Clinical, demographic and histopathological prognostic factors for urothelial carcinoma of the bladder

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INTRODUCTION

Urothelial carcinoma of the bladder (UCB) is the second most common genitourinary malignancy and is associated with a heterogeneous clinical outcome [1-4]. Radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) is currently the gold standard treatment for muscle-invasive UCB [1, 5-9]. Unfortunately, 40% of patients with organ-confined disease at the time of cystectomy subsequently suffer recurrence. Several studies have evaluated the risk factors for recurrence and survival after cystectomy. Advanced pathologic stage, nodal involvement, grade and urinary obstruction have been reported as prognostic factors for survival and recurrence. However, some bladder cancer cases of similar stage and grade have demonstrated variable clinical outcomes after RC, so many attempts have been made to determine new and reliable prognostic factors [10-14]. The aim of the present study is to evaluate the influence of clinical and detailed histopathological pa-

Key Words: urothelial carcinoma of the bladder • overall survival • tumor necrosis • histology
parameters including age, gender, tumor stage, grade, tumor differentiation, necrosis, lymphovascular invasion (LVI), perineural invasion (PNI) and concomitant carcinoma in situ (CIS), on outcomes of patients with UCB treated with RC.

**MATERIAL AND METHODS**

A total of 84 patients who underwent RC (n = 11) and radical cystoprostatectomy (n = 73) for muscle-invasive bladder cancer (MIBC) at our institute between 2007-2013, were included in the study. Of the total, 79 underwent standard PLND. Bladder cancer was diagnosed histopathologically by transurethral resection in all patients before cystectomy. RC and standard PLND were performed using the standard technique. Surgical specimens were re-examined by 2 genitourinary pathologists applying a standardized reporting protocol. Tumor staging and grading were standardized according to the American Joint Committee on Cancer and World Health Organization. Tumor differentiation, depth of tumor invasion, necrosis, LVI, PNI and concomitant CIS were assessed histopathologically.

Statistically analyses of prognostic effects of age (65 years), gender, smoking status, pathologic tumor stage, lymph node metastasis (LNM), tumor differentiation, LVI, PNI and necrosis on overall survival (OS) were performed. Univariate OS after RS were estimated using the Kaplan-Meier method and log-rank statistics. Multivariate Cox regression models addresses OS after RS. The chi-square test was used to determine correlations among the variables. Statistical significance was set at p <0.05. Statistical analyses were performed with SPSS v.15.

**RESULTS**

The mean age at diagnosis was 66.1 (min. 42, max. 84) and there were 75 (89.3%) males and 9 (10.7%) females. Of the 84 patients, 38 (45.2%) were under 65 years, whereas 46 (54.8%) were over 65 years. Mean tumor diameter was 3.66 cm (min: 0.70 cm, max: 8 cm). The average overall follow-up time was 17.6 months (SD ± 15.1). At the time of analysis, 33 (39.3%) patients were alive with disease, whereas 51 (60.7%) were dead. In 75 patients with available habitual data, 64 (85.3%) were recorded as heavy smokers. The pathologic tumor stages were 4 (4.8%), 8 (9.5%), 20 (23.8%), 37 (44%) and 15 (17.9%) for Ta, T1, T2, T3 and T4 respectively. Of the patients with Ta and T1 tumors who had an extensive mass, which could not be totally excised by TUR, or intensive gross hematuria, underwent RC. Of the total 84 cases, 79 underwent standard PLND and LNM was detected in 25 patients (29.8%).

Of the 84 cases, 82 were high grade on histopathological examination. Both of the low grade tumors were stage Ta and exhibited no tumor necrosis, CIS, LVI and PNI. One of the patients was alive and the other one died of a non-tumoral cause.

The histologic type was pure urothelial carcinoma (UC) in 46 (54.8%) cases. Of the 38 (45.2%) cases which showed divergent differentiations or components, 26 (68.4%) had squamous differentiation, 7 (18.4%) sarcomatoid, 1 (2.6%) glandular differentiation, 1 (2.6%) clear cell, 1 (2.6%) neuroendocrine, 1 (2.6%) micropapillary and 1 (2.6%) squamous plus sarcomatoid components.

Concomitant CIS was observed in 30 (30.7%) tumors. 41 (48.8%) cases showed tumor necrosis, 44 (52.4%) PNI and 61 (72.3%) LVI. Demographic, clinical and pathological characteristics are summarized in Table 1.

The relationship of tumor necrosis with pathologic tumor stage and LNM was evaluated. Accordingly, tumor necrosis was found in 25% (1/4) of Ta tumors, 25% (2/8) of T1 tumors, 50% (10/20) of T2 tumors, 48.6% (18/37) of T3 tumors and 66.7% (10/15) of T4 tumors. No statistically significant relationship was found between tumor necrosis and pathologic tumor stage.

| Clinicopathologic factors | Category | n (%) | p values |
|---------------------------|----------|-------|----------|
| Age | >65 | 46 (54.8%) | | 0.001 |
| Gender | Male | 75 (89.3%) | | 0.23 |
| Pathologic stage | Ta | 4 (4.8%) | | 0.15 |
| Lymph node status | N0 | 54 (64.3%) | | 0.001 |
| Histopathologic Differentiation | Absence | 46 (54.8%) | | 0.011 |
| LVI | Absence | 23 (27.7%) | | 0.37 |
| PNI | Absence | 40 (47.6%) | | 0.06 |
| UCIS | Absence | 54 (64.3%) | | 0.24 |
| Tumor necrosis | Absence | 43 (51.2%) | | 0.025 |

Table 1. Univariate analysis of demographic, clinical and pathological characteristics for overall survival.
stage (p = 0.32). Tumor necrosis was found in 60% (15/35) of N1 cases, 46.3% (25/54) of N0 cases and 20% (1/5) of Nx cases. No statistically significant relationship was found between tumor necrosis and LNM (p = 0.21).

The evaluation of OS data revealed that 55.6% (5/9) of female patients, and 37.3% (28/75) of male cases were alive. There was no statistically significant relationship between OS and gender (p = 0.23).

In this study, 57.9% (22/38) of the patients aged ≤65 years and 23.9% (11/46) of patients aged >65 were alive. The rate of OS in patients aged ≤65 years was statistically significantly higher than those aged >65 years (p < 0.001) (Figure 1).

On the other hand, 36.4% (4/11) of non-smokers and 45.3% (29/64) of smokers were alive. No statistically significant relationship was noted between smoking and OS (p = 0.81).

With regard to pathological tumor stage, 75% (3/4) of Ta patients, 75% (6/8) of T1 patients, 40% (8/20) of T2 patients, 37.8% (14/37) of T3 patients, and 13.3% (2/15) of T4 patients were alive. The cause of death in the Ta and T1 patients was not related to the primary tumor. No statistically significant re-
stage and the presence of LNM have been reported to be the most important prognostic factors [1, 2, 12]. However, reports of different clinical outcomes, in patients with similar stages of disease following RC, have prompted the investigation of other factors that may affect prognosis.

A number of studies have reported that the prognosis of UC in females is much worse than that in males [5, 15-18]. A large European epidemiological study of 1.2 million patients reported that the 5-year cancer-specific mortality was 30% lower in females, which, however, was not the case in bladder carcinomas. The study also demonstrated that UC followed a more aggressive clinical course in females than that in males [5]. Horstmann et al. reported that, in a MICB series of 455 patients, 129 of whom were females, the 10-year survival was lower in females compared to that in males [19]. Aggressive tumor biology in females is considered to be responsible for shorter survival [5]. In our series, where most patients were males (89.3%), there were only 9 female patients and there was no statistically significant difference between OS and gender (p = 0.23). The absence of a statistically significant relationship between gender and OS can be attributed to the small number of female patients in this study.

In a study by Mitra et al., where 259 tumors with tumor differentiation were compared with pure UCB, the OS was lower in patients with differentiation and aged >65 years [13]. In our series, the rate of OS was higher in patients aged ≤65 years (57.9%) compared to those aged >65 years (23.9%) and the difference was statistically significant (p <0.001).

Previous studies have demonstrated that tobacco consumption and the number of cigarettes smoked per day are associated with advanced tumor stage and grade in newly-diagnosed UCB [14, 20]. A study of 1506 patients with UCB by Rink et al., reported the association between smoking and cancer-specific mortality, which, however, lost its significance on multivariate analysis [14]. In the mentioned study, cumula-

| Variable                  | Levels          | Hazard Ratio | 95% CI Lower Bound | 95% CI Upper Bound | p value |
|---------------------------|-----------------|--------------|--------------------|--------------------|---------|
| Age (>65)                 | ≤65 years       | 2.969        | 1.550              | 5.684              | 0.001   |
|                           | >65 years       |              |                    |                    |         |
| Lymph node metastasis     | N0              | 2.204        | 1.223              | 3.970              | 0.009   |
|                           | N1              |              |                    |                    |         |
| Differentiation           | Negative        | 2.116        | 1.173              | 3.818              | 0.013   |
|                           | Positive        |              |                    |                    |         |
| Tumor necrosis            | Negative        | 1.601        | 0.878              | 2.917              | 1.124   |
|                           | Positive        |              |                    |                    |         |
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the level of statistical significance (p = 0.21). Similarly, advanced tumor stage was associated with an increased rate of tumor necrosis, but no statistically significant relationship was found due to the small number of patients in our study (p = 0.32). Numerous cytogenetic, molecular, genetic and immunohistologic studies revealed similar molecular changes in CIS and invasive UC [4]. The presence of isolated or concomitant CIS carries a higher risk of the disease progressing to MIBC [29]. There are numerous studies reporting that the presence of CIS and concomitant non-invasive UC following RC is associated with a poor clinical course [4]. On the other hand, a study by Nuhn et al. of 3973 patients treated with RC, reported no association between concomitant CIS and clinical outcome and the prognostic value of concomitant CIS in UCB could not be confirmed [4]. Similarly in our study no statistically significant difference was noted in OS between the patients with and without concomitant CIS (p = 0.24).

CONCLUSIONS

Advanced age (>65), LNM, tumor differentiation and tumor necrosis were found to be independent prognostic risk factors associated with OS after RC. Tumor necrosis did not remain significant on multivariate analysis. The presence of concomitant CIS had no effect on prognosis. These additional factors, which may explain the different clinical course in patients with similar tumor stage and lymph node status, should be taken into consideration in treatment planning.

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