RESEARCH ARTICLE

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Could Concurrent Capecitabine with Hypofractionated Radiotherapy in Elderly Patients with Muscle-Invasive Bladder Cancer be an Option?

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Abstract

Background: Repopulation of tumor cells during radiotherapy of transitional cell bladder carcinoma is believed to be a significant cause for treatment failure, and it was reported from clinical observations that the local control rate decreased with a prolonged treatment time, so accelerated hypofractionated radiotherapy with concurrent capecitabine may provide good local control in elderly patients unfit for surgery. The study aimed to evaluate the tolerability and efficacy of hypofractionated radiotherapy with capecitabine in elderly patients with urothelial carcinoma. **Methods:** Between October 2019 and September 2021, 30 patients with muscle-invasive bladder cancer staged T2-4aN0M0, underwent transurethral resection of bladder tumor followed by capecitabine (825 mg/m^2 orally, 2 times a day) and radiation therapy (55 Gy in 2.2 Gy per fraction). **Results:** Thirty patients with a median age of 73.5 years (range, 65-85) were included in our study. Most patients had T2N0, and T3N0 (28 patients), furthermore 73.3% had an intermediate-grade tumor, Transurethral resection of bladder tumor was incomplete in 43.3. No grade 4 toxicity was documented. Grade 3 urinary toxicities occurred in two patients requiring hospitalization and temporal radiation cessation. Regarding late toxicities, no grade 3 or 4 toxicity was reported. A complete response was obtained in 56.7% of patients. After a median follow-up of 16 months, the locoregional control rate was 63%. Overall survival, local failure-free survival, and event-free survival were 100%, 93.3%, 80% and 43.3%, 33.3%, 30% at one and two years respectively. **Conclusion:** Hypofractionated chemoradiation with capecitabine, appears to be an effective and well-tolerated curative treatment strategy in the selected elderly population with urothelial carcinoma.

Keywords: Bladder cancer- elderly- hypofractionation radiotherapy- capecitabine

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Introduction

Bladder cancer is over four times more common in men than women and the second most common genitourinary cancer in the United State, based on the latest GLOBOCAN data, the average 5-year survival in the United State is 77% (Bray et al., 2018). The disease tends to occur mainly in older people, about 9 out of 10 people with bladder cancer are over the age of 55. When they are diagnosed, the average age of people is 73 (Schltzel et al., 2017). Although radical cystectomy has been a standard curative treatment for muscle-invasive bladder cancer (MIBC) (kulkami et al., 2013). Most frail old patients would otherwise be poor candidates for surgery because of other serious health problems with increased risk of mortality, for patients, concurrent chemoradiation (CRT) continues to pose a significant global health challenge and is considered as a well-established alternative therapy (Chang et al., 2017).

The optimum combination of chemotherapeutic drugs needs to be identified to improve efficacy and minimize toxic effects related to treatment. When chemotherapy is given with radiation, cisplatin, mitomycin-C (MMC) plus 5 fluorouracil (5-FU) are currently the most drugs used (Chang et al., 2017). However, there may be some patients who can't tolerate chemotherapy due to medical co-morbidities, single-agent capecitabine with radiotherapy seemed logical in such patients with a more therapeutic ratio (Patel et al., 2005).

Capecitabine (Xeolda) is an oral prodrug that is converted to 5-FU through the thymidine phosphorylase enzyme. Radiation has been shown to increase the tumor enzyme levels preferentially, improving the likelihood of capecitabine-mediated radiosensitizing and therefore

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increasing the therapeutic benefit (Miwa et al., 1998).

Using a hypofractionated schedule of 55 Gy in 20 fractions over 4 weeks to treat patients with bladder cancer unsuitable for daily radiotherapy was non-inferior to a schedule of 64 Gy in 32 fractions over 6.5 weeks concerning both invasive locoregional control and toxicity, according to data published in The Lancet Oncology (Choudhury et al.,2021).

In this study, we aimed to assess the safety and efficacy of concurrent capecitabine and external-beam irradiation as well as (1-year) locoregional control rate and survival in an elderly patient with urothelial cancer.

Materials and Methods

We enrolled 30 patients in Prospective, one arm trial carried out at radiotherapy department, South Egypt Cancer Institute (SECI), and clinical oncology department at Assuit University Hospital. Between October 2019 and September 2021, the study was approved by the SECI ethics committee (approval number 480), and informed written consent was taken from all patients. Our sample size calculated with its power based on G power as shown in (Figure 1).

Eligible patients had pathologically confirmed urothelial carcinoma of the bladder (cT2-4aN0M0), small tumors (less than 5 cm) and solitary, lack lymph node metastasis, lack carcinoma in situ (CIS), without tumor-related hydronephrosis, have favorable baseline bladder function, and none of the patients were candidates for surgery or cisplatin-based chemotherapy. Preradiotherapy assessment included: full physical examinations, cystoscopy with biopsy, complete blood count (CBC), liver function tests, urinalysis, chest radiography, and computed tomography (CT) or pelvic magnetic resonance imaging before treatment.

CT- based simulation was generated for all patients with bladder empty protocol after completion of transurethral resection of bladder tumor (TURBT), with patients in the supine position using upper and lower alpha cradles custom immobilization.

Three-dimensional treatment planning with 6- 15 megavoltage (MV) photons energy using linear accelerators Elekta synergy platform was applied in all patients except in 5 patients with radiologically suspected positive pelvic lymph node as intensity-modulated radiotherapy was delivered. Our target volumes are gross target volume (GTV) which includes the gross tumor, clinical target volume (CTV) includes the whole urinary bladder and finally adding a 1.5 cm margin to the empty bladder generates the planning target volume (PTV), (Figure 2). Internal and external iliac vessels were contoured plus a 1.5 cm margin modified around bone and muscle to generate the PTV of the intensity-modulated radiation therapy, with the superior border typically at the L5/S1 junction. Capecitabine was administrated at dose 825 mg/ m2 (orally) twice daily with concurrent radiation therapy 45 Gy in 1.8 to 2 Gy/fx to pelvic lymphatic with simultaneous integrated boost technique to the bladder of 55 Gy in 25 fractions (2.2 Gy) per fraction.

After completion of treatment, all patients were evaluated by radiation oncologists and urologic oncologists at 3-month intervals for 1 year and at least 6 months thereafter.

Toxicity and complications

Detailed data of radiation therapy and chemotherapy was obtained, and any treatment interruptions or dose reductions were recorded. Acute (within 90 days, from initiation of treatment)) and late (>90 days from the start of CRT), toxicities were assessed as per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (NCI/NIH,2017). Hematologic and laboratory-related toxicities were assessed for the duration of treatment only. We classified treatment response as a complete or partial response. Clinical findings based upon imaging reports, and the results of cystoscopy. A complete response (CR) was defined disappearance of all target lesions as no residual tumor can be found in the cystoscopy specimen and no evidence of disease on CT. A Partial Response (PR) was defined as at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. Progressive Disease (PD) was defined as at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions (Elsenhauer etal., 2009; Schwartz et al., 2016).

Statistics

By Shapiro-Wilk test, all data were not normally distributed except for age (p=0.4), time to local relapse (p=0.36), time to distant relapse (p=0.93), overall survival (p=0.081), local failure-free survival (p=0.4), and event-free survival (p=0.07). One-way anova was used for the scale-dependent variable (age) after performing inhomogeneity tests for detecting equality of variances, χ^2 test for significances between categorical and nominal variables, however, because >20% of cells had values <5, so likelihood ratio was the type of χ^2 used, all survivals were analyzed by Kaplan-Meier test. Overall survival was calculated from the date of diagnosis to date of death or last follow up (patients under follow up were considered right censored), local failure-free survival was the time passed between diagnosis and either death or local relapse, and event-free survival was the time passed between diagnosis and either death, local or distant relapses. All data were analyzed by IBM SPSS version 26 and considered significant at $p \leq 0.05$. Local failure-free survival estimated from the time of study enrolled. Cumulative incidence estimates local relapse, non-relapse mortality. and event-free survival was the length of time after primary treatment for cancer ends that the patients remain free from certain complications or events (local relapse, distal relapse, or death) that the treatment was intended to prevent or delay.

Results

Clinicopathologic characteristics of 30 patients with bladder transitional cell carcinoma received hypofractionated RT concurrent with capecitabine.

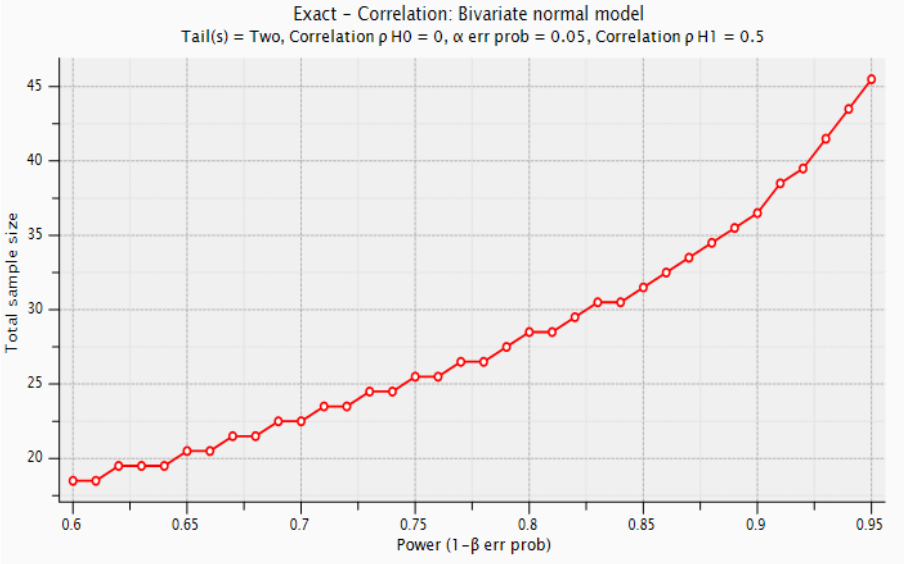

Figure 1. Our Sample Size was Calculated Based on G-power 3.1.9.4 Program to be 30 with a Corresponding Power of 82.5%.

The median age of the studied patients was 73.5 years (range, 65-85), ten patients had age ≥80 years with male to female ratio of 1.7:1. Twenty-two patients had Eastern cooperative oncology group performance status ECOG-PS 2, while 7 patients had PS-3 with the majority of patients had T2N0, and T3N0 (28 patients), furthermore 73.3% (22 patients) of them had intermediate-grade transitional cell carcinoma (TCC), in spite most patients (28 patients) previously underwent 1-2 TURT, but complete TURT was performed in only 17 patients as illustrated in table 1. Figure 3 demonstrated the number of months passed since the date of the last TURT before enrollment into the current study.

Table 1. Baseline Patients' Characteristics

Characteristic	Descriptive (n=30)
Age (mean ±SE)	75.5±1.013
Min-max	61-85 ys
Median	73.5 ys
Sex male/female	19/11 (1.7:1)
ECOG-PS	
PS-1	1 (3.3%)
PS-2	22 (73.3%)
PS-3	7 (23.3%)
TNM stage	
T2N0	16 (53.3%)
T3N0	12 (40%)
T4aN0	2 (6.7%)
Grade	
Intermediate grade TCC	22 (73.3%)
High grade TCC	8 (26.7%)
Number of the previous TURT	
1	19 (63.3%)
2	9 (30%)
3	1 (3.3%)
4	1 (3.3%)
Complete TURT	
Complete	17 (56.7%)
Incomplete	13 (43.3%)

Data expressed as mean ±SE, median, number, percentages, ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; TURT, transurethral resection of the tumor; TCC, transitional cell carcinoma, ys; years

Treatment response and outcomes

The median time of follow-up calculated after the completion of concurrent hypofractionated 3-dimensional conformal radiotherapy 3DCRT with capecitabine was

Table 2. Response among 30 Patients with TCC

Outcome	Description
Response	
Complete response	17 (56.7%)
Stable response	2 (6.7%)
Progressive disease	11 (36.7%)
Local relapse	7 (23.3%)
Time to local relapse (mean ±SE)	14±2.1 ms
Median time	16 ms
Distant relapse	10 (33.3%)
-Pulmonary metastases	5 (16.7%)
-Bone metastases	3 (10%)
-Peritoneal metastases	2 (6.7%)
Time to distant relapse (mean ±SE)	8.9±0.61
Median time	9 ms
Follow up period (mean ±SE)	20.3±0.94 ms
Median	20 ms
Outcome	
Dead	8 (26.7%)
Alive	22 (73.3%)

Data expressed as mean ±SE, number, percentages, and median, ms; months

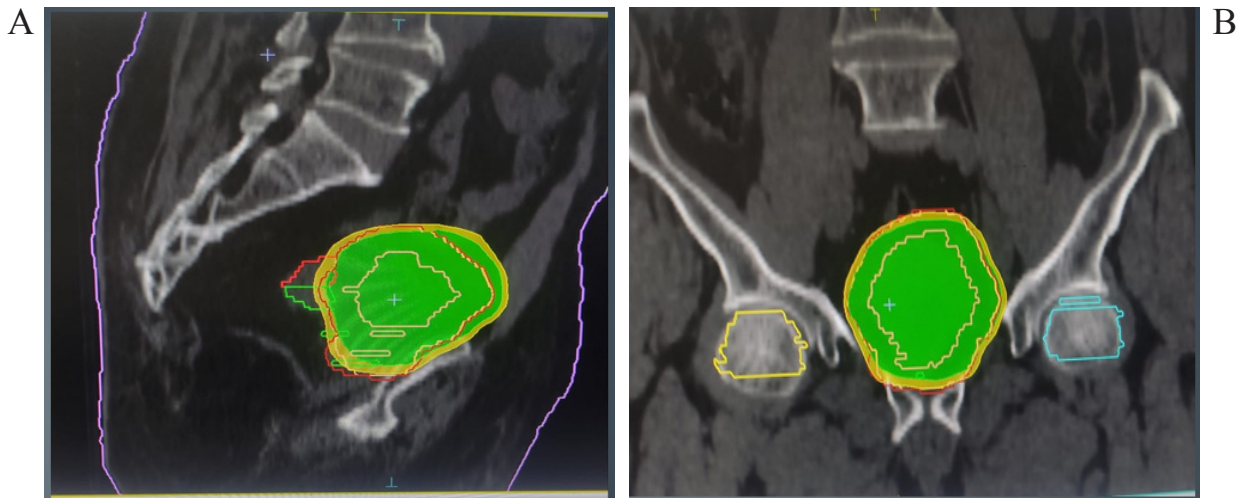

Figure 2. A and B, Showed target volumes and dose distribution in which red color represents 100%dose, green represents 95% and yellow is the 90% of the dose distribution.

20 months (range 10-30 months); Seventeen patients achieved complete response; while two patients had stable disease, and eleven patients achieved progressive disease. Commonly, the locoregional control rate for this protocol was calculated to be 63.3%. After a median time of 16 months, seven patients experienced local relapses, and ten patients developed distant metastases after a median time of 9 months as reported in Table 2, Figure 4.

Regarding age, sex, and performance status, there were no significant differences between response groups. But most patients with complete response to treatment had intermediate-grade TCC (p=0.002), T2N0 (p<0.0001), and no local or distant relapse during the period of follow up (p=0.001, p<0.0001 for local and distant relapses respectively). Conversely, patients with progressive disease had high-grade TCC, T3N0, and more local and distant relapses, all these relations and corresponding p-values were summarized in Table 3).

Survival analysis of 30 TCC elderly patients

The median overall survival (OS) was 23 months, while the median local failure-free survival (LFFS) was 23 months, and median event-free survival (EFS) was 18.5 months as mentioned in the subsequent table (Table 4), and figures 5A, 5B, 5C. OS, LFFS, and EFS at one year were 100%, 93.3%, and 80% respectively, and at two-year were 43.3%, 33.3%, and 30% respectively.

Toxicities among studied patients

Generally, no grade 4 toxicities were reported among our studied patients implying the feasibility of concurrent hypofractionated 3DCRT with capecitabine in elderly patients.

However, ten patients experienced grade 3 hematologic toxicity mainly in the form of anemia and lymphopenia, but it was easily manageable by blood transfusion and steroid injection and didn't necessitate hospitalization, two patients developed grade 3 urinary toxicities in the form of severe cystitis that required hospitalization for catheter fixation, bladder washing, urinary cultures, and antibiotic treatments, 8 patients required temporal

Figure 3. Months Elapsed Since Last TURT before Enrollment in the Current Study; 13 (43.3%) patients had last TURT 2-months ago, while 10 (33.3%) patients had last TURT 3-months ago, 6 (20%) patients had their last TURT one month ago, and 1 (3.3%) patient had last TURT 1.5 months ago.

Table 3. Relations between Response and Clinicopathologic Characteristics

Character	CR[a]	SD[a]	PD[a]	LR, p-value
Age	75.7±1.2	73.5±0.5	75.6±2.1	0.8*
Sex				LR =0.162
Male	11 (64.7%)	1 (50%)	7 (63.6%)	P=0.9
Female	6 (35.3%)	1 (50%)	4 (36.4%)	
ECOG-PS				
PS-1	1 (100%)	0 (0%)	0 (0%)	LR=2.1
PS-2	13 (76.5%)	1 (50%)	8 (72.7%)	P=0.71
PS-3	3 (17.6%)	1 (50 %)	3 (27.3%	
Grade				LR= 12.8
Intermediate	16 (94.1%)	2 (100%)	4 (36.4%)	P=0.002
High	1 (5.9%)	0 (0%)	7 (63.6%)	
Stage				
T2N0	15 (88.2%)	0 (0%)	1 (9.1%)	LR=24.6
T3N0	1 (5.9%)	2 (100%)	9 (81.8%)	P<0.0001
T4aN0	1 (5.9%)	0 (0%)	1 (9.1%)	
Local relapse				LR =14.7
No	17 (100%)	1 (50%)	5 (45.5%)	P=0.001
Yes	0 (0%)	1 (50%)	6 (54.5%)	
Distant relapse				
No	17 (100%)	2 (100%)	1 (9.1%)	LR=31.5
Pulmonary mets.	0 (0%)	0 (0%)	5 (45.5%)	P<0.0001
Peritoneal mets.	0 (0%)	0 (0%)	2 (18.2%)	
Bone mets.	0 (0%)	0 (0%)	3 (27.3%)	

Data were analyzed with one-way anova for *age because the test of homogeneity of variance was insignificant based on mean with p=0.092, all other data were analyzed using $\chi 2$ test with likelihood ratio (LR); [a], all percentages were from the response type.

Table 4. Survival Outcomes among 30 TCC Patients

Statistic	Overall survival	LFFS	EFS
Mean ±SE	28.7±1.3 ms	27.3±1.5 ms	23.9±1.9 ms
95% CI	26.2-31.3 ms	24.3-30.3 ms	20.1-27.6 ms
Median	23 ms	23 ms	18.5 ms

Data analyzed by Kaplan-Meier

interruptions of capecitabine due to grade 2 diahrria and hyperbilluribinemia and while patients discontinued due to preexisting cardiac disease,hand and foot syndrome was mainly of grade 1 that managed with a topical pain reliever such as lidocaine, topical moisturizing exfoliant creams oral NSAIDs like celecoxib without dose reduction of capecitabine. regarding late toxicities, all patients had grade 1-2 urinary frequency as a result of reduced bladder capacity as evaluated by MRI pelvis and cystoscopy

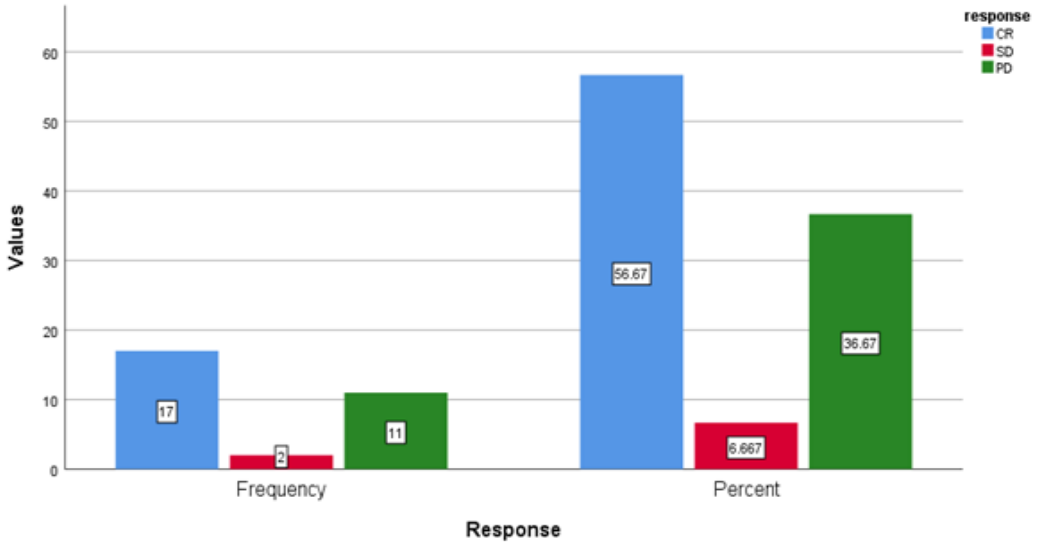

Figure 4. Responses among 30 Elderly TCC patients who Received Hypofractionated RT.

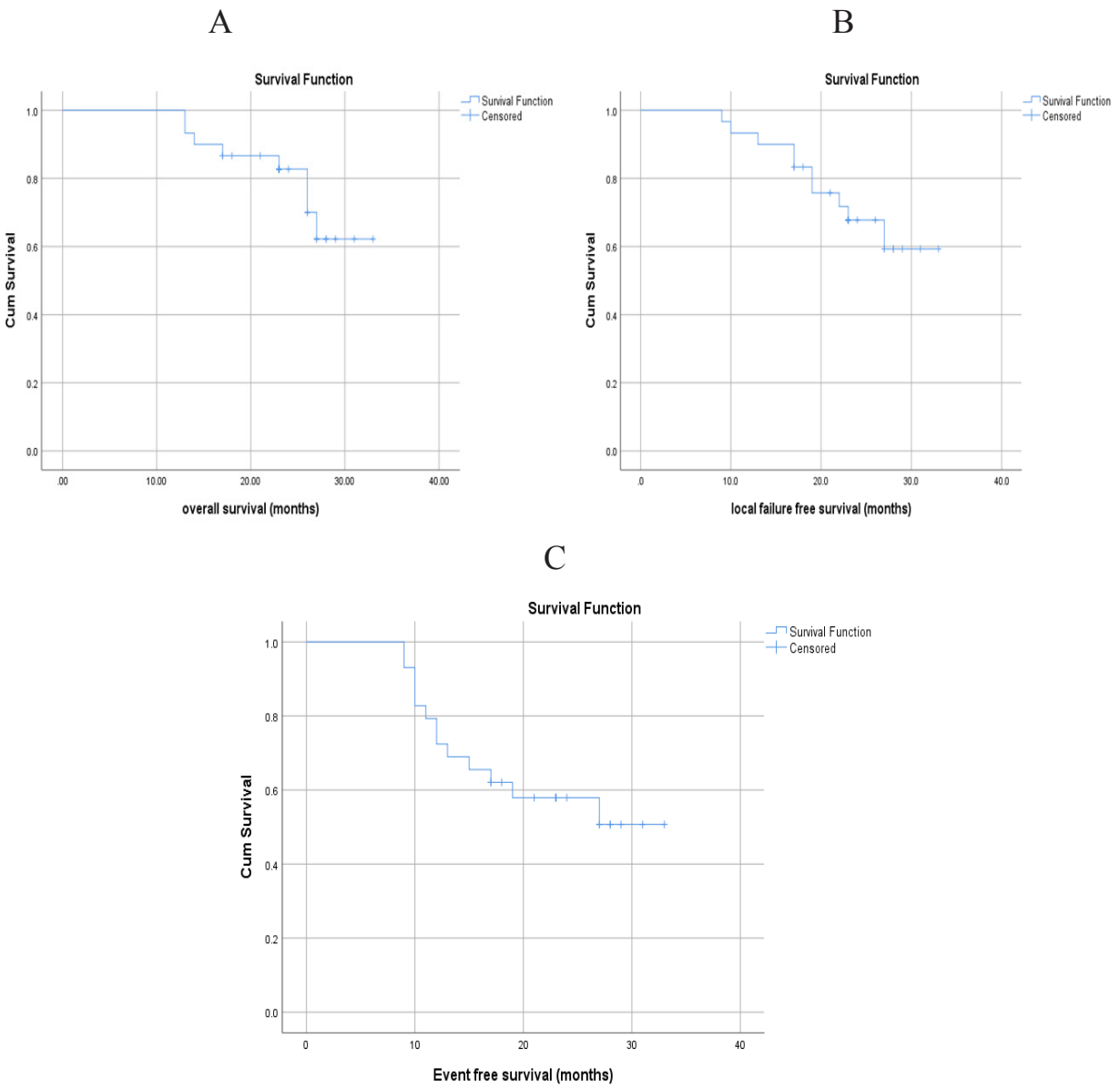

Figure 5. A, Overall survival among 30 TCC patients; B, Local failure-free survival among 30 TCC patients; C, Event-Free Survival among 30 TCC Patients

after treatment (bladder capacity < 200 ml), and only two patients developed chronic constipation which was managed by proctoscopy revealing only chronic inflammatory reactions without ulceration or perforation. Table 5 summarized all toxicities developed in studied patients.

Table 5. Acute and Late Toxicities among 30 TCC Patients

Toxicity	< Grade 3	Grade 3	Grade 4
Acute			
Genitourinary	28 (93.3%)[b]	2 (6.7%)	0 (0%)
Gastrointestinal	30 (100%)	0 (0%)	0 (0%)
Hematologic	20 (66.7%)	10 (33.3%)	0 (0%)
Blood chemistries	30 (100%)	0 (0%)	0 (0%)
Hand & foot syndrome	2 (6.7%)	0 (0%)	0 (0%)
Late			
Genitourinary	30 (100%)	0 (0%)	0 (0%)
Gastrointestinal	2 (6.7%)	0 (0%)	0 (0%)

Data expressed as numbers and percentages; [b], percentages were calculated from the total number of patients

Discussion

Bladder cancer is considered a highly proliferating cancer, with a high α/β ratio of 10 Gy and low fractionation sensitivity. There is evidence that the repopulation of tumor cells can lead to radioresistance and limit the effectiveness of radiotherapy (Maciejewski et al., 1991). The finding that a moderately hypofractionated radiotherapy schedule is non-inferior for locally advanced bladder cancer is most probably due to a combination of α/β ratio lower than 10 and a substantial effect of repopulation. The overall treatment time for rapidly proliferating cancers at high risk of repopulation is very important, with evidence that detrimental outcomes when treatment is interrupted and prolonged (Majewski et al., 2004).

A dataset reported by the National Cancer Institute of Canada (NCIC) that randomized patients with MIBC to RT alone versus with concurrent cisplatin concluded that lower recurrences rate in the pelvis in the chemoradiation group (29.4%) versus the RT alone group (52%) (Nicholas et al., 2012).

Chemoradiation effectiveness in the treatment of urinary bladder cancer was repeatedly demonstrated in results of phase III BC2001 trial which randomized patients with MIBC who completed TURBT to either RT alone or chemoradiation with 5FU/Mitomycin C, the two-year DFS was 67% in the chemoradiation group vs. 54% in the RT alone group (Oh et al., 2009).

Liat Hammer et al gave accelerated hypofractionated radiotherapy 45 GY/15 Fx in frail elder patients staged from T1-T4a N0M0 with maximum TURT in only 45% with no chemosensitizer used, CR, as well as local control rates, were higher than that reported in our study, may be related to that Liat Hammer used volumetric modulated arc therapy (VMAT) in most cases with improved conformity and homogeneity while 1 year and 2 years OS were lesser than our trial and still low rate of acute and late toxicities (liat et al., 2019).

Although there is limited literature on the use of concurrent capecitabine and radiation in MIBC, only two other studies in our knowledge have reported on the use of this strategy. Patel et al., did a cohort of patients (n=14) ineligible for platinum-based chemotherapies and results are tolerable including no grade 4-5 toxicities, complete clinical response in 77% of patients which was higher than the CR rate reported in our study as TURBT was incomplete in 43.3% of our patients, and only 3 relapsed at a median follow up of 10.5 months (Patel et al.,2005).

Our study further supports this finding in Jim et al., (2018) study on hypofractionation radiotherapy concurrent with capecitabine in elder patients where most patients were T2 reaching CR rate 64%. which was slightly more than the CR rate in our study, and one year OS in his study was 82% but in the present series, one year OS was better although the local control rate is slightly lesser than that in Jim et al., (2018) reflecting the fact that in our trial, 40% of cases were T3, higher grade and not all cases had maximum TURBT before radiotherapy, and most cases with CR had intermediate-grade T2N0 TCC. In our study, only 6.7% discontinued capecitabine due to preexisting cardiac disease, but in Jim leng et al study 36% discontinued the drug due to grade 3 hematologic toxicities. Results on distant metastasis-free survival were more than our event in one-year EFS and results of 2 years OS and 2 years local control (LC) showed better values than our trial may be due to that not all patients complete their follow up in our center and patients offered that regimen have typically been non-surgical candidates with various comorbidities and more advanced disease.

Regarding late toxicity rate compared with Jim leng et al are better in our trial and most late toxicities were urinary frequency resulting from diminished bladder capacity (Jim et al., 2018). Advanced radiation techniques such as image-guided radiotherapy (IGRT) as well as VMAT, will be able to better conform high-dose radiation to the target volume, and further reduce long-term side effects.

Turgeon et al., (2014) reported a CR rate of 83 % and a 2 year OS of 69 % and acute grade 3 gastrointestinal or genitourinary toxicities occurred in only 4% of the patients, in a series of 24 patients treated with hypofractionated IMRT (50 Gy in 20 fractions) and concurrent chemotherapy, which was more favorable results than that reported in our study, may be due to better selection criteria in their study with more advanced planning technique.

A study conducted by Ananya et al., (2011) revised the results of hypofractionation with gemcitabine in cases staged T2-3 N0M0 with all patients completed their courses of treatment except 2 patients who discontinued from severe bowel toxicity, this trial showed higher CR and survival rates than our trial as our study reported more unfavorable patient population, but we have good local control in spite high stage and grading.

Similar findings were published by Mohamed et al., (2019) as hypofractionated radiotherapy 52.5Gy in 20 fractions using 3D conformal radiotherapy with concurrent 100mg/m2 gemcitabine weekly as a radiosensitizer, showed high CR reaching 80.6% and high 2 years OS 72.6% and both staging and residual after TURBT adversely affect disease-free survival (DFS).

It is virtually impossible to make valid comparisons between our results and the previous gemcitabine prospective trials, as these data do not represent a head-to-head comparison. However, the current study demonstrated non-inferiority of statistical analysis regarding efficacy and toxicity which may be appropriate in selected frail geriatric patients and may contribute to a change in practice in the future.

Limitation of the study

This current strategy has encouraging results regarding toxicity and efficacy with the use of Concurrent capecitabine and radiation following TURBT, there are several limitations including its small sample size, 40% were T3 and not all patients underwent maximum TURBT and these were influencing the outcomes. Lack of Advanced radiation treatment technologies such as IGRT and VMAT that sculpt the radiation dose to precisely conform to complex geometric targets. Also, the presence of competing risks of mortality has limited the length of follow-up time, making it difficult to estimate longer-term control rates. Lack of molecular subtyping that may offer additional guidance on proper patient selection and prediction of treatment response of MIBC to various chemoradiation regimens. Data on quality of life will be central in the implementation of this Strategy and will be published as a separate report, after an increased follow-up of patients in this trial to better capture late events. More prospective comparative studies will be needed to validate our findings, and better understand which patients are likely to benefit most from this regimen.

In conclusion, hypofractionated chemoradiation with capecitabine in urothelial MIBC appears to be an effective and well-tolerated curative treatment strategy in

selected geriatric populations and should be considered for patients who are not candidates for cystectomy or standard chemotherapy. The use of IMRT and VMAT is now encouraged with improved toxicity and better oncological outcomes.

Abbreviations

CRT: Chemoradiation, CBCT: Cone-beam CT, CR: Complete response, CTV: Clinical target volume, DFS: Disease free survival, FFLR: Freedom from locoregional recurrence, GTV: Gross tumor volume, IMRT: intensity modulated radiotherapy, IGRT: image guided radiotherapy, VMAT: volumetric modulated arc therapy, TRUBT: Transurethral resection of bladder tumor.

Author Contribution Statement

AA is the first author of the manuscript and made contributions to the protocol design. DA and AA Analyzed and interpreted the data, and all authors drafted the manuscript. DA, RA and MS provided support regarding the statistical analysis and discussion. SA and MA performed all methodological procedure and was responsible for data analysis and manuscript revision. All authors have reviewed and approved the final version of the manuscript.

Acknowledgments

Not applicable.

Ethical approval

The study was approved by SECI ethics committee (approval number 480) and informed written consent was taken from all patients.

Availability of data and material

The datasets analyzed during the current study are available from the corresponding author on request.

Competing Interests

The authors indicated no potential conflicts of interest.

References

Ananya C, Ric S, John PL,et al (2011). Phase II Study of Conformal Hypofractionated Radiotherapy With Concurrent Gemcitabine in Muscle-Invasive Bladder Cancer. *J Clin Oncol*, **29**, 733-8.

Bray F, Ferlay J, Soerjomataram I, et al (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, **68**, 394- 424.

Chang SS, Bochner BH, Chou R, et al (2017). Treatment of non-metastatic muscle invasive bladder cancer: AUA/ ASCO/ ASTRO/ SUO guideline. *J Urol*, **198**, 552-9.

Choudhury A, Porta N, Hall E, et al (2021). Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials. *Lancet Oncol*, **22**, 246-5.

Eisenhauer E, Therasse P, Bogaerts J, et al (2009). New 'response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer*, **45**, 228-47.

Jim Leng, Adil S, Russel Z, et al (2018). Safety and Efficacy of Hypofractionated Radiotherapy with Capecitabine in Elderly Patients with Urothelial Carcinoma Clinical Genitourinary. *Cancer*, **17**, 1.

Kulkarni GS, Urbach DR, Austin PC, Fleshner NE, Laupacis A (2013). Higher surgeon and hospital volume improve long term survival after radical cystectomy. *Cancer*, **119**, 3546-54.

Liat H, Menahem L, Zohar D, et al (2019). Accelerated Hypofractionated Radiation Therapy for Elderly Frail Bladder Cancer Patients Unfit for Surgery or Chemotherapy. *Am J Clin Oncol*, **42**, 179-83.

Maciejewski B, Majewski S (1991). Dose fractionation and tumour repopulation in radiotherapy for bladder cancer. *Radiother Oncol*, **21**,163.

Majewski W, Maciejewski B, Majewski S, et al (2004). Clinical radiobiology of stage T2-T3 bladder cancer. *Int J Radiat Oncol Biol Phys*. **60**, 60- 70.

Miwa M, Ura M, Nishida M, et al (1998). Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer*, **34**, 1274–81.

Mohamed H, Salem MA, Elnaggar MS, Gabr A, Abdelrheem AM (2018).Trimodalities for bladder cancer in elderly: Transurethral resection, hypofractionated radiotherapy and gemcitabine. *Cancer Radiother*, **22**, 236-40.

National Cancer Institute (NCI)/National Institute of Health (NIH) (2017). Common Terminology Criteria for Adverse Events v.5.0 (CTCAE). (https://www.meddra.org/).

Nicholas DJ, Syed AH, Emma H, et al (2012). Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer. *N Engl J Med*, **366**, 1477-88.

Oh KS, Soto DE, Smith DC, et al (2009). Combined-Modality Therapy With Gemcitabine and Radiation Therapy as a Bladder Preservation Strategy: Long-Term Results of a Phase I Trial. *Int J Radiat Oncol*, **47**, 511-7.

Patel B, Forman J, Farzier A et al (2005). A single institution experience with concurrent capecitabine and radiation therapy in weak and/or elderly patients with urothelial cancer *Int Radiat Oncol*, **62**, 1332-8.

Schltzel M, Saltzstein SL, Downs TM et al (2017). Late age (85 years or older) peak incidence of bladder cancer. *J Urol*, **98**, 552-9.

Schwartz L, Litière S, Ford R, et al (2016). RECIST 1.1 – Update and Clarification: From the RECIST Committee. *Eur J Cancer*, **62**, 132-7.

Turgeon GA, Souhami L, Cury FL, et al (2014). Hypofractionated intensity modulated radiation therapy in combined modality treatment for bladder preservation in elderly patients with invasive bladder cancer. *Int J Radiat Oncol Biol Phys*, **88**, 326–31.

Erratum: Could Concurrent Capecitabine with Hypofractionated Radiotherapy in Elderly Patients with Muscle-Invasive Bladder Cancer be an Option?
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The original version of this Article contained two errors: 1) Figure 5c was missing it was added. 2) Heading of the Table 4 was corrected. These errors have been corrected in the PDF and HTML versions of the Article.

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