PHASE II TRIAL OF HYPOFRACTIONATED EXTERNAL-BEAM RADIOTHERAPY FOR MACROSCOPIC HEMATURIA IN ADVANCED URINARY BLADDER CANCER

Muhammad Yousaf Khan, Naeem Haider, Shahid Rasul, Ahsan Mahmood, Muhammad Sohaib Nadeem

Combined Military Hospital Rawalpindi Pakistan

ABSTRACT

Objective: The objective of this study was to determine the efficacy of hypofractionated external-beam radiotherapy for management of macroscopic hematuria in patients with advanced urinary bladder cancer.

Study Design: Quasi-experimental study.

Place and Duration of Study: This study was conducted from December 2014 to May 2015, at the department of oncology Combined Military Hospital Rawalpindi.

Material and Methods: Forty patients with macroscopic hematuria grade 2, 3 or 4 associated with advanced stage (III / IV) urothelial urinary bladder cancer unfit for curative treatment, were enrolled. All patients were subjected to hypofractionated radiotherapy (21gray/3fractions). We used Common Toxicity Criteria Adverse Event (CTCAE) Version 4.0 (Hematuria) for grading of macroscopic hematuria before radiotherapy and at day 15 after radiotherapy. Two proformas were designed to get clinical information and grade of hematuria.

Results: Thirty four male and 06 female patients of advanced urinary bladder cancer with macroscopic / gross hematuria were included. Mean age was 60.22 ± 5.72 years. Out of these (n=40) 21 patients (52.5%) presented with grade 3, 17 patients (42.5%) presented with grade 4 while 2 patients (5%) presented with grade 2 hematuria. All patients received hypofractionated radiotherapy (21gray/3fractions). Of these (n=40) 27 patients (67.5%) were hematuria free with complete cessation of bleeding, 10 patients (25%) had ≥1 Grade improvement in gross hematuria) while 3 patients (7.5%) had no improvement in macroscopic hematuria on CTCAE) Version 4.0 (Hematuria).

Conclusion: Hypofractionated radiotherapy (21Gray/3Fractions) is an effective treatment modality for palliation of macroscopic / gross hematuria in advanced urinary bladder cancer patients.

Keywords: Hypo fractionated radiotherapy, Macroscopic hematuria, Urinary bladder cancer.

INTRODUCTION

Urinary bladder cancer is the 9th most common cancer worldwide with more than 12 million new cases occurring annually[1]. Of these 5.4 million cases occur in developed countries and 6.7 million cases in developing countries[1]. A serious increase in urinary bladder cancer incidence is expected in the developing countries in the next decade. This rise is attributed to ongoing shift in the geography of smoking from developed to the developing world which has resulted in an early stage tobacco epidemic in these low-middle income countries[2].

Hematuria is the most common presenting symptom in patients with urinary bladder cancer i.e. a presenting symptom in 54.7% of Pakistani men and 52.9% Pakistani women with urinary bladder cancer[3]. Mean age at presentation in our population is 55.5 years with the male to female ratio being 5 to 13. Moreover 40.2% of Pakistani patients present in advanced stage (III, IV) urinary bladder cancer[4]. Management of gross hematuria is always challenging for clinicians because of the frequent failures of local healing

Correspondence: Dr Muhammad Yousaf Khan, Registrar Oncology Dept, CMH Rawalpindi, Pakistan
Email:usaf909@yahoo.com
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pathways in patients with advanced stage urinary bladder cancer.

Radiotherapy (RT) has long been the standard non-surgical therapy for controlling active and gross hematuria in patients with urinary bladder cancer however paucity exists in literature regarding the optimal regimen with inadequate information about time, dose, and fractionation[5]. Practices ranged from a short course of large daily fractions for achieving palliation to delivering doses up to 35 Gray in the hope of prolonging the duration of palliation and possibly overall survival. Efficacy of radiotherapy up to 91% has been reported in literature[6].

Optimal fractionation scheme for the relief of gross hematuria in advanced urinary bladder cancer needs to be evaluated in our setting. This study was designed to analyze the efficacy of strict hypo fractionated RT schedule of 21 gray in 3 fractions delivered on alternate days in 1 week with the aim that if proven to be efficacious, fewer visits to the hospital would result in improvement in quality of life of the patient, facilitation for the caregivers and reduction in workload on the Linacs. Simplicity and easy scheduling of this regimen are specifically facilitative for oncologists allowing them to pay more attention to patients requiring RT with curative intent.

MATERIAL AND METHODS

This quasi-experimental study was carried out at oncology department CMH Rawalpindi from December 2014 to May 2015. Forty patients with histologically proven transitional cell carcinoma of urinary bladder stage (III/IV) disease unfit for curative treatment, having gross hematuria, age ≥18 years and both genders, Eastern Cooperative Oncology Group performance status (ECOG PS) 2 or 3 and expected survival ≥3 months were included. Patients with history of inflammatory bowel disease, past or present history of concomitant second primary and those who had received previous RT to pelvis were excluded from the study.

Sample size of 40 was calculated using WHO sample size calculator with 95% confidence level, 9% absolute precision and 91% anticipation population. Non-probability consecutive sampling technique was adopted. After enrollment and registration, patients were subjected to following diagnostic work-up: physical and radiological examinations (chest x-ray and computed tomography (CT) scan of abdomen and pelvis). ECOG PS was documented. Disease staging was done according to the 7th edition AJCC TNM classification[7].

Macroscopic / gross hematuria was graded according to Common Toxicity Criteria Adverse Event (CTCAE) version 4.08 (Hematuria) at baseline before radiotherapy and at day 15 after radiotherapy. RT was given at the oncology department, CMH Rawalpindi using Linear Accelerator (LINAC) with two parallel antero-posterior beams covering the gross symptomatic disease with a 2 cm margin. Megavoltage RT with a 6 or 15-MV photon beam was used according to patient parameters. RT consisted of 21 Gray in three fractions, given on alternate days in one week.

All clinical information and grade of hematuria were recorded on two proformas designed for the purpose. At day 15 after RT, all patients were again subjected to history, examination and grading of hematuria on CTCAE Version 4.0 (Hematuria). Data on day 15

Table-1: Results of McNemar's Test applied to post therapy outcomes.

Crosstabs			***p*-value**
Before	After		0.001
	Gross hematuria	No hematuria	
Gross hematuria	13	27	
No hematuria	0	0	

was compared with pre-treatment grade of hematuria in order to determine the efficacy of hypofractionated RT in palliation of macroscopic hematuria associated with advanced urinary bladder cancer. ≥1 grade improvement in gross hematuria was termed as efficacy of RT however post-therapy outcome was stratified in terms of improvement in gross hematuria according to CTCAE Version 4.0. Outcome was stratified in three groups i.e. patients with complete cessation of bleeding / hematuria free, patients with partial response to therapy (≥1 grade improvement in gross hematuria) and patients with no response i.e. no improvement in gross hematuria. Data analysis was computer based with the use of SPSS version 19. Frequency and percentages computed for categorical variables like gender and grade. Mean ± SD was calculated for quantitative variable like age. McNemar's test applied to compare hematuria before and after hypofractionated radiotherapy. P value of < 0.05 considered significant.

RESULTS

Forty patients with macroscopic / gross hematuria and advanced urinary bladder cancer were enrolled in which 34 were males and 6 females (Figure-1). Mean age was 60.22 years (SD=5.72). 21 patients (52.5%) presented with grade 3, 17 patients (42.5%) presented with grade 4 while 2 patients (5%) with grade 2 hematuria. All patients received hypofractionated RT (21gray / 3fractions). 27 patients (67.5%) were hematuria free with complete cessation of bleeding. 10 patients (25%) achieved partial response (≥1 Grade improvement in gross hematuria) while 3 patients (7.5%) had no improvement in macroscopic / gross hematuria assessed on CTCAE Version 4.0 (Hematuria) (Figure 2). McNemar's test applied to post therapy outcomes related to pre-therapy gross hematuria and results (shown in Table-1) were found to be statistically significant (*p* vale =0.01).

DISCUSSION

Although urinary bladder cancer is more prevalent in developed communities, its incidence is increasing in developing and low socio-economic countries[2]. Current early stage tobacco epidemic in developing world is thought to be contributory factor to changing geography of this disease[9]. Gross / macroscopic hematuria being life threatening and distressing for patients, is the most common presenting symptom and complication of urinary bladder cancer[3]. Contrary to the figures in developed countries where >80% patients present with stage I/II disease, unfortunately >40% patients in Pakistan present with advanced stage (III & IV) disease[4].

Gross hematuria / bleeding is presenting symptom in >50% of patients in Pakistan[3] which is always a challenge for clinicians specifically due to failure of local hemostatic and healing pathways. In some patients persistent blood loss may be life threatening. Different strategies including bladder irrigation and surgical interventions including vessel ligation, cystoscopy and interventional radiological procedures have been adopted for control of macroscopic hematuria and blood loss. In this scenario radiotherapy has proved to be a

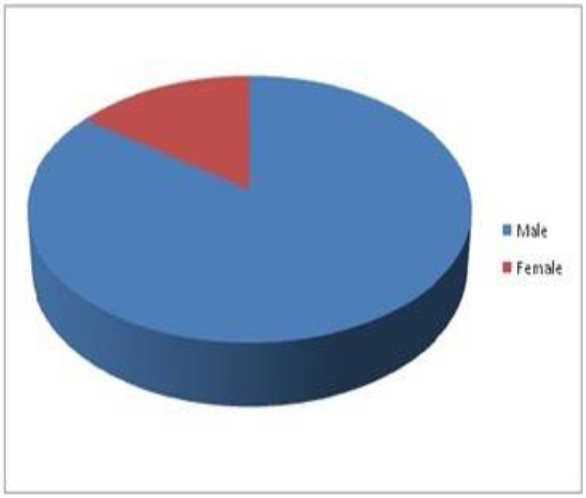

Figure-1: Male: Female ratio of the patients.

potential and practical therapeutic option for controlling local tumor bleeding[10]. RT has been used in various situations and has produced clinically and statistically significant response where other local therapies have failed[11]. External beam RT has been tried as a first-line treatment

for controlling active bleeding associated with tumors. It has been used in various fractionation schedules (hypofractionated or conventional). Radiotherapy (RT) is a safe and effective treatment for cancer related bleeding and has produced clinically and statistically significant control when used as a hemostatic agent[11]. Exact mechanism of radiation acting as a hemostatic agent is not known. Malignancy itself is a pro-thrombotic state exactly as antineoplastic therapies[12]. Probable mechanism of radiotherapy might be local thrombus formation via injury to the vascular endothelium associated with increase in the levels of von Willebrand factor[6]. Gray delivered in 3 Fractions on alternate days of a week. Although not the gold standard, 21 gray / 3 fractions has been encorporated as the recommended regimen by Royal College of Radiologists (RCR) United Kingdom for gross hematuria associated with bladder cancer. This study may explore venue for future research to establish role of hypofractionated radiotherapy as hemostatic agent for management of cancer related bleeding e.g. macroscopic hematuria associated with advanced urinary bladder cancer.

Rasool M et al[6] published their study using external beam radiotherapy as hemostatic agent for gross hematuria associated with advanced

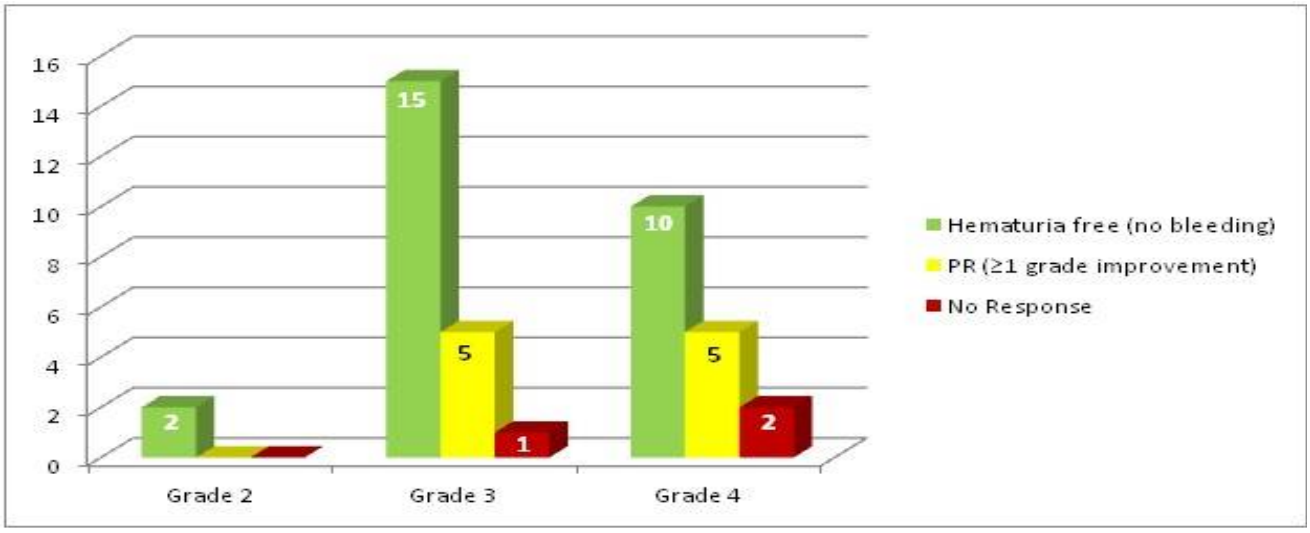

Figure-2: Grade-wise distribution of post-RT outcomes [Hematuria free (no bleeding), Partial Response (PR) & No Response).

Moreover soluble mediators released secondary to anticancer therapies also act on endothelial cells resulting in altered and impaired normal antithrombotic and anti-adhesive functions. Various fractionation schemes have been tried for palliation of gross hematuria associated with advanced urinary bladder cancer however paucity exists in literature regarding optimum dose and fractionation schedules of radiotherapy. High doses up to 35 Gray have been tried with intent to achieve an improved and more durable response rates and possibly survival advantage. In this series we have adopted a strict hypofractionated short protocol consisting of 21 urinary bladder cancer[6]. They used Cobalt 60 teletherapy unit. Two dose/fractionation schemes were used i.e. 20Gray/5Fractions and 15Gray/5 Fractions. They reported 88% response rate with treatment well tolerated and no intermission. In contrast we used modern Mega Voltage Linear Accelerator (LINAC) for radiotherapy instead of Cobalt 60 teletherapy unit. Results of our study differ in regards that 67.5% patients in our series achieved complete cessation of bleeding, whereas in the above mentioned study 88% of the patients were hematuria free after radiotherapy. This difference can possibly be attributed to the diverse

population of cancer patients enrolled in their study i.e. 52% of patients with non-bladder cancer.

Lacarrière E et al used even higher doses of external beam radiotherapy i.e. 30 Gray/10 Fractions delivered over two weeks, as standard regimen in their study[5]. They found 69% of patients hematuria free at 2 weeks after treatment. Although the results of this study are similar to ours, there is a significant difference in the regimen used in our study involving a strict hypofractionated protocol delivering lower dose (21Gray) delivered in only 3 patient visits and achieveing equivalent response rate.

CONCLUSION

Results of this study conclude that hypofractionated radiotherapy with 21gray/3fractions protocol is an effective modality for management of macroscopic hematuria associated with advanced stage urinary bladder cancer. Although this regimen appears to be rapidly effective, cost-effective and involves lesser patient visits, durability of its effect has not been evaluated in our study. Larger cohorts and prospective trials are needed to compare efficacy of this regimen with other radiotherapy protocols and durability of response.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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