Percentage of High-Grade Carcinoma as a Prognostic Indicator in Patients With Renal Cell Carcinoma

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Background: The prognostic value of Fuhrman nuclear grade for patients with renal cell carcinoma has been well-characterized. However, to the authors’ knowledge, the prognostic significance of the amount of high-grade renal cell carcinoma has not been previously analyzed. Methods: The authors identified 898 consecutive renal cell carcinoma cases treated with nephrectomy between 1989 and 2003. Histopathologic features that were captured based on re-review of all slides included histologic type, pathologic stage, conventional Fuhrman grade, and percentage of Fuhrman grade 3 and 4 carcinoma, as ascertained by visual inspection of histologic slides. The clinical endpoints were metastasis-free survival, cancer-specific survival, and overall survival. Results: Kaplan-Meier analysis demonstrated that both conventional Fuhrman grading and the percentage of Fuhrman grade 3 and 4 carcinoma were highly correlated with all 3 measures of patient survival (P < .0001). The creation of 3 categories of the percentage of Fuhrman grade 3 and 4 carcinoma (0%, 1–50%, and 51–100%) generated distinctly separate survival curves. On Cox proportional hazards multivariate analysis, TNM stage, tumor size, and the percentage of Fuhrman grade 3 and 4 carcinoma were all found to be significantly associated with all 3 types of patient survival (all P values <.05). Conclusions: The determination of the percentage of renal cell carcinoma that is 0%, 1% to 50%, or 51% to 100% high Fuhrman grade 3 and 4 is a simple and powerful measurement of patient outcome after surgery that provides additional prognostic information beyond stage, tumor size, and conventional Fuhrman grade. This prognostic information could be useful in the stratification of patients into prognostic groups for the development of more individualized follow-up schedules and for enrollment into clinical trials.

Editorial Comment: For many years the prognosis of renal cell carcinoma has been partly determined by grade and stage of tumor. The Fuhrman system (4 grades) has been the most widely used tool for grading. In this study the amount of high Fuhrman grade (3 to 4) was a simple measurement of patient outcome. For example, patients with 51% to 100% Fuhrman grade 3 to 4 tumor were 170% more likely to die of cancer compared to patients with 0% grade 3 to 4 tumor. Presumably there is a greater chance of genetic mutation and progression, which can produce a population of cells with a greater tendency to metastasize with a higher number of high grade (3 to 4) cells. This article verifies an intuitive hypothesis.

Urological Oncology: Bladder, Penis and Urethral Cancer, and Basic Principles of Oncology

Nomograms for Bladder Cancer

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Introduction: Patients with bladder cancer face a variable risk of recurrence based on their clinical characteristics and the biology of their disease. Physicians need tools to accurately estimate the risk of recurrence and cancer-specific mortality to recommend individualized therapy and to design
appropriate clinical trials. Methods: A MEDLINE literature search was performed on bladder cancer nomograms from January 1966 to July 2007. We recorded input variables, prediction form, number of patients used to develop the prediction tools, the outcome being predicted, prediction tool-specific features, predictive accuracy, and whether validation was performed. Each prediction tool was classified into patient clinical disease state and the outcome being predicted. Results: The literature search generated 11 published prediction tools that may be applied to patients in various clinical stages of bladder cancer. Of the 11 prediction tools, 8 have undergone validation. The following considerations need to be applied when designing and judging predictive models: predictive accuracy (internal and external validation), calibration, generalizability (reproducibility and transportability), and level of complexity, with the intent of determining whether the new model offers advantages relative to available alternatives. Studies comparing decision tools show that nomograms outperform other methodologies such as risk grouping. Conclusions: Nomograms provide the most accurate individualized risk estimations that facilitate management decisions. However, current nomograms still need to be refined. Potential advances may include the incorporation of biomarkers, validation in larger patient cohorts, and prospective data acquisition.

**Editorial Comment:** This is an excellent review for those interested in prognostic tools. It confirms that nomograms perform better than TNM staging alone. This finding is not surprising because important data, in addition to anatomical extensive disease, can be incorporated. A total of 11 recent prognostic models are described.

James E. Montie, M.D.

**Vesicoenteric, Vesicovaginal, Vescicocutaneous Fistula—An Unusual Complication With Intravesical Mitomycin**

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Intravesical instillation of mitomycin C is a routine practice for treatment of superficial transitional cell carcinoma of bladder. Despite usual precautions serious side effects like fistulation can occur with diverse presentation as illustrated by this report. The pathology demonstrates a dense necrotic and massive inflammatory reaction in the peri vesical tissue following the extravasation of an intravesically administered chemotherapeutic agent. The severe inflammatory tissue response and the necrotic effect associated with the extravasated chemotherapeutic agent could potentially lead to local sepsis with a subsequent fistula formation.

**Editorial Comment:** Dangerous complications after mitomycin C are uncommon. The fistula complications described in this report are at the far end of the spectrum but delayed healing, persistent eschar and occasionally dystrophic calcification at the site of resection are common. Immediate mitomycin C should be avoided if the resection is large, deep in the bladder wall, over an orifice or in the prostatic urethra.

James E. Montie, M.D.
Prognostic Factors in Patients With Non-Muscle-Invasive Bladder Cancer Treated With Bacillus Calmette-Guerin: Multivariate Analysis of Data From Four Randomized CUETO Trials


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Objectives: To evaluate the prognostic factors of recurrence and progression after intravesical adjuvant bacillus Calmette-Guerin (BCG) immunotherapy in patients with non-muscle-invasive bladder tumors. Methods: From February 1990 to May 1999, the Spanish Club Urologico Espanol de Tratamiento Oncologico (CUETO) group has performed four randomized phase 3 studies comparing different intravesical treatments in patients with noninvasive bladder cancer. Data from 1062 evaluable patients treated only with BCG were analyzed. Most patients received BCG once weekly for 6 consecutive weeks and a short-term BCG maintenance (once every 2 wk 6 times more). Associated tumor in situ (TIS) was found in 7.5% (n=80) of cases. There were 22.1% (n=235) patients with T1G3 tumors, 22.9% of whom (n=54) were associated with TIS. Stepwise multivariate Cox regression models with stratification by study and dose were used to assess the independent effect of predictive factors and hazard ratios (HRs) were estimated from the Cox model. Results: Multivariate analysis demonstrated that female gender (HR=1.71) compared to male gender, recurrent tumors (HR=1.9) compared to primary tumors, multiplicity, and presence of associated TIS (HR=1.54) increased the risk of recurrence. Recurrent tumors (HR=1.62) compared to primary tumors, high-grade tumors (HR=5.64) compared to G1 tumors, T1 tumors (HR=2.15) compared to Ta tumors, and recurrence at 3-mo cystoscopy (HR=4.6) increased the risk of progression. Conclusion: Significant independent predictors for recurrence were female gender, history of recurrence, multiplicity, and presence of associated TIS. Age, history of recurrence, high grade, T1 stage, and recurrence at first cystoscopy were independent predictors of progression by multivariate Cox analysis.

Editorial Comment: Prognostic factors from more than 1,000 patients treated with BCG in 4 randomized trials from Spain confirm previous observations—recurrent tumors, T1 tumors and a positive 3-month cystoscopy are predictive of muscle invasive disease. A re-staging transurethral resection of bladder tumor was not a specific part of the protocols, so some of the early recurrences were probably due to incomplete initial resection.

James E. Montie, M.D.

Bladder Cancer Detection With CT Urography in an Academic Medical Center

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Purpose: To evaluate the performance characteristics of computed tomographic (CT) urography for the detection of bladder cancer in patients at risk for the disease. Materials and Methods: Institutional review board approval was obtained for this retrospective HIPAA-compliant review of medical records of 2600 consecutive patients undergoing CT urography. Of these, 838 CT urograms in 779 patients (449 men, mean age of 62 years, range of 27–92 years; 330 women, mean age of 56 years, range of 18–86 years) evaluated for hematuria or a history of urothelial cancer, who had undergone cystoscopy within 6 months of the CT urogram, were included in the study. Clinical reports of CT