

# Epidemiology and Staging of Renal Cell Carcinoma

Carole A. Ridge, FFRRCSI<sup>1</sup> Bradley B. Pua, MD<sup>2</sup> David C. Madoff, MD, FSIR<sup>2</sup>

<sup>1</sup> Department of Radiology, Mater Misericordiae University Hospital, Dublin, Ireland

<sup>2</sup> Division of Interventional Radiology, Department of Radiology, New York–Presbyterian Hospital/Weill Cornell Medical College, New York, New York

Address for correspondence David C. Madoff, MD, FSIR, Division of Interventional Radiology, Department of Radiology, New York–Presbyterian Hospital/Weill Cornell Medical College, 525 East 68th Street, Payson Pavilion, 5, New York, NY 10065 (e-mail: dcm9006@med.cornell.edu).

Semin Intervent Radiol 2014;31:3–8

## Abstract

Incidence and mortality trends attributed to kidney cancer exhibit marked regional variability, likely related to demographic, environmental, and genetic factors. Efforts to identify reversible factors, which lead to the development of renal cell carcinoma (RCC), have led not only to a greater understanding of the etiology of RCC but also the genetic and histologic characteristics of renal tumors. This article describes this evolution by discussing contemporary RCC incidence and mortality data, the risk factors for development of RCC, the histologic features, and anatomic and integrated staging systems that guide treatment.

## Keywords

- ▶ renal cell carcinoma
- ▶ kidney cancer
- ▶ epidemiology and staging
- ▶ incidence
- ▶ mortality
- ▶ risk factors

**Objectives:** Upon completion of this article, the reader will be able to identify the current national and international epidemiologic data regarding renal cell carcinoma (RCC) incidence, mortality and survival; the demographic, environmental and genetic risk factors for development of RCC; and the current classification and staging of RCC.

**Accreditation:** This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Tufts University School of Medicine (TUSM) and Thieme Medical Publishers, New York. TUSM is accredited by the ACCME to provide continuing medical education for physicians.

**Credit:** Tufts University School of Medicine designates this journal-based CME activity for a maximum of **1 AMA PRA Category 1 Credit**<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

## Incidence

Kidney cancer is the 14th most common cancer in the world,<sup>1</sup> and its global incidence in 2008 was estimated to be 273,518.

The global age-standardized incidence rate based on this data was 4 per 100,000 people per year. Incidence rates are highest in Europe, North America, and Australia and lowest in India, Japan, Africa, and China.<sup>2</sup> The incidence in the United States between 2006 and 2010 is reported to be 15.3 per 100,000 people per year.<sup>3</sup> In contrast, in the same year, kidney cancer incidence in China<sup>1</sup> was 21,269 in 2008 with an age-standardized rate of 2.8. There has been some improvement in kidney cancer incidence in the United States, however, while the annual percentage change between 1997 and 2008 was +3.2%, incidence then decreased by –3.4% from 2008 to 2010.<sup>3</sup>

## Mortality

The global mortality rate from kidney cancer was estimated to be 72,019 in 2008, with a global age-standardized mortality rate of 2.2 per 100,000 people per year.<sup>1</sup> The mortality rate in the United States between 2006 and 2010 is reported to be 4 per 100,000 people per year.<sup>3</sup> In contrast, kidney cancer mortality in China was 7,053 in 2008 with an age-standardized rate of 0.9 in the same year.<sup>1</sup> Kidney cancer mortality rates have remained stable in the United States in recent

Issue Theme Renal Malignancies; Guest Editors, Bradley B. Pua, MD and David C. Madoff, MD, FSIR

Copyright © 2014 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.  
Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0033-1363837>.  
ISSN 0739-9529.

decades. The annual percentage change between 1975 and 1994 was +1%, which then decreased by -0.6% from 2008 to 2010.<sup>3</sup> In contrast, the overall mortality rate for kidney cancer in Europe peaked at 3.5 per 100,000 from 1990 through 1994, and declined to 3 per 100,000 from 2000 to 2004.<sup>4</sup>

## Survival

Surveillance, Epidemiology, and End Results (SEER) data indicate that 5-year relative survival rates have improved for renal cell carcinoma (RCC) patients diagnosed in the United States<sup>3</sup> between 1983 and 1987 from 56.4 to 71.8% between 2003 and 2009. When subdivided by tumor size, a data analysis of the SEER database from 1983 to 2002 indicated that 5-year relative survival rates improved more for tumors measuring less than 2 cm (278% improvement) compared with those measuring between 2 and 4 cm (193% improvement) and survival for patients diagnosed with tumors measuring > 4 cm, which showed a lesser improvement over the same time period (48–59%).<sup>3,5</sup> Similarly, 5-year relative survival rate is significantly better for patients with localized disease (91.7%) compared with patients with regional (64.2%) and distant (12.3%) metastasis.<sup>3</sup>

## Risk Factors

### Demographics

Racial and gender disparities occur in terms of RCC incidence and survival rate. A population study performed in California demonstrated a significantly increased incidence of RCC and lower associated survival rate in African American and Hispanic patients compared with all other races studied.<sup>6</sup> Survival was lowest among African Americans, despite disease detection at a younger age and more localized disease stage. Several reasons have been proposed for this disparity: first, hypertension, a known risk factor for RCC, affects African populations more often and at a younger age than other racial groups; second, lower socioeconomic status, comorbidities, and reduced access to health care may contribute to a higher incidence, for example, African American patients have been shown to have a lower likelihood of receiving nephrectomy for RCC despite correction for age, gender, cancer stage, tumor size, and comorbidities.<sup>7</sup> Socioeconomic factors such as poverty and education have also been shown to be determinants of nonsurgical management of African American patients with RCC.<sup>8</sup>

RCC incidence indicates that men are at an increased risk of developing RCC.<sup>1</sup> In the aforementioned Californian population analysis, for example, males had twice the incidence rate and a lower survival rate when compared with females.<sup>6</sup> This is echoed in global and U.S. data.<sup>1,3</sup> Females also present with less advanced tumors, leading to a 19% reduced risk of death from RCC compared with men.<sup>9</sup> This survival benefit was only observed, however, in females younger than 59 years.

SEER data indicate that RCC incidence rates increase with age for all racial groups until the age of 70 years.<sup>3</sup> The decline in incidence at this time point may relate in part to less invasive diagnostic testing in the elderly because the RCC

incidence disparity after the age of 85 lessens when cases without pathologic confirmation are included in analysis.<sup>6</sup>

## Cigarette Smoking

Cigarette smoking is an established independent risk factor for RCC.<sup>10</sup> This increased risk is strongly dose dependent and also leads to a more advanced stage at diagnosis (e.g., nodal involvement and distant metastasis) than in nonsmokers.<sup>11</sup> Cumulative exposure is proportional to RCC risk: smokers with less than 10 pack-years of cumulative exposure have a 7% increased risk and smokers with a 30 to 40 pack-years exposure have up to an 80% greater risk of advanced RCC than nonsmokers.<sup>11</sup> This increased risk has been attributed to several biologic mechanisms: smoking induces renal damage by toxic effects on the renal tubules, and hemodynamic alterations including hypertension, endothelial cell dysfunction, and oxidative stress.<sup>12</sup> In addition to this, carcinogenic mechanisms have been proposed, which predispose certain smokers to RCC. 4-Methylnitrosamino-1-(3-pyridyl)-1-butane (NNK) is an abundant carcinogenic N-nitrosamine present in cigarette smoke, and has been shown to lead to greater DNA damage in peripheral blood lymphocytes in smokers who are sensitive to NNK, thus leading to the development of RCC.<sup>13</sup> Benzo- $\alpha$ -pyrene-diol epoxide (BPDE) is also in abundance in cigarette smoke. This substance induces chromosomal aberrations at the 3p locus, which are associated with susceptibility to smoking-associated cancers, including RCC in patients who are susceptible to BPDE.<sup>14</sup>

## Medical Comorbidities

Increased body mass index (BMI) is an independent risk factor for RCC.<sup>15</sup> The hazard ratio for patients with a BMI  $\geq$  35 kg/m<sup>2</sup> is 1.8 compared with patients with BMI < 25 kg/m<sup>2</sup>, among a prospectively analyzed cohort in the United States. There may also be a gender disparity in terms of metabolic risk factors: high BMI, blood pressure, glucose, and triglycerides were associated with a risk of RCC in males in a large prospective study in Europe, whereas high BMI was the only metabolic risk factor demonstrable among women in the same geographic area.<sup>16</sup>

Hypertension doubles the risk of RCC. This risk is greater in poor hypertension control, and differs by ethnicity: a population-based case-control demonstrated an odds ratio of 1.9 for white Americans compared with 2.8 for African Americans. This risk was shown to increase with time after the diagnosis of hypertension, almost doubling for both groups after 25 years.<sup>17</sup>

## Genetic Risk Factors

Hereditary RCC is predominantly caused by von Hippel-Lindau (VHL) syndrome, hereditary papillary renal cell carcinoma (HPRCC), hereditary leiomyomatosis and RCC, and Birt-Hogg-Dubé syndromes.

RCC accounts for 50% of deaths in patients with VHL, which is an autosomal dominant condition with high penetrance.

**Table 1** Robson renal cell carcinoma staging system<sup>23</sup>

| Tumor stage | Description  |
|-------------|--|
| Stage I     | Confined to the kidney                                       |
| Stage II    | Involvement of the perinephric fat, limited to Gerota fascia |
| Stage III   |  |
| IIIa        | Renal vein involvement                                       |
| IIIb        | Nodal involvement  |
| IIIc        | Both renal vein and nodal involvement                        |
| Stage IV    |  |
| IVa         | Direct invasion of adjacent structures                       |
| IVb         | Distant metastasis   |

Clear cell RCC usually develops in the fourth decade of life.<sup>18</sup> VHL arises as a result of a mutation in the VHL tumor suppressor gene on chromosome 3 that produces a protein that targets hypoxia inducible factors for ubiquitin-mediated degradation. Hypoxia is associated with a buildup of these factors that leads to upregulation of vascular endothelial growth factor and other factors that promote angiogenesis and growth of typically hypervascular tumors.<sup>2,19</sup> Extrarenal manifestations include pancreatic cysts and neuroendocrine tumors, pheochromocytomas, paragangliomas, cystadenomas of the epididymis or broad ligament, retinal angiomas, endolymphatic sac tumors, and hemangioblastomas of the cerebellum, brainstem, and spinal cord.<sup>2</sup>

HPRCC is a rare autosomal dominant syndrome due to mutations in the C-met protooncogene on chromosome 7. Affected individuals are at risk of developing bilateral, multifocal papillary type 1 RCC. Unlike VHL, the kidney is the only

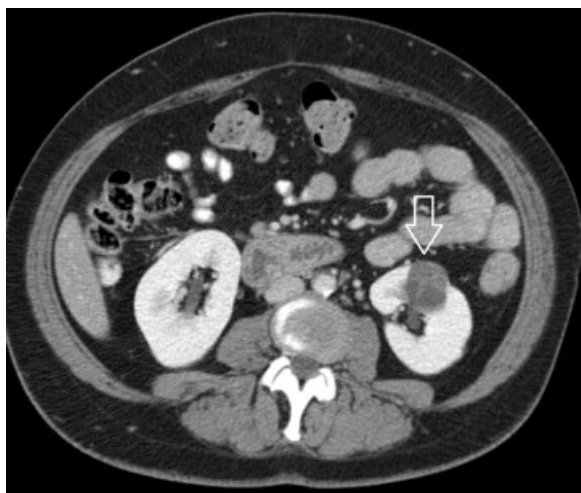
organ affected by HPRCC, and renal tumors can arise between the third and fifth decades.<sup>19</sup> Hereditary leiomyomatosis and RCC is an autosomal dominant disorder that comprises multiple fibroids, cutaneous leiomyomata, and type 2 papillary RCC. It is linked to a mutation or deletion<sup>20</sup> of the fumarate hydratase gene on chromosome 1. Tumors are more frequently solitary and unilateral and are characteristically aggressive, with metastases seen in more than 50% of cases. Birt-Hogg-Dubé syndrome<sup>21</sup> is a rare autosomal dominant disorder caused by a mutation in the folliculin gene on chromosome 17. Affected patients develop cutaneous fibrofolliculomas, lung cysts, spontaneous pneumothoraces, and RCC, most commonly in the sixth decade. Various histologic subtypes of RCC occur including chromophobe RCC, oncocytoma, and, rarely, clear cell carcinoma.<sup>2,22</sup>

## Staging

Staging for RCC has evolved from the Robson classification into the TNM system, developed by the International Union Against Cancer and the American Joint Committee on Cancer.<sup>23,24</sup> The Robson staging system refers largely to the tumor relationship to Gerota fascia, involvement of renal vein, and regional nodes (► **Table 1**).<sup>23</sup> The TNM staging system, originally proposed in 1978, was most recently revised in its seventh edition in 2010. Tumor T stage consists of five stages: T0 to T4. Stages T1 and T2 and their subdivisions are assigned on size alone, while stages T3 and T4 are assigned according to features of locoregional extension into the renal vein, inferior vena cava, Gerota fascia, and the ipsilateral adrenal gland (► **Table 2**).<sup>24</sup> This system takes into account the influence that local factors such as perinephric fat invasion, invasion of IVC wall, as well as lymph node involvement and distant

**Table 2** TNM staging for renal cell carcinoma<sup>24</sup>

| Stage                | Definition  | Subdivision  |
|----------------------|---|--|
| Tumor stage          |   |  |
| T0                   | No evidence of primary tumor  |  |
| T1                   | < 7 cm in greatest dimension, confined to the kidney  | 1a: < 4 cm (► <b>Fig. 1</b> )<br>1b: > 4 cm and < 7 cm   |
| T2                   | > 7 cm in greatest dimension, confined to the kidney  | 2a: > 7 cm < 10 cm (► <b>Fig. 2</b> )<br>2b: > 10 cm   |
| T3                   | Extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland or beyond Gerota fascia              | 3a: Tumor extends into renal vein branches, or invades perirenal and/or renal sinus fat (► <b>Fig. 3</b> ) |
|                      |   | 3b: Tumor extends into the subdiaphragmatic inferior vena cava   |
|                      |   | 3c: Tumor extends into the supradiaphragmatic inferior vena cava   |
| T4                   | Tumor invades beyond the Gerota fascia and/or contiguous extension into the ipsilateral adrenal gland (► <b>Figs. 4 and 5</b> ) |  |
| Regional lymph nodes |   |  |
| N0                   | No regional lymph node metastasis   |  |
| N1                   | Metastasis to regional lymph nodes  |  |
| Distant metastasis   |   |  |
| M0                   | No distant metastasis   |  |
| M1                   | Distant metastasis  |  |

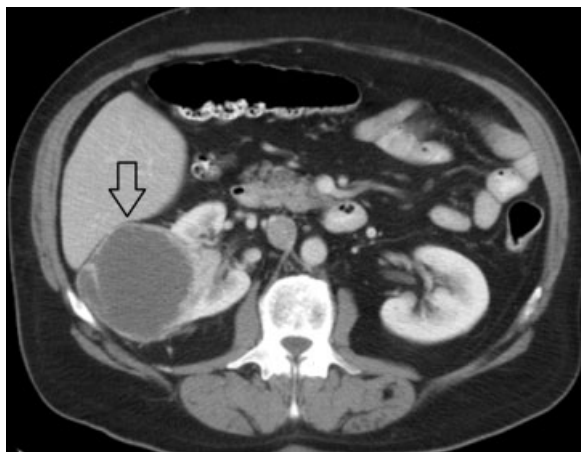


**Figure 1** Axial contrast-enhanced computed tomography of a left clear cell renal cell carcinoma (arrow) measuring 3.7 cm in maximal dimension indicating a T stage of T1a.

metastasis at presentation independently exert on survival.<sup>25</sup> The most recent edition has introduced some modifications from the sixth edition. Specifically, T2 lesions are subdivided into T2a (> 7 cm but ≤ 10 cm) and T2b (> 10 cm), ipsilateral adrenal involvement is classified as T4 if it is contiguous and M1 if it is noncontiguous, and finally renal vein involvement is classified as T3a.

### Histologic Grading

The Fuhrman histologic classification system is the most widely accepted classification of tumor grade.<sup>26</sup> The three World Health Organization histologic RCC types—clear cell RCC (80–90% of cases), papillary RCC (10–15%), and chromophobe RCC (4–5%)—can be further differentiated by histologic features into nuclear grades.<sup>27</sup> Papillary RCC is further divided into two different subtypes, type 1 and type 2, in order of worsening prognosis.<sup>28</sup> Four Fuhrman nuclear grades are assigned according to increasing nuclear size, irregularity,



**Figure 2** Axial computed tomography without intravenous contrast demonstrating a left clear cell renal cell carcinoma measuring 5.2 cm with renal sinus fat invasion (arrow) indicating a T stage of T3a.



**Figure 3** Axial contrast-enhanced computed tomography of a right clear cell renal cell carcinoma (arrow) measuring 7.5 cm in maximal dimension without extrarenal extension indicating a T stage of T2a.

and nucleolar prominence. At the time of its initial description in 1982, nuclear grade was felt to be more effective than pathologic stage, tumor size, cell arrangement, and cell type in predicting development of distant metastasis following nephrectomy.<sup>29</sup> Prognosis estimation has subsequently been enhanced by modifications to RCC staging, in association with histologic features.<sup>30</sup>

### Integrated Staging Systems

Individual clinical factors including patient performance status, localized symptoms, low BMI, and anemia have been shown to independently predict survival, especially in patients with metastatic disease.<sup>26</sup> With this in mind, integrated staging systems have been devised to improve upon the TNM staging system.<sup>31</sup> One such system is the University of California Los Angeles (UCLA) Integrated Staging System.<sup>32</sup> Along with tumor stage, a patient's performance status and Fuhrman grade is used to divide patients



**Figure 4** Axial contrast-enhanced computed tomography of a left medullary renal cell carcinoma in a patient with sickle trait. The tumor is multifocal, with invasion of the main left renal vein (white arrow) and extension outside Gerota fascia (hollow arrow) indicating a T stage of T4.





**Figure 5** Coronal T2-weighted magnetic resonance imaging of a large left chromophobe renal cell carcinoma with direct involvement of the left adrenal gland and extension beyond Gerota fascia (arrow) consistent with a T stage of T4.

into low-, intermediate-, and high-risk groups. For patients with localized kidney cancer, a 5-year survival rate of 91% for the low-risk group, 80% for the intermediate group, and 55% for the high-risk group is estimated. In a subsequent report, the UISS was further enhanced to predict freedom from cancer-specific mortality.<sup>33</sup> Metastatic and nonmetastatic patients are stratified into low-, intermediate-, or high-risk categories for cancer-specific mortality and have been shown to effectively discriminate in terms of cancer-specific mortality in 64% of an Asian population and 86% of a Western population.

## Conclusion

Kidney cancer is the 14th most common cancer in the world. Kidney cancer incidence and mortality has plateaued in North America and Europe in recent years and continues to increase in incidence in developing countries. Survival is significantly better for patients with localized disease compared with patients with regional and distant metastasis, thus underscoring the importance of early detection. This can be enhanced by identifying and modifying known risk factors to the development of RCC such as smoking, hypertension and obesity, and adequate monitoring of those individuals with hereditary syndromes associated with RCC. Once diagnosed, staging, histologic grading, and clinical risk stratification can help guide therapy and predict prognosis accurately.

### Acknowledgment

The authors thank Robert A. Lefkowitz, MD, from Memorial Sloan Kettering Cancer Center, New York, NY, for assistance in image selection.

## References

- 1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127(12):2893–2917
- 2 Ljungberg B, Campbell SC, Choi HY, et al. The epidemiology of renal cell carcinoma. *Eur Urol* 2011;60(4):615–621
- 3 Howlader N, Noone AM, Krapcho M, et al, (eds). SEER Cancer Statistics Review, 1975–2010, National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2010/](http://seer.cancer.gov/csr/1975_2010/), based on November 2012 SEER data submission, posted to the SEER web site, April 2013
- 4 Levi F, Ferlay J, Galeone C, et al. The changing pattern of kidney cancer incidence and mortality in Europe. *BJU Int* 2008;101(8):949–958
- 5 Chow WH, Linehan WM, Devesa SS. Re: Rising incidence of small renal masses: a need to reassess treatment effect. *J Natl Cancer Inst* 2007;99(7):569–570, author reply 570–571
- 6 Chow WH, Devesa SS. Contemporary epidemiology of renal cell cancer. *Cancer J* 2008;14(5):288–301
- 7 Berndt SI, Carter HB, Schoenberg MP, Newschaffer CJ. Disparities in treatment and outcome for renal cell cancer among older black and white patients. *J Clin Oncol* 2007;25(24):3589–3595
- 8 Becker A, Roghmann F, Trinh QD, et al. Sociodemographic disparities in the treatment of small renal masses. *BJU Int* 2013;111(8):E274–E282
- 9 Rampersaud EN, Klatter T, Bass G, et al. The effect of gender and age on kidney cancer survival: younger age is an independent prognostic factor in women with renal cell carcinoma. *Urol Oncol* 2014;32(1):30
- 10 Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. *Nat Rev Urol* 2010;7(5):245–257
- 11 Tsivian M, Moreira DM, Caso JR, Mouraviev V, Polascik TJ. Cigarette smoking is associated with advanced renal cell carcinoma. *J Clin Oncol* 2011;29(15):2027–2031
- 12 Orth SR. Cigarette smoking: an important renal risk factor—far beyond carcinogenesis. *Tob Induc Dis* 2002;1(2):137–155
- 13 Clague J, Shao L, Lin J, et al. Sensitivity to NNKOAc is associated with renal cancer risk. *Carcinogenesis* 2009;30(4):706–710
- 14 Zhu Y, Horikawa Y, Yang H, Wood CG, Habuchi T, Wu X. BPDE induced lymphocytic chromosome 3p deletions may predict renal cell carcinoma risk. *J Urol* 2008;179(6):2416–2421
- 15 Macleod LC, Hotaling JM, Wright JL, et al. Risk Factors for Renal Cell Carcinoma in the Vitamin and Lifestyle (VITAL) Study. *J Urol* 2013;190(5):1657–1661
- 16 Häggström C, Rapp K, Stocks T, et al. Metabolic factors associated with risk of renal cell carcinoma. *PLoS ONE* 2013;8(2):e57475
- 17 Colt JS, Schwartz K, Graubard BI, et al. Hypertension and risk of renal cell carcinoma among white and black Americans. *Epidemiology* 2011;22(6):797–804
- 18 Chauveau D, Duvic C, Chrétien Y, et al. Renal involvement in von Hippel-Lindau disease. *Kidney Int* 1996;50(3):944–951
- 19 Pfaffenroth EC, Linehan WM. Genetic basis for kidney cancer: opportunity for disease-specific approaches to therapy. *Expert Opin Biol Ther* 2008;8(6):779–790
- 20 Tomlinson IP, Alam NA, Rowan AJ, et al; Multiple Leiomyoma Consortium. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. *Nat Genet* 2002;30(4):406–410
- 21 Northrup BE, Jorke CE, Grubb RL III, Menias CO, Khanna G, Siegel CL. Hereditary renal tumor syndromes: imaging findings and management strategies. *AJR Am J Roentgenol* 2012;199(6):1294–1304
- 22 Cohen D, Zhou M. Molecular genetics of familial renal cell carcinoma syndromes. *Clin Lab Med* 2005;25(2):259–277
- 23 Sheth S, Scatarige JC, Horton KM, Corl FM, Fishman EK. Current concepts in the diagnosis and management of renal cell carcinoma: role of multidetector CT and three-dimensional CT. *Radiographics* 2001;21(Spec No):S237–S254
- 24 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer Science and Business Media; 2010
- 25 Cho MC, Kim JK, Moon KC, Kim HH, Kwak C. Prognostic factor for Korean patients with renal cell carcinoma and venous tumor thrombus extension: application of the new 2009 TNM staging system. *Int Braz J Urol* 2013;39(3):353–363

- 26 Ljungberg B, Cowan NC, Hanbury DC, et al; European Association of Urology Guideline Group. EAU guidelines on renal cell carcinoma: the 2010 update. *Eur Urol* 2010;58(3):398–406
- 27 Eble JN, Sauter G, Epstein JI, Sesterhenn IA. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. World Health Organization Classification of Tumours. Lyon, France: IARC Press; 2004:7
- 28 Pignot G, Elie C, Conquy S, et al. Survival analysis of 130 patients with papillary renal cell carcinoma: prognostic utility of type 1 and type 2 subclassification. *Urology* 2007;69(2):230–235
- 29 Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. *Am J Surg Pathol* 1982;6(7):655–663
- 30 Kontak JA, Campbell SC. Prognostic factors in renal cell carcinoma. *Urol Clin North Am* 2003;30(3):467–480
- 31 Meskawi M, Sun M, Trinh QD, et al. A review of integrated staging systems for renal cell carcinoma. *Eur Urol* 2012;62(2):303–314
- 32 Zisman A, Pantuck AJ, Dorey F, et al. Improved prognostication of renal cell carcinoma using an integrated staging system. *J Clin Oncol* 2001;19(6):1649–1657
- 33 Zisman A, Pantuck AJ, Wieder J, et al. Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. *J Clin Oncol* 2002;20(23):4559–4566