Original Paper

Urologia Internationalis

Urol Int 2010;85:23–29
DOI: 10.1159/000318994

Received: September 14, 2009
Accepted after revision: December 21, 2009
Published online: July 26, 2010

Impact of Lymph Node Invasion and Sarcomatoid Differentiation on the Survival of Patients with Locally Advanced Renal Cell Carcinoma

Francisco Rodríguez-Covarrubias[a] Ricardo Castillejos-Molina[a]
Mariano Sotomayor[a] Carlos E. Méndez-Probst[a] Martha Olivia Gómez-Alvarado[a]
Norma Uribe-Uribe[b] Fernando Gabilondo[a] Guillermo Feria-Bernal[a]

Departments of [a]Urology and [b]Pathology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Key Words
Renal cell carcinoma · Prognosis · Staging · Radical nephrectomy

Abstract
Introduction: The application of current prognosticators in locally advanced nonmetastatic renal cell carcinoma (RCC) is controversial. We analyzed the impact of clinical and pathological variables on the survival of this subset of patients. ***Patients and Methods:*** We studied patients with RCC in stages III and IV without metastases, treated surgically between 1980 and 2009. We calculated disease-free (DFS) and cancer-specific survival (CSS), and the relation of clinical and pathological variables with these end-points. ***Results:*** We identified 126 patients with locally advanced RCC; 8.7% had sarcomatoid differentiation. Tumor stage was pT3a in 48% and pT3b in 42%; 11.9% had lymph node invasion (N+). Patients with N– and N+ had a 10-year DFS of 49.0 and 23.4%, respectively ($p = 0.0001$). In multivariate analysis N+ ($p = 0.0002$) was the strongest predictor of DFS. The 10-year CSS of patients without sarcomatoid differentiation was 53.1% while those with sarcomatoid differentiation did not reach the median time to death ($p < 0.0001$). In multivariate analysis, sarcomatoid differentiation ($p = 0.01$) was the strongest predictor of CSS. ***Conclusions:*** Locally advanced RCC portends poor prognosis. Preoperatively, weight loss and Eastern Cooperative Oncology Group performance status are predictors of recurrence and mortality, respectively. However, the most powerful predictors of DFS and CSS in our cohort were lymph node status and sarcomatoid differentiation.

Introduction

Renal cell carcinoma (RCC), considered one of the most lethal urological malignancies, is the third most common neoplasm of the urinary tract and accounts for up to 5% of all cancers in adults [1, 2]. In 2009, a total of 57,760 new cases and 12,980 RCC related deaths are expected to occur in the United States [3]. Despite technological advances in imaging modalities, 30–50% of contemporary cases are diagnosed in advanced stages of the disease [1] of which 25% will have lymph node invasion at diagnosis [4]. Although the outcome in this setting appears to have high variability [5], the majority of series evaluating patients with locally advanced RCC uniformly demonstrate a poor prognosis [4, 5], with 5-year disease-specific survival rates in excess of 60% and 30% for stages III and IV, respectively [1].

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0042–1138/10/0851–0023$26.00/0

Accessible online at:
www.karger.com/uin

Francisco Rodríguez-Covarrubias, MD, Department of Urology
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán
Vasco de Quiroga 15, Col. Sección XVI. Tlalpan 14000, Mexico City (Mexico)
Tel. +52 55 5487 0900 ext. 2145, Fax +52 55 5485 4380
E-Mail frodriguez.covarrubias@gmail.com

Several variables have been analyzed in order to predict the evolution of localized and metastatic RCC. Among the most useful prognostic factors are pathological stage, tumor size, nuclear grade and necrosis [6]. Nevertheless, the application of current prognostic information, in case of locally advanced RCC, is a matter of debate and it is difficult to determine the current role of each factor in the outcome of this subset of patients. Furthermore, the accuracy of some well-known prognostic tools could be limited [7]. Therefore, some efforts have been conducted to improve the efficacy of such instruments [7, 8] and additional factors have been evaluated, including histopathological features [9–11], laboratory parameters and molecular markers [12].

In this study, we analyzed the prognostic impact of clinical and pathological variables in order to determine their role in the long-term survival of a single-center cohort of patients with locally advanced RCC.

Patients and Methods

After obtaining institutional review board approval, we analyzed our prospective, renal solid-tumor database of 388 consecutive patients treated surgically, of whom 343 had undergone radical nephrectomy or nephron-sparing surgery for sporadic RCC between March 1980 and May 2009 at our institution; of these, only those with locally advanced RCC were included in the study whereas patients with distant metastases were excluded. Locally advanced disease was defined as pathologically confirmed stages III (pTxN1M0/pT3N0M0) and IV (pT4N0-N1M0/pTxN2M0) in the absence of metastatic disease. All patients underwent radical nephrectomy and adjuvant therapy was offered at the discretion of the treating oncologist rather than in a routine fashion.

Preoperative variables studied included age, gender, hemoglobin, Eastern Cooperative Oncology Group performance status (ECOG-PS), involuntary weight loss in kilograms and clinical stage according to the American Joint Committee on Cancer TNM 2002 staging system [13]. Normal thresholds for hemoglobin were 13.0–15.0 g/dl for females and 14.5–17.7 g/dl for males. Postoperative variables evaluated were tumor diameter (pT stage), histological subtype [14], nuclear grade, lymph node status, and presence of sarcomatoid differentiation.

For statistical analysis, the χ^2 test and the Student t test were used, respectively, to compare means and proportions. Survival intervals were calculated from the date of surgery to the date of disease recurrence (disease-free survival, DFS) or death from cancer (cancer-specific survival, CSS). These were calculated with the Kaplan-Meier method and the differences of the results were determined with the log-rank test. We assessed the relation of clinical and pathological variables with recurrence and death from RCC using Cox proportional hazards regression models. All analyses were performed with StatView for Windows (SAS Institute, Cary, N.C., USA). Results were considered significant with a p value less than 0.05.

Table 1. Clinical and pathological characteristics of 126 patients with locally advanced RCC

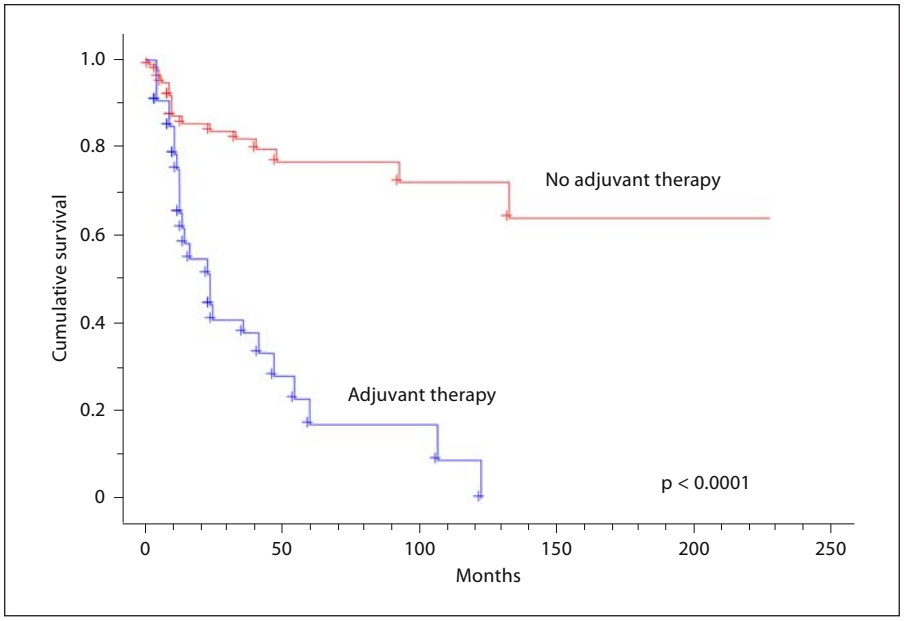
Age, mean ± SD, years	60.1 ± 13.3
Age, range, years	27 – 85
Gender	
Female	55 (43.7%)
Male	71 (56.3%)
Weight loss	
No	66 (52.4%)
Yes	60 (47.6%)
ECOG-PS	
0	101 (80.2%)
1+	25 (19.8%)
Tumor size	
Mean ± SD, cm	9.03 ± 5.2
Range, cm	2.0 – 23.3
Pathological tumor stage	
pT1	1 (0.8%)
pT2	1 (0.8%)
pT3a	61 (48.4%)
pT3b	53 (42%)
pT3c	5 (4%)
pT4	5 (4%)
Lymph node status	
pN0	41 (32.5%)
pN1–2	15 (11.9%)
pNx	70 (55.6%)
Pathologic stage	
III	114 (90.5%)
IV	12 (9.5%)
Sarcomatoid differentiation	
No	115 (91.3%)
Yes	11 (8.7%)

Results

We identified a total of 126 patients with locally advanced RCC in the absence of distant metastases. Mean follow-up was 39.1 ± 46.4 months (median 20.5, range 2–228). The clinical and pathological characteristics are summarized in table 1.

Clinical Parameters

As expected, mean hemoglobin concentration was lower in females than in males (12.4 ± 2.30 vs. 13.92 ± 2.73 g/dl, p = 0.002). However, the frequency of anemia was similar between both genders (47.2% vs. 47.7%, p = 0.94). Mean involuntary weight loss was 9.97 ± 6.19 kg (range 1.5–30.0). The majority of patients (80.2%) had an ECOG-PS of 0.



Color version available online

Fig. 1. CSS according to adjuvant therapy.

Pathological Characteristics

Maximum tumor diameter was ≥7cm in 64% of cases. Histology was clear-cell RCC in 81%, papillary in 7.9%, chromophobe in 1.6% and unclassified in 9.5%; sarcomatoid differentiation was found in 8.7%. Regarding nuclear (Fuhrman) grade, 15.7% of cases had grade 1, 35.3% grade 2, 24.5% grade 3 and 24.5% grade 4. Most of the patients were in stage pT3a (48%) or pT3b (42%). Of those who underwent lymph node dissection, 11.9% had positive lymph nodes (53.3% were classified as N1 and 46.7% as N2). Finally, 9.5% were in stage IV.

Adjuvant Therapy

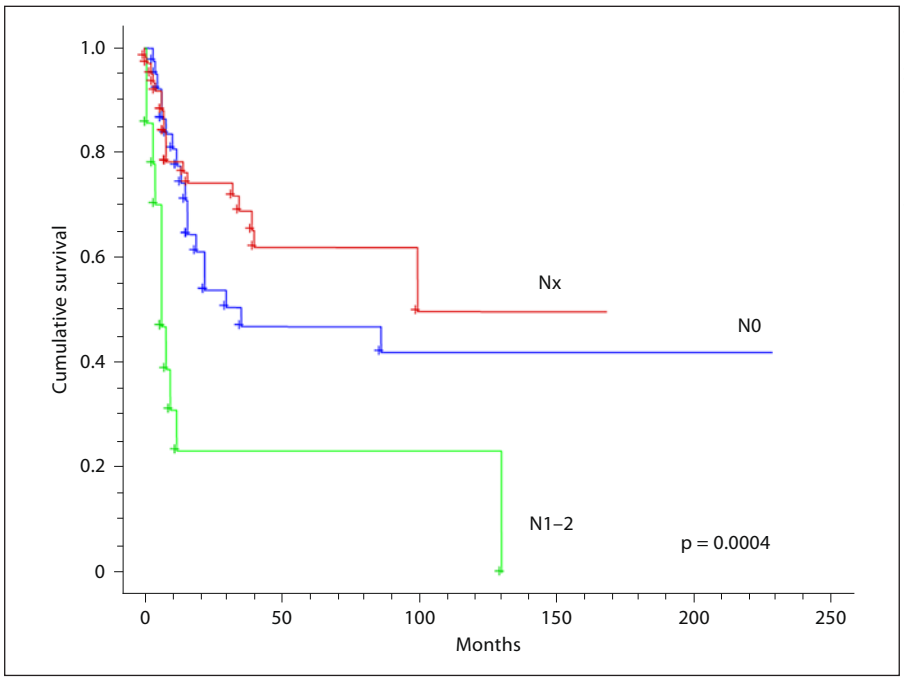
34 patients (26.9%) received adjuvant therapy consisting of chemotherapy (initial years of this series) in 15.1%, immunotherapy in 6.3%, immunotherapy plus chemotherapy in 3.1% and thalidomide in 2.3%. As expected, those in stage IV were more prone to receive additional treatment than their counterparts in stage III (41.6 vs. 25.4%; p = 0.22). Despite complementary treatments, patients receiving adjuvant therapy had a worse prognosis, with 5- and 10-year CSS of 17 and 1 vs. 76% and 72% in patients without additional therapy ($p < 0.0001$, fig. 1).

Disease-Free Survival

Overall, 48 patients (38.1%) had disease recurrence after a mean time of 17.2 months (median 8). Preoperatively, they had lower hemoglobin concentrations (mean 12.4 ± 2.5 vs. 13.7 ± 2.6 g/dl, p = 0.006) and a higher frequency of weight loss (66.6 vs. 35.8%, p = 0.0008) in comparison with those free of disease. There was no difference in ECOG-PS (p = 0.25). Regarding postoperative characteristics, patients with recurrence had larger tumors (mean tumor diameter 10.5 ± 7.3 vs. 8.1 ± 3.2 cm, p = 0.01), more frequent Fuhrman 3–4 tumors (71.8 vs. 34.9%, p = 0.0003), and a higher frequency of lymph node invasion (22.9 vs. 5.1%, p = 0.002). Although the pathological evidence of sarcomatoid differentiation was also more common in the group with recurrent RCC (14.6 vs. 5.1%), this trend did not reach statistical significance (p = 0.06). The 10- and 15-year DFS in the whole cohort was 46.1 and 42.5%, respectively. Patients without and with lymph node invasion had a 10-year DFS of 49.0 and 23.4%, respectively (p = 0.0001). When stratified in Nx, N0 and N1–2 the 10-year DFS was 49, 42 and 23%, respectively (p = 0.0004; fig. 2). In those without sarcomatoid differentiation, the 10-year DFS was 49.3% whereas those with sarcomatoid differentiation did not reach the median time to recurrence ($p < 0.0001$). The multivariate Cox proportional hazards regression model showed that weight loss (p = 0.02), lymph node invasion (p = 0.0002) and the evidence of sarcomatoid differentiation (p = 0.03) were associated with disease recurrence (table 2).

Cancer-Specific Survival

Overall, 41 patients (32.5%) died from RCC, with a mean time to death of 27.7 months (median 13). Preoperatively, they had lower hemoglobin concentrations



Color version available online

Fig. 2. DFS according to lymph node status.

Table 2. DFS according to clinicopathological features in 126 patients with locally advanced RCC treated surgically

	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Anemia	3.04	1.64–5.63	0.0004	1.28	0.57–2.84	0.54
ECOG-PS	2.11	1.09–4.11	0.02	1.50	0.70–3.23	0.29
Weight loss	3.46	1.87–6.39	<0.0001	2.69	1.13–6.40	0.02
Tumor diameter	1.05	1.01–1.08	0.002	1.02	0.97–1.07	0.35
Nuclear grade	1.88	1.36–2.61	0.0001	1.13	0.74–1.72	0.56
Positive lymph nodes	3.46	1.76–6.83	0.0003	6.42	2.41–17.08	0.0002
Sarcomatoid differentiation	6.72	2.82–16.01	<0.0001	3.33	1.12–9.92	0.03

HR = Hazards ratio; 95% CI = 95% confidence interval.

(mean 12.1 ± 2.8 vs. 13.7 ± 2.3 g/dl, p = 0.001), a higher frequency of weight loss (70.7 vs. 36.4%, p = 0.0003) and a worse ECOG-PS (p = 0.001) in comparison with survivors. Postoperatively, they also had larger tumors (mean tumor diameter 10.9 ± 7.8 vs. 8.1 ± 3.1 cm, p = 0.005), more frequent Fuhrman 3–4 tumors (74.2 vs. 38.0%, p = 0.0008) and a higher frequency of lymph node invasion (26.8 vs. 4.7%, p = 0.0003). Although sarcomatoid differentiation was more frequent among patients dying from RCC (14.6 vs. 5.8%) this difference was not statistically significant (p = 0.1). The 10- and 15-year CSS in the whole cohort was 49.8 and 40.6%, respectively. Patients without and with lymph node invasion had a 10-year CSS of 54.8 and 14.0%, respectively (p < 0.0001). When stratified in Nx, N0 and N1–2, the 10-year CSS was 73, 41 and 14%, respectively (p = 0.0001, fig. 3). Those without sarcomatoid differentiation had a 10-year CSS of 53.1% while patients with sarcomatoid differentiation did not reach the median time to death (p < 0.0001). The multivariate Cox proportional hazards regression model showed that ECOG-PS (p = 0.009), lymph node invasion (p = 0.01) and the presence of sarcomatoid differentiation (p = 0.01) were independent predictors of cancer-related mortality in this cohort of patients (table 3).

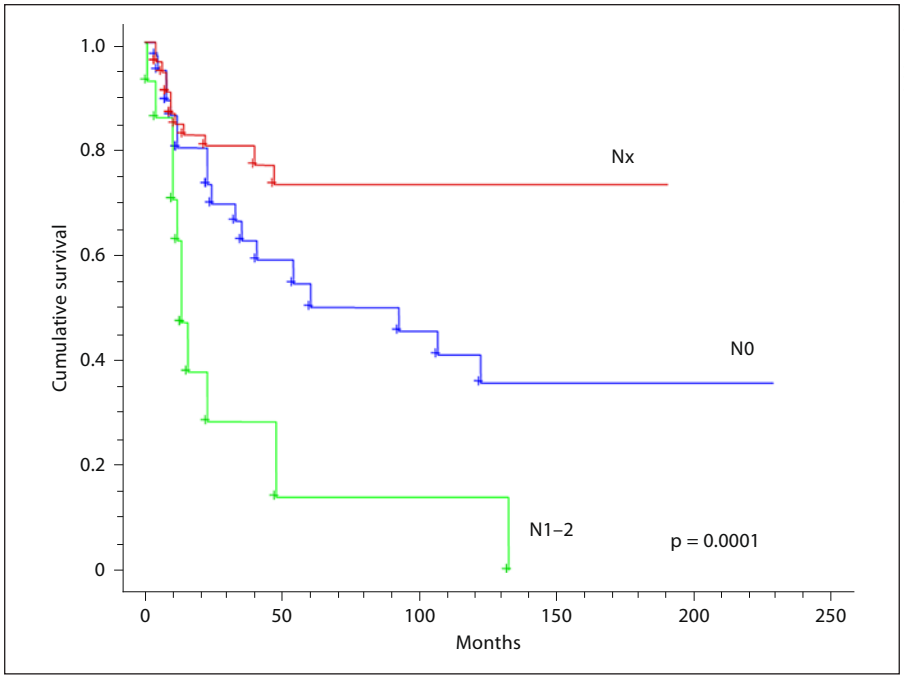


Fig. 3. CSS according to lymph node status.

Table 3. CSS according to clinicopathological characteristics in 126 patients with locally advanced RCC treated surgically

	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Anemia	3.30	1.68–6.49	0.0005	1.11	0.44–2.79	0.81
ECOG-PS	4.20	2.18–8.11	<0.0001	2.77	1.29–5.96	0.009
Weight loss	3.98	2.01–7.85	<0.0001	2.20	0.84–5.74	0.10
Tumor diameter	1.06	1.03–1.10	0.0002	1.04	0.99–1.10	0.07
Nuclear grade	1.95	1.34–2.84	0.0004	1.18	0.70–2.00	0.52
Positive lymph nodes	3.66	1.81–7.38	0.0003	3.15	1.20–8.26	0.01
Sarcomatoid differentiation	7.42	2.93–18.77	<0.0001	4.09	1.31–12.72	0.01

HR = Hazards ratio; 95% CI = 95% confidence interval.

Discussion

Several clinical, pathological and molecular factors have been identified as having prognostic implications in localized and metastatic RCC [15]. Moreover, some staging systems [6, 16] have been created in order to improve the prognostic accuracy of well-known risk factors. However, the existing information could be limited when it comes to predict the outcome of locally advanced disease and this category remains a diagnostic, prognostic and therapeutic challenge for urologists and oncologists. Furthermore, since this cohort of patients might be of particular interest in the context of modern adjuvant therapies, a correct understanding of the prognostic effect of clinical and pathological variables in this cohort is crucial.

The aim of our study was the identification of clinical and pathological predictors of recurrence and cancer-related mortality. Our results demonstrate that preoperatively only weight loss is associated with the risk of recurrence. On the other hand, the postoperative characteristics that influenced DFS were lymph node status and the evidence of sarcomatoid differentiation.

From a practical perspective, the most important endpoint is cancer-related mortality. Our findings suggest

that, clinically, ECOG-PS is associated with CSS. However, pathological characteristics were the strongest prognostic factors, since the presence of sarcomatoid differentiation and positive lymph nodes increased the risk of death from RCC 4.09 and 3.15 times, respectively.

Previously, sarcomatoid RCC was considered an independent variety within the classification of RCC. Nevertheless, it is no longer a unique category because it has been demonstrated that sarcomatoid differentiation can be found as a component of all subtypes of RCC [14, 17]. Recently, Cheville et al. [10] analyzed the evolution of patients with sarcomatoid RCC. The frequency of that pattern in their cohort was 5% and was strongly associated to RCC-related death regardless of the underlying histological subtype [10]. In another study evaluating 365 patients with pT3a RCC (including those with metastatic disease), Margulis et al. [18] found that, after adjusting for the effects of lymph node invasion and systemic metastases, sarcomatoid differentiation independently predicted the risk of death from cancer. In a more recent analysis, Bertini et al. [9] evaluated 105 patients with pT3a RCC; an interesting finding of that study, as discussed by the investigators, was the independent role of sarcomatoid differentiation in CSS as it raised the risk of death by more than 5 times [9]. In agreement with these reports, our results suggest that the pathological evidence of sarcomatoid differentiation is one of the most important prognosticators, regardless of histological subtype, increasing the likelihood of cancer-related death by more than 3 times.

Lymph node invasion is a well-known predictor of poor outcome; in our series it showed the strongest association with DFS and the second with CSS. Although lymph node dissection was not standardized, patients with N1–2 had a worse prognosis. The better survival in Nx patients reflects the less aggressive nature of the disease in those not undergoing lymphadenectomy. According to a recent study [4], finding positive lymph nodes should prompt urologists to perform aggressive surgical treatment; moreover, patients harboring nodal metastases could benefit from being enrolled in adjuvant therapy protocols with novel agents.

Interestingly, tumor size showed a trend towards association with CSS regardless of pathological tumor stage. This issue is a matter of debate due to conflicting findings among series. While two recent series [19, 20] demonstrate an important role of tumor size in case of RCC with perinephric fat invasion, a study from Mayo Clinic [21] contradicts those findings. Even though our patients were in different tumor stages, the vast majority (90.5%) was in stage pT3a-b. Moreover, tumor diameter showed a trend towards the likelihood of death from RCC (hazards ratio 1.04, 95% confidence interval 0.99–1.10, $p = 0.07$). Surprisingly, nuclear grade did not predict the possibility of recurrence or death. This finding could be explained, in part, by the fact that, in the context of aggressive disease, the predictive value of this feature could be undermined.

We found a statistically significant difference in terms of CSS between patients with and without adjuvant therapy. In our opinion, this finding should be taken with caution since it could be the consequence of tumor aggressiveness rather than a detrimental effect of adjuvant therapy.

Our study has some limitations. First, regional lymph node dissection was not routinely performed in all cases and the extension of the procedure was not standardized. To minimize the effect of this issue, we analyzed CSS stratifying patients according to lymph node status and found that those with Nx had a survival advantage. Second, the power of our findings may be limited by the retrospective nature of this investigation which allowed some biases to influence our results. Third, due to the number of cases, we were not able to demonstrate prognostic differences among histological subtypes (data not shown). Although the number of patients in our series is somewhat limited, it is similar to that in previous reports [9] and reflects the experience of a single tertiary-referral center. Furthermore, because of the rarity of locally advanced disease in the absence of metastatic disease [4], few studies have focused on analyzing the outcome in this scenario. Therefore, our results and those of other investigators highlight the need of large-scale studies evaluating the prognostic factors in patients with high-risk RCC and no metastatic disease, especially in the era of multikinase inhibitors and other targeted therapies.

In conclusion, patients with locally advanced RCC have a poor prognosis. Preoperatively, a history of weight loss and ECOG-PS are predictors of disease recurrence and cancer-related mortality, respectively. The most powerful predictors of DFS and CSS in this subset of patients are lymph node status and the pathological evidence of sarcomatoid differentiation, respectively. Those individuals presenting such characteristics should be enrolled in clinical trials of adjuvant therapy with targeted strategy agents.

References

1 Pantuck AJ, Zisman A, Belldegrun AS: The changing natural history of renal cell carcinoma. J Urol 2001;166:1611–1623.
2 Otaibi MA, Tanguay S: Locally advanced renal cell carcinoma. Can Urol Assoc J 2007; 1(2 suppl): s55–s61.
3 Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2009. CA Cancer J Clin 2009;59:225–249.
4 Canfield SE, Kamat AM, Sanchez-Ortiz RF, et al: Renal cell carcinoma with nodal metastases in the absence of distant metastatic disease (clinical stage TxN1–2M0): the impact of aggressive surgical resection on patient outcome. J Urol 2006;175:864–869.
5 Karakiewicz PI, Trinh QD, Bhojani N, et al: Renal cell carcinoma with nodal metastases in the absence of distant metastatic disease: prognostic indicators of disease-specific survival. Eur Urol 2007;51:1616–1624.
6 Frank I, Blute ML, Cheville JC, et al: An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. J Urol 2002;168:2395–2400.
7 Ficarra V, Novara G, Iafrate M, et al: Proposal for reclassification of the TNM staging system in patients with locally advanced (pT3–4) renal cell carcinoma according to the cancer-related outcome. Eur Urol 2007; 51:722–729.
8 Ficarra V, Galfano A, Guillé F, et al: A new staging system for locally advanced (pT3–4) renal cell carcinoma: a multicenter European study including 2,000 patients. J Urol 2007;178:418–424.
9 Bertini R, Roscigno M, Freschi M, et al: Renal sinus fat invasion in pT3a clear cell renal cell carcinoma affects outcomes of patients without nodal involvement or distant metastases. J Urol 2009;181:2027–2032.
10 Cheville JC, Lohse CM, Zincke H, et al: Sarcomatoid renal cell carcinoma: an examination of underlying histologic subtype and an analysis of associations with patient outcome. Am J Surg Pathol 2004;28:435–441.
11 Klatte T, Said JW, de Martino M, et al: Presence of tumor necrosis is not a significant predictor of survival in clear cell renal cell carcinoma: higher prognostic accuracy of extent based rather than presence/absence classification. J Urol 2009;181:1558–1564.
12 Rodriguez A, Sexton WJ: Management of locally advanced renal cell carcinoma. Cancer Control 2006;13:199–210.
13 Greene FL, Page DL, Fleming ID, et al: AJCC Cancer Staging Manual, ed 6. New York, Springer, 2002.
14 Kovacs G, Akhtar M, Beckwith BJ, et al: The Heidelberg classification of renal cell tumours. J Pathol 1997;183:131–133.
15 Motzer RJ, Mazumdar M, Bacik J, et al: Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530–2540.
16 Zisman A, Pantuck A, Dorey F, et al: Improved prognostication of renal cell carcinoma using an integrated staging system. J Clin Oncol 2001;19:1649–1657.
17 Storkel S, Eble JN, Adlakha K, et al: Classification of renal cell carcinoma: Workgroup No 1. Union Internationale contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer 1997;80:987–989.
18 Margulis V, Tamboli P, Matin SF, et al: Location of extrarenal tumor extension does not impact survival of patients with pT3a renal cell carcinoma. J Urol 2007;178:1878–1882.
19 Lam JS, Klatte T, Patard JJ, et al: Prognostic relevance of tumour size in T3a renal cell carcinoma: a multicentre experience. Eur Urol 2007;52:155–162.
20 Yoo C, Song C, Hong JH, et al: Prognostic significance of perinephric fat infiltration and tumor size in renal cell carcinoma. J Urol 2008;180:486–491.
21 Siddiqui SA, Frank I, Leibovich BC, et al: Impact of tumor size on the predictive ability of the pT3a primary tumor classification for renal cell carcinoma. J Urol 2007;177:59–62.