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Palliative Hypofractionated Radiotherapy in Urinary Bladder Cancer

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Abstract

Aim: Evaluation different hypofractionation dose schedules for palliation of haematuria and pelvic pain in urinary bladder cancer. **Patients and methods**: Eighty patients with locally advanced and metastatic bladder cancer, were divided into 4 arms, Each group had 20 patients as the following ,arm A 30 Gy with fraction size 3 Gy in 10 fractions, five days/week, Arm B 20 Gy with fraction size 4 Gy in 5 fractions, five days/ week, Arm C 21 Gy with fraction size 7 Gy in 3 fractions, day after day in 1 week. And Arm D 8 Gy in single fraction. The primary end points were duration of such symptoms improvement and toxicity. **Results**: Hypofractionated radiotherapy for palliative management of hematuria and pain from bladder cancer showed improvement and acceptable toxicities. The response to palliative radiotherapy in 4 arms showing the following the arm A complete stop of macroscopic haematuria in 75% of patients and 90% of pain with GI and GII diarrhea in 4 patients, arm B complete stop of macroscopic (gross) haematuria in 70 % and 85% of pain with GI and GII diarrhea in 3 patients, in arm C complete stop of macroscopic haematuria in 78 % and 85% of pain with GI and GII diarrhea in 4 patients and in arm D complete stop of macroscopic haematuria in 65 % and 75% of pain with GI and GII diarrhea in 3 patients from our results the 4 arms are nearly similar in toxicities and more in response in arm A and C without statistical significance. **Conclusion**: Hypofractionated radiotherapy is effective to alleviate tumor-related pain and hematuria with acceptable toxicities and decrease burden in patients and machines.

Introduction

In Gharbia Governorate; Egypt the incidence of cancer bladder was estimated to be 24.4 per 100,000 population [1] and urinary bladder cancer accounts for 30.3% of all cancer incidence [2-3]. Painless haematuria is the commonest symptoms of bladder cancer [4] and incidence of gross haematuria represents 10 -20 % [5-8].

Radiotherapy with palliative intent commonly makes up 40% to 50% of the workload of any radiation oncology department [7–8]. The hypo-fractionation, usually implies daily doses that ranging between 3 Gy and 8 Gy per fraction. The human body structures are divided into early responding and late responding tissues which depends on whether they are more to manifest radiation damage during time of treatment course or months to years later, and usually fraction s of larger size are associated with greater damage to the late responding tissues [9].

The patients with advanced bladder cancer who are treated for symptom palliation commonly have limited survival, physical discomfort with transportation, and emotional physical discomfort from prolonged radiotherapy courses and financial burden. Make shorter courses exemplify common sense end-of -life care, especially because most patients who are treated for symptom palliation will not survive to face the increased risk of long-term side effects associated with hypofractionated regimens [10]. Study by Hall et al was delivery of a single fraction 10-Gy radiotherapy was shown to palliate advanced cervical and endometrial primary tumors, with bleeding controlled in 60% of patients and with many of the palliated symptoms remaining under control till end of life [11].

A comparison of a hypofractionated course (short course) and a more prolonged course of radiotherapy for symptomatic bladder cancer was done by Srinivasan et al, showed an improvement in symptom control with shortened course. Patients with grade II or III, stage T3 or T4N0M0 tumors that caused pain and/or hematuria received either 45 Gy in 12 fractions over 26 days or 17 Gy in 2 fractions over 3 days. The rates of clearing of hematuria and relief from pain were 59%

and 73%, respectively, in the 2-fraction group and 16% and 37%, respectively, in the 12-fraction group. The side effect profiles of the 2 regimens were similar and mild, whereas the survival of patients in the shorter course group was just under 10 months compared with almost 15 months for patients in the longer course group [12]. A second prospective, randomized trial compared hypofractionated regimens of either 35 Gy in 10 fractions or 21 Gy in 3 fractions for patients with locally advanced, inoperable bladder carcinoma: Seventy-one percent of patients who received 35 Gy and 64% of patients who received 21 Gy had symptomatic relief. Along with similar palliation rates, neither side effects nor overall survival rates differed between the two groups [13]. We completed a prospective study of advanced bladder cancer at our institutions using different dose schedules and primary end point is assessment of symptoms palliation and toxicities of every dose schedule. bleeding controlled in 60% of patients and with many of the palliated symptoms remaining under control till end of life [11].

A comparison of a hypofractionated course (short course) and a more prolonged course of radio-therapy for symptomatic bladder cancer was done by Srinivasan et al, showed an improvement in symptom control with shortened course. Patients with grade II or III, stage T3 or T4N0M0 tumors that caused pain and/or hematuria received either 45 Gy in 12 fractions over 26 days or 17 Gy in 2 fractions over 3 days. The rates of clearing of hematuria and relief from pain were 59% and 73%, respectively, in the 2-fraction group and 16% and 37%, respectively, in the 12-fraction group. The side effect profiles of the 2 regimens were similar and mild, whereas the survival of patients in the shorter course group was just under 10 months compared with almost 15 months for patients in the longer course group [12]. A second prospective, randomized trial compared hypofractionated regimens of either 35 Gy in 10 fractions or 21 Gy in 3 fractions for patients with locally advanced, inoperable bladder carcinoma: Seventy-one percent of patients who received 35 Gy and 64% of patients who received 21 Gy had symptomatic relief. Along with similar palliation rates, neither side effects nor overall survival rates differed between the two groups [13]. We completed a prospective study of advanced bladder cancer at our institutions using different dose schedules and primary end point is assessment of symptoms palliation and toxicities of every dose schedule.

Patients and method

Study design, settings and time

A prospective cohort study for patients with bladder cancer received radiotherapy during the period from November 2010 to April 2014 at Clinical Oncology and Nuclear Medicine Department, Zagazig University, Fakous Cancer Center and Clinical Oncology Department, Menoufia university

The target groups

80 patients with T3-T4N0, N1, M0, M1 bladder cancer were chosen during the studied period with the following inclusion criteria; pathologic proven carcinoma of bladder, European Co -operative Oncology Group (ECOG) performance status 3 and 4, American Joint Committee on Cancer (AJCC) stage III and IV, acceptable complete blood count, no prior pelvic radiotherapy, unfit for chemotherapy or surgery at time of treatment, informed consent.

Technique of Radiotherapy was delivered as the following, clinical target volume CTV= The bladder, The PTV = The CTV + 1.5 cm and Field Arrangement 2 parallel opposing (anterior and posterior). The given doses was as in the following schedule; arm A 30 Gy with fraction size 3 Gy in 10 fractions, five days/week, Arm B 20 Gy with fraction size 4 Gy in 5 fractions, five days/week, Arm C 21 Gy with fraction size 7 Gy in 3 fractions, day after day in 1week and Arm D 8 Gy in single fraction. Each group composed of 20 patients and radiotherapy was delivered by external beams with Cobalt-6o and linear machines availability.

All patients underwent complete history and physical examination, biopsy and histopathologic proven carcinoma, computerized tomography (CT) scan with contrast and/or MRI pelvis to determined the tumors extensions, chest x-ray and/or CT chest if indicated, bone scan if indicated, complete blood picture, liver functions and renal functions tests. Patients characteristics are shown in table (1).

Evaluation of Treatment

We evaluated the patients before, during and every month after completion of treatment in term effectiveness of palliative radiotherapy on bladder cancer. The duration of response is the time from end of haematuria till recurrence of symptom and toxicities. Assessment was according to RTOG acute radiation scoring criteria [14] and Pain assessment according visual analogue scale (VAS) from local bladder infiltration by tumours [15].

Ethical consideration

Informed consent was taken from each participant after explaining to them the aim of this work.

Data management

The collected data were presented, summarized, tabulated and analyzed using computerized software statistical packages (EPI -info version 6.04 and SPSS version 19). $P < 0.05$ was considered to be statistically significant at 95% confidence

interval. Chi-square and Fisher exact tests were used to compare proportions. Paired t-test was used to compare means. In addition to logistic regression analysis for risk factors.

Results

The majority of patients were aged above 60 years in all the studied groups with range between 53 to 70 and median 62 (table 2). Table (3) shows that the male patients represented higher percentages in all groups than females and highest sector was in group C (80%) Heamaturia constituted the main symptom among all the studied groups which was more in group B (100%) and A (90%) respectively. Also pain symptom had high percentages among group A and C followed by group D and group B respectively (table 4).

Table 1. Distribution of patients characteristics

Variable	No of patient	%
Center		
Clinical Oncology Dept.	40	50
Fakous Cancer Center	20	25
Menoufia Clin Onc Dept.	20	25
Age		
Median	62	
Range	53-70	
Gender		
Male	58	27.5
Female	22	72.5
Performance status		
PS III	20	25
PS IV	60	75
Pathology Transitional		
GII	15	18.8
GIII	35	43.7
Squamous		
GII	14	17.5
GIII	16	20.0
Stage		
III	35	43.75
IV	45	65.25

Table 2. Age distribution among the studied groups

Age	Group A		Group B		Group C		Group D		Chi P value
	No.	%	No.	%	No.	%	No.	%	
51-60	8	40	7	35	5	25	3	15	Chi square = 3.6 p = 0.307
≥60	12	60	13	65	15	75	17	85	
Total	20	100	20	100	20	100	20	100	
Range	55-70 years		58-67 years		50-65 years		53-70 years		
Median	61		62		60		65		

Table 3. Sex distribution among the studied groups

Gender	Group A		Group B		Group C		Group D		Chi square P value
	No.	%	No.	%	No.	%	No.	%	
Male	14	70	12	60	16	80	14	70	Chi square = 1.9 p = 0.592
Female	6	30	8	40	4	20	6	30	
Total	20	100	20	100	20	100	20	100	

Table 4 frequency distribution of Clinical presentation among the studied groups after palliative radiotherapy.

Groups	Group A		Group B		Group C		Group D		Chi square P value
	No.	%	No.	%	No.	%	No.	%	
Haematuria	18	90	20	100	12	60	15	75	Chi square =12.2 P=0.006*
Pelvic pain	10	50	6	30	10	50	8	40	Chi square =2.3 P=0.522

The response to palliative radiotherapy in our 4 arms showing the following, in the arm A complete stop of macrscopic haematuria in 75% and 90% for pain with GI and GII diarrhea in 4 patients, arm B complete stop of macroscopic haematuria in 70 % and 85% of pain with GI and GII diarrhea in 3 patients, in arm C complete stop of macroscopic haematuria in 78 % and 85% of pain with GI and GII diarrhea in 4 patients and in arm D complete stop of macroscopic haematuria in 65 % and 75% of pain. The duration of response ranged from 3.5 to 7 months with median 5.5 month. In 80% of patients the palliation continues till end of life with good quality of life. The improvement of performance status of all patients was observed in 30% of patients in all therapeutic groups, with no statistically significant among groups A, B, C and D. the response was more in transitional carcinoma than squamous carcinoma. There is improvement in anemia of all patients after stop of haematuria and decrease needing for blood transfusion and decrease in doses of analgesics with decrease hospitalization and decrease cost of supportive care with acceptable toxicities GI and GII diarrhea in 4 patients in group A, 4 patients in arm B, 6 patient in arm C and 4 patients in arm D with no statistically significant difference between groups, from our results the 4 (20%) arms are nearly similar in response and toxicities but more in response in arm A and C, with the best loss of pain and haematuria with no statistically significant difference between groups after 1 month.

Discussion

The radiotherapy can be effective in treating symptoms associated with local progression of bladder cancer, regarding disease progression even when an inoperable or locally advanced tumor, Radiotherapy can also alleviate tumor-related pain and pressure, and control hematuria associated with tumor hemorrhage [16].

Hypofractionated radiotherapy provides efficient palliation of end-of-life symptoms. Many patients who receive treatment near the end of life require an intense effort to achieve transportation out of the home; thus, the optimal intervention for this group is 1 visit that includes consultation, dose planning, and delivery of a single-fraction treatment; a series of tasks that may be completed within 2 hours at most radiotherapy centers. If additional fractions are necessary, then those treatments should require only approximately 15 minutes each. Symptomatic relief after radiation therapy occurred 7 to 10 days, it achieves its full benefit within 1 month, and it lasts for most of a patient's remain in lifetime [17].and palliative radiotherapy is cost effective compared with systemic chemotherapy. [17].

In our study the response to palliative radiotherapy in our 4 arms showing the following, arm A complete stop of macroscopic haematuria in 75% and 90% of pain with GI and GII diarrhea in 4 (20%) patients, arm B complete stop of macroscopic haematuria in 70 % and 85% of pain with GI and GII diarrhea in 3 (15%) patients, in arm C complete stop of macroscopic haematuria in 78 % and 85% of pain with GI and GII diarrhea in 4 (20%) patients and in arm D complete stop of macroscopic haematuria in 65 % and 75% of pain with GI and GII diarrhea in 3 (15%) patients from our results the 4 arms are nearly similar in response and toxicities but more in response in arm A and C which is comparable to the following studies in response and toxicities, first study ,the delivery of a single, 10-Gy fraction of radiotherapy was shown to palliate advanced cervical and endometrial primary tumors, with bleeding controlled in 60% of patients and with many of the palliated symptoms remaining under control for the remainder of the patients' lifespan. Once again, however, late bowel toxicity was a concern for those who had a life expectancy of >9 months [11]. A second prospective, randomized trial compared hypofractionated regimens of either 35 Gy in 10 fractions or 21 Gy in 3 fractions for patients with locally advanced, inoperable bladder carcinoma: Seventy-one percent of patients who received 35 Gy and 64% of patients who received 21 Gy had symptomatic relief. Along with similar palliation rates, neither side effects nor overall survival rates differed between the 2 groups [13].

Conclusion

Short course radiotherapy founded to be effective to alleviate tumor-related pain and hematuria with acceptable toxicities in patients with locally advanced and metastatic bladder cancer with decreasing load to machines and decrease number of visits of poor performance status and elderly patients which is good cost-effective to our low resources areas.

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