The Impact of Histological Reclassification during Pathology Re-Review—Evidence of a Will Rogers Effect in Bladder Cancer?

Brian J. Linder, Stephen A. Boorjian, John C. Cheville, William R. Sukov, Prabin Thapa, Robert F. Tarrell and Igor Frank*,†

From the Departments of Urology (BJL, SAB, IF), Pathology (JCC, WRS) and Health Sciences Research (PT, RFT), Mayo Clinic, Rochester, Minnesota

Abbreviations and Acronyms

CSS = cancer specific survival
OS = overall survival
RC = radical cystectomy
UC = urothelial carcinoma

Accepted for publication May 13, 2013.
Study received institutional review board approval.

* Correspondence: 200 First St. Southwest, Rochester, Minnesota 55905 (telephone: 507-266-0191; FAX: 507-284-4951; e-mail: Frank.Igor@mayo.edu).

† Financial interest and/or other relationship with Rochester Medical.

Purpose: We investigated the association of histological reclassification during pathology re-review of radical cystectomy specimens with clinicopathological outcomes in patients initially classified with urothelial carcinoma.

Materials and Methods: We identified 1,211 patients initially diagnosed with urothelial carcinoma at radical cystectomy between 1980 and 2005. All pathological specimens were re-reviewed by a urological pathologist. Survival was estimated using the Kaplan-Meier method and compared with the log rank test.

Results: Of 1,211 cases previously recorded as pure urothelial carcinoma 406 (33%) were reclassified as variant histology. The most common variant histologies identified were squamous in 151 patients (37%) and micropapillary in 62 (15%). Variant histology on re-review was associated with a higher rate of extravesical disease (71%) than urothelial carcinoma at initial diagnosis (52%) or pure urothelial carcinoma on re-review (42%, $p < 0.0001$). Median postoperative followup was 11.1 years, during which 976 patients died, including 564 of bladder cancer. Notably, reclassification resulted in significant stratification of 10-year cancer specific survival, which was 50% in patients with pure urothelial carcinoma after re-review, 47% in those with urothelial carcinoma on initial interpretation and 42% in those with variant histology on re-review ($p = 0.03$). Ten-year overall survival in patients with urothelial carcinoma on re-review, urothelial carcinoma at initial interpretation and variant histology on re-review was 29%, 27% and 24%, respectively ($p = 0.04$).

Conclusions: Pathological re-review of radical cystectomy specimens identified variant histology in a third of patients. These variants are associated with a high rate of locally advanced disease, which may impact the noted rates of cancer specific and overall survival. Thus, it is critical to be aware of re-review status when interpreting outcomes from historical data sets and stratifying risk.

Key Words: urinary bladder, urothelium, carcinoma, pathology, diagnosis

Bladder UC has the unique propensity for differentiation into distinct histological subtypes.[1–3] While pure UC remains the most common reported histology diagnosed in patients with bladder cancer (90% to 95%), various pathological subtypes have now been described.[2] Recognizing these histological variants has diagnostic, prognostic and in some cases therapeutic importance.[2] For instance, compared to patients with pure UC, those with variant histology have a greater incidence of locally

0022-5347/13/1905-1692/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.05.040
Vol. 190, 1692-1697, November 2013
Printed in U.S.A.

advanced disease[4–6] and for select histologies they have adverse survival outcomes.[7,8]

Previous reports of prostate, lung and breast cancer demonstrate that a change in classifying or staging in a subpopulation of an entire cohort may result in a significant change in the expected survival of patients remaining in the cohort.[9–11] After recognizing this statistical pattern secondary to advancements in diagnostic imaging for lung cancer, Feinstein et al labeled the pattern the Will Rogers phenomenon after the 1930s humorist.[9] One of the famous comments of Rogers refers to the alteration in statistical effects caused by reclassifying a group.

In a large population of patients treated with RC we evaluated a potential Will Rogers effect with histological reclassification during pathological specimen re-review. Specifically, we compared oncological outcomes in patients with UC at initial pathological interpretation, those with pure UC on pathological re-review and those with variant UC histology on pathological re-review.

MATERIALS AND METHODS

Study Population

After receiving institutional review board approval, we reviewed the cystectomy registry at our center and identified 1,211 patients treated with RC at our institution between 1980 and 2005 who were initially classified with UC. RC was performed by various surgeons during the study using standard techniques. The limits of lymph node dissection varied during the study period. They currently extend from the mid-common iliac artery proximal to the Cooper ligament distal, lateral to the genitofemoral nerve and inferior to the internal iliac vessels.

A urological pathologist (JCC) re-reviewed all 1,211 RC pathological specimens. In accordance with published classification recommendations, a case was considered to represent UC with histological variant differentiation if any UC component was present and associated with a second variant histology.[12–14] Also, a sample of 45 cases (4%) was re-reviewed by a second urological pathologist (WRS) to assess for interobserver reliability. During this re-review, the pathologist was blinded to the original pathological diagnosis and to patient clinical outcomes. Clinicopathological variables recorded included age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, pathological tumor stage, grade, lymph node status, total number of lymph nodes dissected, surgical margin status and receipt of perioperative (neoadjuvant/adjuvant) chemotherapy. Tumor staging was determined by the 2010 American Joint Committee on Cancer/UICC TNM classification, 7th edition.[15]

Followup

The retrospective nature of this study precluded a standardized followup protocol. However, followup after RC at our institution has generally been recommended quarterly for the first 2 years postoperatively, semiannually for the next 2 years and annually thereafter in patients without evidence of recurrent disease. This evaluation included history, physical examination, urine cytology and imaging of the chest/abdomen/pelvis. Stomal cytology and urethral wash cytology (in males) in patients with a cutaneous urinary diversion and voided cytology in those with an orthotopic diversion were done at least annually. Local recurrence was defined as tumor recurrence in the soft tissue of the initial surgical bed or lymph node metastasis in the dissection template. Vital status was identified from death certificates or physician correspondence. For patients followed elsewhere the cystectomy registry at our institution monitors outcomes annually via correspondence with the patient and treating physician.

Statistical Analysis

We compared clinicopathological features among the cohorts using conditional logistic regression with results shown as the OR and 95% CI. Recurrence-free survival was determined at the diagnosis of local recurrence or death, whichever came first. Survival was estimated as time from RC to the event of interest using the Kaplan-Meier method and compared with the log rank test. Interrater reliability was calculated via κ coefficient. Statistical analysis was done using SAS®. All statistical tests were 2-sided with $p < 0.05$ considered statistically significant.

RESULTS

As a result of pathological re-review, 406 cases (33%) previously designated as UC were reclassified as variant histology and 805 remained pure UC. The most common variant histologies identified were squamous differentiation in 122 (30%) patients, the micropapillary variant in 62 (15%) and the nested variant in 51 (13%) (see table). The median rate of tumors with variant histology was 90% (range 1% to 100%). For the interobserver reliability rate between the 2 urological pathologists $\kappa = 0.97$.

The supplementary table (http://jurology.com/) lists patient clinicopathological features. Patients with variant histology on re-review were significantly more likely to have extravesical disease at

Histological UC subtypes identified at pathological re-review in 406 patients

	No. Variant UC (%)
Squamous differentiation	122 (30)
Micropapillary	62 (15)
Nested variant	51 (13)
Pure squamous Ca	39 (10)
Small cell Ca	36 (9)
Glandular differentiation	33 (8)
Adenoca	30 (7)
Sarcomatoid	14 (3)
Mixed differentiation	11 (3)
Inverted growth pattern	4 (1)
Plasmacytoid	1 (0.2)