

# External Validation of Bladder Cancer Predictive Nomograms for Recurrence, Cancer-Free Survival and Overall Survival following Radical Cystectomy

Michael Brooks,\* Guilherme Godoy,\* Maxine Sun, Shahrokh F. Shariat, Gilad E. Amiel and Seth P. Lernert

From the Scott Department of Urology, Baylor College of Medicine (MB, GG, SPL), Houston, Texas, University of Montreal Health Center (MS), Montreal, Québec, Canada, Center for Surgery and Public Health, Brigham and Women's Hospital, Harvard School of Medicine (MS), Boston, Massachusetts, Bladder Cancer Research Consortium (SFS, GEA, SPL), Department of Urology, Comprehensive Cancer Center, Vienna General Hospital, Medical University of Vienna (SFS), Vienna, Austria, Weil Medical College Cornell University (SFS), New York, New York, and Department of Urology, Rambam Health Care Campus (GEA), Haifa, Israel

**Purpose:** We externally validated 3 previously published nomograms to predicting recurrence, and cancer specific and overall survival following radical cystectomy and pelvic lymph node dissection for urothelial carcinoma of the bladder.

**Materials and Methods:** Two surgeons from a single institution performed a total of 197 consecutive radical cystectomies and pelvic lymph node dissections for bladder cancer from January 2003 to September 2009. A total of 23 patients were excluded from analysis. Examined parameters were those used in the original nomograms, including patient age, gender, pathological T stage, N stage, tumor grade, presence of carcinoma in situ and lymphovascular invasion, neo-adjuvant chemotherapy, adjuvant chemotherapy and adjuvant radiation therapy. Nomogram predictions were compared to actuarial outcomes and predictive accuracy was quantified using measures of discrimination and calibration.

**Results:** At the time of analysis 34 patients had experienced recurrence, of whom 28 died of disease and 6 were currently alive with disease. Discrimination at 2, 5 and 8 years was 0.776, 0.809 and 0.794 for recurrence, 0.822, 0.840 and 0.849 for cancer specific survival, and 0.812, 0.820 and 0.825, respectively, for overall survival. Calibration plots revealed nomogram overestimation of all 3 end points.

**Conclusions:** Nomograms for bladder cancer recurrence, cancer specific survival and overall survival following radical cystectomy and pelvic lymph node dissection performed well in our series with accuracy comparable to that in the original series. The use of nomogram predictions should be further explored in clinical trials to assess the impact on patient care in clinical practice.

## Abbreviations and Acronyms

ACH = adjuvant chemotherapy

AJCC = American Joint Committee on Cancer

AXRT = adjuvant external beam radiotherapy

IBCNC = International Bladder Cancer Nomogram Consortium

NACH = neoadjuvant chemotherapy

PLND = pelvic lymph node dissection

RC = radical cystectomy

UC = urothelial carcinoma

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\* Equal study contribution.

† Correspondence: Scott Department of Urology, Baylor College of Medicine, 7200 Cambridge St., Suite 10B, Houston, Texas 77030 (telephone: 713-798-6841; FAX: 713-798-5553; e-mail: [slerner@bcm.edu](mailto:slerner@bcm.edu)).

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**Key Words:** urinary bladder neoplasms, cystectomy, nomograms, validation studies, mortality

THE natural history of bladder UC varies considerably from noninvasive low grade disease, which has a high probability of recurrence but low mortality following local treatment, to high grade muscle invasive disease, which has rates of recurrence and mortality that depend on a variety of clinical, pathological and treatment factors. Although treatment modalities continue to evolve, RC with PLND remains the primary treatment for muscle invasive and refractory high grade nonmuscle invasive UC of the bladder.<sup>1</sup> Despite treatment with curative intent oncologic outcomes still vary considerably and recurrence-free survival after RC and PLND at 5 years ranges from 58% to 62%.<sup>2,3</sup>

As defined by AJCC after RC for UC of the bladder prognostic pathological stages represent the gold standard for outcome prediction and are based on pathological staging and lymph node status.<sup>4</sup> Longitudinal outcome based studies using AJCC stages alone have demonstrated less than ideal recurrence and mortality predictions due to the relatively low predictive accuracy and significant outcome heterogeneity for individuals in AJCC stages.<sup>3,5</sup> In contrast, nomograms use a multivariable approach that incorporates significant clinical, pathological and treatment factors to improve overall predictive accuracy and provide individualized risk assessments for each patient.<sup>6</sup>

Multivariable nomograms were previously developed to predict recurrence, and overall and cancer specific survival following RC for bladder UC.<sup>7,8</sup> These nomograms, which are based on the patient outcomes observed in a single multi-institutional series from March 11, 1984 through January 24, 2003, use patient characteristics including age, pathological T stage and N stage, presence of lymphovascular invasion, presence of carcinoma in situ and use of neoadjuvant chemotherapy, adjuvant chemotherapy and adjuvant external beam radiotherapy. In the study group both nomograms demonstrated statistically significant improvement in predictive accuracy over the accuracy of AJCC predictions.

At the time of the current study the recurrence, overall survival and cancer specific survival nomograms had not been externally validated in the United States. This critical step was required before these predictive models could finally be tested in clinical trials and/or be incorporated into clinical practice for patient treatment.<sup>6</sup>

The objective of the current study was external validation of the previously published nomograms. We hypothesized that in our series of patients with

UC of the bladder treated with RC and extended PLND by 2 experienced surgeons using a standardized technique the nomogram predictions of recurrence, and overall and cancer specific survival would be accurate and highly correlate with actual oncological outcomes.

## MATERIALS AND METHODS

### Study Group

Patient consent was obtained during the initial evaluation and patient data were entered into a prospectively updated institutional review board approved database (Caisis, <http://caisis.org/>). The study group included 197 consecutive patients who underwent RC and PLND performed by 2 experienced urological oncologists at a tertiary academic medical center from January 2003 to September 2009. All patients were treated with curative intent and 7 had pathologically positive margins at cystectomy. All patients underwent RC using a standardized approach as well as bilateral extended PLND, including para-aortic and paracaval lymph nodes above the bifurcation of the aorta up to the level of the inferior mesenteric artery as the proximal limit of dissection. PLND also included the presacral nodes and the bilateral presciatic nodes as well as the common iliac, external iliac, obturator and hypogastric nodes by removing all potential node bearing tissue surrounding those vessels.

Indications for RC and PLND included refractory, high grade, nonmuscle invasive disease and muscle invasive UC of the bladder. Neoadjuvant and adjuvant chemotherapy regimens varied but typically included 4 cycles of methotrexate, vinblastine, doxorubicin and cisplatin or gemcitabine and cisplatin. Salvage external beam radiation was performed in only 3 cases and regimen and radiation dose varied depending on treatment facility. After excluding 23 patients from analysis, including 12 because of nonUC histology, 8 because of lack of sufficient data and 3 because they had undergone salvage RC, the final study group included 174 patients.

### Pathology Evaluation

All surgical specimens were evaluated by pathologists with expertise in genitourinary cancer. Pathological staging was performed in accordance with the 2002 AJCC staging system to provide consistency with definitions used in the original nomogram development.

### Followup

Patients were typically followed at 4-month intervals for the first year, at 6-month intervals for the second year and annually thereafter. The majority of patients were followed by the treating surgeon. Outcome information was obtained from patients, primary physicians, referring urologists and death certificates. As with the original definitions used for nomogram development patients in

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