Radiotherapy for muscle-invasive urinary bladder cancer in elderly patients

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Objective: *To review retrospectively the outcome and toxicity of Radiotherapy (RT) in the cohort of elderly patients (EP) with muscle-invasive urinary bladder carcinoma (MIUBC).*

Methods: *Thirty-six EP were treated with RT with radical intent. The age of the cohort ranged from 71 to 89 years with a median of 79 years. Eighty percent of the patients had Easter Cooperative Oncology Group (ECOG) 0 and 1 performance status. Conventional and accelerated fractionation RT regimen were utilized.*

Results: *With median follow up of 45.8 months, the median survival was 23.9 months. There was a trend toward better survival in patients treated with the accelerated fractionation regimen. The median survival for that group (12) has not yet been reached, where it is 9.7 months for the group (24) treated with conventional fractionation. Treatment related toxicity was low for any RT regimens.*

Conclusion: *RT is well tolerated by EP with good baseline performance status. The role of accelerated fractionation should be tested by conducting randomized trials.*

Key Words: muscle-invasive carcinoma of urinary bladder, elderly patients, radical radiation therapy, accelerated fractionation

Introduction

Urinary bladder carcinoma (UBC) is the fourth most common cancer in men and thirteenth in women. Projections for Canada for the year 2000 included 4850 new cases, and 1510 deaths.[1] In about 25% of cases bladder tumors are muscle-invasive at presentation; another 10%-25% of initially superficial tumors are muscle-invasive at recurrence. Muscle invasion portends a poor prognosis, and generally signifies the need for aggressive intervention. Radical Cystectomy (RC) and urinary diversion remains the most frequently employed treatment in North America.[2] Many patients also receive adjuvant or neo-adjuvant chemotherapy, although the value of this remains debatable.[3]

Carcinoma of the urinary bladder mainly affects the elderly, with the incidence increasing 2-3 fold beyond age 70. Therefore management of MIUBC may be complicated by the comorbid medical conditions of these EP and by their limited tolerance of radical surgery and aggressive chemotherapy. RT is well-established method of treatment for MIUBC[4-9]. However, the role of age as a prognostic variable for patients treated with RT[6-12] remains uncertain. Our

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study represents a retrospective review of the outcome and toxicity of radical RT (RTT) in an elderly group of patients with MIUBC.

Materials and methods

All patients receiving RRT were treated by Linear Accelerator using an 18 MV energy photon beam. Three-dimensional CT-based conformal planning was utilized. The most common field arrangement was a 4 field box with extensive conformal shielding. The Planning Target Volume (PTV) normally would include the entire empty bladder with a margin from 1 cm to 2 cm. Regional lymph nodes usually were not treated unless they were radiologically positive for metastases (N_1, N_2). Twenty-four patients were treated with daily fractionation regimen with total dose from 50-66 Gy in 20 – 34 fractions over 4 – 7 weeks. Twelve patients were treated on an accelerated fractionation regimen ("concomitant boost regimen") that included delivery of 40 Gy in 20 fractions to the entire bladder with a 2-cm margin, and a concomitantly administered 20 Gy in 10 fractions boost to the bladder and a 1-cm margin. Thus, in this particular regimen patients received twice-daily treatment for 2 out of the 4 weeks of the overall course, with fractions given 6 hours apart. The RT dose regimen was chosen based only on the preference of the individual radiation oncologist. Eleven out of 12 patients treated with "concomitant boost regimen" participated in the prospective nonrandomized study assessing the tolerance and compliance with this alternative fractionation regimen.[14] Therefore in these patients the outcome and toxicity data was collected prospectively.

All available and compliant patients were followed with history, physical examination and cystoscopy every 3 months for the first year, 6-monthly for the second year and annually thereafter. In cases where a patient was not available for follow-up visits the information regarding patient's status was obtained by personal correspondence with the general practitioner or urologist office.

Survival curves were plotted using the method of Kaplan and Meier, with differences between curves assessed by two-sided log-rank test. The Cox proportional hazards model was used to evaluate the association of survival with baseline parameters and treatment, in both univariate and multivariate fashion.

Results

From April 1, 1995 until July 1, 1999, 146 patients with UBC were referred to the Fraser Valley Cancer Centre including 21 with superficial UBC and 125 with MIUBC. Among those with MIUBC, 76 had documented metastatic spread at the time of referral.

Amongst the 46 patients with localized MIUBC treated with RRT, 36 were over 70 years in age at the time of RRT. This latter group is the subject of our analysis. All patients had transurethral resection of the tumor (TUR) prior to RT. Two patients received a course of neo-adjuvant chemotherapy.

The patients and tumors characteristics are presented in Table 1.

Three different radiotherapy regimens were employed. Seventeen patients (47.2%) received 5500 cGy-6600 cGy with 180 cGy-200 cGy per fraction. Twelve patients (33.3%) received a concomitant boost regimen

TABLE 1. **Patient and tumor characteristics**

		N (%)
Age	Median 79.3	
	Range 71-89	
Gender	M	26 (72)
	F	10 (28)
T stage	Tx	1 (3)
	T2	15 (42)
	T3a	5 (14)
	T3b	8 (22)
	T4a	5 (14)
	T4B	2 (6)
N stage	N0	29 (81)
	N1	1 (3)
	N2	1 (3)
	Missing	5 (14)
Grade	1	1 (3)
	2	2 (6)
	3	33 (91)
Histology	TCC	33 (91)
	Squamous carcinoma	
	Adenocarcinoma	1 (3)
Hydronephrosis	None	26 (72)
	Unilateral	8 (22)
	Bilateral	2 (6)
ECOG performance status	0	7 (67)
	1	22 (61)
	2	6 (17)
	3	1 (3)
Baseline hemoglobin	Median 125 g/l	
	Range 84-153 g/l	
	Missing	10 (28)
Baseline creatinine	Median 107 mmol/l	
	Range 50-188 mmol/l	
	Missing	12 (33)

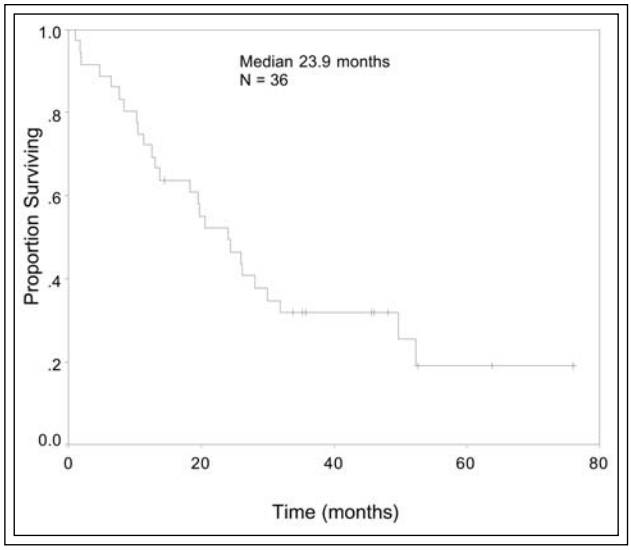

Figure 1. Overall survival from the time of start of radiotherapy.

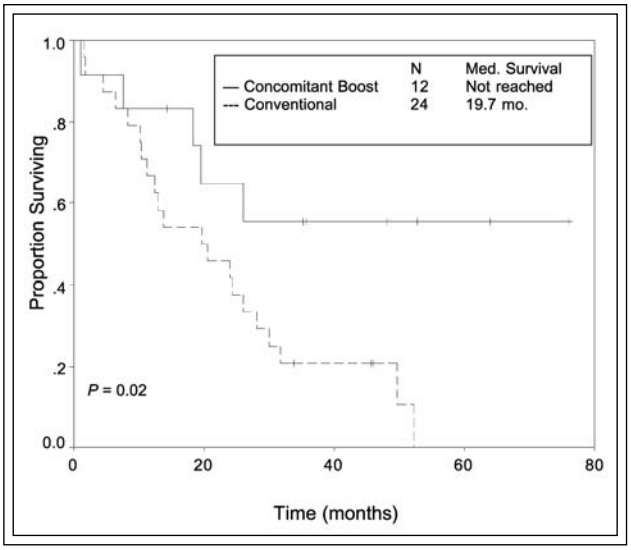

Figure 2. Survival from start of radiotherapy according to radiotherapy regimen received.

of 6000 cGy in 30 fractions, with twice daily treatment for the last 2 weeks of the course. Seven patients (19.4%) received a hypofractionated regimen of 5000 cGy-5250 cGy in 20 fractions (250 cGy – 262.5 cGy per fraction). Three patients did not complete their treatment: one who was initially scheduled to receive concomitant boost regimen and two who were scheduled to have hypofractionated regimen. Among them one presented with metastatic spinal cord compression while on treatment (no metastases were detected before RT started) and two with weakness, anemia and debilitation related to progression of the malignancy.

For the purpose of analysis we divided the patients into two groups: 1) 24 patients who received RT with once a day fractionation (conventional and hypofractionated regimens); and 2) 12 who received RT according to concomitant boost regimen (accelerated). One should keep in mind, however, that among "conventional" group, 7 were treated with hypofractionated regimens (250 cGy – 262.5 cGy per fraction).

With a median follow up of 45.8 months (range 14.4 – 76 months) the median survival of the entire group is 23.9 months Figure 1. Thirteen patients (36%) have remained free of recurrence 14.4 – 57.6 months from treatment. Five (14%) have died without evidence of disease recurrence 10.2 – 49.7 months from treatment, and two others have died of unknown causes 7.6 and 8.4 months from treatment (they are considered to have relapsed for the purposes of analysis).

Univariate analysis of potential prognostic factors Table 2 demonstrated that normal baseline creatinine (dichotomized at the median value), excellent performance status and utilization of the concomitant boost regimen (60 Gy in 30 fractions over 4 weeks) were associated with better survival. Figure 2

TABLE 2. **Univariate analysis of potential prognostic factors**

Factor	N	Risk ratio	P
Age at RRT (70-<80, vs ≥ 80)	36	1.4	0.3
Gender (female vs male)	36	0.9	0.9
T stage (<T3 vs ≥ T3)	36	0.8	0.6
Baseline hemoglobin*	26	0.9	0.9
Baseline creatinine*	22	3.8	0.03
Presence of hydronephrosis	36	1.1	0.7
ECOG performance status 0 vs > 0	36	4.2	0.05
Use of concomitant boost RRT	36	3.0	0.03

Higher risk ratio indicates worse prognosis with higher value of prognostic factor.
*Dichotomized at median value

demonstrates the difference in survival of the patients treated with once a day and accelerated ("concomitant boost" regimens) fractionation. On multivariate analysis, however, no factors retained independent prognostic significance.

Toxicity of the treatment

Table 3 outlines the toxicity data. Three patients (8%) developed acute grade 3 genitourinary (GU) toxicity and no patients developed acute grade 3 gastrointestinal (GI) toxicity. One patient died of acute cardiac death shortly after the initiation of RT course (accelerated regimen was planned).

No grade 3 late toxicity was documented in survivors. One patient had grade 2 late GU toxicity and three patients (6.5%) had grade 1 late GI toxicity. There was no correlation between any particular regimen of RT with increased acute or late toxicity.

Discussion

Radical Cystectomy remains the "gold standard" treatment for MIUBC in North America. Post-cystectomy, 5-year survival ranges between 48% and 78% depending on pathological stage.[2] There is a considerable risk of major operative morbidity (20.5%) and a low risk of operative mortality (2.3%).[13] These figures may well be higher in patients of advanced age and in patients with significant comorbidity. Therefore RC may be precluded for a number of patients with MIUBC. In some cases age alone may be felt to dictate the use of palliative-intent rather than radical-intent treatment. With the overall "aging" of the population one might foresee facing this dilemma more and more often.

Radiotherapy is considered an alternative to RC, particularly in Europe. There has been no modern direct randomized comparison of these two primary treatment modalities, and the presumed superiority of radical cystectomy is based largely on conjecture.[14]

Our study indicates that in a group of EP not felt to be candidates for RC, RRT provided useful disease control. Forty percent of the patients survived 4+ years from treatment, 13 (36%) have yet to recur, and an additional 5 (14%) died without evidence of disease.

Historically most of the large retrospective RRT series report age as being one of the adverse prognostic factors in MIUBC.[7,10,11] This negative impact of age on survivorship however is not universal. Large retrospective reviews done by Mameghan[8] and Gospodarowicz[9] suggested that the age of the patient was not a significant determinant of the 5-year actuarial relapse free survival when assessed in multivariate analysis. In these studies the factors statistically associated with relapse were advanced T stage, bulk of tumor, presence of ureteric obstruction and multiplicity of the lesions. Other prognostic factors which are frequently reported are: hemoglobin, hydronephrosis, grade of the tumor, extent of Transurethral Resection (TUR), creatinine and performance status. In our study only baseline creatinine and ECOG performance status were statistically significant on Univariate Analysis (besides radiotherapy regimen). We believe that other common prognostic factors did not reach significance for several reasons. Firstly, our cohort was not large enough. If we look at the grade of the tumor, we see that 33 out of 36 patients had tumor of grade 3 histologically and there were not enough variables to detect the difference. With regard to the lack of significance of clinical stage, one should remember that it is to a great deal a reflection of urologic (endoscopic) assessment. In a number of instances there was a lack of detailed description of bimanual examination prior to and after Transurethral Resection. If it happened we tended to stage patients as having stage T2, but it might be that in reality, many of them had more advanced stage. Therefore it is quite possible that the majority of the patients belonged to T3A or higher category and thus we could not observe a great deal of difference of survival according to the clinical stage. The same is true for the extent of

TABLE 3. **Radiation toxicity**

Grade	**N (%)**				
	Acute GU	**Acute GI**	**Acute other**	**Late GU**	**Late GI**
1	10 (28)	7 (19)	3 (8)	2 (6)	3 (8)
2	9 (25)	15 (42)	3 (8)	1 (3)	0
3	3 (8)	0	0	0	0
4	0	0	1 (3)	0	0

*National Cancer Institute of Canada Cancer Treatment Group (NCIC CTG) tosicity criteria

Transurethral Resection (TUR). We found that it was difficult to document it accurately based on available surgical reports and therefore did not include it in the list of potential prognostic variables. In majority of cases urologists reported complete or near complete TUR, but there was no way to verify it retrospectively.

Sengelov et al reported their experience with RRT for EP with MIUBC.[10] The authors treated 94 patients in the age range of 75-93 years. They reported 2 and 5 year overall survival of 29% and 7% respectively. The factors significantly associated with a poor survival on multivariate analysis were advanced stage of the cancer (T3-T4), poor performance status and RT regimen. Some of the findings of that study fully corresponded with our own, e.g. performance status of the patient was more important than patient's age as a selection criterion for RRT. The RRT regimen used by Sengelov et al, however, was of a more controversial nature. They found that survival of the 76 patients treated with a split regimen was significantly better than survival of the 18 patients treated with a continuous course. On the other hand they found that unplanned treatment pauses were associated with worse survival. In our study we were guided by a different treatment philosophy. We believed that the overall treatment time should be short for RRT of MIUBC, to reflect its biology.[16] Therefore a number of our patients were treated with a 4 week course of RRT without planned interruption and a core of the patients had a so-called concomitant boost regimen which utilizes accelerated fractionation for half of the course. If we assume that a/b for fast reacting tumors (and we believe that high grade MIBC belongs to this category) is 10 and also introduce a time factor after 4 weeks of treatment we may derive Biologically Effective Dos (BED_{10}) for each of the 3 regimens we utilized in our cohort:

60 Gy/30 fractions/6 weeks: $BED_{10} = 66$
60 Gy/30 fractions/4 weeks: $BED_{10} = 72$
51 Gy/20 fractions/4 weeks: $BED_{10} = 64$

On the other hand BED_3 (for late responding tissues) will be:

60 Gy/30 fractions/6 weeks: $BED_3 = 100$
60 Gy/30 fractions/4 weeks: $BED_3 = 100$
51 Gy/20 fractions/4 weeks: $BED_3 = 116$[17]

Interestingly enough, when we divided our patients according to overall duration of RT (4 weeks versus 6 weeks), we found that the difference in their survival is statistically significant in favor of 4-week regimens. This may be another indication that MIUBC may be controlled better with accelerated or hypofractionated RT regimens.

Another indirect indication that accelerated fractionation may be advantageous in MIUBC is a degree of local control. Among 12 patients in our study who developed local recurrence based on cystoscopic evaluation, 3 out of 12 (25%) were treated with "concomitant boost" RT regimen and 9 out of 24 (37.5%) with once a day fractionation. Undoubtedly, to verify this a proper prospective randomized trial should be conducted.

Similar observations regarding the importance of patient performance status were made in the other large retrospective studies of RRT for MIUBC.[14] Unfortunately performance status is only rarely included in the list of potential prognostic factors in many retrospective studies. On the other hand this factor is frequently included in the eligibility criteria for enrollment in randomized prospective studies. There is a tendency to enroll into the randomized study the patients with better performance status and therefore to introduce a natural bias in assessment of treatment results. We believe, and our study illustrated this, that in selecting patients for RRT the performance status should take precedence over the age.

We found that toxicity related to RT was relatively modest, no matter what RT regimen was utilized. One potential explanation for this may be utilization of 3D conformal planning which led to reduced volume of normal tissues treated with the high dose RT.

There are reports of chemotherapy used in combination with RT in EP.[18,19] Our institution experience with chemotherapy in EP, however, was rather limited and we would hesitate to compare our results with these studies.

The role of accelerated fractionation in management of MIUBC, as it was mentioned before, should be addressed by conducting proper randomized study. This strategy, however, appears promising to us and we will continue to collect the data. □

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