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PARANEOPLASTIC SIGNS AND SYMPTOMS OF RENAL CELL CARCINOMA: IMPLICATIONS FOR PROGNOSIS

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ABSTRACT

Purpose: Renal cell carcinoma (RCC) can present with a wide range of signs and symptoms. To our knowledge we report the first study to describe the frequency of paraneoplastic findings in a modern RCC series and assess the prognostic significance of each finding.

Materials and Methods: Using the kidney cancer database at our institution 1,046 patients undergoing nephrectomy for RCC between 1989 and 2001 were assessed. The prognostic significance of symptoms present at diagnosis and findings on preoperative laboratory evaluation were examined in a univariate analysis as well as on multivariate analysis controlling for TNM stage, Fuhrman grade and Eastern Cooperative Oncology Group performance status (ECOG-PS).

Results: Mean followup to date of death or last contact for all patients was 40.3 months. Median time to death was 19.3 months. Most paraneoplastic signs and symptoms correlated with poor survival, although on multivariate analysis hypoalbuminemia, weight loss, anorexia and malaise predicted shorter survival. The frequency of each of these findings was 19.9%, 22.9%, 10.6% and 19.1%, respectively. Cachexia, defined as the presence of at least 1 of these findings, was noted in 35.3% of patients. Cachexia did not predict a higher recurrence rate in patients with localized disease and only malaise correlated with a decreased likelihood of responding to immunotherapy.

Conclusions: Cachexia, defined as hypoalbuminemia, weight loss, anorexia or malaise, predicts worse survival after controlling for well established indicators of prognosis (TNM stage, Fuhrman grade and ECOG-PS). Consideration should be given to expanding the ECOG-PS to include measures for cachexia when applied to patients with RCC.

KEY WORDS: kidney; carcinoma, renal cell; signs and symptoms; cachexia; prognosis

Renal cell carcinoma (RCC) is the third most common genitourinary malignancy.[1] It is estimated that more than 30,000 new cases were diagnosed in 2002. Approximately 20% of patients diagnosed with RCC present with paraneoplastic symptoms.[2] Another 10% to 40% of patients have paraneoplastic symptoms during the disease course. The paraneoplastic syndrome represents a constellation of signs and symptoms that result from the release of various tumor associated proteins rather than as a consequence of local invasion. Proteins responsible for the paraneoplastic effects may be elaborated directly by the tumor cells or by the immune system in response to the tumor.

With the widespread use of radiological imaging RCC is being detected at earlier stages. In modern series approximately 15% to 48% of RCC cases are diagnosed incidentally during evaluation for an unrelated disorder.[3,4] However, to our knowledge the frequency of paraneoplastic signs and symptoms in a modern series has never been reported. Furthermore, paraneoplastic findings at presentation have been assumed to indicate a poor prognosis, although to our knowledge the implications for prognosis have never been clearly defined.

Many previous studies have examined presenting symptoms in the context of incidentally diagnosed RCC.[3,4] The hypothesis for these studies was that incidentally discovered tumors are more likely to be diagnosed at a lower stage and, therefore, they carry a better prognosis. Patients presenting with symptoms were grouped together to serve as the control group and no attempt was made to discriminate among symptoms.

In this study we examined the assumption that all symptomatic tumors are similar. The frequency of various paraneoplastic signs and symptoms in a modern RCC series is reported and their prognostic significance is assessed. This information may allow for a better determination of prognosis and better patient selection for standard as well as experimental treatments.

PATIENTS AND METHODS

Patients and definitions. Using the kidney cancer database at our institution 1,046 patients were identified who underwent partial or a radical nephrectomy for RCC between 1989 and 2001. Presenting signs and symptoms were determined at the time of preoperative history and physical examination using a standard patient questionnaire. Hypertension was defined as new hypertension or worsening of existing hypertension, as determined by the primary physician. Weight loss was defined as an unintended decrease of at least 5 pounds within 3 months. Hematuria included gross and microscopic hematuria. Flank or abdominal masses were noted by the patient or examining physician. Fever, chills, night sweats, anorexia and malaise were reported by the patient. Anorexia was defined as a loss of appetite and malaise was defined a prolonged decrease in energy level. Hematuria, flank pain and flank mass are part of the classic triad of presenting symptoms for RCC and, therefore, they were included in the study, although it is unlikely that they represent paraneoplastic effects.

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Preoperative laboratory studies from our institution or elsewhere were used to assess presenting signs. Anemia was defined as hematocrit less than 40% in men and less than 36% in women. Erythrocytosis was defined as hematocrit greater than 50% in men and greater than 44% in women. Thrombocytosis and hypoalbuminemia were defined as a platelet count of greater than 440,000/μl and a serum albumin of less than 3.6 gm/dl, respectively. For all analyses of hepatic dysfunction and hypercalcemia all patients with known liver or bone metastasis were excluded. Alanine transaminase greater than 50 IU/l, aspartate transaminase greater than 50 IU/l and alkaline phosphatase greater than 105 IU/l were considered evidence of hepatic dysfunction. Calcium was adjusted for albumin less than 4 gm/dl according to the formula, measured calcium + 0.8 $\times$ (4 $-$ serum albumin). Patients with corrected calcium greater than 10 mg/l were considered to have hypercalcemia. A diagnosis was considered incidental if RCC was discovered during evaluation of an unrelated symptom or disorder.

Cases were staged according to the 1997 TNM criteria proposed by the American Joint Committee on Cancer. Performance status was determined using the Eastern Cooperative Oncology Group Performance Score (ECOG-PS). Tumor grade was categorized using Fuhrman grade. Patients were also categorized according to the University of California-Los Angeles Integrated Staging System (UISS).[5] Following surgery patients were evaluated for disease recurrence by physical examination, liver function tests, chest x-ray and computerized tomography of the abdomen/pelvis every 6 to 12 months. Most patients with metastatic RCC were treated with interleukin (IL)-2 based immunotherapy and then evaluated radiologically in 3 months to determine the response to therapy. A positive response was defined as a complete or partial response. Patients with stable disease or progressive disease following immunotherapy were considered to have a negative response.

Statistical analysis. The Kaplan-Meier method was used to determine disease specific survival and tumor recurrences rates. Survival and recurrence rates between groups with and without each paraneoplastic finding were compared using the log rank test. Each finding was used in a multivariate Cox proportional hazard model that included T category, N category, M category, ECOG-PS and Fuhrman grade. To compare responses to immunotherapy binary logistic regression analysis was performed. Patients with incomplete data were included when all necessary information was available for analysis of a particular sign or symptom. All statistical analyses were performed using StatsDirect, version 2.2 (StatsDirect, Ltd., Cheshire, United Kingdom) software package with $p < 0.05$ considered significant.

TABLE 1. *Patient characteristics*

	No. Pts (%)
Overall	1,046
Men/women	2/1
Localized	593 (57)
Histological pattern:	
Clear cell	730 (77)
Papillary	139 (15)
Chromophobe	28 (3)
Sarcomatoid	49 (5)
Fuhrman grade:	
1	117 (13)
2	446 (49)
3	307 (34)
4	45 (5)
1997 TNM stage:	
1	290 (30)
2	93 (10)
3	182 (19)
4	397 (41)
ECOG-PS:	
0	395 (42)
1	503 (54)
Greater than 1	36 (4)
UISS:	
1	243 (29)
2	218 (26)
3	65 (8)
4	200 (34)
5	26 (3)

TABLE 2. *Presentation of localized and metastatic, renal cell carcinoma and effect on disease specific survival*

	% (No./total No.)	Localized/ Metastatic Ratio	HR	p Value (univariate)
Anemia	52.1 (396/760)	0.7	2.0	<0.0001
All hematuria types	35.2 (358/1,016)	0.8	1.2	0.1852
Gross hematuria	24.3 (247/1,016)	0.7	1.2	0.0744
Hepatic dysfunction	31.5 (167/531)	0.6	2.1	<0.0001
Wt loss	22.9 (232/1,011)	0.3	3.0	<0.0001*
Malaise	19.1 (192/1,005)	0.6	2.9	<0.0001*
Hypoalbuminemia	19.9 (105/528)	0.6	2.3	<0.0001*
Flank pain	19.5 (197/1,010)	0.6	1.3	0.0631
Hypercalcemia	13.0 (61/470)	0.6	1.8	0.0223
Anorexia	10.6 (106/1,004)	0.4	3.1	<0.0001*
Thrombocytosis	9.2 (60/654)	0.6	2.6	<0.0001
Night sweats	8.4 (85/1,009)	0.6	2.5	<0.0001
Fever	7.8 (79/1,016)	0.5	2.0	<0.0001
Flank/abdominal mass	4.4 (45/1,012)	0.4	1.8	0.0064
Hypertension	2.5 (25/1,013)	0.6	1.4	0.3945
Erythrocytosis	3.7 (28/755)	0.47	1.4	0.1810
Chills	3.1 (31/1,013)	0.6	1.7	0.0457
Cachexia related findings†	35.3 (359/1,018)†	0.4	3.5	<0.0001*

* Significant on multivariate analysis using each finding separately combined with T category, N category, M category, ECOG-PS and Fuhrman grade.

† Hypoalbuminemia less than 3.6 gm/dl, weight loss greater than 5 lbs, anorexia or malaise.

RESULTS

Table 1 lists patient characteristics. Mean age was 59 years and the male-to-female ratio was 2:1. Nephrectomy was performed for localized RCC (N0M0) in 593 patients. Before 1995, 28% of RCC cases were diagnosed incidentally, while 36% were diagnosed incidentally beginning in 1995 ($p = 0.004$). Overall mean and median followup, including patients who died, was 40.3 and 24.5 months, respectively. Median time to death was 19.3 months.

Table 2 lists the frequency of presenting signs and symptoms for all patients and the ratio of the percent of each finding in patients with localized and metastatic RCC. Anemia (52.1% of cases), hematuria (35.2%) and hepatic dysfunction (31.5%) were the most common findings. On univariate analysis correlation between findings (table 2) and disease specific survival were statistically significant or approached statistical significance for all findings except hypertension and hematuria. When the same findings were assessed separately in a multivariate analysis controlling for T category, N category, M category, ECOG-PS and Fuhrman grade, the correlation with disease specific survival remained statistically significant for 4 findings, namely hypoalbuminemia, weight loss, anorexia and malaise (tables 2 and 3).

TABLE 3. *Presentations predicting disease specific survival after controlling for stage, grade and ECOG-PS*

	Hazard Ratio	95% CI	p Value
Hypoalbuminemia	1.4	1.0–2.1	0.0402
Wt loss	1.4	1.1–1.8	0.0079
Anorexia	1.5	1.1–2.0	0.0193
Malaise	1.6	1.2–2.1	0.0005
Cachexia related findings*	2.8	2.1–3.8	<0.0001

TNM stage was controlled as T, N and M category.

* Hypoalbuminemia less than 3.6 gm/dl, weight loss greater than 5 lbs, anorexia or malaise.

The findings that remained significant on multivariate analysis were categorized as cachexia related findings, and their frequency and correlation with disease specific survival were determined (tables 2 and 3). Figure 1 shows that an increasing total number of cachexia related findings resulted in a trend towards progressively worse prognosis. However, disease specific survival associated with 1 vs 4 cachexia related findings was not statistically different ($p = 0.08$). Therefore, patients with any cachexia related finding were assessed without regard to the number of cachexia related findings. When patients with localized RCC were stratified according to the presence or absence of cachexia, the difference in disease specific survival was statistically significant ($p < 0.0001$, fig. 2). When patients with metastatic RCC were stratified by the presence or absence of cachexia, the difference in disease specific survival was also different ($p < 0.0001$, fig. 3).

UISS stratifies patients into 5 prognostic categories based on complex interactions among stage, tumor grade and performance status. Figure 4 shows that for UISS stage 4, representing 80% of patients with metastatic RCC, cachexia related findings further stratified patients into statistically different survival groups ($p < 0.0001$). When stratified by cachexia for the other UISS stages, the difference in survival was not statistically significant. For patients with localized RCC none of the individual findings categorized as cachexia related correlated on multivariate analysis with increased risk of recurrence following nephrectomy. For patients with metastatic disease malaise correlated with response to immunotherapy on multivariate analysis ($p = 0.012$).

DISCUSSION

Hypoalbuminemia, weight loss, anorexia and malaise were predictors of poor survival after controlling for traditional indicators of prognosis, including TNM stage, Fuhrman grade and ECOG-PS. All 4 of these paraneoplastic findings may be related to cachexia that is often associated with malignancy. There was a trend toward worse survival with increasing number of cachexia related findings. Median survival for patients with 1 cachexia related finding was approximately 24 months, while median survival for those with all 4 cachexia related findings was approximately 9 months. However, the difference between these 2 groups did not attain statistical significance ($p = 0.08$). Therefore, patients with any 1 cachexia related finding were considered to be positive for cachexia in our analysis.

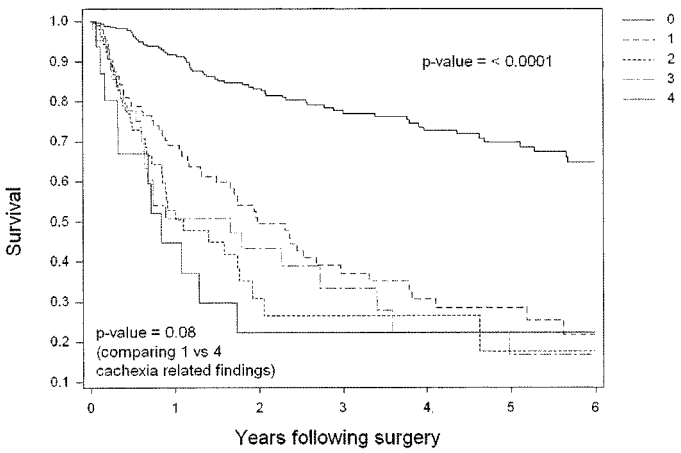

FIG. 1. Disease specific survival in patients with renal cell carcinoma stratified by number (*0* to *4*) of cachexia related findings, namely hypoalbuminemia, weight loss, anorexia and malaise.

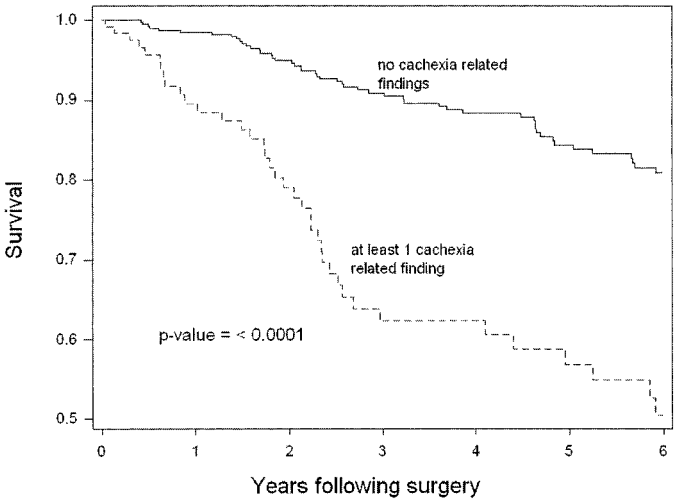

FIG. 2. Disease specific survival in patients with localized renal cell carcinoma stratified by presence or absence of cachexia.

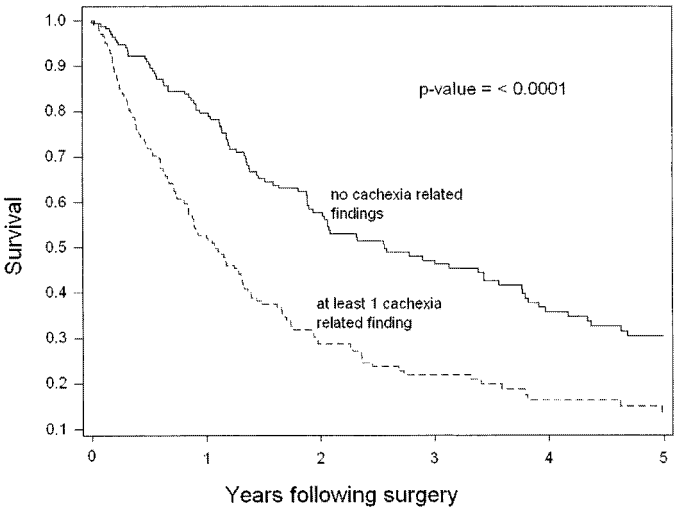

FIG. 3. Disease specific survival in patients with metastatic renal cell carcinoma stratified by presence or absence of cachexia.

Cachexia predicts worse survival in patients with localized as well as metastatic RCC. For localized RCC the 2-year survival rate was 95% vs 79% in patients without vs with cachexia ($p < 0.0001$). However, cachexia did not predict a higher risk of recurrence, suggesting that cachexia at initial presentation predicts a worse prognosis for patients after recurrence. For metastatic RCC median survival was 12 vs 31 months in patients with vs without cachexia ($p < 0.001$). However, cachexia did not decrease the likelihood of responding to immunotherapy in patients with metastatic disease.

Currently the most commonly used measure of performance status is ECOG-PS, which defines performance as the ability to perform the daily activities of life, such as housework and self-care. ECOG-PS has been shown to predict survival in patients with localized and metastatic RCC. In addition, patients with metastatic RCC who have a good ECOG-PS are more likely to respond to immunotherapy.[5] Therefore, at most centers IL-2 based immunotherapy is administered only to patients with good PS. ECOG-PS is also widely applied to determine eligibility for investigational protocols. However, it does not include measures of presenting signs and symptoms, and it is not surprising that other parameters that predict survival can be identified. To better predict prognosis our findings suggest that ECOG-PS should be expanded to include cachexia related findings when applied to RCC.

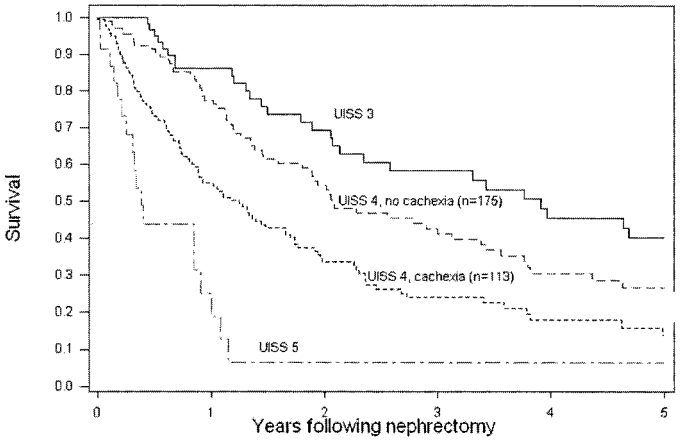

FIG. 4. Disease specific survival in patients with UISS stage 4 renal cell carcinoma stratified by presence or absence of cachexia ($p < 0.0001$). Disease specific survival curves for UISS stages 3 and 5 are shown for reference.

UISS was developed to account for the complex interactions of stage, grade and ECOG-PS in affecting survival and it stratifies patients with localized and metastatic RCC into 5 survival groups.[5] However, the usefulness of UISS is somewhat limited for metastatic RCC because most cases are categorized as UISS stage 4. Therefore, a parameter that further stratifies this group is needed. In this study patients with UISS stage 4 disease with (110) and without (167) cachexia had median disease specific survival of 14 and 25 months, respectively ($p < 0.0001$). The 2 groups contained similar numbers of patients.

All presenting signs and symptoms that we report were found in localized as well as metastatic RCC cases, suggesting that these findings reflect tumor biology rather than simply the local or distal extent of tumor. Many presenting symptoms and signs in RCC represent paraneoplastic effects that result from the elaboration of various proteins by the tumor. A parathyroid hormone-like peptide has been implicated as the cause of hypercalcemia.[6,7] Erythrocytosis is thought to result from the production of erythropoietin by RCC and it may even predict the response to immunotherapy.[8] Hepatic dysfunction (Stauffer's syndrome) and hypertension have been documented previously in the absence of metastatic disease and resolve following nephrectomy.[9,10] It has been suggested that cachexia and malaise may be due to the secretion of tumor necrosis factor-α, IL-1 or IL-6 by the tumor or infiltrating immune cells.[11,12]

Although paraneoplastic effects are well recognized in RCC, previously the implication for prognosis had not been clearly defined. In our study only cachexia related findings correlated with survival on multivariate analysis. This result is consistent with a study of Elson et al showing that weight loss as well as time to metastasis, ECOG-PS, previous chemotherapy and number of metastatic sites predict survival.[13] In a similar study Motzer et al reported that anemia and hypercalcemia (Ca greater than 10 ng/ml) predict worse survival on multivariate analysis.[14] In our analysis anemia and hypercalcemia correlated with poor survival on univariate analysis but not on multivariate analysis controlling for TNM stage, grade and ECOG-PS. In the study by Motzer et al multivariate analysis did not include grade or T category, which may account for the differing results.

Other studies compared survival in patients with and without symptoms, although no attempt was made to separate patients based on presenting symptoms, which may account for conflicting conclusions reached by various investigators. Two previous reports concluded that there was no difference in prognosis for patients with RCC presenting with vs without symptoms.[15,16] However, others reported that symptomatic presentation portends a worse prognosis.[4,17,18] The current study suggests that certain signs and symptoms (ie cachexia related findings) and not simply the presence or absence of symptoms have a prognostic significance that is independent of stage, grade and ECOG-PS.

Our study provides the frequency of presenting symptoms and paraneoplastic signs in a modern RCC series. McDougal and Garnick reported a 24% frequency of hypertension.[2] However, when we defined hypertension as the new onset or worsening of existing hypertension, we reported a frequency of 2.5%. Although flank pain, flank mass and hematuria are not paraneoplastic findings, they represent the classic triad for the presentation of RCC and were included in this study. Historically the frequency of presentation with the classic triad of hematuria, palpable mass and pain is quoted as 10%.[19] However, we report that these 3 findings are almost never seen in the same patient, and the frequency of finding 1 of these 3 symptoms (a palpable mass) was only 4.4%. Because more tumors are being incidentally detected on computerized tomography and ultrasound imaging at an earlier stage, fewer tumors can be expected to present with a palpable mass. In addition, as radiographic technology improves, examining patients for a palpable flank mass may be less critical.

CONCLUSIONS

Cachexia, defined as hypoalbuminemia, weight loss, anorexia and malaise, predicts worse survival after controlling for well established indicators of prognosis, including TNM stage, Fuhrman grade and ECOG-PS. Consideration should be given to expanding ECOG-PS to include measures for cachexia.

REFERENCES

1. Jemal, A., Thomas, A., Murray, T. and Thun, M.: Cancer statistics, 2002. CA Cancer J Clin, **52:** 23, 2002
2. McDougal, W. S. and Garnick, M. B.: Clinical signs and symptoms of renal cell carcinoma. In: Comprehensive Textbook of Genitourinary Oncology. Edited by N. J. Vogelzang, P. T. Scardino, W. U. Shipley and D. S. Coffey. Baltimore: Williams & Wilkins Co., pp. 154–159 and 111–115, 1995
3. Konnak, J. W. and Grossman, H. B.: Renal cell carcinoma as an incidental finding. J Urol, **134:** 1094, 1985
4. Tsui, K.-H., Shvarts, O., Smith, R. B., Figlin, R., deKernion, J. B. and Belldegrun, A.: Renal cell carcinoma: prognostic significance of incidentally detected tumors. J Urol, **163:** 426, 2000
5. Zisman, A., Pantuck, A. J., Dorey, F., Said, J. W., Shvarts, O., Quintana, D. et al: Improved prognostication of renal cell carcinoma using an integrated staging system. J Clin Oncol, **19:** 1649, 2001
6. Strewler, G. J., Stern, P. H., Jacobs, J. W., Eveloff, J., Klein, R. F., Leung, S. C. et al: Parathyroid hormonelike protein from human renal carcinoma cells. Structural and functional homology with parathyroid hormone. J Clin Invest, **80:** 1803, 1987
7. Suva, L. J., Winslow, G. A., Wettenhall, R. E., Hammonds, R. G., Moseley, J. M., Diefenbach-Jagger, H. et al: A parathyroid hormone-related protein implicated in malignant hypercalcemia: cloning and expression. Science, **237:** 893, 1987
8. Janik, J. E., Sznol, M., Urba, W. J., Figlin, R., Bukowski, R. M., Fyfe, G. et al: Erythropoietin production. A potential marker for interleukin-2/interferon-responsive tumors. Cancer, **72:** 2656, 1993
9. Hollifield, J. W., Page, D. L., Smith, C., Michelakis, A. M., Staab, E. and Rhamy, R.: Renin-secreting clear cell carcinoma of the kidney. Arch Intern Med, **135:** 859, 1975
10. Rosenblum, S. L.: Paraneoplastic syndromes associated with renal cell carcinoma. J S C Med Assoc, **83:** 375, 1987
11. Sufrin, G., Mirand, E. A., Moore, R. H., Chu, T. M. and Murphy, G. P.: Hormones in renal cancer. J Urol, **117:** 433, 1977
12. Laski, M. E. and Vugrin, D.: Paraneoplastic syndromes in hy-

pernephroma. Semin Nephrol, **7:** 123, 1987
13. Elson, P. J., Witte, R. S. and Trump, D. L.: Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma. Cancer Res, **48:** 7310, 1988
14. Motzer, R. J., Mazumdar, M., Bacik, J., Berg, W., Amsterdam, A. and Ferrara, J.: Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol, **17:** 2530, 1999
15. Jayson, M. and Sanders, H.: Increased incidence of serendipitously discovered renal cell carcinoma. Urology, **51:** 203, 1998
16. Mevorach, R. A., Segal, A. J., Tersegno, M. E. and Frank, I. N.: Renal cell carcinoma: incidental diagnosis and natural history: review of 235 cases. Urology, **39:** 519, 1992
17. Thompson, I. M. and Peek, M.: Improvement in survival of patients with renal cell carcinoma—the role of the serendipitously detected tumor. J Urol, **140:** 487, 1988
18. Kattan, M. W., Reuter, V., Motzer, R. J., Katz, J. and Russo, P.: A postoperative prognostic nomogram for renal cell carcinoma. J Urol, **166:** 63, 2001
19. deKernion, J. B., Lowitz, B. and Casciato, D.: Urinary tract cancers. In: Manual of Clinical Oncology. Edited by D. Casciato and B. Lowitz. Boston: Little, Brown & Co., pp. 198–219, 1998