Change in Management Based on Pathologic Second Opinion Among Bladder Cancer Patients Presenting to a Comprehensive Cancer Center: Implications for Clinical Practice

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OBJECTIVE To evaluate the incidence and degree of change from a pathologic second opinion of bladder biopsies at a Comprehensive Cancer Center that were initially performed at referring community hospitals. The secondary objective was to determine the impact the potential changes would have on a patient's treatment.

MATERIALS AND METHODS Dedicated genitourinary pathologists reviewed 1191 transurethral biopsies of the bladder and/or prostatic urethra from 2008 to 2013. Major and minor treatment changes were defined as altering recommendations for cystectomy, systemic chemotherapy, or primary cancer diagnosis, and alterations in intravesical regimens, respectively.

RESULTS There were 326/1191 patients (27.4%) with a pathologic change on second opinion: grade (62/1191, 5.2%), stage (115/1191, 9.7%), muscle in the specimen (29/1191, 2.4%), presence or absence of carcinoma in situ (34/1191, 2.9%). Outside pathology did not address the presence or absence of lymphovascular invasion in 620/759 (81.7%) of invasive cases (≥cT1), of which 35/620 (5.6%) had lymphovascular invasion. There were 212 mixed, variant, or nonurothelial histologies detected in 199/1191 (16.7%) patients, with 114/212 (53.7%) resulting in reclassification by our pathologists. Potential treatment alterations accounted for 182/1191 (15.3%) of cases, with 141/1191 (11.8%) imparting major changes. There were 82/1191 (6.8%) changes in recommendation for a radical cystectomy, 38/1191 (3.2%) had a complete change in primary tumor type, and 21/1191 (1.8%) for change in chemotherapy regimen.

CONCLUSION The amount and degree of pathologic changes and its potential impact on treatment emphasize the importance of bladder cancer patients having their histology reviewed by genitourinary-dedicated pathologists. In our cohort, 15.3% of patients could see a treatment alteration, with 11.8% being a major change. UROLOGY 93: 130–134, 2016. © 2016 Elsevier Inc.

Pathologic grade, stage, and histology obtained from transurethral biopsy and/or resection are key sources of information that drive management decisions in bladder cancer. However, discrepancies, missing information, or incomplete reporting are important factors that may misguide treatment. As the bladder cancer landscape has become more complicated with recognition of aggressive, atypical variants and other adverse pathologic features, such as lymphovascular invasion, accurate pathologic assessment of bladder biopsy and resection specimens has become even more important. Concerns regarding variable pathology in reports and the impact on clinical treatment decisions were studied as early as 1983.[1] Even today, variations in pathologic evaluations continue to be problematic and reports often do not include all key information.

Components of pathology reports, such as presence or absence of lymphovascular invasion, are of paramount importance, given the prognostic and treatment implications conferred by the recognition of high-risk or adverse pathologic features.[2] For example, identification of mixed or variant histologies (MVH), such as micropapillary variant,

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is critical, but under- or misdiagnosis is still common in the community.[3,4]

The benefit of a second opinion performed by pathologists who specialize in a particular disease has been shown in other fields. For example, previous studies have demonstrated high levels of discordance in recognition and reporting of extracapsular extension, high-grade Gleason scores, and margin status when prostatectomy specimens are reviewed at high-volume institutions. Specialized pathology reviews not only allowed for better risk stratification for clinical outcomes such as biochemical failure and prognosis after radical prostatectomy, but also improved the quality of clinical studies.[5-7] A recent report regarding second opinions for breast cancer pathology performed at a referral cancer center demonstrated a change in patient care in over 10% of cases.[8] Additionally, the review of melanoma histology by an expert dermatopathologist changed surgical excision margins and the need for sentinel node biopsies in 12% and 16% of patients, respectively.[9]

Despite the documented importance of correct staging and grading of bladder cancer, there is still a paucity of data supporting the benefit of having biopsy tissue reexamined by dedicated genitourinary (GU) pathologists. The primary objective was to assess and report on changes resulting from a pathologic second opinion of bladder biopsies originally performed and read at referring hospitals. Our secondary objective was to determine the potential impact the changes could have on patient's treatment for bladder cancer.

MATERIALS AND METHODS

All patients with a primary diagnosis of bladder cancer, or resection of a bladder or prostatic urethral tumor obtained by referring urologists at a non-Moffitt Cancer Center facility from October 2008 to March 2013, were eligible for this study. There were 1386 cases that were reevaluated by 2 GU-dedicated pathologists (S.D. and J.D), of which 1191 had a transurethral biopsy of the bladder and/or prostatic urethra. Case retrieval was performed utilizing the PathNet pathology case retrieval system. A spreadsheet was prepared for all retrieved cases with a SNOMED code pertaining to urothelial carcinoma (UC), bladder or prostatic urethral tumors. The PathNet anatomic pathology system is fully integrated, and it supports surgical pathology providing history review, SNOMED coding, case review, and case retrieval.

If a patient had multiple biopsies, only the original and/or first was used in this study. Exclusion criteria were those specimens of the upper tract or from a metastatic site (eg, UC metastasis to the liver). Pathologic variables that were recorded included: stage, grade, lymphovascular invasion (LVI), presence or absence of carcinoma in situ (cis), absence or presence of detrusor muscle present in the specimen, MVH, or nonurothelial histologies. Potential alterations in treatment that could occur were recorded; this was then further subdivided into "major" or "minor" treatment changes. Treatment alterations were based on the pathological change, if it occurred, and the assumption that the tissue reviewed was of the first resection in the patient's care plan.

Major Treatment Change

Major treatment changes were defined as altering recommendations for cystectomy, systemic chemotherapy regimen, or primary cancer diagnosis. These differences were secondary to changes in stage, primary pathology, MVH, or nonurothelial histologies.

Cystectomy Change. Alterations that changed the recommendation for cystectomy were the following: an upgrade from ≤ cT1 to cT2 or downgrade from cT2 to ≤ cT1, cT1 with a change to aggressive MVH (either micropapillary, plasmacytoid, or sarcomatoid).

Systemic Chemotherapy Change. Decisions that would change the systemic chemotherapy regimen were based on the primary bladder cancer malignancy (ie, if the referring facilities diagnosed the malignancy as UC and on review it was changed to adenocarcinoma, squamous, small cell, or prostate cancer). Those patients that changed to pure squamous cell carcinoma fit into this category as they would not receive neoadjuvant chemotherapy. Another instance that would be considered is an original diagnosis of adenocarcinoma changed to UC with glandular differentiation as this patient would now receive neoadjuvant chemotherapy (UC based) as opposed to immediate cystectomy.

Primary Cancer Diagnosis. Defined as cases where bladder cancer was present or not present. A change between benign, UC, or nonurothelial histology fit into this category.

Minor Treatment Change

Minor treatment changes were considered to be reclassifications in grade or stage that would potentially alter intravesical instillation regimens. Examples would include Ta High Grade (HG) to Ta Low Grade (LG), TaHG to T1HG, dysplasia to cis, or vice versa. Intravesical regimens used at our institution that were incorporated into this study include the following: TaLG (for study purposes, they were considered as "not receiving intravesical therapy" as specific factors such as size of the tumor, multiple locations, and/or recurrences could not be assessed), TaHG (induction bacillus Calmette–Guerin [BCG]) ± 1 year of maintenance therapy, and T1HG/cis (induction ± 3 years of maintenance therapy maintenance BCG).

RESULTS

Overall, there were 326/1191 patients (27.4%) with 360 pathologic changes on second opinion (Table 1). This would have resulted in 182/1191 (15.3%) potential treatment changes.

Grade

A change of grade was seen in 62/1191 (5.2%) of cases. There were 48/62 (77%) changed from LG to HG and 14/

Table 1. Pathologic change on review

	Change on Review (%)
Stage	115/1191 (9.7)
Grade	62/1191 (5.2)
Presence or absence of carcinoma in situ	34/1191 (2.9)
Presence of lymphovascular invasion*	35/620 (5.6)
Mixed, variant, or nonurothelial histology†	114/212 (53.8)

* For biopsies ≥cT1.
† There were 212 mixed or variant histologies, or nonurothelial histologies seen in 199 patients.