Chapter 13
Kidney Cancer

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Introduction

Approximately 58,000 people in the United States were diagnosed with kidney cancer in 2011, and an estimated 13,000 people will die as a result of the disease [1]. Cancer of the kidney represents 3.9% of all U.S. cancers and 2% of all cancer deaths. During their lifetime, 1 in 70 men and women will be diagnosed with cancer of the kidney or renal pelvis [2]. Worldwide, the mortality from renal cell carcinoma (RCC) is estimated to exceed 100,000 per year [3].

Kidney cancer is subdivided into two major histologic subtypes: RCC and transitional cell carcinoma. RCC arises within the renal parenchyma and accounts for about 85% of all primary renal neoplasms. RCC is further subdivided into multiple subtypes that exhibit differential biologic and prognostic features. Transitional cell carcinoma arising from the renal pelvis accounts for 7% of primary renal neoplasms, and its biology is similar to that of transitional cell carcinoma of the bladder. Several other rare parenchymal epithelial tumors, such as oncocytomas, collecting duct tumors, and renal sarcomas, account for the remaining tumors. Herein, we will review the advances and treatment of RCC at The University of Texas MD Anderson Cancer Center.

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Historical Perspective

For localized disease, the mainstay of treatment for RCC has been surgical excision. In the 1960s, radical nephrectomy became the procedure of choice, with a reported 66% 5-year survival rate, which compared favorably with that of simple nephrectomy at 48%. For almost 35 years, the procedure was relatively static, with only slight modifications associated with the excision of the ipsilateral adrenal gland and the management of regional lymph nodes. In the 1990s, minimally invasive surgical techniques (laparoscopy) were heralded, followed by the adoption of partial nephrectomy techniques (nephron-sparing surgery). In properly selected patients, partial nephrectomy has yielded equivalent oncologic outcomes and has become the standard of care for many patients with small renal masses [4]. Although initially used only to perform radical nephrectomy, the laparoscopic approach is now used for some nephron-sparing surgeries.

In the 2000s, further advances in technology have spawned ablative technologies (cryotherapy and radiofrequency ablation) for small renal masses as well as robotic extirpative and reconstructive techniques. The durability of oncologic outcomes with the use of ablative techniques remains to be proven.

Even more recently, active surveillance of the small (less than 4 cm) renal mass has gained increasing popularity for those with a reduced life expectancy due to age, severe medical conditions, or a high surgical risk. The use of partial nephrectomy for small renal masses has an equivalent cancer-specific survival rate and possibly an improved overall survival rate compared with radical nephrectomy [4]. The increased overall survival is purported to be due to a decrease in the comorbid chronic medical conditions associated with the development of chronic renal insufficiency. As in many aspects of oncologic treatment, surgical therapy for RCC is best modified for each individual patient. Systemic agents are also tailored to the individual patient with use of a multifaceted analysis of histologic subtype, patient comorbid medical conditions, burden of disease, and other characteristics.

Risk Factors

Numerous environmental and clinical factors have been implicated in the etiology of RCC [5]: tobacco use; occupational exposure to toxic compounds such as cadmium, asbestos, and petroleum by-products; obesity; acquired polycystic disease of the kidney (typically associated with dialysis); and analgesic abuse nephropathy. Cigarette smoking doubles the likelihood of RCC and contributes to as many as one-third of all cases [6–8]. The risk of developing RCC in patients with acquired polycystic disease of the kidney has been estimated to be 30 times greater than in the general population [9].

Although most RCCs are sporadic (>90%), factors suggesting a hereditary cause include first-degree relatives with the disease [10–13], onset before age 40, and

bilateral or multifocal disease [14]. An enhanced risk of RCC has been observed in patients with certain inherited disorders (von Hippel–Lindau disease, hereditary papillary renal cancer, hereditary leiomyomatosis renal cancer syndrome, and Birt–Hogg–Dube syndrome), thereby implicating various genetic abnormalities in its etiology. In addition, patients with tuberous sclerosis and hereditary polycystic kidney disease, although not having a substantially increased incidence of renal cancer, can have cancers with unique features.

Staging

Approximately 75% of patients present with clinically localized disease amenable to surgical treatment. Despite the initial presentation, up to 40% of these patients will experience recurrence of disease after the primary lesion is treated. In RCC, the most consistent predictor of patient outcome is stage. Multiple modifications to the American Joint Committee on Cancer (AJCC) staging system have occurred to further improve the prognostic accuracy of the staging system. In 2002, the T1 stage was further subdivided into T1a and T1b [15]. In 2009, the T2 and T3 staging categories were modified and the nodal stage simplified to better reflect outcome in patients with advanced-stage disease (Table 13.1) [16].

The overall incidence of RCC in the United States for all races has been increasing and is now three times higher than the mortality rate. Since 1950, there has been a 126% increase in the incidence of RCC, accompanied by a 37% increase in annual mortality [17, 18]. Moreover, the 5-year survival rate of patients diagnosed with RCC has improved, from 34% for those diagnosed in 1954 to 67% for those diagnosed in 2004 [19].

With the widespread introduction of cross-sectional imaging in the mid-1980s, the incidence of low-stage tumors increased substantially. Incidental discovery of RCC increased from approximately 10% in the 1970s to 60% in 1998, and the mortality rate between 1990 and 2005 decreased by approximately 5% [18, 20].

Stage migration has been continuous: the incidence of stage I disease has continued to increase, whereas that of stages II and III disease has shown a statistically significant decline. The incidence of stage IV disease has remained stable over the past two decades [20]. Stage grouping (Table 13.2) shows the poor 5-year survival rates in patients with locally advanced and metastatic disease.

Although the decrease in mortality during the past 20 years is most likely a result of the increased incidence of lower-stage tumors (stage migration), multiple advances in understanding the biology of RCC have led to novel targeted treatments for patients with advanced/metastatic disease. Although complete responses are anecdotal, these targeted agents are providing extended survival in a large percentage of stage IV patients—survival times not previously seen in the recorded history of the disease.

Table 13.1 AJCC Version 7.0 staging of renal cell carcinoma

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney
T2b	Tumor more than 10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis

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Table 13.2 Correlation of stage grouping with survival in patients with renal cell cancer

Cancer stage	Tumor category	Node category	Metastasis category	5-year survival rates
I	T1	N0	M0	90–95
II	T2	N0	M0	70–85
III	T3a	N0	M0	50–65
	T3b	N0	M0	50–65
	T3c	N0	M0	45–50
	T1	N1	M0	25–30
	T2	N1	M0	25–30
	T3	N1	M0	15–20
IV	T4	Any N	M0	10

The MD Anderson Cancer Center Experience

The MD Anderson Tumor Registry data set was derived from 10,308 patients diagnosed with kidney cancer between 1944 and 2004. Of this total group, 4,601 received no prior treatments. After excluding patients with other primary noncutaneous malignancies and those previously treated at other institutions, survival data were calculated from the remaining 2,839 patients. The number of patients presenting by time interval is summarized in Table 13.3.

Until the early 1990s, there were no FDA-approved treatments for metastatic RCC, represented by the high percentage of new referrals for patients with distant metastatic disease. With the approval of high-dose interleukin 2 (HD IL-2) in 1992 and more recently with the approval of multiple targeted agents for the treatment of metastatic RCC (2005–present), the percentage of referrals for advanced disease may plateau.

The Kaplan–Meier survival curves for patients with RCC reveal significantly improved 5- and 10-year outcomes over the 60-year analysis period (Fig. 13.1). Equally apparent is the stage migration, noted since the mid-1980s with the prevalent use of cross-sectional imaging; analyzing outcome on the basis of stage provides better insight into the historical improvements in the treatment of this disease. Significant improvements in the treatment of localized and regional disease have increased survival rates, as shown in Figs. 13.2 and 13.3, respectively.

Unfortunately, up to 40% of patients with localized/regional disease will experience recurrence of disease after treatment of the primary lesion; however, no adjuvant treatments have been approved for these patients at high risk of recurrence. Since the approval of the first targeted agent in 2005, overall survival rates for patients with metastatic disease have increased significantly. As shown in Fig. 13.4, survival rates for those with distant disease have not substantially improved over the analysis period, but these data do not include the survival rates achieved since the introduction of newer effective agents. For the time periods surveyed, the only

Table 13.3 Patients with kidney cancer treated at MD Anderson, 1944–2004

	SEER stage at presentation				
	Local	Regional	Distant	Unstaged	Total
Decade	[No. (%) of patients]				
1944–1954	3 (50.0)	0 (0)	2 (33.3)	1 (16.7)	6 (100.0)
1955–1964	15 (21.1)	12 (16.9)	43 (60.6)	1 (1.4)	71 (100.0)
1965–1974	35 (19.1)	18 (9.8)	126 (68.9)	4 (2.2)	183 (100.0)
1975–1984	74 (18.2)	65 (16.0)	262 (64.5)	5 (1.2)	406 (100.0)
1985–1994	167 (22.3)	130 (17.4)	444 (59.4)	7 (0.9)	748 (100.0)
1995–2004	513 (36.0)	232 (16.3)	651 (45.7)	29 (2.0)	1,425 (100.0)
Total	807 (28.4)	457 (16.1)	1,528 (53.8)	47 (1.7)	2,839 (100.0)

SEER Surveillance, Epidemiology, and End Results program

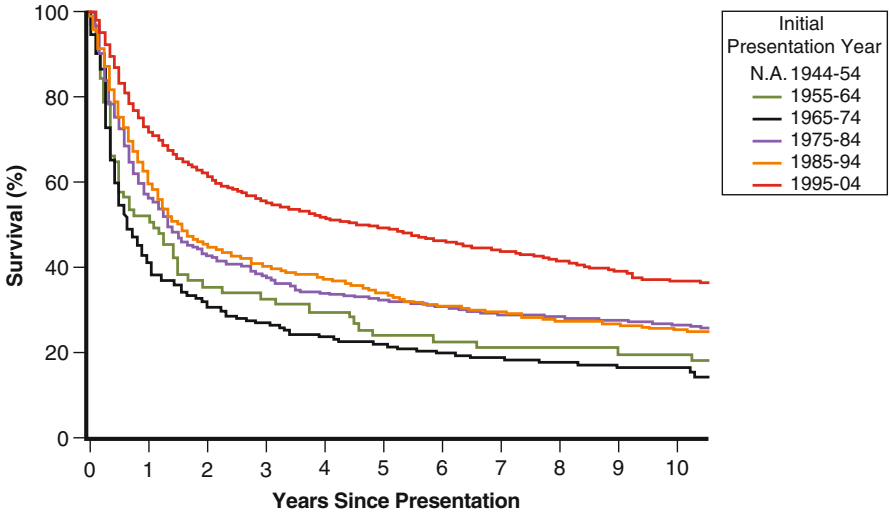

Fig. 13.1 Overall survival rates for patients with kidney cancer (1944–2004) ($P < 0.0001$, log-rank test for trend). Because of the very small number of individuals with kidney cancer seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

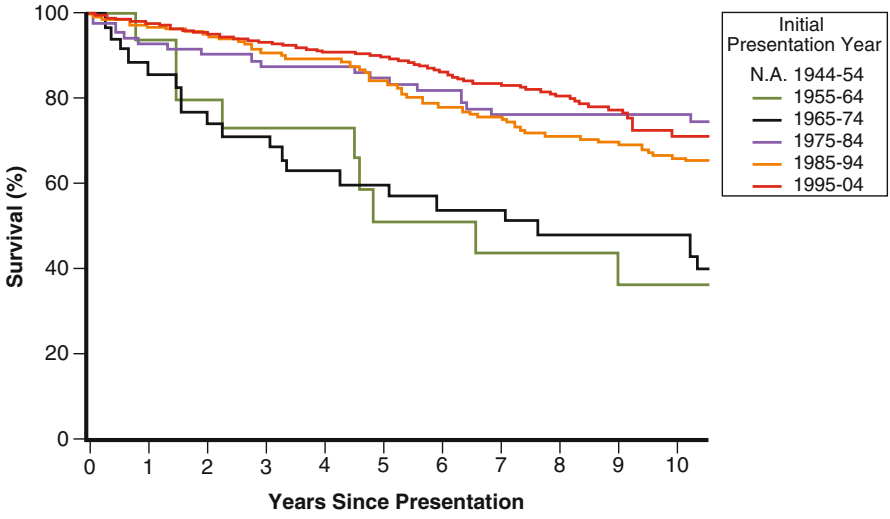

Fig. 13.2 Survival rates for patients with local (SEER stage) kidney cancer (1944–2004) ($P < 0.0001$, log-rank test for trend). Because of the very small number of individuals with local kidney cancer seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

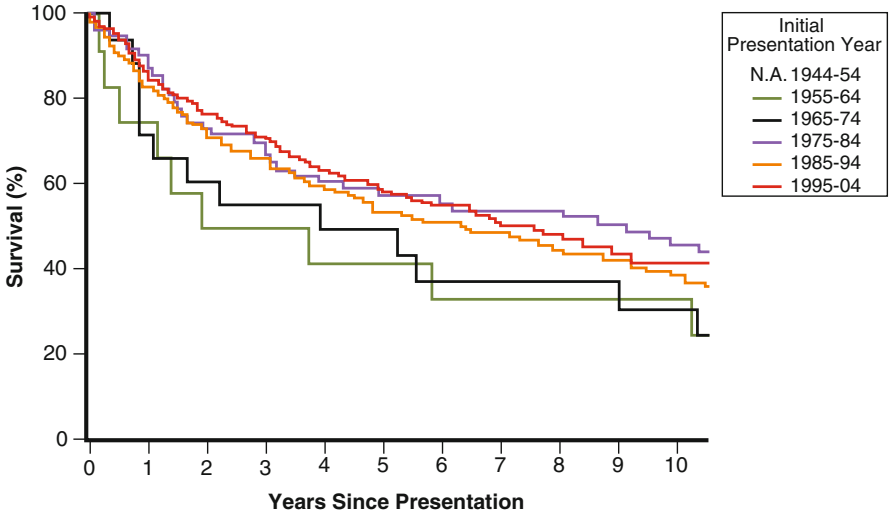

Fig. 13.3 Survival rates for patients with regional (SEER stage) kidney cancer (1955–2004) ($P=0.56$, log-rank test for trend). Because no individuals with regional kidney cancer were seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

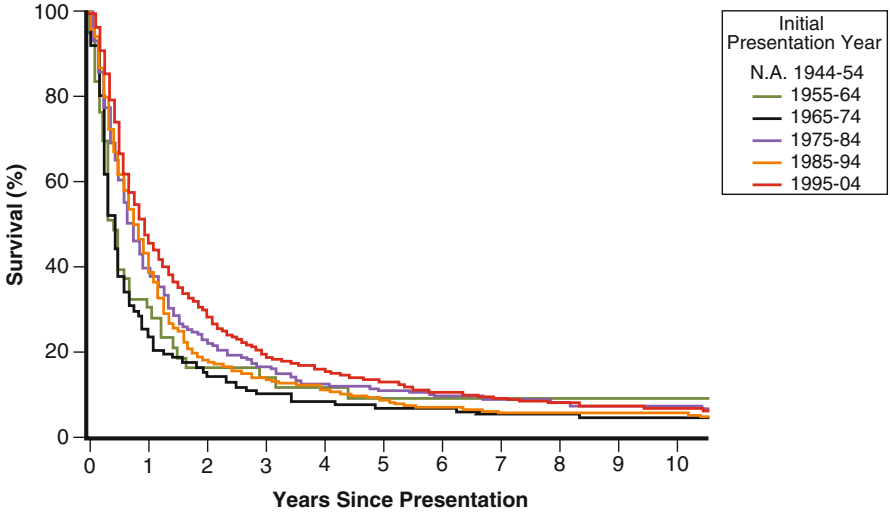

Fig. 13.4 Survival rates for patients with distant (SEER stage) kidney cancer (1944–2004) ($P<0.0001$, log-rank test for trend). Because of the very small number of individuals with distant kidney cancer seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

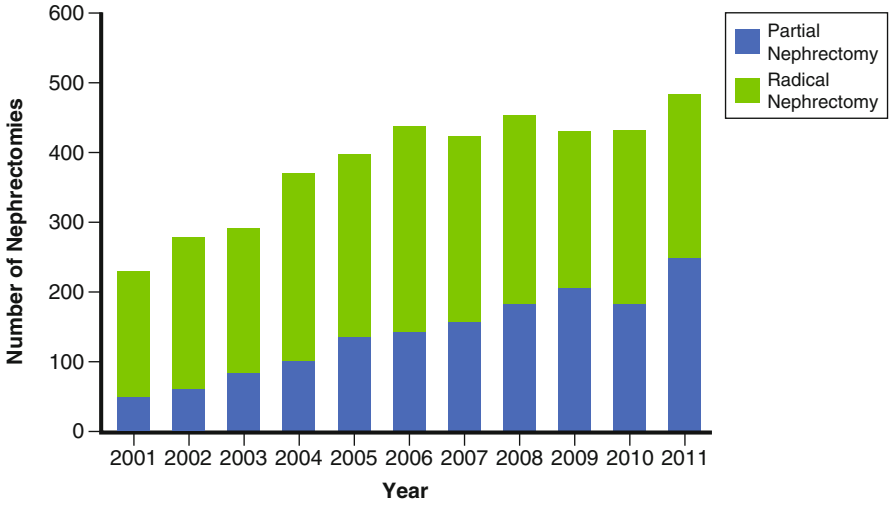

Fig. 13.5 Number of patients treated with partial versus radical nephrectomies at MD Anderson Cancer Center between 2001 and 2011.

effective treatment for metastatic RCC (outside of a clinical trial) has been HD IL-2 therapy [21]. Although associated with the highest durable long-term survival (7% complete durable responders), this treatment is difficult to tolerate and therefore cannot be used by most patients with metastatic disease. Multiple agents targeted at the angiogenesis pathway have been widely used since the first agent was approved in December 2005. At MD Anderson Cancer Center, many of these same targeted agents used for metastatic disease are currently being tested in the adjuvant setting for high-risk patients, and results are forthcoming.

The use of partial nephrectomy rather than radical nephrectomy for treatment of small localized lesions has provided an overall survival benefit by decreasing the comorbidities associated with the development of chronic renal insufficiency [4]. Figure 13.5 shows the relative number of partial to radical nephrectomies performed at MD Anderson Cancer Center between 2001 and 2011. The increasing number of partial nephrectomies is due to both the ever-increasing number of small renal masses (resulting from earlier detection) and improvements in technique allowing more complex masses to be removed while sparing the remaining renal parenchyma.

Oncologic outcomes with the use of partial and radical nephrectomy are equivalent in properly selected patients. The technique of partial nephrectomy is now the standard of care for many patients with tumors amenable to this procedure. Application and adoption of minimally invasive techniques (robotic and laparoscopic) has further augmented the surgical treatment of RCC.

Current Management Approach

Our current approach to the management of RCC is stratified by clinical and pathologic stage. For systemic disease, histologic subtyping of RCC is particularly important since the biologic mechanisms, and therefore the response rates to targeted agents, are varied. For tumors with a predominance of sarcomatoid dedifferentiation, traditional cytotoxic agents are also offered on the basis of multiple small single-institution studies and an ongoing study at MD Anderson Cancer Center.

Future improvements in survival for patients with metastatic disease will likely come from several strategies. First, development of an effective adjuvant treatment for patients with a high risk of recurrence after primary treatment could significantly affect the overall survival of the 40% of patients whose disease is destined to recur. Second, delineation of the biologic pathways involved in the development of resistance to targeted and standard chemotherapeutics could enable the design of agents specific to resistant tumors or of agents to be used up front to prevent resistance. Third, further advances in surgical technology and techniques with appreciation for surgical morbidity as well as oncologic outcome will aid patients diagnosed with this disease. Historic advances have been achieved in the past 20 years, and with continued research, we hope to continue to advance the treatment of patients with all stages of RCC.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics 2010. CA Cancer J Clin. 2010;60(5): 277–300.
2. Horner M, Ries L, Krapcho M, Neyman N, Aminou R. SEER cancer statistics review 1975–2006. Bethesda, MD 2009;(11):11.1–28. http://seer.cancer.gov/csr/1975_2006/. Accessed 1 Dec 2009.
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008, cancer incidence and mortality worldwide: IARC CancerBase No. 10 [Internet]. Lyon: International Agency for Research on Cancer; 2010. http://globocan.iarc.fr. Accessed 1 Dec 2009.
4. Thompson RH, Boorjian SA, Lohse CM, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. J Urol. 2008;179(2):468–71 [discussion 72–3].
5. Mandel JS, McLaughlin JK, Schlehofer B, et al. International renal-cell cancer study. IV. Occupation. Int J Cancer. 1995;61(5):601–5.
6. La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Smoking and renal cell carcinoma. Cancer Res. 1990;50(17):5231–3.
7. Yu MC, Mack TM, Hanisch R, Cicioni C, Henderson BE. Cigarette smoking, obesity, diuretic use, and coffee consumption as risk factors for renal cell carcinoma. J Natl Cancer Inst. 1986;77(2):351–6.
8. Hunt JD, van der Hel OL, McMillan GP, Boffetta P, Brennan P. Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. Int J Cancer. 2005;114(1):101–8.
9. Brennan JF, Stilmant MM, Babayan RK, Siroky MB. Acquired renal cystic disease: implications for the urologist. Br J Urol. 1991;67(4):342–8.

10. Gago-Dominguez M, Yuan JM, Castelao JE, Ross RK, Yu MC. Family history and risk of renal cell carcinoma. Cancer Epidemiol Biomarkers Prev. 2001;10(9):1001–4.
11. Schlehofer B, Pommer W, Mellemgaard A, et al. International renal-cell-cancer study. VI. the role of medical and family history. Int J Cancer. 1996;66(6):723–6.
12. McLaughlin JK, Mandel JS, Blot WJ, Schuman LM, Mehl ES, Fraumeni Jr JF. A population–based case–control study of renal cell carcinoma. J Natl Cancer Inst. 1984;72(2):275–84.
13. Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH. Occupational risk factors for renal-cell carcinoma in Denmark. Scand J Work Environ Health. 1994;20(3):160–5.
14. Gnarra JR, Glenn GM, Latif F, et al. Molecular genetic studies of sporadic and familial renal cell carcinoma. Urol Clin North Am. 1993;20(2):207–16.
15. Green FL, Blach CM, Haller DG, Morrow M. AJCC cancer staging manual. 6th ed. New York: Springer; 2002.
16. Edge SB, Byrd DR, Compton CA, editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.
17. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. CA Cancer J Clin. 2006;56(2): 106–30.
18. Pantuck AJ, Zisman A, Belldegrun AS. The changing natural history of renal cell carcinoma. J Urol. 2001;166(5):1611–23.
19. Jemal A, Siegel R, Ward E, Hao Y, Xu J. Cancer statistics 2009. CA Cancer J Clin. 2009;59: 225–49.
20. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. Cancer. 2008;113(1):78–83.
21. Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Fyfe G. High-dose aldesleukin in renal cell carcinoma: long-term survival update. Cancer J Sci Am. 1997;3 Suppl 1:S70–2.