

## Value of Low Dose Short Hypofractionated Palliative Radiation Therapy in the Management of Bladder Cancer

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### ABSTRACT

**Background:** In locally advanced and metastatic urinary bladder carcinoma, palliative radiation therapy aims to palliate symptoms with acceptable toxicity.

**Objective:** Evaluation of the role of low dose short hypofractionated radiotherapy in improving symptoms of bladder cancer indefinitely, as long as it does not cause unacceptable toxicity.

**Patients and Methods:** From July 2018 to July 2020, 24 patients with advanced bladder cancer were included in a trial at Zagazig University Hospitals' Clinical Oncology & Nuclear Medicine Department. All patients received a total dose of 21Gy of conformal radiation (7 Gy/fraction in 3 fractions, a fraction every other day over one week).

**Results:** There was statistically significant improvement in haematuria symptoms among the studied patients. Also, there were no statistically significant changes in bowel frequency symptoms, diarrhea symptoms and bleeding symptoms. There were no significant changes in symptoms at 3-month assessment compared to end of treatment assessment while there was increase in percent of patients with symptomatic improvements especially in haematuria, dysuria and nocturia symptoms.

**Conclusion:** Low dose hypofractionated radiation therapy protocol showed effective palliation of urinary symptoms with an acceptable toxicity.

**Keywords:** Hypofractionated radiotherapy, Bladder symptoms, Bowel symptoms, Bladder cancer.

### INTRODUCTION

Bladder cancer is one of the most frequent cancers in developed countries, with the largest incidence occurring between 70 and 75 years of age <sup>(1)</sup>.

After prostate cancer, it is the second most frequent urogenital malignancy. When it comes to cancer mortality, it is the 8th most common cause of death in the United States for both men and women <sup>(2)</sup>.

In the United States, it is responsible for 3% of all cancer fatalities in men and 2.5% of all malignancy-related deaths <sup>(3)</sup>. Urothelial carcinomas in Egypt are more commonly diagnosed in urban areas as the control of schistosomiasis in the rural areas led to a drop in squamous cell carcinoma incidence <sup>(4)</sup>.

At time of diagnosis, about 25% of patients presented with muscle-invasive cancer bladder. About 10%-15% of the remaining 75% who initially presented with early disease will progress to muscle invasive one <sup>(5)</sup>. Many of the 25 percent of patients who may be identified with a deadly muscle-invasive disease will be unable to endure the aggressive treatment because of their comorbid conditions. In some cases, the disease has progressed to the point where curative treatment is no longer possible. The majority of individuals with this disease suffer from bothersome symptoms like dysuria and hematuria, which necessitate treatment for the length of the patient's life <sup>(6)</sup>.

As long as possible, palliative care should strive to alleviate the patient's symptoms, but it should not cause unacceptable toxicities <sup>(7)</sup>. As a result, hypofractionated radiotherapy is used to treat the symptoms of advanced and metastatic bladder cancer that have spread locally. Only the tumor and bladder will be treated with a dose of 21 Gy in three segments using this approach, not the entire pelvis <sup>(8)</sup>.

We wanted to check if low dosage, short hypofractionated radiation could improve symptoms of bladder cancer for as long as possible, with no undesirable side effects.

### PATIENTS AND METHODS

This prospective cohort study was conducted through the period from July 2018 to July 2020 at the Clinical Oncology and Nuclear Medicine Department of Zagazig University Hospital in Egypt. This research included 24 patients with locally advanced or metastatic bladder cancer who were unfit for any type of radical treatment.

#### Inclusion criteria:

Pathologically, they were verified as muscle-invasive cancer of the bladder causing local symptoms, a normal haematological profile, an expected life span of at least three months, and no concurrent or planned use of cytotoxic chemotherapy were the criteria for this clinical research, with either: (1) T3 and T4a tumors are appropriate for radical treatment, but the patient's age or general medical state prevents him or her from receiving it, or (2) Treatment options are limited due to the stage of the tumor's development (T4b, N1, and M1).

#### Exclusion Criteria:

Patients fit for radical treatment, previous cystectomy, and decompensated liver failure (ascites).

#### Ethical approval:

All participants signed informed permission papers and submitted them to the Research Ethics Committee, Zagazig University. The study was

permitted (ZU-IRB#6835). Ethics guidelines for human experimentation were adhered to in line with the Helsinki Declaration of the World Medical Association.

**A) Pretreatment evaluation:** Complete medical history, clinical examination & per rectal examination. Assessment of patients' WHO performance status <sup>(9)</sup>. Cystoscopy and resection to confirm histological diagnosis. Complete blood count. Liver and kidney functions tests. Chest x-ray or CT chest with contrast. Pelvi-abdominal CT with contrast, and Bone scan.

**A) Treatment:**

**Radiotherapy schedule:** All patients were treated with a conformal radiotherapy to the tumor and the bladder only with a total dose of 21Gy (7 Gy/fraction in 3 fractions, a fraction every other day over one week)

**Preparation – positioning:** Patients had their lower extremities fixed and stabilized using "knee sponge" during CT simulations while lying supine. In order for the simulation to run smoothly, patients were told to keep their bladders full. A special diet with reduced fiber content was prescribed to prevent diarrhoea while they were receiving therapy as well.

**Immobilization:** Repeated CT simulator sessions were used to determine the patient's treatment position. Tattoos on the body, as well as orthogonal laser lights, assured the patient's fixation and a consistent set-up for each procedure.

**Target Volume Definition:** CTV= the bladder and the PTV = the CTV + 1.5 cm.

**Field arrangements:** A 3D conformal planning was used, and 2, 3 or 4 field techniques were permissible.

**Dose/Fractionation:** A total dose of 21 Gy was given in 3 fractions (7 Gy /fraction) in one week, a fraction every other day

**Machine:** Linear accelerator was used with energy appropriate to deliver the prescribed dose to the midline of the bladder.

**B) Treatment evaluation and follow up:**

Patients were evaluated at the end of palliative treatment. At 2 weeks following the conclusion of radiation. Patients were evaluated for toxicity and palliation as well as at 3 months for symptomatic improvement of specific complaints. Then, three-month intervals were set for follow-up visits. At each follow up visit WHO performance status, bladder and bowel related symptoms were recorded.

**Response to treatment (change in bladder and bowel related symptoms):** Symptomatic improvement, symptomatic worsening and no response.

**Bladder related symptoms that were assessed (usually disease related):** Haematuria, urine frequency, nocturia, and dysuria.

**Bowel related symptoms that were assessed (usually treatment related):** Bowel frequency, diarrhea, and bleeding/discharge.

**Table (1):** ECOG / WHO Performance status <sup>(9)</sup>

GRADE	
0	All pre-disease activities can be carried out without restriction.
1	Only mobile and capable of mild or sedentary employment, including light housework or office work, but unable to engage in physically taxing activities.
2	Able to perform all self-care tasks, but unable to perform any work activities; out and about more than half of the time.
3	Being bedridden for more than half of the waking hours of one's waking life; only able to perform minimal self-care tasks
4	Disabled to the point where they are unable to perform any self-care; they are confined to their beds or chairs.
5	Dead

**Statistical analysis**

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc., Chicago, IL, USA). Numbers and percentages are used to represent data (percent) or mean ± SD. Different qualitative factors were examined using the Chi square (X<sup>2</sup>) test. The results were judged statistically significant and highly statistically significant if the significant probability was less than 0.05, which was the threshold for statistical significance. P value ≤ 0.05 was considered significant.

**RESULTS**

The patients' average age was 72.87 ± 2.52, 83.3% of them were male and only 16.7% were female (Table 2).

Fifty percent of the studied patients showed WHO performance status, 54.1% of them were unfit for radical treatment (Table 3).

**Pretreatment bladder and bowel symptoms were compared to end-of-treatment results:**

Hematuria symptoms improved statistically significantly. Urinary frequency and dysuria symptoms did not alter significantly among the patients investigated. No significant changes in stool frequency, diarrhea, and bleeding symptoms were found (Table 4).

**Change in bladder and bowel related symptoms at 3-month assessment compared to pretreatment assessment:** Among the patients studied, hematuria symptoms improved significantly but dysuria symptoms did not alter statistically. In addition, the

symptoms of frequent bowel movements, diarrhea, and bleeding remained highly significant (Table 5).

**Improvement of individual symptoms at 3-month assessment compared to pretreatment assessment:**

The most common symptomatic improvement at 3-month assessment of the studied patients was hematuria 82.4 % followed by dysuria 72.7% while nocturia improvement was 44.4% and the urine frequency improvement was 40% (Table 6).

**Comparison of the symptomatic improvement between the end of treatment assessment and 3-month assessment:**

A three-month evaluation compared to the end-of-treatment assessment revealed no significant changes in symptoms while there was increase in percent of patients with symptomatic improvements especially in haematuria, urine frequency, nocturia and dysuria symptoms (Table 7).

**Table (2):** Age and sex distribution of the studied patients (n=24)

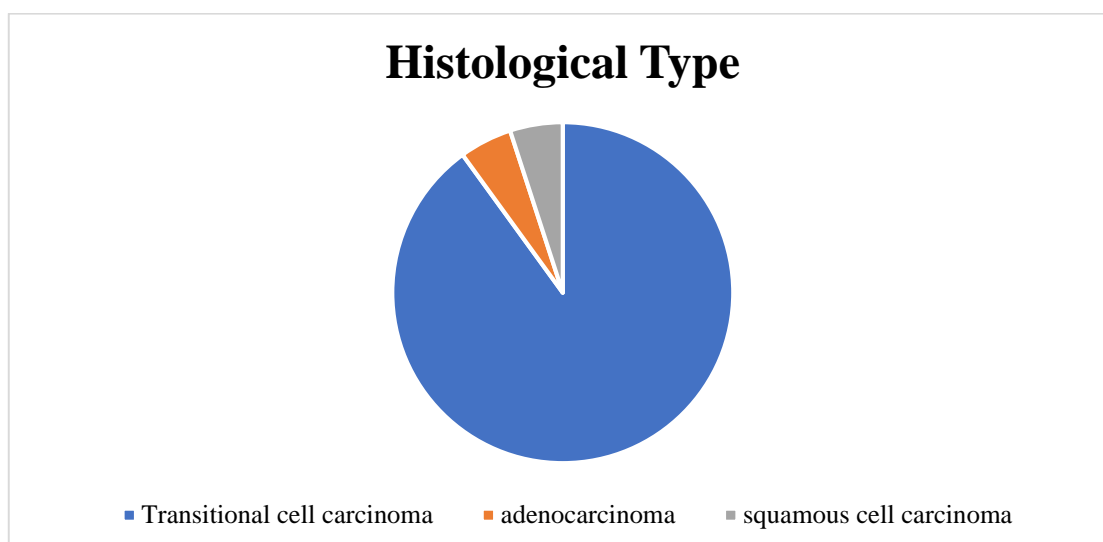
Age and sex	Studied patients(n=24)	
Age (years)	72.87 ± 2.52	
Mean ± SD	69-78	
Min-Max		
	N	%
<b>Sex:</b>		
Male	20	83.3
female	4	16.7

**Table (3):** Frequency distribution of the studied patients regarding WHO status, disease stage and resection type (n=24)

Variables	Studied patients(n=24)	
	N	%
<b>WHO performance status:</b>		
0	3	12.5
1	12	50.0
2	7	29.2
3	2	8.3
<b>Disease stage at entry:</b>		
Unfit for radical treatment	13	70.8
Too advanced for radical treatment	11	29.2

**Table (4):** Pretreatment bladder and bowel symptoms were compared to end-of-treatment results for the participants investigated in this study (n=24)

Symptoms	Studied patients(n=24)						X <sup>2</sup>	p-value
	Same		Better		Worse			
	N	%	N	%	N	%		
<b>Hematuria</b>	7	29.1	16	66.7	1	4.2	13.8	<0.001**
<b>Urine frequency</b>	13	54.2	4	16.7	7	29.2	7.9	0.02*
<b>Nocturia</b>	12	50.0	6	25.0	6	25.0	4.5	0.10
<b>Dysuria</b>	13	54.2	7	29.2	4	16.6	7.8	0.02*
<b>Bowel frequency</b>	15	52.5	2	8.3	7	29.2	16.1	0.001**
<b>Diarrhea</b>	16	66.7	1	4.2	7	29.2	21.4	<0.001**
<b>Bleeding/discharge</b>	21	87.5	1	4.2	2	8.3	47.6	<0.001**



**Figure (1):** Frequency distribution of the histological type among the studied patients (n=24)

**Table (5):** Change in bladder and bowel related symptoms at 3-month assessment compared to pretreatment assessment after exclusion of the dead patients (n=20)

Symptoms	Studied patients(n=20)						X <sup>2</sup>	p-value
	Same		Better		Worse			
	N	%	N	%	N	%		
Hematuria	3	15.0	16	80.0	1	5.0	11.8	<b>0.001**</b>
Urine frequency	10	50.0	6	30.0	4	20.0	4.2	0.12
Nocturia	8	40.0	9	45.0	3	15.0	4.6	0.09
Dysuria	11	55.0	8	40.0	1	5.0	11.8	<b>0.002*</b>
Bowel frequency	14	70.0	2	10.0	4	20.0	18.6	<b>&lt;0.001**</b>
Diarrhea	16	80.0	1	5.0	3	15.0	29.8	<b>&lt;0.001**</b>
Bleeding/discharge	18	90.0	1	5.0	1	5.0	43.3	<b>&lt;0.001**</b>
Dead patients	N			%				
	4			16.7				

**Table (6):** Improvement of individual symptoms at 3-month assessment compared to pretreatment assessment (n=24)

Pretreatment symptoms	3-month symptoms assessment	Studied patients(n=24)		Symptoms improvement
		N	%	
Hematuria (any) (n= 17)	No symptoms	14	82.4	82.4%
	Symptoms	1	5.9	
	Dead	2	11.8	
Urine frequency(≥2 per h) (n=5)	No symptoms	2	40.0	40%
	Symptoms	1	20.0	
	Dead	2	40.0	
Nocturia (≥4) (n= 9)	No symptoms	4	44.4	44.4%
	Symptoms	3	33.3	
	Dead	2	22.2	
Dysuria(any) (n= 11)	No symptoms	8	72.7	72.7%
	Symptoms	1	9.1	
	Dead	2	18.2	

**Table (7):** Comparison of the symptomatic improvement between the end of treatment assessment and 3-month assessment of the studied patient (n = 24)

Symptoms	End of treatment assessment N=24		3-month assessment N=20		X <sup>2</sup>	p-value
	N	%	N	%		
<b>Hematuria:</b>						
Same	7	29.1	3	15.0	1.2	0.5
Better	16	66.7	16	80.0		
Worse	1	4.2	1	5.0		
<b>Urine frequency:</b>						
Same	13	54.2	10	50.0	1.2	0.5
Better	4	16.7	6	30.0		
Worse	7	29.2	4	20.2		
<b>Nocturia:</b>						
Same	12	50.0	8	40.0	2.05	0.3
Better	6	25.0	9	45.0		
Worse	6	25.0	3	15.0		
<b>Dysuria :</b>						
Same	13	54.2	11	55.0	1.6	0.4
Better	7	29.2	8	40.0		
Worse	4	16.6	1	5.0		
<b>Bowel frequency:</b>						
Same	15	52.5	14	70.0	0.4	0.7
Better	2	8.3	2	10.0		
Worse	7	29.2	4	20.0		
<b>Diarrhea:</b>						
Same	16	66.7	16	80.0	1.2	0.5
Better	1	4.2	1	5.0		
Worse	7	29.2	3	15.0		
<b>Bleeding/discharge:</b>						
Same	21	87.5	18	90.0	0.2	0.9
Better	1	4.2	1	5.0		
Worse	2	8.3	1	5.0		

## DISCUSSION

Urothelial carcinoma (formerly known as transitional cell carcinoma) accounts for 90% of all bladder malignancies, making it the most common malignancy affecting the urinary system. With a median age of 69 in males and 73 in women, bladder cancer is more common among the elderly. Age has a negative impact on survival <sup>(10)</sup>.

Patients with high-risk non-MIBC and T2-T4aN0M0 muscle invasive bladder cancer (MIBC) should undergo a radical cystectomy (RC) as the standard of care. For those MIBC patients who are not candidates for radical cystectomy (RC) or who prefer to keep their bladder, trimodality therapy (TMT) combining radiation therapy (RT), transurethral resection of bladder tumor (TURBT), and concurrent chemotherapy (CMT) is an option <sup>(11)</sup>.

As a treatment option for patients with primary tumors and metastases in the brain and liver, hypofractionated palliative radiation can help alleviate symptoms such as obstruction due to the tumors, neurologic symptoms, pain caused by localized bulky

disease, and bleeding caused by tumors in the rectum and bladder. It may be as successful at relieving symptoms as lengthier courses of radiation therapy while taking up less time, costing less, and causing less harm. There may be an alternative to surgery or chemotherapy for medically inoperable patients with low performance status, such as radiotherapy (RT) <sup>(12)</sup>.

The mean age of our studied patients was 72.87 ± 2.52, 83.3% of them were male and only 16.7% were female. Nearly, the same results were considered in the study of **Whalley et al.** <sup>(13)</sup> as they reported that the cohort included 22 males and six females, with a median age of 83 years (range 58-92).

The present study showed that 50% of the studied patients showed ECOG/WHO performance status <sup>(9)</sup>, 54.1% of them were unfit for radical treatment. Our results are supported by study of **Hafeez et al.** <sup>(14)</sup> as they demonstrated that 16% of the studied patients showed ECOG/WHO performance status <sup>(9)</sup>. On the other hand, **Mohamed et al.** <sup>(15)</sup> revealed that hematuria was the most common symptom in groups B (100%) and A (90%) than in any other group. In addition, pain

symptom prevalence was highest in groups A and C, followed by groups D and B. a total of eighty patients with locally advanced or metastatic bladder cancer took part in this study, who were randomly assigned to four groups: Twenty patients were included in each group: 30 Gy in 10 fractions, five days a week, for group A, group B a week of five days of training at a rate of 20 Gy with fractions of 4 Gy each, three 7-Gyr-fractions of group C (21 Gy in total) during the course of one week, three 7-Gyr-fractions of group C (21 Gy in total) during the course of one week and three 7-Gyr-fractions of group C (21 Gy in total) during the course of one week (day after day), as well as a single fraction of 8 Gy for group D.

When cystectomy or radical radiation therapy are not an option, research shows that hypo fractionated radiation therapy (21 Gy in 3 fractions given every other day) can alleviate local symptoms for the duration of survival. A greater biological effective dose is expected to lead to better outcomes in terms of disease control in the local area. Several retrospective investigations have shown that 30 to 36 Gy in six weekly portions is effective in the treatment of MIBC <sup>(16)</sup>.

The present study showed that there were statistically significant improvement in hematuria symptoms. While there were no statistically significant changes in urine frequency symptoms and dysuria symptoms among the studied patients. Also, there were no statistically significant changes in bowel frequency, diarrhea and bleeding symptoms. At 3 months assessment, there was significant improvement in haematuria symptoms. While, there was no statistically significant change in dysuria symptoms among the studied patients. Also, there were no significant changes in bowel frequency symptoms, diarrhea symptoms and bleeding symptoms. While there was significant improvement in hematuria symptoms. The most common symptomatic improvement at 3-month assessment of the studied patients was haematuria 82.4% followed by dysuria 72.8% while nocturia improvement was 44.4% and the urine frequency improvement was 40%. There were no significant changes in symptoms at 3-month assessment compared to end of treatment assessment, while there was increase in percent of patients with symptomatic improvements especially in haematuria, urine frequency, nocturia and dysuria symptoms.

In the study of **Mohamed *et al.*** <sup>(15)</sup>, palliative radiation showed the following results in its four arms: for Arm A, complete stop of macroscopic haematuria in 75% and 90% of pain with GI and GII diarrhea in 4 (20%) patients. Arm B had a complete cessation of macroscopic hematuria in 70% and 85% of pain with GI and GII diarrhea in three (15 percent) patients, Patients in arm C experienced a full cessation of macroscopic hematuria in 78 percent of cases, as well as an 85 percent decrease in pain with GI and GII diarrhea in 4

(20%) patients, three (15 percent) individuals who had diarrhea (GI) and diarrhea (GII) with full cessation of macroscopic hematuria in arm D. It appears that the 4 arms are similar in response and toxicities but with better response in arm A and C, which is comparable to the present study, which is in line with other studies that have looked at response and side effects, such as one in which a single 10-Gy radiotherapy fraction was shown to relieve symptoms in patients with advanced cervical and endometrial primary tumors, with 60% of patients reporting that their bleeding had been controlled and that many other symptoms had been kept under control for at least six months. In the study of **Kouloulis *et al.*** <sup>(17)</sup>, hematuria was relieved in 94.8% of the 58 individuals studied, while 19 out of 58 reported no change in frequency or dysuria following treatment. All patients reported significant improvement for pain ( $P < 0.01$ ). For example, as regards visual analogue scores before and after radiation therapy. There was a median of 14 months of progression-free survival.

## CONCLUSION

Hypofractionated radiation therapy, delivered with a plan of this approach offers a good local control with acceptable toxicity in a patient population not suitable for radical bladder treatment. In this study, at the end of treatment there was statistical significant improvement in hematuria symptoms while there were no significant changes in symptoms at 3-month assessment compared with end of treatment assessment while there was increase in percent of patients with symptomatic improvements especially in haematuria, urine frequency, nocturia and dysuria symptoms.

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