The Impact of Tumor Diameter and Tumor Necrosis on Oncologic Outcomes in Patients With Urothelial Carcinoma of the Bladder Treated With Radical Cystectomy

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OBJECTIVE To evaluate the influence of tumor diameter and tumor necrosis on oncologic outcomes in patients with urothelial carcinoma of the bladder treated with radical cystectomy (RC).

MATERIALS AND METHODS We treated 517 consecutive patients with urothelial carcinoma of the bladder treated with RC without neoadjuvant chemotherapy at our institution between 1996 and 2011. All RC specimens were meticulously re-reviewed for the largest residual tumor diameter and for the presence and extent of tumor necrosis. Cox regression models evaluated the association with disease recurrence and cancer-specific survival.

RESULTS At RC, 155 patients (30.0%) had a residual tumor diameter ≥3 cm and tumor necrosis was present in 156 patients (30.2%). Tumor diameter and necrosis were significantly correlated (P <.001). Both a tumor diameter ≥3 cm and the presence of tumor necrosis were associated with an older age, advanced tumor stage, higher tumor grade, lymph node metastasis, positive surgical margin status, lymphovascular invasion, and administration of adjuvant chemotherapy (P values ≤.009). A tumor diameter ≥3 cm and the presence of tumor necrosis were associated with disease recurrence and cancer-specific mortality in Kaplan-Meier analyses, respectively (pairwise P values <.001). In addition, a tumor diameter ≥3 cm was an independent predictor of cancer-specific mortality in multivariate analysis that adjusted for standard clinicopathologic features.

CONCLUSION Tumor diameter and necrosis are closely correlated and associated with aggressive tumor features and inferior oncologic outcomes. A residual tumor diameter ≥3 cm is an independent predictor of cancer-specific mortality. This additional information should be considered to be reported in every pathology report for consideration in patient counseling and treatment decision making. In addition, these results underscore the importance of a thorough transurethral resection of the bladder tumor before RC. UROLOGY 86: 92–98, 2015. © 2015 Elsevier Inc.

Several patients with urothelial carcinoma of the bladder (UCB) have durable long-term outcomes after radical cystectomy (RC) with pelvic lymph node dissection, the standard surgical treatment for muscle-invasive and recurrent high-grade UCB.[1] In contrast, other patients die of UCB particularly once the disease recurs.[2] Although various clinicopathologic risk factors were identified predicting UCB outcomes,[2,3] the prognostication based on established risk factors remains imperfect.[4,5] Thus, additional parameters may improve counseling of UCB patients regarding multimodal treatment after RC.

Tumor size and tumor necrosis are predictors for poor survival in various epithelial malignancies,[6-8] including urothelial carcinoma of the upper urinary tract (UTUC).[9] In addition, tumor diameter is an established risk factor for disease recurrence and progression in non–muscle-invasive UCB.[10] Moreover, tumor size and necrosis have improved prognostic models in UTUC patients.[9] In UCB patients treated with RC,

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however, the impact of tumor size and necrosis on oncologic outcomes has sparsely been investigated, with variable findings.[11-13]

The aim of this study was to analyze the impact of the residual tumor diameter and the presence and extent of tumor necrosis on oncologic outcomes in UCB patients treated with RC. We hypothesized that a large tumor diameter and the presence of tumor necrosis in the RC specimen would negatively affect outcomes.

MATERIALS AND METHODS

Patient Population

We retrospectively collected clinical and pathologic data of 638 consecutive patients treated with RC and bilateral pelvic lymphadenectomy for UCB between 1996 and 2011 at the University Medical Center Hamburg-Eppendorf. Indications for RC were recurrent Ta, T1, or carcinoma in situ (CIS) refractory to transurethral resection of the bladder (TURB) with or without intravesical immunotherapy or chemotherapy or muscle invasive disease. No patient received chemotherapy and/or radiotherapy preoperatively. In total, 57 patients were excluded because of missing clinicopathologic data or follow-up. In addition, 64 patients were excluded because of incomplete pathologic specimens, resulting in 517 patients available for statistical analyses. No patient had known metastatic disease at the time of RC. In total, 101 patients (19.5%) received adjuvant chemotherapy (94% platin based) at the clinicians' decision based on tumor stage, renal function, health status, and patient's desire. The study was approved by the institutional review board.

Pathologic Evaluation

For pathologic evaluation, the complete surgical cystectomy specimen was inked, and multiple sections were obtained from the bladder and the tumor in addition to the regional lymph nodes and ureters. Tumor stage and nodal status were assessed according to the tumor, lymph nodes and metastasis system. Tumor grade was assessed according to the 1998 World Health Organization grading system.[14] Concomitant CIS was defined as the presence of CIS in conjunction with another tumor other than CIS alone. Lymphovascular invasion was defined as the unequivocal presence of tumor cells within an endothelium-lined space without underlying muscular walls.[15] A positive soft-tissue surgical margin (STSM) was defined as the presence of tumor at inked areas of soft tissue on the RC specimen.[16]

All pathologic specimens were meticulously re-reviewed for the largest residual tumor diameter and the presence and extent of tumor necrosis. Tumor diameter was defined as the largest measurable diameter of UCB. It was assessed by measuring the largest diameter of the tumor on gross and/or microscopic examination of the RC specimen. Tumor diameter was stratified in $\geq$3 and <3 cm according to the generally accepted European Organization for Research and Treatment of Cancer cutoff value in non–muscle-invasive UCB.[17] In accordance with previous studies,[18,9] tumor necrosis was defined as the presence of coagulative necrotic areas in the RC specimen. In contrast, residual cautery artifacts from TURB, as characterized by thermoablative necrosis and tissue contusion, were not classified as tumor necrosis. The extent of tumor necrosis was assessed by a detailed workup of each slide using a subjective method by dividing the microscopic view of the cancer in each slide into successive 10ths. Consecutive analysis of each section allowed estimating the percentage of tumor necrosis within UCB by 5% steps. As previously described,[18,9] tumor necrosis was recorded as absent, focally present (<10% extent of tumor necrosis within UCB), or extensively present ($\geq$10% extent of tumor necrosis within UCB).

Follow-up Regimen

Generally, patients were seen every 3-4 months for the first year after RC, every 6 months from the second to fifth years, and annually thereafter. Follow-up comprised a history, serum chemistry evaluation, and physical examination. Diagnostic imaging of the abdomen including the urinary tract (eg, ultrasonography and/or intravenous urography, computed tomography of the abdomen/pelvis with intravenous contrast) and chest radiography were conducted at least annually or when clinically indicated. Additional radiographic evaluations (ie, bone or brain scans, magnetic resonance imaging, etc) were performed at the discretion of the treating physician when clinically indicated.

Disease recurrence was defined as local failure in the operative site, regional lymph nodes, or distant metastasis. UTUC was not considered disease recurrence but metachronous tumor. For recurrence-free survival analysis, patients who did not experience disease recurrence were censored at time of the last follow-up. Cancer-specific mortality was defined as death from UCB. The cause of death was determined by the treating physician, chart review corroborated by death certificates, or death certificates alone.[19] Perioperative mortality (ie, death within 30 days of surgery) was censored at the time of death for bladder cancer–specific survival analyses.

Statistical Analysis

First, we analyzed differences between UCB with a largest residual tumor diameter of $\geq$3 and <3 cm. Second, we analyzed differences according to the presence or absence of tumor necrosis. Third, we analyzed differences between UCB without and with presence of an extent of $\geq$10% and <10% tumor necrosis, respectively. The indicator variables (tumor diameter, tumor necrosis, and the extent of tumor necrosis) were analyzed as categorical variables. Differences in continuous variables were analyzed using the Mann-Whitney *U* test (2 categories) and the Kruskal-Wallis test ($\geq$3 categories). Associations between categorical variables were assessed using the Fisher exact and chi-square test. Correlations between tumor necrosis and tumor diameter were evaluated using the Spearman rho test. Recurrence- and cancer-specific survival probabilities were estimated using the Kaplan-Meier method, and differences between groups were assessed using the log-rank statistic. Univariate and multivariate Cox regression models assessed time to disease recurrence and cancer-specific mortality. All tests are 2 sided, and a *P* value of <.05 was set to be statistically significant. All analyses were performed with SPSS 20 (SPSS Inc., IBM Corp., Armonk, NY).

RESULTS

Association of Tumor Diameter and Necrosis With Clinicopathologic Characteristics

A residual tumor diameter <3 cm was found in 362 patients (70.0%), and tumor necrosis was present in 156 patients (30.2%). In patients with the presence of tumor necrosis, the extent was $\geq$10% in 34 patients (21.8%)