

Radiotherapy of Primary or Recurrent Bladder Cancer in the Very Elderly

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Abstract. *Aim: The number of very elderly patients with cancer is growing and requires particular attention. The role of organ-sparing irradiation in patients with bladder cancer aged ≥ 80 years was investigated. Patients and Methods: In 29 very elderly (≥ 80 years) patients irradiated for bladder cancer, 12 characteristics were analysed for survival: indication, gender, age, Karnofsky performance score (KPS), T-/N-category, tumour grade, pack years, smoking during irradiation, radiation dose, interruption of irradiation >5 days and concurrent chemotherapy. Results: On univariate analysis, primary treatment ($p=0.001$), KPS >70 ($p=0.026$) and not smoking during radiotherapy ($p<0.001$) were associated with better survival. A strong trend for such association was observed for female gender ($p=0.054$), <40 pack years ($p=0.064$) and concurrent chemotherapy ($p=0.061$), and a trend for no interruption of irradiation ($p=0.09$). On multivariate analysis, primary treatment ($p=0.006$) and not smoking during radiotherapy ($p=0.038$) maintained significance. Conclusion: Very elderly patients irradiated for bladder cancer may benefit from concurrent chemotherapy. Smoking during irradiation and interruptions of irradiation should be avoided.*

Due to demographic changes, the numbers of elderly and very elderly cancer patients are constantly increasing (1-6). This trend also applies to patients with cancer of the urinary bladder (4). For patients with non-metastatic bladder cancer, many oncology centres consider a radical cystectomy the standard of care. However, radical cystectomy has been reported to be associated with significant complications in up to 30% of patients and has a perioperative mortality rate of up

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to 3% (7-9). Very elderly patients often present with significant co-morbidities that preclude aggressive treatment such as radical cystectomy. Alternatively, these patients can be treated with less aggressive organ-preserving approaches, mostly including a transurethral resection of the bladder (TURB) and subsequent local irradiation (10). Irradiation can be intensified by administration of concurrent radio-sensitizing chemotherapy. However, the addition of chemotherapy may not be possible in many very elderly patients due to their co-morbidities affecting organs such as the heart, liver or kidneys. These patients often undergo TURB plus radiotherapy alone.

Since bladder cancer is relatively uncommon, few data are available regarding the treatment of very elderly patients presenting with this particular malignancy. The present study aimed to provide additional data regarding very elderly patients with urinary bladder cancer who received local irradiation or radio-chemotherapy for a primary or recurrent tumour. Several characteristics and their potential impact on the patients' survival prognosis were investigated.

Patients and Methods

A cohort of 29 very elderly patients aged 80 years or older was investigated in this retrospective study. The patients were irradiated for primary (N=17) or recurrent (N=12) non-metastatic bladder cancer. All but one patient had undergone upfront TURB. Concurrent chemotherapy with either cisplatin (N=5), paclitaxel (N=6), cisplatin/paclitaxel (N=1) or gemcitabine (N=1) was administered to 13 patients. In 15 patients, the three-dimensional conformal irradiation was delivered to a total dose of 59.4 Gy given in 28 fractions of 1.8 Gy. In the other 14 patients, total doses ranged from 27 Gy to 55.8 Gy, with doses per fraction ranging from 1.8 to 3.0 Gy. The patient characteristics are shown in Table I.

For these 29 patients, 12 characteristics were investigated for potential impact on survival following irradiation: indication of irradiation (primary vs. recurrent tumour), gender, age at irradiation (≤ 83 vs. >83 years; median age=83 years; range=80-91 years), Karnofsky performance score (KPS; ≤ 70 vs. >70), T-category (T1-2a vs. T $>2a$ vs. T3-4), N-category (N0 vs. N+), grading (G2 vs. G3), pack years of smoking (<40 vs. ≥ 40), smoking during the irradiation period (no vs. yes), equivalent radiation dose in 2-Gy fractions

Table I. Characteristics that were investigated for a potential impact on survival.

	Number of patients	Proportion (%)
Indication for irradiation		
Primary treatment	17	59
Treatment of a recurrence	12	41
Gender		
Female	11	38
Male	18	62
Age at irradiation		
≤83 Years	15	52
>83 Years	14	48
Karnofsky performance score		
≤70	11	38
>70	18	62
T-Stage		
1-2a	6	21
>2a	9	31
3-4	14	48
N-Stage		
0	23	79
1-3	6	21
Grading		
G2	4	14
G3	25	86
Pack years		
<40	25	86
≥40	4	14
Smoking during irradiation		
No	26	90
Yes	3	10
EQD2		
≤54.9 Gy	14	48
<58.4 Gy	15	52
Interruption of irradiation		
No	25	86
Yes	4	14
Concurrent chemotherapy		
No	16	55
Yes	13	45

EQD2: Equivalent dose in 2 Gy fractions.

(EQD2; ≤54.9 Gy vs. 58.4 Gy), interruption of irradiation by >5 days (no vs. yes) and delivery of concurrent chemotherapy (no vs. yes).

Survival rates were estimated with the Kaplan–Meier method supplemented with the log-rank test (11). The characteristics that were found to be significant on univariate analyses ($p < 0.05$) or found to have a strong trend ($p < 0.07$) for association with survival, were additionally included in a multivariate analysis using the Cox proportional hazards model.

Results

On univariate analysis, primary treatment ($p = 0.001$), a KPS >70 ($p = 0.026$) and not smoking during radiotherapy ($p < 0.001$) were significantly associated with better survival

Table II. Univariate analysis including survival rates at 1 and 3 years.

	At 1 year	At 3 years	p-Value
Indication for irradiation			
Primary treatment	82	74	
Treatment of a recurrence	33	8	0.001
Gender			
Female	81	69	
Male	50	29	0.054
Age at irradiation			
≤83 Years	59	39	
>83 Years	64	48	0.52
Karnofsky performance score			
≤70	42	n.a.	
>70	72	58	0.026
T-Stage			
1-2a	67	44	
>2a	56	56	
3-4	62	36	0.72
N-Stage			
0	61	41	
1-3	67	67	0.36
Grading			
G2	75	75	
G3	59	39	0.38
Pack years			
<40	68	49	
≥40	0	0	0.064
Smoking during irradiation			
No	69	49	
Yes	0	0	<0.001
EQD2			
≤54.9 Gy	55	39	
<58.4 Gy	67	48	0.69
Prolongation of irradiation			
No	63	53	
Yes	50	0	0.09
Concurrent chemotherapy			
No	50	29	
Yes	76	65	0.061

EQD2: Equivalent dose in 2 Gy fractions, n.a.: not available. Significant p -values are shown in bold.

rates. A strong trend for an improved survival was observed for female gender ($p = 0.054$), <40 pack years ($p = 0.064$) and the administration of concurrent chemotherapy ($p = 0.061$). In addition, a trend was found for avoiding breaks of >5 days ($p = 0.09$). The complete results of the univariate analyses are shown in Table II.

On multivariate analysis, primary treatment [hazard ratio (HR)=4.85; 95%-confidence interval (CI)=1.57-18.12; $p = 0.006$] and not smoking during radiotherapy (HR=6.09; 95%-CI=1.12-29.22; $p = 0.038$) maintained significance. A KPS >70 (HR=2.13; 95%-CI=0.68-96.54; $p = 0.19$), female gender (HR=1.58; 95%-CI=0.33-8.94; $p = 0.57$), <40 pack years (HR=2.08; 95%-CI: 0.21-52.63; $p = 0.57$) and the

administration of concurrent chemotherapy (HR=1.95; 95%-CI=0.55-7.87; $p=0.31$) did not achieve significance in the multivariate analysis.

Discussion

Very elderly patients with non-metastatic urinary bladder cancer requiring local treatment are often unable to tolerate radical cystectomy and are treated with less aggressive approaches including irradiation (7-10). Since these patients are uncommon, only very few studies are available that focused particularly on this subgroup. The current study was conducted to provide additional information regarding their radiotherapy outcomes to help optimize future patient care.

Treatment for a primary tumour resulted in significantly better outcomes than that of a recurrence on both univariate and multivariate analyses. This is not surprising because at the time of a recurrence, patients often have a worse performance status and have already received anticancer treatment, moreover, recurrent tumours are frequently more difficult to control than primary lesions (12). Smoking during the period of irradiation was also significantly associated with a worse survival on both univariate and multivariate analyses. A negative association between smoking and treatment outcomes has been reported for patients irradiated for non-small-cell lung cancer (13). In the multivariate analysis of a retrospective study of 181 patients, smoking during treatment resulted in worse locoregional control ($p=0.029$). In the present study, a strong trend was observed for an association between <40 pack years of smoking and favourable survival on univariate analysis. A similar correlation has been reported for patients with cancer of the oropharynx (14). In the present study, female gender showed a strong trend for being associated with improved survival in the univariate analysis. A positive association between female gender and survival was also demonstrated in patients with metastatic disease (15). Another important finding of the present study is that very elderly patients appear to benefit from the addition of concurrent chemotherapy to irradiation, which has already been shown in studies of bladder cancer in patients of any age with primary or recurrent tumours (10, 12). In addition, a certain trend was identified that interruptions of irradiation reduce survival. This has also been found in patients of any age treated for locally advanced head and neck cancer (16). The comparisons with the literature show that the factors having an impact on the results of irradiation of localized bladder cancer in very elderly patients are consistent with the outcomes of many other treatment situations.

Weaknesses of this study include the cohort size and the retrospective nature of this analysis. However, there are so few available data on very elderly patients with bladder

cancer; the Authors feel that these data are important in order to help optimize therapy in elderly patients, who present more commonly these days as people live longer than they did in the past.

In conclusion, very elderly patients irradiated for bladder cancer appear to benefit from the addition of concurrent chemotherapy. In order to achieve best possible outcome, smoking and interruptions during treatment should be avoided if possible. Very elderly patients irradiated for bladder cancer require maximum support from their medical staff to accomplish these goals.

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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