Prognostic Significance of Measured Depth of Invasion of Urothelial Carcinoma of the Bladder Compared to the 2010 American Joint Committee on Cancer pT2 and pT3 Classifications

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Abbreviations and Acronyms

CSS = cancer specific survival

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Purpose: We compared the prognostic ability of the current American Joint Committee on Cancer (AJCC) staging system to direct measurement of the depth of tumor invasion into the muscularis propria and perivesical fat.

Materials and Methods: We identified 148 patients with pT2N0 and 206 with pT3N0 who underwent radical cystectomy between 1990 and 2003. Clinicopathological features were reviewed. A measurement in mm was recorded of the depth of tumor invasion into the muscularis propria for pT2 cases and into perivesical fat for pT3 cases. Cancer specific survival between the pT2a and pT2b, and the pT3a and pT3b patient groups was estimated using the Kaplan-Meier method and compared with the log rank test. Optimal cutoff points for invasion depth in mm were estimated using an iterative estimation process to find the minimum p value with the maximum HR.

Results: Of 148 patients with pT2 bladder cancer, including 76 with pT2a and 72 with pT2b, and 206 with pT3 bladder cancer, including 144 with pT3a and 62 with pT3b, there was no significant difference in cancer specific survival between the substages ($p = 0.94$ and 0.37, respectively). However, patients with measured invasion less than 4.5 mm into perivesical fat had significantly improved cancer specific survival compared to that in patients with invasion 4.5 mm or greater (5-year cancer specific survival 53% vs 40%, $p = 0.02$).

Conclusions: We found no significant difference in cancer specific survival when pT2 and pT3 tumors were stratified by AJCC substage. However, for pT3 tumors direct measurement of the depth of tumor invasion into perivesical fat identified a significant stratification of cancer specific survival at 4.5 mm.

Key Words: urinary bladder, carcinoma, urothelium, neoplasm invasiveness, mortality

The 2010 AJCC staging system for bladder cancer divides pathological stage pT2 into superficial muscle invasion (involvement of the inner half of the muscularis propria or pT2a) and deep muscle invasion (into the outer half of the muscularis propria or pT2b).[1] Pathological stage pT3 is likewise divided into microscopic perivesical invasion (pT3a) and gross or macroscopic fat invasion with the parenthetical extravesical mass (pT3b). However, the clinical significance of these substratifications continue to be debated with conflicting data from large studies in regard to outcome, and pT2 and pT3 substages.[2–11]

To our knowledge none of the studies to date that evaluated the prognostic significance of pathological

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substaging included a centralized pathological review by urological pathologists. In our experience there is interobserver variability in the current definition of pT3 substaging in regard to microscopic vs macroscopic invasion, while an extravesical mass is not well defined. Therefore, the interpretation varies by pathologist.

We compared the outcomes of patients with AJCC pT2a vs pT2b, and pT3a vs pT3b bladder cancer treated with radical cystectomy at a single institution whose surgical pathology material had undergone centralized pathology review by a urological pathologist. In addition, we determined whether an objective measure of the depth of invasion into the muscularis propria and perivesical fat was more predictive of outcome than the current AJCC staging system.

METHODS

After receiving approval by the Mayo Clinic institutional review board, we identified 354 patients who underwent radical cystectomy at our institution between 1990 and 2003 and were found to have lymph node negative pT2 and pT3 urothelial carcinoma. In each case the diagnostic tissue slide material and surgical pathology reports were reviewed by a urological pathologist (JCC). Slides and reports were reviewed and tumors were staged according to the 2010 AJCC staging system. Staging in each case was based on review by the urological pathologist and not by the original signing pathologist.

In the review of pT2 tumors the pT2a and pT2b substages were readily identified by microscopic examination. In the case of pT3 tumors the tissues slides (on which gross features of the tumor and bladder are retained) were examined macroscopically, and depth was assessed visually and confirmed microscopically. In addition, the depth of invasion in mm into the muscularis propria for pT2 tumors was obtained using an Olympus® micrometer at 20× magnification, measured from the most superficial aspect of the muscularis propria to the deepest point of invasion. In cases in which the prior transurethral resection tissue reaction was evident, invasion depth was assessed from the closest intact muscularis propria to a line drawn over the deepest point of invasion. In the case of pT3 tumors invasion depth into perivesical fat was measured from the base of the muscularis propria to the deepest point of invasion. The superficial and deep aspects of the muscularis propria are not a continuous layer of muscle. Thus, the superficial aspect and base of the muscularis propria were defined as a line drawn perpendicular to the highest and lowest extent, respectively, of the muscularis propria across the entire tissue section on the glass slide (fig. 1).

Clinical information, including CSS, is routinely recorded in our institutional cystectomy registry for all patients who undergo radical cystectomy. CSS was estimated for patients with pT2a, pT2b, pT3a and pT3b tumors using the Kaplan-Meier method. It was compared for the pT2a vs pT2b substages as well as for pT3a vs pT3b and all T2 vs T3 cases using the log rank test. Optimal cutoff points for invasion depth in mm were estimated using an iterative estimation process of finding the minimum p value with the maximum HR. Finally, invasion depth was correlated with nodal status for patients with pT2 and pT3 cancers to determine the association of invasion depth with the frequency of positive lymph nodes.

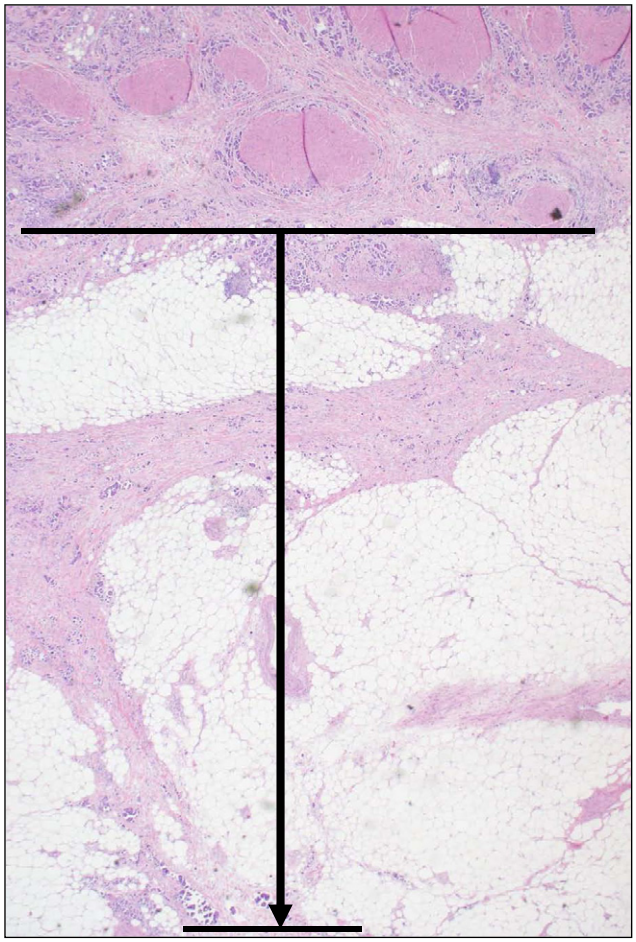

Figure 1. Depth of invasion into perivesical fat was measured from base of muscularis propria across tissue section to deepest point of invasion. In this case invasion depth into fat was 11 mm. Based on AJCC staging system, tumor was staged as pT3a since no mass was discerned in perivesical fat on gross examination of slide and fibrous strands in fat could not be distinguished from prior resection reaction.

RESULTS

Of 148 patients with pT2 bladder cancer 76 and 72 were classified with pT2a and pT2b disease, respectively. Of 206 patients with pT3 bladder cancer 144 and 62 were identified with pT3a and pT3b tumors, respectively. The table lists the clinical and pathological features of all 354 patients by pT stage.

By the last followup 250 patients had died, including 156 of bladder cancer. These patients had