Histologic Tumor Necrosis Is an Independent Prognostic Indicator for Clear Cell and Papillary Renal Cell Carcinoma

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Key Words: Prognosis; Renal cell carcinoma; Tumor necrosis; Papillary type

During the last decade, enormous advances in the development of novel anticancer drugs for the treatment of metastatic renal cell carcinoma (RCC) have driven the replacement of nonspecific monotherapy with immunomodulating agents with compounds that selectively target clearly defined molecular pathways, such as vascular endothelial growth factor and mTOR inhibitors.¹ The successful introduction of these clinically efficient targeted drugs in the setting of metastatic disease has prompted the initiation of adjuvant treatment trials with some of these agents for high-risk patients with earlier tumor stages.² Considering the high costs and toxic effects of most of these drugs, the accurate identification and validation of prognostic factors that might predict the development of distant metastases might enable a better risk-stratified strategy for patient selection for adjuvant treatment modalities.³ The diagnosis of RCC comprises different histologic subtypes, including clear cell, papillary, chromophobe, collecting duct, and not otherwise specified cases.⁴

Because clear cell histology accounts for approximately 80% of all RCCs, most data regarding prognostic factors have been generated for this subtype. It is important to note that a particular histologic subtype is accompanied by different clinical behaviors, genetic changes, and pharmacologic responsiveness.⁵-⁷ Therefore, ideally, the clinical significance of a particular prognostic factor should always be independently validated for each histologic subtype.

The presence of histologic tumor necrosis (TN) has been proposed as an independent prognostic factor for different solid tumors, including colorectal and transitional carcinomas of the upper urinary tract, and in a series of studies evaluating clear cell RCC.⁸-¹² In clear cell RCC, TN has been repeatedly associated with larger tumors, higher grade, and higher metastasis-free survival (HR, 2.32; CI, 1.86-2.9; P < .001) and overall survival (HR, 1.52; CI, 1.31-1.76; P < .001) survival. Regarding papillary RCC, the presence of histologic TN represented an independent predictor of metastasis-free (HR, 5.22; CI, 2.2-12.5; P < .001) and overall survival (HR, 1.69; CI, 1.11-2.58; P = .015) survival.

Our findings suggest that the presence of TN is an independent predictor of clinical outcome in clear cell and papillary RCC. Thus, histologic TN might be a reliable prognostic indicator and should, therefore, routinely be examined during pathologic analysis of RCC specimens.

During the last decade, enormous advances in the development of novel anticancer drugs for the treatment of metastatic renal cell carcinoma (RCC) have driven the replacement of nonspecific monotherapy with immunomodulating agents with compounds that selectively target clearly defined molecular pathways, such as vascular endothelial growth factor and mTOR inhibitors.¹ The successful introduction of these clinically efficient targeted drugs in the setting of metastatic disease has prompted the initiation of adjuvant treatment trials with some of these agents for high-risk patients with earlier tumor stages.² Considering the high costs and toxic effects of most of these drugs, the accurate identification and validation of prognostic factors that might predict the development of distant metastases might enable a better risk-stratified strategy for patient selection for adjuvant treatment modalities.³ The diagnosis of RCC comprises different histologic subtypes, including clear cell, papillary, chromophobe, collecting duct, and not otherwise specified cases.⁴

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Tumor necrosis (TN) is a histologic feature characterized by the presence of coagulative necrosis, which can be observed in a variety of tumors, including renal cell carcinoma (RCC). TN is associated with increased proliferative activity, and, although the pathogenesis of TN remains largely unknown, it is believed that TN represents an indirect indicator of biologically aggressive tumor behavior.13

Papillary RCC represents the second most common histologic subtype, accounting for 10% to 15% of all RCCs.4 Data reporting the prognostic significance of TN in this particular histologic subtype are conflicting, and controversy still exists concerning the role of TN as an independent risk factor for papillary RCC. The majority of published studies have reported that the presence of TN in papillary RCC has no prognostic significance. However, most of these studies included only a limited number of cases.14-16 In contrast to these findings, a recently published large study demonstrated that the extent of TN actually represents an independent prognostic indicator for papillary RCC, and the authors therefore incorporated it into a novel prognostic nomogram, specifically developed for patients with papillary RCC.17

As the first adjuvant trials with clear cell RCC have been initiated and TN constitutes one of the prognostic risk factors to select patients in some of these adjuvant trials, the validation of the prognostic value of TN in the papillary subtype might influence future therapeutic decisions.2 To further clarify the prognostic value of TN in papillary RCC, the aims of this study were to evaluate whether the presence of TN has a prognostic impact on metastasis-free and overall survival in a large cohort of patients with papillary RCC and to compare the results between patients with clear cell and papillary subtypes.

**Materials and Methods**

**Pathologic and Clinical Evaluation**

This retrospective analysis included data from 2,333 consecutive patients who underwent a radical or partial nephrectomy for RCC at the Department of Urology, Medical University of Graz, Graz, Austria, between 1984 and 2006. All clinicopathologic data were retrieved from medical records at the Department of Urology and from pathology records from the Institute of Pathology at the same institution.

The routine pathologic assessment of RCC specimens was based on a minimum of 3 formalin-fixed, paraffin-embedded tissue blocks per tumor. All histologic subtypes were adjusted according to the Heidelberg classification system as clear cell, papillary, chromophobe, collecting duct, or not otherwise specified.4 Since the TNM classification system for RCC changed during the study period, pathologic T stages were uniformly adjusted according to the 2002 edition of this system. In addition, tumor size was defined according to the greatest tumor diameter in centimeters reported in the pathology report. Tumor grade was assessed according to the 4-tiered classification, described by Fuhrman et al.18 The presence or absence (not quantitative assessment) of histologic coagulative necrosis was analyzed according to established histologic criteria.15 Tumor necrosis was defined as the presence of microscopic coagulative necrosis, characterized by homogeneous clusters and sheets of degenerating and dead cells. Image 1. Histopathologic regressive changes, such as cystic transformation, hyalinization, and fibrosis, were not considered to represent necrosis. In patients with bilateral metachronous RCCs, only the first tumor was chosen for analyses.

The assessment of patient-related characteristics included age, sex, date and type of surgery, tumor side, bilateral tumors, metastatic disease at initial examination, and histologically confirmed secondary malignancies other than RCC diagnosed at any time during a patient’s history. Postoperative surveillance included routine clinical and laboratory examination; regarding imaging methods, radiographs of the chest and abdominal ultrasound were predominantly used, especially in patients with a low risk for relapse (pT1 G1-2), whereas computed tomography or magnetic resonance imaging was performed in all other patients or to further clarify “suspicious” lesions. Follow-up evaluations were performed every 6 months for 5 years and annually thereafter for locally advanced tumor stages. In organ-confined cancers, imaging was performed twice in the first year after surgery and annually thereafter.

No neoadjuvant or adjuvant treatment was administered, and survival data were retrieved from the electronic patient records at our institution and from the central registry of the Austrian Bureau of Statistics. Metastasis-free survival was defined as the time (in months) from date of surgery to the recurrence of radiologically or histologically confirmed metastases.
disease. Overall survival was defined as the time (in months) from date of surgery to death.

Statistical Analyses

The relationship between TN and other clinicopathologic parameters was studied by nonparametric tests; metastasis-free and overall survival were calculated with the Kaplan-Meier method, compared by the log-rank test. Backward stepwise multivariate Cox proportion analysis was performed to determine the influence of histologic subtype, T stage, grade, age, sex, and TN on metastasis-free and overall survival. Hazard ratios (HRs) estimated from Cox models were reported as relative risks with corresponding 95% confidence intervals (CIs). All statistical analyses were performed using the Statistical Package for Social Sciences, version 17.0 (SPSS, Chicago, IL). A 2-sided P value of less than .05 was considered statistically significant.

Results

Of the 2,333 consecutive patients, 1,931 (82.8%) had clear cell, 255 (10.9%) papillary, 70 (3.0%) chromophobe, 69 (3.0%) non–clear cell histologic features, and 8 (0.3%) collecting duct RCC. Complete data, including histopathologic parameters and follow-up information, were available for 2,285 patients (97.9%).

Table I shows the clinicopathologic parameters stratified by histologic subtype (clear cell and papillary). Overall, the presence of TN was noted in 775 (33.9%) of 2,285 cases, including 616 (32.6%) of 1,891 clear cell RCCs and 100 (40.3%) of 248 papillary RCCs (P < .001). We investigated the correlation between the presence of TN and established clinicopathologic parameters, including T stage, grade, age, sex, sarcomatoid component, and vascular invasion. The presence of TN was statistically significantly associated with high T stage, large tumor size, poor differentiation, sarcomatoid component (all P < .001), non–clear cell histologic features (P = .015), and vascular invasion (P < .001). No statistically significant association between age or sex and the presence of TN was observed (data not shown).

To investigate whether the presence of TN is associated with the clinical outcome of patients with RCC of different histologic subtypes, an analysis of metastasis-free and overall survival was done. To perform the clinical outcome analysis with enough statistical power, we restricted our study to the 2 main histologic subtypes, ie, clear cell and papillary RCC. Regarding clear cell histologic features, the presence of TN was statistically significantly associated with T stage, tumor size, grade, vascular invasion, and sarcomatoid component (all P < .001); however, no differences could be observed for age or sex. Regarding papillary RCC, the presence of TN was statistically significantly associated with T stage (P = .001), tumor size (P = .007), grade (P = .015), and vascular invasion (P = .003), whereas no statistically significant association was found for sex, sarcomatoid component, or age.

The mean follow-up duration was 86 months (range, 0-281 months). Of the 1,891 patients with clear cell RCC, metastatic disease developed in 491 (26.0%) by the most recent follow-up visit. Of the 248 patients with papillary RCC, metastatic disease developed in 49 (19.8%). Among the 1,891 patients with clear cell RCC, metastatic disease was diagnosed in 299 (48.5%) of 616 with presence of TN and in 192 (15.1%) of 1,275 without (P < .001). Regarding the 248 patients with papillary RCC, progression to metastatic disease occurred in 35 (35.0%) of 100 with TN and in 14 (9.5%) of 148 without (P < .001). Figure 1 shows the Kaplan-Meier curves for metastasis-free and overall survival analysis and reveals that TN is a factor for poor prognosis in papillary RCC. It is noteworthy that patients with RCC with signs of TN had statistically significantly higher rates of 5- and 10-year cancer-related deaths (P < .001; data not shown).

To determine the independent prognostic value of TN on metastasis-free and overall survival, multivariate analysis using a Cox proportional hazards model was done. In multivariate analyses that included the presence of TN, T stage, grade, vascular invasion, age, and sex, the presence of TN was

Table I

| Parameter                      | Clear Cell RCC (n = 1,891) | Papillary RCC (n = 248) |
|-------------------------------|---------------------------|-------------------------|
| Age at operation (y)          |                           |                         |
| ≤65                           | 1,028 (54.4)              | 129 (51.6)              |
| >65                           | 863 (45.6)                | 120 (48.4)              |
| Sex                           |                           |                         |
| Male                          | 1,063 (56.2)              | 173 (69.8)              |
| Female                        | 828 (43.8)                | 236 (30.2)              |
| Mean ± SD primary tumor size (cm) | 5.51 ± 2.96              | 5.27 ± 3.03             |
| T stage                       |                           |                         |
| pT1a                          | 621 (32.8)                | 93 (37.5)               |
| pT1b                          | 362 (19.1)                | 50 (20.2)               |
| pT2                           | 108 (5.7)                 | 20 (8.1)                |
| pT3a                          | 452 (23.9)                | 65 (26.2)               |
| pT3b                          | 327 (17.3)                | 18 (7.3)                |
| pT3c                          | 5 (0.3)                   | 1 (0.4)                 |
| pT4                           | 16 (0.8)                  | 1 (0.4)                 |
| Tumor grade                   |                           |                         |
| G1                            | 423 (22.4)                | 52 (21.0)               |
| G2                            | 1,186 (62.7)              | 153 (61.7)              |
| G3                            | 253 (13.4)                | 41 (16.5)               |
| G4                            | 29 (1.5)                  | 2 (0.8)                 |
| Tumor necrosis                |                           |                         |
| Absent                        | 1,275 (67.4)              | 148 (59.7)              |
| Present                       | 616 (32.6)                | 100 (40.3)              |
| Sarcomatoid component         |                           |                         |
| No                            | 1,785 (94.4)              | 238 (96.0)              |
| Yes                           | 106 (5.6)                 | 10 (4.0)                |
| Vascular invasion             |                           |                         |
| Absent                        | 1,435 (75.9)              | 211 (85.1)              |
| Present                       | 456 (24.1)                | 37 (14.9)               |

RCC, renal cell carcinoma.

* Data are given as number (percentage) unless otherwise indicated.
identified as an independent predictor for metastatic disease in clear cell (HR, 2.32; CI, 1.86-2.9; \( P < .001 \)) and in papillary (HR, 5.22; CI, 2.17-12.54; \( P < .001 \)) RCC. Statistically highly significant results were also obtained for a high T stage, high grade, sarcomatoid component, and vascular invasion (all \( P < .001 \)), whereas sex and age were not highly significantly associated with metastasis-free survival. The presence of TN was also found to be an independent predictor for overall survival in clear cell (HR, 1.52; CI, 1.31-1.76; \( P < .001 \)) and papillary (HR, 1.69; CI, 1.11-2.58; \( P = .015 \)) RCC.

### Table 2

| Parameter                  | Metastasis-Free Survival | Overall Survival |
|----------------------------|--------------------------|------------------|
|                           | HR (95% CI)              |          | HR (95% CI)   |          |
| Age at operation (y)      |                          |           |               |               |
| <65                       | 1 (reference)            | .2       | 1 (reference) | <.001     |
| >65                       | 1.16 (0.94-1.44)         | .018     | 1.84 (1.6-2.11)| <.001     |
| Sex                       |                          |           |               |               |
| Female                    | 1 (reference)            | .9       | 1 (reference) | .77 (1.46-2.16)| <.001     |
| Male                      | 1.29 (1.04-1.6)          |          | 1.27 (1.1-1.46)| <.001     |
| T stage                   |                          |           |               |               |
| pT1-2                     | 1 (reference)            | <.001    | 1 (reference) | <.001     |
| pT3-4                     | 2.16 (1.63-2.88)         |          | 1.5 (1.27-1.79)| <.001     |
| Tumor grade               |                          |           |               |               |
| G1 + G2                   | 1 (reference)            | <.001    | 1 (reference) | <.001     |
| G3 + G4                   | 1.78 (1.32-2.39)         |          | 1.77 (1.46-2.16)| <.001     |
| Presence of tumor necrosis|                          |           |               |               |
| No                        | 1 (reference)            | <.001    | 1 (reference) | <.001     |
| Yes                       | 2.32 (1.85-2.9)          |          | 1.52 (1.31-1.76)| <.001     |
| Sarcomatoid component     |                          |           |               |               |
| No                        | 1 (reference)            | <.001    | 1 (reference) | <.001     |
| Yes                       | 1.85 (1.26-2.7)          |          | 1.66 (1.27-2.17)| <.001     |
| Vascular invasion         |                          |           |               |               |
| Absent                    | 1 (reference)            | <.001    | 1 (reference) | <.001     |
| Present                   | 2.32 (1.83-2.96)         |          | 1.86 (1.58-2.20)| <.001     |

CI, confidence interval; HR, hazard ratio.

### Discussion

Progress in the field of discovering differences in molecular pathways that might influence the development...
and progression of different RCC subtypes has prompted the idea for more personalized medicine, depending on a tumor’s underlying molecular background.\textsuperscript{19-21} Despite advances in the detection of genetic and cellular changes in RCC during the last years, the diagnostic and prognostic assessment of RCC currently relies on pathologic examination and the traditional TNM classification system. The complexity of molecular changes, high costs of analyses, time-consuming preparation steps, and a lack of evidence demonstrating that the newly discovered molecular markers might influence diagnostic or therapeutic decisions have rendered none of the markers available ready for routine testing. Histopathologic parameters, such as assessment of the histologic subtype, vascular invasion, and TN, are easy to assess without additional laborious efforts and, therefore, remain attractive parameters for an individualized risk assessment.

In the present study that included a cohort of almost 1,900 patients with clear cell and 250 patients with papillary RCC, we were able to demonstrate that the presence of TN was an independent negative predictor for metastasis-free and overall survival in a model of well-established prognostic indicators for both histologic subtypes. The presence of TN has been previously shown to be a prognostic factor in different cancers, including breast cancer, transitional carcinomas of the upper urinary tract, and colorectal and lung cancer.\textsuperscript{22-24} In renal malignancies, comprehensive evidence exists for the most common histologic subtype, clear cell RCC. Studies evaluating clear cell RCC include several thousands of patients and have established the presence of TN as a negative prognostic predictor.\textsuperscript{8,9} Consecutively, the stage, size, grade, and necrosis (SSIGN) score and the Leibovich score were developed, and these well-designed prognostic models have incorporated this histologic feature (TN) in an outcome prediction tool for patients with clear cell histologic features.\textsuperscript{25,26} According to the Leibovich score, patients’ assignment into the low-, intermediate-, or high-risk group can accurately assess the risk for the occurrence of metastatic disease after radical nephrectomy.\textsuperscript{26} On the basis of this tool, the UK Medical Research Council phase 3 SORCE trial (NCT00492258) is currently recruiting patients with clear cell RCC with intermediate and high risk to be randomized into groups for the multikinase inhibitor sorafenib and placebo.\textsuperscript{2}

However, data regarding TN in papillary RCC and its prognostic impact are controversially reported, and most prior studies were restricted to a small number of patients. For example, Moch et al\textsuperscript{15} reported that in contrast with the negative impact in clear cell and chromophobe RCC, the presence of TN was not associated with a dismal prognosis in 64 patients with papillary RCC. In another study, Kim and colleagues\textsuperscript{27} found no statistically significant association between the presence of TN and overall survival in 54 patients with papillary RCC. A larger retrospective analysis by Sengupta et al\textsuperscript{28} confirmed the presence of TN as an independent predictor in clear cell and chromophobe RCC, but found no influence in the risk of death for papillary RCC. In contrast with these findings and consistent with our data, a recently published study by Klatte et al\textsuperscript{17} analyzed 435 cases of the papillary subtype and identified the extent of TN as an independent prognostic predictor. It is important to note that this study currently represents the largest study analyzing TN as a

\begin{table}[h]
\centering
\caption{Multivariate Analysis of Clinicopathologic Parameters for the Prediction of Metastasis-Free and Overall Survival in Patients With Papillary Renal Cell Carcinoma}
\begin{tabular}{|l|l|l|l|}
\hline
Parameter & Metastasis-Free Survival & Overall Survival \\
\hline
 & HR (95\% CI) & P & HR (95\% CI) & P \\
\hline
Age at operation (y) & & & & \\
\leq 65 & 1 (reference) & .79 & 1 (reference) & .002 \\
>65 & 0.89 (0.4-1.99) & .03 & 1.95 (1.27-3) & .06 \\
Sex & Female 1 (reference) & .<.001 & 1 (reference) & .04 \\
 & Male 3 (1.12-8.2) & .9 & 1.56 (0.97-2.53) & 1.59 (1.02-2.51) \\
T stage & pT1-2 1 (reference) & .005 & 1 (reference) & .<.001 \\
 & pT3-4 9 (2.65-30) & 3.68 (1.47-9.22) & 3.28 (1.99-5.4) & .015 \\
Tumor grade & G1 + G2 1 (reference) & .<.001 & 1 (reference) & .009 \\
 & G3 + G4 3.68 (1.47-9.22) & 5.22 (2.17-12.54) & 1.69 (1.11-2.58) & .009 \\
Presence of tumor necrosis & No 1 (reference) & 1 (reference) & 1 (reference) & .<.001 \\
 & Yes 5.22 (2.17-12.54) & 2.92 (1.29-6.6) & 1.99 (1.23-3.2) & \\
Vascular invasion & Absent 1 (reference) & .009 & 1 (reference) & .004 \\
 & Present 2.92 (1.29-6.6) & .009 & 1 (reference) & .004 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{CI, confidence interval; HR, hazard ratio.}
prognostic factor for papillary RCC. The observed differences in prior studies can be explained by several factors, including heterogeneity in pTNM stage in the populations studied, biased selection of patients, and the method of TN assessment and sample size, the latter being the most critical aspect in this type of retrospective study.

It is noteworthy that papillary RCC has been divided for histologic reasons into 2 subtypes (1 and 2).29 Although controversial data exist regarding the prognostic meaning of these 2 subtypes, there is no consensus about the prognostic relevance of this subclassification, and, therefore, we have not separately analyzed these subtypes.29,30

The potential influence of TN on the poor clinical outcome for patients with cancer has been hypothesized on the basis that increased tumor cell death indicates more aggressive clinical behavior. In this context, a common hypothesis for the development of TN, although unproven, is that rapid tumor cell growth in more aggressive subtypes outgrows its own blood supply with subsequent creation of hypoxic conditions that result in massive tumor cell death. This theory is underlined by the observation that hypovascular tumors, such as papillary RCC, show higher frequencies of TN and that high proliferation rates indicated by proliferation markers such as Ki-67 are associated with TN.3 However, whether a high proliferation index or an insufficient oxygen supply is the major factor for TN remains controversial. In a recent report on clear cell RCC, Minervini et al31 reported that histologic necrosis was not associated with high Ki-67 expression and that it did not correlate with expression of von Hippel-Lindau gene (VHL) or with the hypoxic response of hypoxia inducible factor-1 a (HIF-1a) expression. Tollefson and colleagues32 stated that TN and the proliferation marker Ki-67 are not interchangeable and, therefore, do not support the hypothesis that TN is solely the consequence of rapid tumor growth. Immunologic factors, such as differential expression of chemokines, have also been involved with the presence of TN, although the real nature of immunologic triggers and this histologic feature remains largely unknown.33

In the present study, we analyzed whether the presence/absence of TN influences the clinical outcome for patients with clear cell or papillary RCC. A few studies have analyzed TN in a quantitative manner by assessing its actual extent. The first report about a cohort of 311 patients with RCC by Lam et al13 demonstrated that the presence of histologic TN was an independent predictor of survival in patients with localized disease. The authors graded the extent of histologic TN in quartiles but did not identify the extent of TN as an independent predictor of survival.13 In concordance with these data, Minervini et al31 found no independent prognostic impact of the extent of histologic TN in a cohort of 213 patients by stratifying them into groups with 1% to 30% TN, 30% to 75% TN, and more than 75% TN. In contrast with these findings, in a prospective sample collection, Klatte and colleagues34 reported that a cutoff value of 20% provides superior prognostic information to the presence or absence of histologic TN. Katz et al35 reported a study comprising data for more than 800 patients regarding the role of the extent of histologic TN in RCC. They were able to demonstrate that a high extent of TN (cutoff >50%) was an independent predictor for disease-specific and overall survival.35 However, both aforementioned studies34,35 found no independent prognostic information for the presence of histologic TN, which is in contrast with the findings of the present and several other larger studies.9,28

Whether the actual extent of histologic TN represents a better prognosticator than the absence or presence of TN remains unclear, albeit larger studies should be able to validate conflicting results. In addition, it still needs to be clarified which cutoff value should be ideally used, optimizing predictive accuracy predictions, and providing high interobserver reproducibility.

As with all retrospective studies, limitations of our study are inherent in the design and include retrospective data collection. Our institutional standard for sampling tumor tissue was at least 3 blocks per RCC. Most current recommendations support sampling at least 1 block per centimeter of tumor tissue. Unfortunately, this criterion was not fulfilled by our retrospective study. Moreover, the patients from this study underwent surgical treatment by multiple surgeons at our academic institution. In an attempt to control for the homogeneity of the study population, we excluded the data for patients with hereditary RCC, patients with metachronous secondary RCC, and patients with competitive invasive cancers originating from other sites if metastatic spread was not assessed by histologic examination. Nevertheless, even regarding the aforementioned limitations, our data clearly indicate that TN is a relevant and powerful parameter for clear cell and papillary RCC.

The presence of TN represents an independent predictor with respect to metastasis-free and overall survival in patients with clear cell and papillary RCC. For future adjuvant trials, this feature should be prospectively evaluated as a selection criterion for risk factor–stratified patient management in RCC. Surgical pathologic assessment of RCC samples should, therefore, be routinely recorded for this assessable histologic feature.

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Acknowledgment: We thank Ariane Angelsreiter, MD, for critically reviewing the manuscript and providing the photomicrograph of tumor necrosis for Image 1.

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References

1. Flaherty KT, Puzanov I. Building on a foundation of VEGF and mTOR targeted agents in renal cell carcinoma. Biochem Pharmacol. 2010;80:638-646.

2. Bex A, Jonasch E, Kirkali Z, et al. Integrating surgery with targeted therapies for renal cell carcinoma: current evidence and ongoing trials. Eur Urol. 2010;58:819-828.

3. Crispin PL, Boorjian SA, Lolse CM, et al. Predicting disease progression after nephrectomy for localized renal cell carcinoma: the utility of prognostic models and molecular biomarkers. Cancer. 2008;113:450-460.

4. Kovacs G, Akhtar M, Beckwith BJ, et al. The Heidelberg classification of renal cell tumours. J Pathol. 1997;181:133-133.

5. Klatte T, Pantuck AJ. Molecular biology of renal cortical tumors. Urol Clin North Am. 2008;35:573-580, vi.

6. Leibovich BC, Lohse CM, Crispen PL, et al. Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. J Urol. 2010;183:1309-1315.

7. Schrader AJ, Ollert PJ, Hegle A, et al. Metastatic non-clear cell renal cell carcinoma: current therapeutic options. BJU Int. 2008;101:1343-1345.

8. Cheville JC, Blute ML, Zincke H, et al. Stage pT1 conventional (clear cell) renal cell carcinoma: pathological features associated with cancer specific survival. J Urol. 2001;166:453-456.

9. Cheville JC, Lohse CM, Zincke H, et al. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Am J Surg Pathol. 2003;27:612-624.

10. Langner C, Hutterer G, Chromekti T, et al. Tumor necrosis as prognostic indicator in transitional cell carcinoma of the upper urinary tract. J Urol. 2006;176:910-914.

11. Pollheimer MJ, Komprat P, Lindner RA, et al. Tumor necrosis is a new promising prognostic factor in colorectal cancer. Hum Pathol. 2010;41:1749-1757.

12. Ramsey S, Lamb GW, Atchison M, et al. Prospective study of the relationship between the systemic inflammatory response, prognostic scoring systems and relapse-free and cancer-specific survival in patients undergoing potentially curative resection for renal cancer. BJU Int. 2008;101:959-963.

13. Lam JS, Shvarts O, Said JW, et al. Clinicopathologic and molecular correlations of necrosis in the primary tumor of patients with renal cell carcinoma. Cancer. 2005;103:2517-2525.

14. Delahant B, Ebbe JN. Papillary renal cell carcinoma: a clinicopathologic and immuno-histochemical study of 105 tumors. Mod Pathol. 1997;10:537-544.

15. Moch H, Gasser T, Amin MB, et al. Prognostic utility of the recently recommended histologic classification and revised TNM staging system of renal cell carcinoma: a Swiss experience with 588 tumors. Cancer. 2000;89:604-614.

16. Onishi T, Ohishi Y, Goto H, et al. Papillary renal cell carcinoma: clinicopathological characteristics and evaluation of prognosis in 42 patients. BJU Int. 1999;83:937-943.

17. Klatte T, Remzi M, Zageruener RE, et al. Development and external validation of a nomogram predicting disease specific survival after nephrectomy for papillary renal cell carcinoma. J Urol. 2010;184:53-58.

18. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol. 1982;6:655-663.

19. Jones J, Pantuck AJ. Genomics and proteomics in renal cell carcinoma: diagnosis, prognosis, and treatment selection. Curr Urol Rep. 2008;9:9-14.

20. Macher-Goeppinger S, Aulmann S, Tagscherer KE, et al. Prognostic value of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and TRAIL receptors in renal cell cancer. Clin Cancer Res. 2009;15:650-659.

21. Macher-Goeppinger S, Aulmann S, Wegener N, et al. Decoy receptor 3 is a prognostic factor in renal cell cancer. Neoplasia. 2008;10:1049-1056.

22. Leek RD, Landers RJ, Harris AL, et al. Necrosis correlates with high vascular density and focal macrophage infiltration in invasive carcinoma of the breast. Br J Cancer. 1999;79:991-995.

23. Llompart-Bosch A, Contesso G, Henry-Amar M, et al. Histopathological predictive factors in Ewing’s sarcoma of bone and clinicopathological correlations: a retrospective study of 261 cases. Virchows Arch A Pathol Anat Histopathol. 1986;409:627-640.

24. Swinson DE, Jones JL, Richardson D, et al. Tumour necrosis is an independent prognostic marker for non–small cell lung cancer: correlation with biological variables. Lung Cancer. 2002;37:235-240.

25. 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.

26. Leibovich BC, Blute ML, Cheville JC, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. Cancer. 2003;97:1663-1671.

27. Kim H, Cho NH, Kim DS, et al. Renal cell carcinoma in South Korea: a multicenter study. Hum Pathol. 2004;35:1556-1563.

28. Sengupta S, Lohse CM, Leibovich BC, et al. Histologic coagulative tumor necrosis as a prognostic indicator of renal cell carcinoma aggressiveness. Cancer. 2005;104:511-520.

29. Picaara V, Brunelli M, Cheng L, et al. Prognostic and therapeutic impact of the histopathologic definition of parenchymal epithelial renal tumors. Eur Urol. 2010;58:655-668.

30. Mejean A, Hopirtean V, Bazin JP, et al. Prognostic factors for the survival of patients with papillary renal cell carcinoma: meaning of histological typing and multifocality. J Urol. 2003;170:764-767.

31. Minervini A, Di Cristofano C, Gacci M, et al. Prognostic role of histological necrosis for nonmetastatic clear cell renal cell carcinoma: correlation with pathological features and molecular markers. J Urol. 2008;180:1284-1289.

32. Tolleson MK, Thompson RH, Sheinin Y, et al. Ki-67 and coagulative tumor necrosis are independent predictors of poor outcome for patients with clear cell renal cell carcinoma and not surrogates for each other. Cancer. 2007;110:783-790.

33. Gacci M, Serri S, Lapini A, et al. CXCR3-B expression correlates with tumor necrosis extension in renal cell carcinoma. J Urol. 2009;181:843-848.

34. 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.

35. Katz MD, Serrano MF, Grubb RL III, et al. Percent microscopic tumor necrosis and survival after curative surgery for renal cell carcinoma. J Urol. 2010;183:909-914.