



# Gender-specific outcomes of bladder cancer patients: A stage-specific analysis in a contemporary, homogenous radical cystectomy cohort

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## Abstract

**Introduction:** Controversial findings regarding gender-specific oncological outcomes of urothelial carcinoma of the bladder (UCB) have recently been reported. The aim of this study was to analyze gender-specific outcomes using a stage-adjusted approach in a homogenous, contemporary radical cystectomy (RC) cohort.

**Material and methods:** We prospectively collected data of 517 UCB patients treated with RC and pelvic lymphadenectomy without neoadjuvant chemotherapy at our institution between 1996 and 2010. Stage-adjusted uni- and multivariable Cox regression models analyzed the association of gender with disease recurrence, cancer-specific mortality and overall survival.

**Results:** In total, 398 (77%) patients were male and 119 (23%) were female. Compared to men, women were more likely to have advanced tumor stages ( $p = 0.017$ ), nodal metastasis ( $p = 0.047$ ) and received more frequently adjuvant chemotherapy ( $p = 0.009$ ). At a median follow-up of 44 months, there was no statistical difference in disease recurrence, cancer-specific mortality and overall survival between both genders when analyzed as a group. In stage-adjusted analyses, only women with non-invasive UCB were more likely to die of UCB compared to the male counterparts ( $p = 0.013$ ). In gender-specific multivariable analyses that adjusted for standard clinico-pathologic features, pathologic tumor stage was an independent predictor for disease recurrence ( $p$ -values  $\leq 0.047$ ) and cancer-specific mortality ( $p$ -values  $\leq 0.049$ ), respectively.

**Conclusion:** Women present with more aggressive tumor biologic features at RC, however this did not translate into inferior outcomes compared to men in stage-specific analyses in our cohort. Tumor stage is the most important factor influencing the course of disease in both genders. Validation of our findings is warranted in a larger cohort.

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**MeSH keywords:** Urinary bladder cancer; Urothelial carcinoma; Radical cystectomy; Gender; Outcome; Survival

## Introduction

Urothelial carcinoma of the bladder (UCB) is the second most common urological malignancy after prostate cancer and the fourth and eleventh most common malignancy in

men and women, respectively.<sup>1</sup> Radical cystectomy (RC) with pelvic lymph node dissection is the standard surgical treatment for muscle invasive and high-risk UCB.<sup>2</sup> Gender-specific differences in UCB prevalence and prognosis have been described with men developing UCB more frequently than their female counterparts.<sup>3</sup> However, women seem to present with more aggressive tumor biologic features and advanced tumor stages at RC.<sup>4–7</sup>

Gender has been considered an important factor in clinical decision-making regarding UCB management<sup>5</sup> and is

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implemented in bladder cancer prediction tools as a strong prognosticator for UCB outcomes in patients treated with RC.<sup>8–10</sup> Nevertheless, recent studies challenged the impact of gender on RC outcomes, as some investigators did not find gender-specific differences across all disease stages.<sup>7,11,12</sup> Surprisingly, stage-adjusted outcome analyses were only carried out in a minority of these reports.<sup>13</sup> Disparate findings across studies may be explained by differences inherent to the heterogeneous study populations, small cohort sizes, regional and country-specific differences and other data inhomogeneities.

Finally, the impact of gender on UCB outcomes is still insufficiently understood and thus further clarification is urgently warranted. The aim of this study was to investigate gender-specific outcomes in a stage-specific approach in a homogenous, contemporary UCB cohort treated with RC. We hypothesized that women present with more advanced disease stages, but the course of disease is comparable in men and women with the same disease stage. Further we assumed that tumor stage is predominantly impacting outcomes compared to gender in a stage-dependent analysis.

## Material and methods

### *Patient population*

We prospectively enrolled and retrospectively analyzed 671 consecutive patients treated with RC and bilateral pelvic lymphadenectomy for UCB between 1996 and 2010 at the University Medical Center Hamburg-Eppendorf. In total, 14 surgeons all trained for the RC at the same institution under the supervision of one chairman performed the RCs. Indications for RC were muscle invasive disease or recurrent Ta, T1, or carcinoma in situ (CIS) refractory to transurethral resection of the bladder (TURB) with or without intravesical chemo- or immunotherapy. No patient received preoperative chemo- and/or radiotherapy. In total, 154 patients were excluded due to missing data on clinical parameters and outcomes, resulting in 517 patients available for statistical analyses. No patient had known metastatic disease at time of surgery. A total of 91 patients (17.6%) received adjuvant chemotherapy (95% platin-based) at the clinicians' decision based on tumor stage, overall health status, renal function and patient's desire. The study was approved by the institutional review board.

### *Pathological evaluation*

The pathological evaluation of surgical specimens followed the previously described criteria.<sup>14</sup> In brief, genitourinary pathologists assigned tumor stage according to the tumor, lymph nodes and metastasis (TNM) system. Tumor grade was assessed according to the 1998 World Health Organization (WHO) grading system.<sup>15</sup> The entire surgical cystectomy specimen was inked, and multiple sections were obtained from the tumor, the bladder wall, and mucosa adjacent to and distant from the tumor in addition to

the ureters and regional lymph nodes. Concomitant CIS was defined as the presence of CIS in conjunction with another tumor other than CIS alone. Lymphovascular invasion (LVI) was defined as the unequivocal presence of tumor cells within an endothelium-lined space without underlying muscular walls.<sup>16</sup> A positive soft tissue surgical margin (STSM) was defined as the presence of tumor at inked areas of soft tissue on the RC specimen.<sup>17</sup>

### *Follow-up regimen*

Patients were generally seen every three to four months for the first year after surgery, every six months from the second to fifth years, and annually thereafter. Follow-up consisted of a history, physical examination and serum chemistry evaluation. Diagnostic imaging of the abdomen including the urinary tract (e.g. ultrasonography and/or intravenous urography, computed tomography of the abdomen/pelvis with intravenous contrast) and chest radiography were performed at least annually or when clinically indicated. Additional radiographic evaluations (i.e., 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. Upper tract urothelial carcinoma was considered metachronous tumors and not disease recurrence. Patients who did not experience recurrence were censored at time of last follow-up for recurrence-free survival analysis. Cancer-specific mortality was defined as death from UCB. Death from UCB was defined as patients who deceased from local recurrence and/or distant metastases of their disease. Cause of death was determined by the treating physician, by chart review corroborated by death certificates, or by death certificates alone.<sup>18</sup> Perioperative mortality (i.e., death within 30 days of surgery;  $n = 14$ ) was censored at time of death for bladder cancer-specific survival analyses.

### *Statistical analysis*

To evaluate the association of gender, stage and outcomes, we analyzed the data two-fold: First, we analyzed male and female patients separately to identify differences in outcomes and risk factors in each subgroup. Second, we analyzed both genders as one group and stratified for each pathologic parameter to identify differences between both genders.

Differences in variables with a continuous distribution across categories were assessed using the Mann–Whitney  $U$  test (two categories). The Fisher's exact test and the  $\chi^2$ -test were used to evaluate the association between categorical variables. Recurrence-, cancer-specific and overall survival probabilities were estimated using the Kaplan–Meier method and differences between groups were assessed using the logrank test. Uni- and multivariable Cox regression models assessed time to disease recurrence and cancer-specific mortality. All tests are two-sided and a  $p$ -value of  $<0.05$  was set to be

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