

Combined Modality Treatment Using Hypofractionated IMRT for Bladder Preservation in Elderly Patients With Invasive Bladder Cancer

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Abstract

Purpose

Long-term results of bladder-preserving combined treatment modalities (CMT) for muscle invasive bladder cancer have confirmed that this approach is safe and effective in selected patients. Here we report our preliminary results of CMT for bladder preservation in elderly patients using hypofractionated IMRT.

Materials/Methods

A retrospective review was performed on a population aged ≥ 70 years treated with maximally feasible TURBT followed by concomitant chemoradiation using hypofractionated IMRT. All patients were treated between January 2008 and August 2012. Eligibility criteria were: a proven diagnosis of muscle invasive transitional cell carcinoma stage T2-T3N0M0; to have received CMT with curative intent; and to have been planned for a course of hypofractionated IMRT regimen of 50Gy in 20 fractions (fx). IMRT was delivered to the bladder volume only in 7 patients (29%). The remaining 17 patients received 50Gy/20fx to the bladder and 40Gy/20fx to the pelvic lymph nodes. All patients received concomitant chemotherapy either with Gemcitabine 100 mg/m² weekly (21 patients) or Cisplatin 40 mg/m² weekly. Of the patients receiving weekly gemcitabine, six also received everolimus as part of an on-going phase I/II trial.

Results

Twenty-four patients with a median age of 79 years were eligible for our study. Nine patients refused cystectomy and the remaining 15 were not considered medically fit for cystectomy. TURBT was not possible or judged incomplete by the urologist in five patients. The median follow-up was 16 months (range: 6-55 months). A cystoscopically and/or biopsy proven complete response in the bladder was confirmed in 83% of the patients. Of the remaining patients, one of them underwent salvage cystectomy and no disease was found in the bladder

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on histopathological assessment. Seven patients recurred, four loco-regionally and three with distant metastasis. Disease-free, cause-specific and the overall survival rates at 2 years were 81%, 74% and 63%, respectively. Grade 2 acute genitourinary (GU) and/or gastrointestinal (GI) toxicities occurred in 42% of the patients. A single patient had febrile neutropenia with combined grade 3 GU and GI acute toxicities. Grade 3 hematologic and/or liver enzymes toxicity were seen in 17% of our cohort. There was no grade 4-5 toxicity.

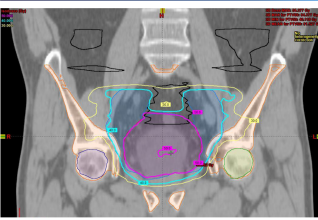
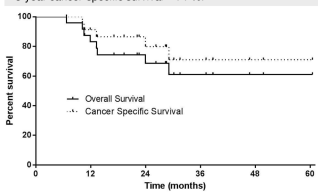
Conclusions

In our preliminary results, CMT using hypofractionated IMRT appears to be an effective and generally well tolerated regimen for elderly, frail patients with muscle invasive bladder cancer undergoing bladder preservation strategy. Hypofractionated IMRT appears to be an attractive alternative option to conventionally fractionated radiotherapy in the elderly population.

Combined Modality Treatment Using Hypofractionated IMRT for Bladder Preservation in Elderly Patients With Invasive Bladder Cancer

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Purpose/Objectives	Materials/Methods (cont'd)	Results (cont'd)																																																																			
<ul style="list-style-type: none"> Tri-modality therapy (TMT) for muscle-invasive transitional cell carcinoma (TCC) of the bladder is an appealing alternative to radical cystectomy, resulting in comparable overall survival rates to surgical series and complete pathological response rate of 60-90% [1]. The most effective TMT involves: <ol style="list-style-type: none"> Maximally feasible transurethral resection of the bladder tumor (TURBT) Followed by concomitant chemotherapy and radiotherapy (RT), with or without adjuvant chemotherapy. There is an underutilization of curative bladder therapies in the elderly population. Up to 23-59% of patients aged ≥ 70 year-old do not receive curative therapy [2]. <p>Objectives : Demonstrate that elderly patients (age ≥ 70) not considered good surgical candidates can be treated effectively and tolerate well a curative TMT approach consisting of :</p> <p style="text-align: center; color: red;">A maximal TURBT</p> <p style="text-align: center; color: red;">↓</p> <p style="text-align: center; color: red;">A hypofractionated IMRT course with concomitant weekly radiosensitizing chemotherapy [3]</p>	 <p>Fig. 1. Dose distribution of an IMRT plan: PTV_{0.450} receiving 50Gy/20fx (magenta) and PTV_{0.200} 40Gy/20fx (cyan). Sparring of organ at risk including: small bowel (black), femoral heads (blue & green), pelvic bones (orange) and rectum (not visible).</p> <p style="text-align: center; background-color: #0056b3; color: white; padding: 2px;">Results</p> <ul style="list-style-type: none"> Demographic Data : <ul style="list-style-type: none"> Between January 2008 and August 2012, 24 pts were eligible. Median age = 79 years (range: 72-88 years). Pts median follow-up is 25 months (range 7-60 months). <table border="1" style="width: 100%; border-collapse: collapse; font-size: small;"> <caption>Table 1. Patient and treatment characteristics</caption> <thead> <tr> <th>Characteristics</th> <th>Number of patients</th> </tr> </thead> <tbody> <tr> <td>Sex</td> <td></td> </tr> <tr> <td>Male</td> <td>20</td> </tr> <tr> <td>Female</td> <td>4</td> </tr> <tr> <td>Clinical Stage</td> <td></td> </tr> <tr> <td>T2</td> <td>22</td> </tr> <tr> <td>T3</td> <td>2</td> </tr> <tr> <td>Reason for treatment decision</td> <td></td> </tr> <tr> <td>Not surgical candidate</td> <td>15</td> </tr> <tr> <td>Cystectomy Refusal</td> <td>9</td> </tr> <tr> <td>ECOG</td> <td></td> </tr> <tr> <td>0</td> <td>15</td> </tr> <tr> <td>1</td> <td>7</td> </tr> <tr> <td>2</td> <td>2</td> </tr> <tr> <td>Hydronephrosis</td> <td>4</td> </tr> <tr> <td>Visually complete pre-treatment TURBT</td> <td>19</td> </tr> <tr> <td>Lymph nodes irradiation</td> <td>17</td> </tr> <tr> <td>Chemotherapy</td> <td></td> </tr> <tr> <td>Cisplatin only</td> <td>3</td> </tr> <tr> <td>Gemcitabine only</td> <td>15</td> </tr> <tr> <td>Gemcitabine + Everolimus</td> <td>6</td> </tr> </tbody> </table> <ul style="list-style-type: none"> Treatment-related toxicities (Table 2) : <ul style="list-style-type: none"> TMT was well tolerated. No grade 4 gastro-intestinal (GI) or genito-urinary (GU) toxicity. The single pt with acute grade 3 GI and GU toxicity also required hospitalization because of febrile neutropenia. 	Characteristics	Number of patients	Sex		Male	20	Female	4	Clinical Stage		T2	22	T3	2	Reason for treatment decision		Not surgical candidate	15	Cystectomy Refusal	9	ECOG		0	15	1	7	2	2	Hydronephrosis	4	Visually complete pre-treatment TURBT	19	Lymph nodes irradiation	17	Chemotherapy		Cisplatin only	3	Gemcitabine only	15	Gemcitabine + Everolimus	6	<table border="1" style="width: 100%; border-collapse: collapse; font-size: small;"> <caption>Table 2. 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Metastatic: 1 pt regionally (20 cm), and 3 pts distally (5, 6 & 11 cm). Overall and cancer specific survival (Fig. 2) : <ul style="list-style-type: none"> 3-year overall survival = 61 %. 3-year cancer-specific survival = 71 %.  <p>Fig. 2. Overall and cancer-specific survival rates.</p> <ul style="list-style-type: none"> 75% of the surviving pts have a disease free and functioning bladder. 	Grade	GI	GU	Hematologic	Hepatic	1	12 (50%)	10 (42%)	14 (58%)	0	2	7 (29%)	7 (29%)	4 (17%)	0	3	1 (4%)	1 (4%)	2 (8%)	2 (8%)	4	0	0	1* (4%)	0
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<p style="text-align: center; background-color: #0056b3; color: white; padding: 2px;">Materials/Methods</p> <ul style="list-style-type: none"> Eligibility criteria : <ul style="list-style-type: none"> ≥ 70 year-old treated in our institution Received a curative intent hypofractionated IMRT regimen of 50 Gy in 20 fractions (fx) and concomitant chemotherapy Diagnosed with an invasive bladder TCC stage T2-T3N0M0 Non-surgical candidates due to comorbid disease or personal preference. TREATMENT <ul style="list-style-type: none"> Maximal TURBT : 4-12 weeks prior the start of the RT. Radiotherapy : Delivered daily, five days a week. An inverse IMRT technique was used to deliver 50 Gy in 20 fx to the bladder. When treated (bx), the lymph nodes received 40 Gy in the same 20 fx using a field-in-field technique. The bladder clinical target volume (CTV_{bladder}) and the CTV_{node} were expanded 1.5-2.0 and 0.7 cm, respectively, to generate the planning target volumes (PTV). Chemotherapy : Patients (pts) received concomitant weekly Gemcitabine 100 mg/m² or Cisplatin 40 mg/m² (on RT day 1, 8, 15 and 22). Treatment response : Evaluated 1-3 months after chemoradiation. A complete response was defined as: <ol style="list-style-type: none"> Negative cystoscopy and cytology or Negative biopsy at the previous lesion site. 	<p style="text-align: center; background-color: #0056b3; color: white; padding: 2px;">Conclusions</p> <ul style="list-style-type: none"> Our preliminary results show that hypofractionated IMRT with concurrent radiosensitizing chemotherapy, after maximum TURBT, appears to be an effective and well-tolerated curative treatment strategy in the elderly population and should be considered for patients who are non-candidates or wish to avoid cystectomy. <p style="text-align: center; background-color: #0056b3; color: white; padding: 2px;">References</p> <p style="font-size: x-small;">[1] Rodol C, et al. Trimodality treatment and selective organ preservation for bladder cancer. J Clin Oncol 2006; 24: 5536-5544. [2] Gray PJ, et al. Use of Potentially Curative Therapies for Muscle-Invasive Bladder Cancer in the United States: Results from the National Cancer Data Base. Eur Urol 2013; 63: 823-829. [3] Sangar WK, et al. Phase I study of conformal radiotherapy with concurrent gemcitabine in locally advanced bladder cancer. Int J Radiat Oncol Biol Phys 2005; 61: 420-425. Author contact: guy.ame.turgeon@mail.mcgill.ca</p>																																																																				