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Treatment Related Toxicity of Hypofractionated Radiation Therapy with Capecitabinein Muscle Invasive Bladder CancerElderly Patients

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ABSTRACT

Background: Bladder cancer can be clinically classified by stage as either muscle invasive or non-muscle invasive based on involvement of the detrusor muscle.Radical cystectomy and selective bladder preserving therapy are bothconsidered standard of care treatment options for non-metastatic, muscle-invasive bladder cancer. **Purpose:** To decrease the toxicity of concurrent chemoradiation in old age non metastatic bladder cancer patients.**Patients and method:** 24 Patients ineligible for radical cystectomy or high-intensity chemoRT underwent transurethral resection of bladder tumour followed by capecitabine (median 850 mg/m2/d BID) and hypofractionatedradiotherapy (total dose of 55 Gy was given in 25 fr) at the Clinical Oncology and Nuclear Medicine department, Zagazig University Hospitals from August 2019 to August 2021. **Results:**A total of 24 patients (with a median age of 67 years) were treated. Only grade 1 (anaemia in one patient (4.2 %), leucopenia in three patients (12.5%), hyperbiliribinemia in two patients(8.3 %), grade 2 (diarrhea in two patients (8.3 %), skin toxicity in one (4.2 %) of patients, hand foot syndrome in two patients (8.3 %), and acute urogenital toxicity were present;G1 dysuria was reported by 58.3%, G1 frequency by 45.8%, G1 urgency by 37.5 %, and G1 hematuria by 29.1%.**Conclusions:** For elderly patients, Hypofractionated chemo-RT with capecitabine is a tolerable regimen with effective local control that may increase the utilization of definitive treatment for bladder cancer**.**

Keywords:Cancer bladder, Elderly ,Hypofractionated radiotherapy,capecitabine,Toxicity.

INTRODUCTION

In Egypt, where bladder cancer is the second most common malignancy among men and and it comes as the fourth type among both sexes (7.2%) according to the recent Global Cancer Observatory with a peak incidence at 85 years, bladder cancer is a disease of the elderly (**1).** Bladder cancer can be clinically classified by stage as either muscle invasive or non-muscle invasive based on involvement of the detrusor muscle. Around 70-85% of patients present with superficial disease and are now commonly named non-muscle invasive bladder cancer (NMIBC) , Muscle invasive bladder cancer (MIBC) (T2-T4) on the other hand represents a potentially grave danger **(2).** Radical cystectomy and selective bladder preserving therapy are bothconsidered standard of care treatment options for non-metastatic, muscle-invasive bladder cancer **(3)**.

Although it is clear that CRT is superior to radiation alone the ideal concurrent chemotherapy regimen has not yet been determined, No comparative radiosensitizer data for the treatment of MIBC exist and CRT is currently administered with cisplatin, mitomycin-C (MMC) plus 5- fluorouracil (5-FU), gemcitabine or tumor hypoxia-reducing drugs such as carbogen and nicotinamide**(4).** However, not all patients are candidates to receive these chemotherapies due to pre-existing medical comorbidities or poor performance status so for such patients; single agent capecitabinewithhypofractionated radiotherapy may provide a more suitable therapeutic ratio (**5).** Capecitabine is an oral prodrug that is converted to 5-FU ,The choice of capecitabine over 5-FU

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is primarily based on ease of administration, avoiding hospital admission, the need for intravenous catheters and infusion pumps, and administration related complications **(6).**The present study aimed to decrease the toxicity of concurrent chemoradiation in old age non metastatic bladder cancer patients.

PATIENTS AND METHODS:

This prospective study was conducted at Clinical Oncology and nuclear medicine department, Zagazig University Hospitals from August 2019 to August 2021 on 24 patients with locally advanced non metatstatic muscle invasive bladder cancer,The patients were treated by Hypofractionated Radiotherapy concurrent with capecitabine.

Inclusion criteria:

Patients with locally advanced Non-metastatic or locally recurrent muscle invasive bladder cancer , Pathologically proved transitional cell carcinoma , ECOG performance status ≥2 , Patients not previously received chemotherapy or radiotherapy , Unfit for radical surgery ,Unfit for high-intensity chemoRT with cisplatin or 5-FU/MMC , Age ≥ 65 years , Medically unfit for high intensity chemotherapy regimens , All patients diagnosed by transurethral resection of bladder tumor (TURBT).

Exclusion criteria

Patients with metastatic bladder cancer , Fit for surgery or high-intensity chemoRT with cisplatin or 5-FU/MMC , previously received chemotherapy or radiotherapy were excluded.

Treatment:

The patients underwent CT-simulation, in supine position, using “knee sponge” for fixation and stabilization of lower extremities. Patients were instructed to be with empty bladder during simulation and during the course of treatment, multi-slice CT was done every 0.3-0.5cm on the same simulated position. GTV = pre-TURBT tumor volume (as assessed on cystoscopy, CT, PET, or MRI). CTV = GTV + entire bladder + proximal urethra + prostate and prostatic urethra (in men) or proximal 2 cm of the female urethra + regional lymphatics (internal iliac, external iliac, and obturators).PTV = CTV + margin (1.5 to 2 cm). CTV boost = GTV + 0.5 cm, If GTV not well defined, entire bladder (empty) is CTV. PTVboost = CTVboost + 1 to 2 cm margin. Atotal dose of 55 Gy was given in 25 fractions (2.2 Gy /fraction) every day from Saturday to Wednesday for atotal 5 weeks, Linear accelerator was used with energy 6MV or 15 MV,Greater than 99% of the PTV should receive at least 95% of the prescription dose (V95%>99%) with less than10% of the PTV receiving 105% (V105%<10%) and no volume receiving greater than 115% of the prescription dose.Patients received capecitabine at a median dose of 850mg/m2/day using twice-daily dosing on all days of RT with the last dose administered at the end of RT One of the daily doses was given approximately one hour before RT.

Follow up:

Patients were followed at 3-month intervals with physical examinations, cystoscopy, cytology,and surveillance CTs for the first 2 years after therapy.

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Response evaluation criteria in solid tumors (7) was used to classify treatment response treatment-related toxicities was recorded prospectively at each clinical evaluation by the treating physician using Common Terminology Criteria for Adverse Events (CTCAE) version3.0 toxicity grading criteria, Acute toxicities define as toxicities during treatment and within 90 days of treatment completion, Late toxicities define as toxicities occurring ≥90 days post-treatment.

Statistical analysis

The analyzed by computer using a data base software program, Statistical Package for Social Science (SPSS) version 16,Qualitative data was represented as percents,For quantitative variables mean and standard deviation (SD) were computed,Chi square (X^2) test was used to detect relation between different qualitative variables.The results were considered statistically significant when the significant probability (P value) was ≤0.05*.

RESULTS

The median age was 67years range(60 to 77), Regarding sex 75% of them were male **,** About 37.5% of them were non-smoker, 29.2% were ex-smoker while 33.3% were smoker, 20.8% had bilhariziasis**,** All cases were high grade and half of the cases were stage 3 also half of the cases were T2 and 25% had +ve N, Regarding tumor size 58.3% had tumor size > 3cm , LVI and extracapsular invasion were +ve in 20.8% of the cases , Finally 20.8% had incomplete TURBT **(Table 1)**.Acute hematological toxicity was founded in the form of anemia in 4.2% of the patients , leucopenia in 25 % of the patients and no cases had thrombocytopenia. Regarding acute urogenital toxicity it was founded that 58.3% had dysuria, 45.8% had frequency, 37.5 % had urgency and 29.1% had hematuria. Other toxicity was founded (16.7% diahrea, 12.5% skin toxicity and 20.8% hand and foot syndrome , 8.3% hyperbilirubinemia) **(Table 2).**

Table 1: Clinicopathologic data among the studied patients:

Variable		(n=24)	
Age:	Mean ± SD Range	68.88 ± 4.79 60 – 77	
Variable		No	%
Sex:	Male Female	18 6	75 25
Smoking:	Non smoker Ex-smoker Smoker	9 7 8	37.5 29.2 33.3
Bilharziasis:	Absent Present	19 5	79.2 20.8
Grade:	Low High	0 24	0 100
AJCC Stage:	Stage 2 Stage 3	12 12	50 50
T:	T2 T3 T4	12 9 3	50 37.5 12.5
N:	-ve +ve	18 6	75 25
Tumor size:	Small ≤ 3 cm Large > 3 cm	10 14	41.7 58.3
LVI:	-ve +ve	19 5	79.2 20.8
Extracapsular invasion:	-ve +ve	19 5	79.2 20.8
TURBT:	Complete Incomplete	19 5	79.2 20.8

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Table (2): Toxicitydata among the studied patients:

Acute Hematological toxicity:	Anemia:	Absent Present G1	23 1	95.8 4.2
	Leucopenia:	Absent Present G1 Present G2	18 3 3	75 12.5 12.5
	Thrombocytopenia:	Absent	24	100
Acute Urogenital toxicity:	Dysuria:	Absent Present G1	10 14	41.6 58.3
	Frequency:	Absent Present G1	13 11	54.1 45.8
	Urgency:	Absent Present G1	15 9	62.5 37.5
	Hematuria:	Absent Present G1	17 7	70.8 29.1
Other:	Diarrhea	Absent Present G1 Present G2	20 2 2	83.3 8.3 8.3
	Hyperbilirubinemia:	Absent Present G1	22 2	91.7 8.3
	Skin toxicity:	Absent Present G1 Present G2	21 2 1	87.5 8.3 4.2
	Hand Foot syndrome	Absent Present G1 Present G2	19 3 2	79.2 12.5 8.3

DISCUSSION

Bladder cancer is the most common malignancy involving the urinary system, of which urothelial carcinoma is the most prevalent histology, comprising 90% of bladder cancers, Bladder cancer is more common in the elderly, with a median age at diagnosis of 69 years in men and 73 years in women Survival decreases with increased age (**8).**Elderly patients are often unfit for surgery and are thus referred for trimodality treatment , Yet many frail elderly patients with potentially curative bladder cancer are unfit for chemoradiotherapy with high intensity chemotherapy regimen Furthermore, many of these patients are often unable to complete a 6-week course of radiotherapy **(9).**

This clinical conundrum provides motivation to explore an alternative approach. Hypofractionation has been investigated as a strategy to increase the therapeutic ratio of RT and provides potential advantages and convenience for elderly patients with bladder cancer (**10),**andcapecitabine is well tolerated,effective as a radiosensentizig agent**(11).**

In our study patients median age was found to be 69 years (range 60 – 77years) this was comparable to that reported by **Leng et al** , who reported a median age 80 years (range 63-87 years),75% of our patients were male and 25% were female,62.5% were current or prior smokers and this was comparable to that reported by **Leng et al** who reported that 73% of patients were male while 27% were female and 73% were current or prior smokers **(12)**.

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The current study showed that (100%) of the tumors were transitional cell carcinoma and high in grade, Half (50%) of the tumors were in T2 stage, Regarding lymph nodes; 75% of the patients their lymph nodes were negative (N0), 25%were node positive and all (100%) of them had no metastasis (M0), Our results were supported by **Choudhuryet al. (13)** reported that the majority of the studied group (97%) had transitional cell carcinoma and grade III, 95% of them were in T2 stage**.**

Leng et al.(12)assessed Safety and Efficacy of Hypofractionated Radiotherapy With Capecitabine , Eleven patients with locally advanced non metastatic bladder cancer were thought to be unfit for standard chemo-RT with cisplatin or 5-FU/MMC on the basis of multidisciplinary discussion, and they were treated with maximal TURBT followed by concurrent capecitabine and RT. They observed that during the course of treatment, there was one patient with grade 3 non hematologic toxicity consisting of severe urinary urgency leading to catheter placement for 1 week and discontinuation of RT during the last week of treatment,no grade 4 non hematologic toxicity was observed Furthermore, no clinically significant hematologic toxicities were observed; the only cases of grade 3 hematologic toxicity included lymphopenia, and there were no grade 3 or higher neutropenia events. While in our study there was no grade 3,4 toxicites our patients presented by only grade 1(anemia in 4.2% of patients ,leucopenia in 12.5% of patients,hyperbiliribinemia 8.3% of patients),grade 2(diarrhea in 8.3% of patients,skintoxcity in 4.2% of patients,hand foot syndrome in 8.3% of patients), Regarding acute urogenital toxicity it was founded that 58.3% had G1 dysuria, 45.8% had G1 frequency, 37.5 % had G1 urgency and 29.1% had G1 hematuria no need for catheter placement , our study was consistent with **Patel et al. (14)**that included a small cohort of patients (n = 14) ineligible for platinum-based chemotherapies and demonstrated results which were similar to our study in terms of tolerability and efficacy, including no grade 4/5 toxicities**.**

The encouraging findings of the current study are of particular importance given that the availability of a more tolerable, curative-intent chemo-RT treatment option may lessen the underutilization of definitive treatment and overutilization of suboptimal therapies such as radiation alone for MIBC as a result of concerns of toxicity for elderly patients as capecitabine is well tolerated , has an acceptable toxicity profile, available ,oral drug and hyopfractionated radiotherapy more conveinence especially for elderly patients with good response rate and disease free survival.

While this study provides encouraging results on toxicity and efficacy with the use of concurrent capecitabine and radiation following TURBT there are some limitations wihthin our findings need to be interpreted carefully first is the insufficient sample size for statistical measurmentand second is the lackof previous research studies,last the machine errors.

CONCLUSION

For well-selected elderly patients, chemo-RT with capecitabine is a tolerable regimen with effective local control that may increase the utilization of definitive treatment for MIBC, Patient characteristics such as poor performance status, renal failure, and other comorbidities are essential to guide clinical decision making regarding eligibility for therapy.

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No conflict of interest.

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