

Factors Impacting the Overall Survival of Patients Irradiated for Invasive Carcinoma of the Urinary Bladder

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Abstract. *Background/Aim: To contribute to personalisation of treatment for patients with carcinoma of the urinary bladder, 11 factors were analyzed for survival. Patients and Methods: Data from 61 patients receiving definitive irradiation for carcinoma of the urinary bladder were retrospectively evaluated, namely gender, age, T-stage, N-stage, grading, pack years, smoking during irradiation, upfront transurethral resection of the bladder tumour (TURBT), equivalent dose in 2-Gy fractions (EQD2), chemotherapy and Karnofsky performance score (KPS). Results: On univariate analysis, female gender ($p=0.007$), <40 pack years ($p=0.029$), not smoking during irradiation ($p=0.037$), TURBT ($p=0.007$) and KPS >70 ($p<0.001$) led to improved survival; EQD2 >55 Gy showed a trend ($p=0.065$) for such association. On Cox regression, gender [risk ratio (RR)=2.81; $p=0.039$], TURBT (RR=4.44; $p=0.033$) and KPS (RR=3.45; $p=0.018$) remained significant. Conclusion: This study identified independent predictors of survival in patients irradiated for carcinoma of the urinary bladder and contributes to creation of personalised treatment programs.*

A considerable number of patients with carcinoma of the urinary bladder are treated with an organ-preserving approach, mostly consisting of transurethral resection of the bladder tumour (TURBT) followed by irradiation with or without concurrent chemotherapy (1-3). Since many of these patients present with significant comorbidities, a personalised treatment program is often required. Such a program should ideally consider several patient-related factors, including the patient's social situation, patient

treatment preference, additional diseases, general condition and remaining life-span. It has been reported for other situations of patients with carcinoma of the urinary bladder, such as metastatic or recurrent disease, that those patients with a poor survival prognosis should receive shorter-course and less aggressive treatments, since low treatment-related toxicity not impairing the patient's quality of life is very important for this group (4-7). Those patients with a much better prognosis should benefit from more aggressive longer-course treatments including systemic therapies leading to better control of the malignant disease and significant prolongation of the patient's survival time.

In order to tailor the treatment regimen to the patient's individual situation, the ability to estimate their survival time is desirable. This goal could be achieved with a clear understanding of the independent predictors of survival identified specifically for patients with carcinoma of the urinary bladder. This study aimed to identify such predictors in a cohort of patients who received organ-preserving treatment including local irradiation.

Patients and Methods

This retrospective study included 61 patients treated with definitive irradiation for carcinoma of the urinary bladder cancer. Irradiation was performed as computed tomography-based conformal radiotherapy with 6-18 MV photons. The median dose was 59.4 Gy (range=50.4 to 63.0 Gy), which was delivered with conventional fractionation of 1.8 to 2.0 Gy on five consecutive days per week. In two-thirds of the patients (N=40), the total dose was 59.4 Gy given with 1.8 Gy per fraction. In 45 patients, irradiation was supplemented with simultaneous chemotherapy, which was mainly cisplatin- or carboplatin-based (N=27). The characteristics of the 61 patients are summarized in Table I.

For the 61 patients, a total of 11 potential predictive factors were analysed with respect to an association with overall survival. These factors were gender, age (≤ 77 vs. >77 years; median age=77 years), T-stage (T1-2 vs. T $>2a$ vs. T3-4), N-stage (N0 vs. N1/2), histological grading (G2 vs. G3), pack years smoked prior to irradiation (<40 vs. ≥ 40 years), smoking during irradiation (no vs. yes), transurethral resection of the bladder tumour prior to irradiation (TURBT; no vs.

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Table I. Distribution of the factors evaluated for an association with overall survival.

Characteristic	Number of patients	Proportion (%)
Gender		
Female	23	38
Male	38	62
Age at irradiation of local recurrence		
≤77 Years	33	54
>77 Years	28	46
T-Stage		
T1-2	25	41
T>2a	17	28
T3-4	19	31
N-Stage		
N0	52	85
N1-2	8	15
Histological grading		
G2	10	16
G3	51	84
Pack years		
<40	46	75
≥40	15	25
Smoking during irradiation		
No	45	74
Yes	16	26
Upfront TURBT		
No	6	10
Yes	55	90
EQD2		
≤55 Gy	16	26
>55 Gy	45	74
Concurrent chemotherapy		
No	16	26
Yes	45	74
Karnofsky performance score		
≤70	16	26
>70	45	74

TURBT: Transurethral resection of the bladder tumour, EQD2: equivalent dose in 2-Gy fractions.

yes), radiation dose given as equivalent dose in 2-Gy fractions (EQD2; ≤55 vs. >55 Gy), simultaneous chemotherapy (no vs. yes) and Karnofsky performance score (KPS; ≤70 vs. >70).

Initially, we performed univariate analyses for these 11 factors using the Kaplan–Meier method and the Wilcoxon test (8). Those factors that achieved significance ($p < 0.05$) or showed a trend ($p < 0.07$) for an association with overall survival were subsequently investigated for independence in a multivariate manner using the Cox regression model.

Results

On univariate analysis of overall survival, female gender ($p = 0.007$, Figure 1), <40 pack years ($p = 0.029$), not smoking during irradiation ($p = 0.037$), upfront TURBT ($p = 0.007$,

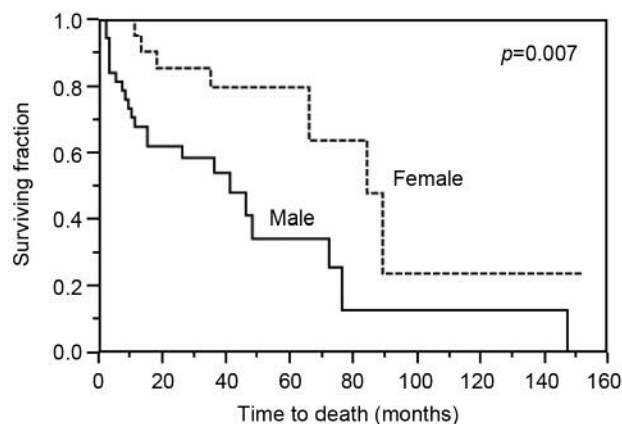


Figure 1. Comparison of female vs. male patients (Kaplan–Meier curves). The p -value (univariate analysis) was calculated using the Wilcoxon test.

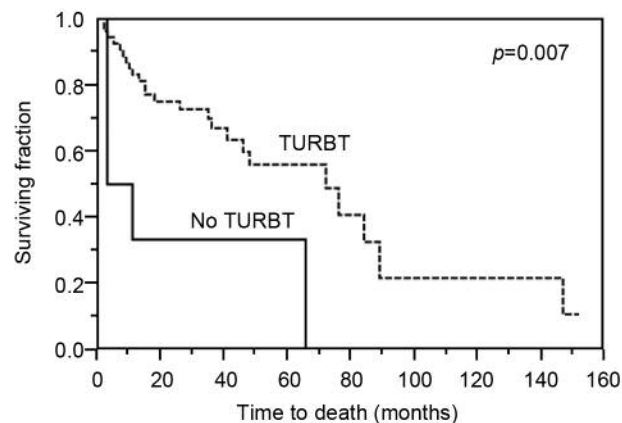


Figure 2. Comparison of patients who underwent an upfront transurethral resection of the bladder tumour (TURBT) vs. patients not doing so (Kaplan–Meier curves). The p -value (univariate analysis) was calculated using the Wilcoxon test.

Figure 2) and a KPS >70 ($p < 0.001$, Figure 3) were significantly associated with an improved survival outcome. Furthermore, treatment with an EQD2 >55 Gy showed a trend towards conferring better overall survival ($p = 0.065$, Table II). The results of the univariate analysis are summarised in Table II.

These six factors were incorporated into the subsequent multivariate analysis. In the Cox regression analysis, female gender [risk ratio (RR)=2.81; 95% confidence interval (CI)=1.05-8.29; $p = 0.039$], upfront TURBT (RR=4.44; 95% CI=1.13-16.39; $p = 0.033$) and KPS >70 (RR=3.45; 95% CI=1.25-9.52; $p = 0.018$) were significant, whereas <40 pack years (RR=1.04; 95% CI=0.38-2.62; $p = 0.94$), not smoking

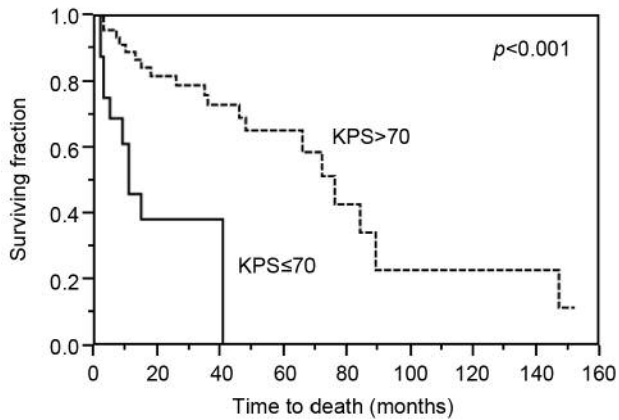


Figure 3. Comparison of patients with a Karnofsky performance score (KPS) of ≤ 70 vs. patients with a KPS of > 70 (Kaplan-Meier curves). The *p*-value (univariate analysis) was calculated using the Wilcoxon test.

during irradiation (RR=1.07; 95% CI=0.42-2.57; $p=0.88$) and an EQD2 >55 Gy (RR=1.40; 95% CI=0.53-4.14; $p=0.51$) were not.

Discussion

In patients with carcinoma of the urinary bladder, standard cystectomy may not be possible or may be refused by the patients. The alternative organ-sparing approach includes local irradiation with or without chemotherapy, mostly preceded by upfront TURBT (1-3). Many of these patients present with other significant diseases in addition to their bladder cancer. Therefore, it is important to tailor the planned treatment approach to each patient. One relevant aspect that needs to be considered when individualizing care is the patient's remaining life-span. Therefore, it is important to be able to predict the expected survival time as precisely as possible. Like for definitive treatment of other malignant disease, this goal can be best achieved with a clear knowledge of predictive factors independently associated with the survival prognosis of the patients (9-11).

Therefore, the present study was initiated, which aimed to identify the independent predictors of survival specifically for patients with carcinoma of the urinary bladder assigned to an organ-sparing treatment approach. According to the results of this study, female gender, upfront TURBT and a KPS >70 were independently associated with improved survival. In addition to these three factors, <40 pack years, not smoking during the period of irradiation were associated with survival at least on univariate analysis, and treatment with an EQD2 >55 Gy showed a trend towards better survival. These factors, particularly those that proved to be

Table II. Univariate analysis of survival including survival rates at 3 and 5 years.

Characteristic	Survival rate (%)		<i>p</i> -Value
	At 3 years	At 5 years	
Gender			0.007
Female	80	80	
Male	54	34	
Age at irradiation			0.15
≤ 77 Years	53	40	
> 77 Years	77	71	
T-Stage			0.18
T1-2	64	57	
T $>2a$	75	50	
T3-4	55	55	
N-Stage			0.49
N0	61	54	
N1-2	88	58	
Histological grading			0.60
G2	69	69	
G3	63	50	
Pack years			0.029
<40	72	63	
≥ 40	41	27	
Smoking during irradiation			0.037
No	69	61	
Yes	50	38	
Upfront TURBT			0.007
No	33	33	
Yes	67	56	
EQD2			0.065
≤ 55 Gy	55	55	
< 55 Gy	67	56	
Concurrent chemotherapy			0.72
No	60	48	
Yes	66	57	
Karnofsky performance score			<0.001
≤ 70	38	0	
> 70	73	65	

TURBT: Transurethral resection of the bladder tumour, EQD2: equivalent dose in 2-Gy fractions. Bold: Significant *p*-values.

independent predictors of survival in the multivariate analysis, may guide physicians who aim to provide a personalised approach for a patient assigned to organ-preserving treatment for carcinoma of the urinary bladder.

The impact of the KPS on the survival of patients with carcinoma of the urinary bladder has been previously shown for patients irradiated for a local recurrence of urinary bladder carcinoma or for metastatic disease (4, 7). In a previous study of patients with metastatic bladder cancer, a greater EQD2 was also significantly associated with improved survival (4). The importance of an upfront TURBT in achieving optimal results has been previously reported (2). The prognostic impact of the number of pack years and

smoking during the period of irradiation has also already been demonstrated for other tumours such as lung and head-and-neck cancer (12-15). The fact that the findings of the present study agree with the results of previous studies demonstrates consistency of the data obtained from the present analyses. When using the factors identified in this study to judge the survival time of a patient with a carcinoma of the urinary bladder, the retrospective nature of the data source should be kept in mind. Such retrospective studies always bear the risk of including hidden selection biases. However, prospective trials with an appropriate statistical power are unlikely to be available soon.

In summary, this study identified three independent predictors of survival in patients with carcinoma of the urinary bladder assigned to organ-sparing treatment including irradiation. These predictors can support physicians when aiming to create a personalised treatment program for a patient belonging to this particular group and when designing trials using these factors for the proper stratification of patients.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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