Does Tumor Size or Microvascular Invasion Affect Prognosis in Patients with Renal Cell Carcinoma?

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Background: We retrospectively evaluated the effects of tumor size and microvascular tumor invasion on the clinical outcomes of patients who had undergone radical nephrectomy for renal cell carcinoma (RCC).

Methods: One-hundred and sixty-two patients who received radical nephrectomy for localized or locally invasive RCC from 1989 to 2002 were included. We evaluated a new cut-off value for tumor size by dividing patients into groups by tumor diameter from 3.0 to 7.0 cm in 1.0 cm increments and compared the prognosis with that predicted by the 2002 TNM classification. We also re-classified localized microvascular tumor invasion as invasive disease.

Results: Univariate analyses showed a 5.0 cm cut-off provided the greatest difference in recurrence (p = 0.004) and survival (p = 0.001). Microvascular invasion made no significant difference in tumor recurrence and tumor-specific survival. However, in the new categories used in this study, survival in the locally invasive group was poor compared with the localized group.

Conclusion: Our study showed that a tumor diameter of 5.0 cm might be the critical size to determine the prognosis of patients with localized RCC. Microvascular invasion seemed to have the necessity of re-evaluation in the TNM classification for patients with RCC.

Key words: renal cell carcinoma – tumor size – microvascular tumor invasion

INTRODUCTION

In most carcinomas, proliferative activity and metastatic potential, which are reflected in the size, grade and venous and lymphatic infiltration of the tumor, have been identified as important markers for patient prognosis. For example, there is good evidence that tumor size is an important prognostic factor in cutaneous squamous cell carcinoma (1), hepatic cell carcinoma (2) and lung cancer (3). It is also reported that patients with lung adenocarcinoma without vascular invasion clearly have a better outcome after resection (4).

Because no promising treatment exists for patients with metastatic renal cell carcinoma (RCC), predictive markers of RCC should be evaluated precisely at the time of nephrectomy. To date, the pathological stage has been the most important predictor of cancer-specific survival in patients with RCC (5). Although the TNM classification system for evaluation of pathological stage has been generally accepted, several studies have shown that the current TNM staging system does not always correlate well with patient survival in RCC (6–10).

The 1997 TNM staging system (11) considered 7 cm in tumor size as the cut-off point between T1 and T2 RCC. The 2002 TNM staging system (12) introduced a subdivision of T1 into T1a and T1b with a 4.0 cm cut-off. However, recent studies have shown that current staging category of T1 may not be appropriate because a tumor diameter of 4.5–5.5 cm is a better point to divide T2 from T1 in patients who have undergone radical nephrectomy (6–10). In addition, it is significant that microvascular tumor invasion is not included in the TNM classification. It has been reported that microvascular tumor invasion is a poor prognostic factor in the patients with localized RCC (13, 14).

Therefore, we re-evaluated the current staging system in terms of the factors correlated with a poor prognosis described above. In this study, we retrospectively evaluated...
the effects of tumor size and microvascular tumor invasion on clinical outcomes by analyzing the records of patients with localized and locally invasive RCC who had undergone radical nephrectomy.

PATIENTS AND METHODS

PATIENTS

Between 1989 and 2002, 162 patients received radical nephrectomy for localized or locally invasive disease (that is, from T1a to T3c in the 2002 TNM classification) at Tsukuba University Hospital. Patients were pre-operatively evaluated by ultrasonography, computerized tomography, magnetic resonance imaging and chest X-rays. The histological type and grade were determined according to the 1997 WHO classification and Fuhrman criteria, respectively. Tumors were pathologically staged according to the 2002 TNM classification proposed by the American Joint Committee on Cancer. For this study, tumor size and T classification were obtained from the final pathology reports. The pathological T stage and patient characteristics are shown in Table 1. Of 162 patients, 114 cases were localized disease. The mean tumor size was 4.6 cm (median 5.0 cm, range 1–20 cm). The histology showed clear cell carcinoma in 135 (83%) cases. In nine cases, the Fuhrman grade was unknown. The median follow up period was 97 months (range 1–390 months). The follow-up schedule as well as the pre-operative evaluation and survival after nephrectomy were investigated using the patients’ files.

NEW CRITERIA FOR STAGE CLASSIFICATIONS

We re-evaluated the TNM staging by means of new cut-off value of tumor size in the localized diseases. The patients with T1 and T2 tumors were re-divided into two groups of tumor diameters from 3.0 to 7.0 cm by 1.0 cm increments. To evaluate the significance of microvascular invasion as a risk for recurrence, RCC patients with microvascular invasion were included in the invasive disease category and were categorized together with T3a.

STATISTICAL ANALYSES

Disease-specific probability and disease-specific survival based on the 2002 TNM classification criteria and on the new values were calculated using the Kaplan–Meier method and a log-rank test was used to compare survival curves for gender, age, Fuhrman criteria and, tumor size and microvascular invasion in localized disease. Additionally, Cox’s proportional hazard model was used to evaluate the independent predictive value of the prognostic variables that were significant in the univariate analysis and odds ratio for tumor diameter was calculated.

RESULTS

Tumor-specific survival curve is shown in Fig. 1. There was no pathological T3c tumor in the present series. In the patients with T1 and T2 tumors, microvascular invasion was seen in 16 (three in T1a, nine in T1b and four in T2) cases. These tumors were able to be categorized as locally invasive tumors and combined with T3a in the 2002 TNM classification, as shown in Table 2.

Additionally, 99 patients with T1 and T2 tumors were divided into six groups at each cut-off of tumor diameter from 3.0 to 7.0 cm by 1.0 cm increments (Table 2). In the follow-up period, the tumor recurred in 16 cases at an average of 24.9 months (median 19.5 months, range 1–63 months).

Table 1. Patient characteristics and pathological stages according to 2002 TNM classification

<table>
<thead>
<tr>
<th>Gender*</th>
<th>pT1a</th>
<th>pT1b</th>
<th>pT2</th>
<th>pT3a</th>
<th>pT3b</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>42</td>
<td>30</td>
<td>11</td>
<td>14</td>
<td>18</td>
<td>115</td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>13</td>
<td>4</td>
<td>5</td>
<td>11</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>43</td>
<td>15</td>
<td>19</td>
<td>29</td>
<td>162</td>
</tr>
<tr>
<td>Mean age (year)</td>
<td>57.4</td>
<td>58.4</td>
<td>56.1</td>
<td>63.8</td>
<td>62.1</td>
<td>59.5</td>
</tr>
<tr>
<td>Mean tumor size (cm)</td>
<td>2.8</td>
<td>5.7</td>
<td>10.2</td>
<td>7</td>
<td>9.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Pathology*</td>
<td>Clear cell</td>
<td>47</td>
<td>43</td>
<td>13</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>12</td>
<td>27</td>
</tr>
<tr>
<td>Grade*</td>
<td>G1</td>
<td>19</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>G2</td>
<td>34</td>
<td>30</td>
<td>6</td>
<td>14</td>
<td>16</td>
<td>100</td>
</tr>
<tr>
<td>G3</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Vascular invasion* (IVC thrombus)</td>
<td>3</td>
<td>9</td>
<td>4</td>
<td>6</td>
<td>29</td>
<td>51</td>
</tr>
</tbody>
</table>

*Number of the patients.
months), and nine patients died at an average of 61 months (median 47.3 months, range 7–115 months).

The tumor-specific survival curves according to the 2002 TNM classification are shown in Fig. 1. There was no statistical difference in the survival by gender \((p = 0.327)\), age \((p = 0.351)\), or Fuhrman nuclear grade \((p = 0.114)\). The survival rate in the T2 group was poor compared with the T3a group.

In the 5-year disease-specific survival rates of patients with localized disease, univariate analysis of 1.0 cm increments between 3.0 and 7.0 cm showed that the 5.0 cm cut-off provided the greatest difference in recurrence (odds ratio 2.65, \(p = 0.004\)) and survival (odds ratio 3.97, \(p = 0.001\)) rates. The tumor size cut-off of 5.0 cm provided the most significant difference in recurrence among the groups \((p = 0.004)\). Multivariate statistics including age, Fuhrman nuclear grade and tumor size showed that the cut-off point of 5.0 cm was the highest hazard ratio for recurrence and survival rates (odds ratio and \(p\) value in each subgroup are 3.13 and 10.8, and \(p = 0.001\) and 0.001, respectively—Figs 2 and 3).

In patients with microvascular invasion in localized disease, there was no significant difference in tumor recurrence \((p = 0.09)\) and tumor-specific survival \((p = 0.10)\). However, in the new category used in this study, the locally invasive group had a poorer survival rate than the localized group (Fig. 4). Five year survival rate in a new classification was 98% in localized <5 cm, 85% in localized >5 cm, 76% in pT3a/v(+) and 50% in pT3b. The log-rank test revealed significant differences between \(T < 5 \text{ cm}\) and \(T > 5 \text{ cm}\), \(T > 5 \text{ cm} \text{ and } \text{T3a/v}(+)\), and \(\text{T3a/v}(+)\) and T3b \((p = 0.039, < 0.001 \text{ and } 0.023, \text{ respectively})\).

**DISCUSSION**

The pathologic stage remains the main predictor for disease-specific recurrence and death in patients with RCC (5). The 1987 version of the TNM classification introduced the 2.5 cm breakpoint to distinguish T1 from T2 tumors in localized RCC on the basis of tumor size. With 2.5 cm as a cut-off point, no difference in survival between T1 and T2 groups was observed (15). In 1997, the classification for RCC was revised and the criterion for tumor size of T1 was raised from 2.5 cm to 7.0 cm (11). In the present study, therefore, we analyzed a large cohort of patients who underwent radical nephrectomy and were followed for a long

**Table 2.** A number of the patients whose tumor size in local disease and new classification of locally invasive disease

<table>
<thead>
<tr>
<th>Size (cm)</th>
<th>&gt;3</th>
<th>3–4</th>
<th>4–5</th>
<th>5–6</th>
<th>6–7</th>
<th>&lt;7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>23</td>
<td>30</td>
<td>10</td>
<td>12</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Locally invasive disease</td>
<td>v(+)</td>
<td>pT3a</td>
<td>pT3b</td>
<td>pT3c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>16</td>
<td>19</td>
<td>29</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3.** Like Fig. 2, multivariate analysis showed the cut-off point of 5.0 cm was the highest hazard ratio for the 5-year disease-specific survival rates of patients with organ-confined RCC.

**Figure 4.** Tumor-specific survival for the new classification in this study showed the prognosis of patients with RCC better than the 2002 TNM system. The log-rank test revealed significant differences between \(T < 5 \text{ cm}\) and \(T > 5 \text{ cm}\), \(T > 5 \text{ cm} \text{ and } \text{T3a/v}(+)\), and \(\text{T3a/v}(+)\) and T3b \((p = 0.039, < 0.001 \text{ and } 0.023, \text{ respectively})\). RCC, renal cell carcinoma.
period to re-assess the validity of the 1997 classification division between T1 and T2. Previous studies have shown that tumor size is critical to survival of patients after radical nephrectomy and have suggested that the ideal breakpoint is 4.5–5.5 cm. Zisman et al. (6) proposed a tumor diameter of 4.5 cm as the most accurate breakpoint to predict cancer-specific survival in patients with localized RCC. Similarly, Elmore et al. (7) reported that 5.0 cm was the optimal cut-off point for tumor size for the prediction of patient prognosis. In addition, Kinouchi et al. (8) and Ficarra et al. (9) suggested a tumor size of 5.5 cm as an optimal cut-off using retrospective studies, that analyzed patients with radical nephrectomy. In the present study, we propose 5.0 cm as an optimal breakpoint based on the survival rate of patients with T1 disease. As shown in previous studies, a tumor diameter of 7.0 cm may be too large to assess the prognosis of patients with stage 1 tumor of any TNM classification system. Indeed, Ficarra et al. (10) previously showed no apparent difference between pT1b and pT2 tumors in the cancer-specific survival of patients.

In patients with similar pathological stages of RCC, different clinical courses have frequently been observed after radical nephrectomy. This finding allows us to better consider additional parameters that might predict disease outcome. The significance of vascular invasion in the prognosis of RCC has elicited great discussion. In terms of microvascular tumor invasion of tissue surrounding the tumor, several previous studies attempted to establish whether microvascular invasion could be considered a negative prognostic factor. According to a study by Goncalves et al. (13), microvascular invasion is a significantly associated with poor prognosis in patients with RCC. Ishimura et al. (14) also showed that disease recurrence after radical nephrectomy in patients with pT1 and pT2 RCC could be predicted. In our study, although patients with microvascular invasion did not show a poor prognosis in univariate analysis, the new categories used in this study showed that the locally invasive group had a poor survival rate compared with the localized group (Fig. 4). The TNM classification system should predict the disease-specific survival. However, the survival rate in the T2 group of our series was poor compared with that in T3a group, as shown in Fig. 1. Although the number of T2 patients was small, this might indicate that the 2002 TNM system is not optimal to predict the prognosis of patients with T2 and T3a RCC. The new criteria proposed in this study could predict the prognosis of patients with RCC more accurately than the 2002 TNM system.

In conclusion, our retrospective analysis showed that a tumor diameter of 5.0 cm might be the critical size to determine the prognosis of the patients with localized RCC. Microvascular tumor invasion may need to be re-evaluated in the TNM classification for patients with RCC.

Conflict of interest statement
None declared.

References