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Original Research Paper

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EFFECTIVENESS OF PALLIATIVE RADIATION FOR MACROSCOPIC HEMATURIA CAUSED BY UROTHELIAL CANCERS

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KEYWORDS :

INTODUCTION

Urothelial cancers (UC) are one of the most commonly occurring tumors in the world. Over a half of the patients with UC show recurrence or progressive disease even after definitive treatments[1]. In patients with UC, hematuria, especially macroscopic hematuria (MH), is the most common presenting symptom; it is often intractable, adversely affecting the quality of life of the patients. Uncontrollable MH is sometimes fatal. Several treatment approaches have been suggested, limited by poor treatment compliance or absence of proven efficacy, including intrvesical formalin treatment, alum irrigation, intravesical instillation of prostaglandin, hydrostatic bladder distention, urinary diversion and embolization[2].

Palliative radiation therapy (RT) is sometimes used as a treatment option, with the reported treatment response rate varying from 45% to 100%[3]. Only a few report of retrospective analysis of palliative RT for hematuria in patients with urothelial carcinomas have been published. In 2016, a survey conducted by the palliative RT working group of the Japanese Radiation Oncology Study Group (JROSG) suggested that hemostatic irradiation is rarely performed and further, that the number of fraction used varied significantly among facilities[4].

Hence, the purpose of this study was to conduct a retrospective analysis of the efficacy and toxicity of palliative RT for MH in patients with urothelial cancer at Swami Ram Cancer Hospital and Research Institute, Haldwani, Uttrakhand.

MATERIAL AND METHODS

Patients

The study was conducted in 40 urothelial cancer patients with MH who received palliative RT between 2014 and 2019 at Swami Ram cancer Hospital & Research Institute, Haldwani. MH is defined as blood in the urine that can be seen with the naked eye. The patients were retrospectively enlisted from our record section, and patients in whom the MH was caused by direct bleeding from the bladder tumor, which was established, based on the clinical and/or diagnostic imaging findings, were analyzed. The clinical tumor stage was determined based on the findings of contrast-enhanced computed tomography (CECT) and/or magnetic resonance imaging (MRI).

Complete resolution of the MH after RT was deemed as representing treatment success, while reappearance of the MH was considered as relapse. Adverse events were classified according to the Common Terminology Criteria for Adverse Events version 4.0.

The overall survival (OS) time was defined the period from the initiation of palliative RT to the last follow-up examination or death. The hematuria free survival (HF) time was defined as the period from complete resolution of the MH to the recurrence of MH, death, or the last follow-up examination. The variables used of the statistical analysis were the age, gender, ECOG performance status (PS), hemoglobin, serum creatinine, history of pre-treatment blood transfusion, and history of chemotherapy prior to the palliative RT.

RESULTS

The characteristics of the 40 patients included in the analysis are shown in table1. The study population included 32 males and 8 females, with a median age of 66 years (range 43-81 years); 24 patients (60%) had an ECOG PS of 0 to 1. The dominant histology was transitional cell carcinoma (34 patients; 85%) and the primary site of the tumor was the bladder in 36 patients (90%). Of the 40 patients, 38 were not suitable candidates for radical surgery because of advanced age (14; 35%), poor general condition (8; 20%), widespread metastasis (5; 12.5%), recurrence after surgery (6; 15%), or patient's refusal to undergo definitive treatment (5; 12.5%).

The median hemoglobin level prior to the palliative RT was 8.1 g/dl (range; 5.7-11.2 g/dl).

Table-1

Patient Characterstics Total (n=40)			Tumor Characterstics	T Stage	
	Age (years)			T1	0
	>70	23		T2	01
	<70	17		T3	27
	Gender			T4	12
	Male	32		N Stage	
	Female	08		0	01
	1	24		1	19
	2	11		2	07
	3	04		3	02
	4	01		X	11
				Stage	
				Locally advanced	35
				Metastatic	05
				Histology	
				TCC	34
				Unknown	06
				Tumor Grade	
				1	09
				2	13
				3	07
				Unknown	11

The median hemoglobin level in the 16(40%) patients who had received blood transfusion prior to the RT was 7.8g/dl (range: 5.7-10.8 g/dl),while that in remaining 24(60%) patients was 9.8 g/dl (range: 6.9-11.2 g/dl) (p=0.02).All the patients received palliative RT alone,as follows: 15 Gy in 3 fractions in 16 (40%) patients, 20Gy in 05 fractions in 14(35%) patients, and 30Gy in

10 fractions in 10(25%). The fractionation scheme was determined by the condition of the patients and/or the irradiated bladder volume. The median follow-up period after completion of the RT was 72 days (range:23-546 days).

Complete resolution of the MH was achieved in 29 patients (72.5%). The median interval from the start of the RT to complete resolution of the MH was 13 days (range:4-79 days). At 2 weeks after the start of the RT, 24 (60%) patients showed no evidence of MH. Among the 03 patients who failed to show resolution of the MH, 01 died of multiple organ failure at the age of 76 years, after surviving for 11 days; the remaining 02 patients survived for 54 and 91 days, respectively. No significant intergroup differences in the rate of resolution of the MH were found, including between those with/without pretreatment blood transfusion history (14/16 vs. 21/24, P=0.53). 18 of the 29 (62%) patients who showed resolution of the MH developed recurrence MH, and the median period to recurrence of MH was 107 days (range: 36-582 days). Among the 09 patients with recurrent MH, 02 patients died within a week of recurrence due to severe anemia.

The median survival duration of the 09 patients was 263 days (range: 54-682 days).

The OS rate and HFS rate are shown in Fig.01. The 3 month OS and HFS rates were 71.1% and 52.1%, respectively. There were significant differences in both the 3 month OS rate and 3 month HFS rate between patients with and without a history of pretreatment blood transfusion (OS rate: 62.5% vs. 76.9%, P= 0.005, HFS rate: 34.6% vs 61.5%, P=0.03) (Fig.02). Among these factors, patient with a history of blood transfusion prior to the palliative RT had significantly worse HF and OS rates (P=0.01/P=0.04). The period from the start of treatment to the day of resolution of the MH was significantly longer in the patients with T3 and T4 disease than in those with T2 disease (median duration: 20 days and 6 days, respectively; P=0.01).

Figure-1 Overall survival (OS) and Hematuria free survival (HFS) for 3 months

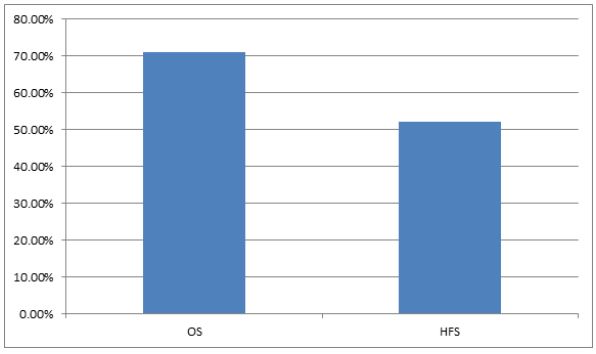
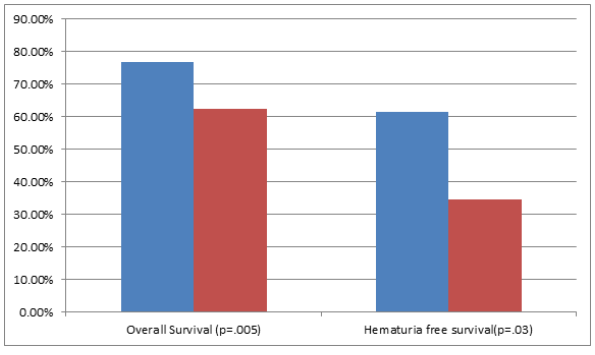


Figure-2 Differences on basis of pretreatment blood transfusion in OS and HFS



None of the patients developed grade 04 or grade 05 toxicities. The toxicities in the 40 patients include 2 95%) patient with grade 01 urinary pain, 01 (2.5%) patient with grade 01 dermatitis, 05 (12.5%) patients with grade 01 diarrhes, and 06 (15%) patients with grade 01 increased urinary frequency. One patient each (2.5%) developed grade 02 urinary pain and grade 03 diarrhea.

DISCUSSION

The result of this retrospective single-institution study indicated that palliative RT may be an effective treatment method to manage MH caused by tumor recurrence or tumor progression, with acceptable toxicity.

Surgery is the standard treatment of choice for the management of advanced urothelial cancer[6] while definitive RT with or without chemotherapy has also been used as an alternative approach[7].However no optimal treatment option have been established and treatment option are also limited, especially for patients who have no opportunity to undergo radical surgery or other treatments with radical intent, and those who develop loco-regional recurrence after radical treatments, including surgery and RT.

Palliative RT still has a place due to its high time efficacy, good tolerance, and good cot-performance characteristics[8]. The main aim of palliative RT is to provide adequate symptomatic relief throughout a patient's anticipated life span. The efficacy of palliative RT for MH in patients with urological cancers has been reported in several retrospective studies[3 5]. In regard to the mechanism induced by RT, platelet aggregation, injury of vascular endothelial cells, and induction of vascular embolization have been considered as the main underlying mechanisms, in addition to tumor shrinkage [9,10]. To obtain symptomatic relief or hemostasis, a high RT dose, as in definitive RT, is not necessary. Only one randomized controlled trial, MRC BA09[11] , has been conducted until date to evaluate the efficacy and toxicity of palliative RT for symptomatic improvement in patients with bladder cancer who are deemed as unsuitable candidates for curative treatment option this tudy, 500 patients from 20 centers received palliative RT at a dose of 35 Gy in 10 fractions or 21 Gy in 3 fractions. Symptomatic improvement was noted in approximately 68% of patients. Among the patients suffering from hematuria, 88% were alleviated. The median time to deterioration of one more bladder-related symptom from the start of RT was 9 months.

However, the optimal total radiation dose or fractionation schema have not been established, especially for palliative RT to treat MH, due to the limited clinical data available from retrospective studies In a survey conducted in the Netherlands, 9 distinct palliative RT schedules for bleeding tumors were indentified, including 1x8 Gy, 2x8 Gy, 5x4 Gy, 5x5Gy and 10-13x3 Gy[12] . In Japan also, the fractionation schedule for palliative RT used to achieve resolution of MH varied widely according to the sites of the primary tumor, such as gastrointestinal and genitourinary tumors, and/or the patients' general condition. The most frequently used fractioned scheme was 30 Gy administered in 10 fractions.

In patients in a poor general condition with a limited survival prognosis, hypo fractionated RT may be beneficial[13,14]. Several studies have suggested that short-course RT was as efficient as RT administered in a higher number of fractions or long-course RT for obtaining bleeding control. Both longer RT regimens (>5fraction) and shorter regimens (<5fractions) exerted equal hemostatic effect (P=0.497) for an equal duration (P=0.652). Longer regimens, However, caused frequent treatment interruptions and increase in hospital days (22.2% vs 5.3%, P=0.020). Similarly, in the MRC BA09 study, there was no difference in the survival, symptomatic improvement rate or toxicity between two hypo fractionated RT schedules (35 Gy in 10 fractions v 21 Gy in 3 fractions).

Lacarriere et al[3]. Compared 2 RT schedules retrospectively: the tandard treatment arm consisted of 30 Gy administered in 10 fractions over a period of 2 weeks and study treatment arm consisted of a hypo fractionated regimen of 20 Gy administered in 5 fractions over a period of one week to patients with ECOG P>2. No statistically significant difference was observed in respect of the MH control rate at 2 weeks after the start of treatment (54% vs. 79%, P=0.139) or rate of relapse of MH at 6 months (62% vs. 71%).

In the current study, resolution of the MH was noted in 72.5% of all patients, and 60% of the patients showed no sign of MH after 15 of palliative RT. The duration of hemostasis lasted for about 3 months. In addition, the toxicity of palliative RT was also acceptable only 1 patient developed grade 3 diarrhes. In addition, the results of the current study showed that the time to resolution of the MH was longer in the patients with T3 or T4 disease as compared to those with T2 disease, and the majority of patients who developed recurrent hematuria were patients with T3 or T4 disease. This may indicated the possibility of the need for a higher dose of radiation in patients with more advanced or larger tumors. The outcome in patients with/without a history of pre-treatments blood transfusion history differed, and probable reason is deterioration of the patient's condition before the palliative RT manifested it efficacy, Several limitations of this study must be pointed out, including the small sample size, retrospective nature of the study and short follow-up time. Therefore, further accumulation of patients is needed to arrive at a more concrete conclusion.

CONCLUSIONS

Our study findings suggest that palliative RT could be an effective and safe treatment option to control macroscopic bleeding in patients with urothelial cancer. RT plays a pivotal role in the management of urothelial cancer, while palliative RT needs more attention. To date only a handful of studies have shown the effects of palliative RT.

Further research is required to determine the optimal individual treatment schedule and to select appropriate candidate for treatment.

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