Epidemiology and Staging of Renal Cell Carcinoma

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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.

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Incidence

Kidney cancer is the 14th most common cancer in the world,[1] 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.[2] The incidence in the United States between 2006 and 2010 is reported to be 15.3 per 100,000 people per year.[3] In contrast, in the same year, kidney cancer incidence in China[1] 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.[3]

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.[1] The mortality rate in the United States between 2006 and 2010 is reported to be 4 per 100,000 people per year.[3] In contrast, kidney cancer mortality in China was 7,053 in 2008 with an age-standardized rate of 0.9 in the same year.[1] Kidney cancer mortality rates have remained stable in the United States in recent

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decades. The annual percentage change between 1975 and 1994 was +1%, which then decreased by – 0.6% from 2008 to 2010.[3] 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.[4]

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[3] 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%).[3,5] 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.[3]

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.[6] 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.[7] Socioeconomic factors such as poverty and education have also been shown to be determinants of nonsurgical management of African American patients with RCC.[8]

RCC incidence indicates that men are at an increased risk of developing RCC.[1] In the aforementioned Californian population analysis, for example, males had twice the incidence rate and a lower survival rate when compared with females.[6] This is echoed in global and U.S. data.[1,3] Females also present with less advanced tumors, leading to a 19% reduced risk of death from RCC compared with men.[9] 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.[3] 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.[6]

Cigarette Smoking

Cigarette smoking is an established independent risk factor for RCC.[10] 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.[11] 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.[11] 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.[12] In addition to this, carcinogenetic mechanisms have been proposed, which predispose certain smokers to RCC. 4-Methylnitrosamino-1-(3-pyridyl)-1-butanone (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.[13] Benzo-α-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.[14]

Medical Comorbidities

Increased body mass index (BMI) is an independent risk factor for RCC.[15] The hazard ratio for patients with a BMI $\geq$ 35 kg/m^2 is 1.8 compared with patients with BMI $<$ 25 kg/m^2, 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.[16]

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.[17]

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[23]

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.[18] 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.[2,19] 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.[2]

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.[19] 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[20] 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[21] 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.[2,22]

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.[23,24] The Robson staging system refers largely to the tumor relationship to Gerota fascia, involvement of renal vein, and regional nodes (►**Table 1**).[23] 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**).[24] 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[24]

Stage	Definition	Subdivision
Tumor stage		
T0	No evidence of primary tumor	
T1	$<$ 7 cm in greatest dimension, confined to the kidney	1a: $<$ 4 cm (►**Fig. 1**) 1b: $>$ 4 cm and $<$ 7 cm
T2	$>$ 7 cm in greatest dimension, confined to the kidney	2a: $>$ 7 cm $<$ 10 cm (►**Fig. 2**) 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 (►**Fig. 3**)
		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 (►**Figs. 4** and **5**)	
Regional lymph nodes		
N0	No regional lymph node metastasis	
N1	Metastasis to regional lymph nodes	
Distant metastasis		
M0	No distant metastasis	
M1	Distant metastasis	

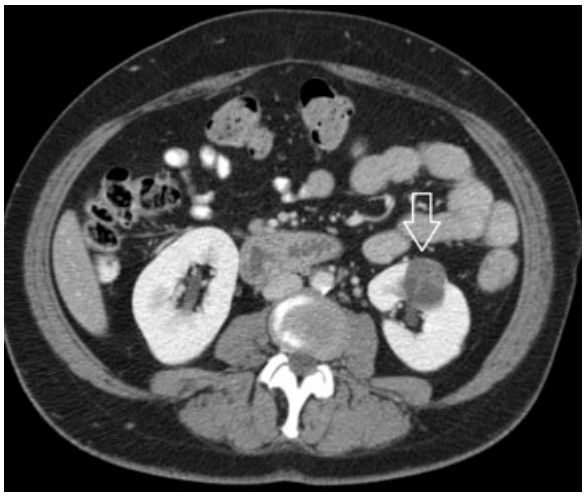

Figure 1 Axial contrast-enhanced computed tomography of a left clear cell renal cell carcinoma (arrow) measuring 3.7 cm in maximal dimension indicating a T stage of T1a.

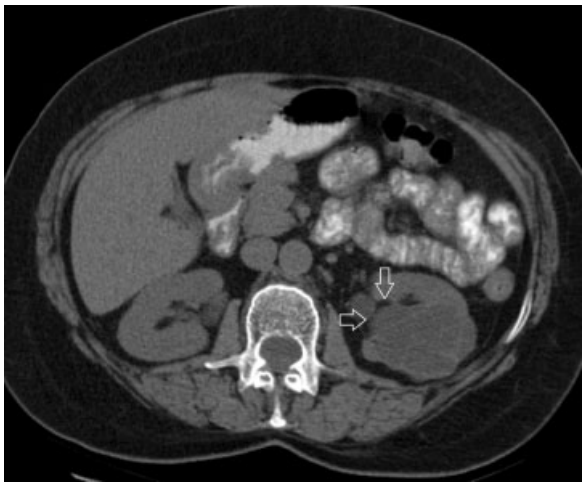

Figure 3 Axial contrast-enhanced computed tomography of a right clear cell renal cell carcinoma (arrow) measuring 7.5 cm in maximal dimension without extrarenal extension indicating a T stage of T2a.

metastasis at presentation independently exert on survival.[25] The most recent edition has introduced some modifications from the sixth edition. Specifically, T2 lesions are subdivided into T2a ($>$ 7 cm but $\leq$ 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.[26] 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.[27] Papillary RCC is further divided into two different subtypes, type 1 and type 2, in order of worsening prognosis.[28] Four Fuhrman nuclear grades are assigned according to increasing nuclear size, irregularity, 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.[29] Prognosis estimation has subsequently been enhanced by modifications to RCC staging, in association with histologic features.[30]

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.[26] With this in mind, integrated staging systems have been devised to improve upon the TNM staging system.[31] One such system is the University of California Los Angeles (UCLA) Integrated Staging System.[32] Along with tumor stage, a patient's performance status and Fuhrman grade is used to divide patients

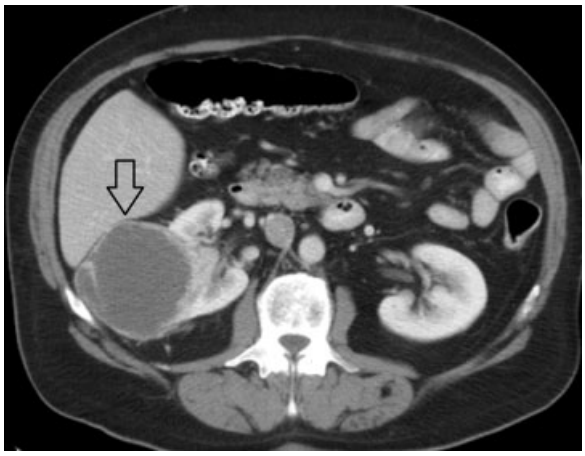

Figure 2 Axial computed tomography without intravenous contrast demonstrating a left clear cell renal cell carcinoma measuring 5.2 cm with renal sinus fat invasion (arrow) indicating a T stage of T3a.

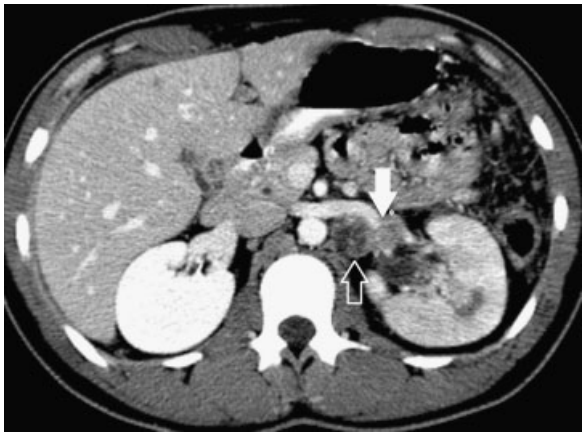

Figure 4 Axial contrast-enhanced computed tomography of a left medullary renal cell carcinoma in a patient with sickle trait. The tumor is multifocal, with invasion of the main left renal vein (white arrow) and extension outside Gerota fascia (hollow arrow) indicating a T stage of T4.

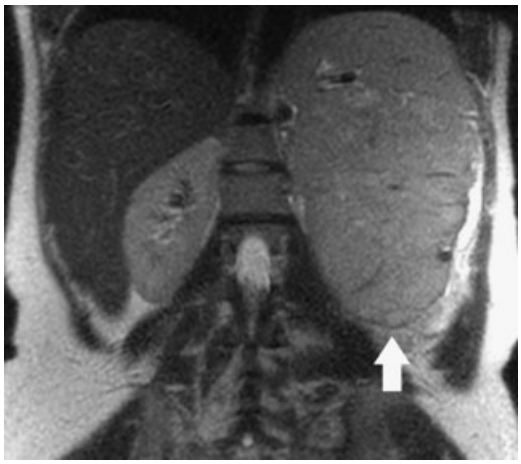

Figure 5 Coronal T2-weighted magnetic resonance imaging of a large left chromophobe renal cell carcinoma with direct involvement of the left adrenal gland and extension beyond Gerota fascia (arrow) consistent with a T stage of T4.

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.[33] 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.

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