RESEARCH ARTICLE

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# Trimodality Therapy in which Concurrent Chemoradiation with Concomitant Boost in Muscle Invasive TCC Urinary Bladder Cancer

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## Abstract

**Background:** Bladder cancer is the most common genitourinary tract malignancy among Egyptian males (16%). bladder sparing therapy can be considered an alternative for patients refusing surgery or are not candidates for surgery. The objective of this study was to determine the safety and feasibility of external-beam irradiation with concomitant boost in muscle invasive bladder cancer and to determine the short-term (1-year) risk of recurrence of bladder cancer. **Methods:** Between October 2019 and November 2021, we enrolled 42 patients in Prospective, one arm trial. Eligible patients had pathologically confirmed TCC transitional cell carcinoma of the bladder cT2-4aN0M0, who refused surgery or had contraindications to surgery, and treated conservatively with radiotherapy. All patients underwent maximal TURB before beginning of chemoradiation therapy which was delivered in all patients The patients received radiotherapy dose 45 Gy/25 fractions (1.8 Gy) per fraction to the whole bladder+ 3 cm. with concurrent cisplatin 20 mg/ $m^2$ over 30 minutes before radiation on days 1,2,15,16,29, and 30. Additionally, concomitant boost limited to the bladder plus1.5 cm margin was deliverd during the last ten days of the treatment with a minimum 6 h gap between fractions, to a total dose 60 Gy, with the overall treatment time equal to 5 weeks. **Results:** The median overall survival OS for 42 patients with transitional cell carcinoma( TCC) of bladder treated with 3D conformal radiotherapy 3DCRT and concomitant boost was 28 months, the mean OS was 29.9±1.04, and (95% confidence interval=27.9-32). The one-year OS was 100%, 2-year OS was 81%, and 3-year OS was 26.2%.The mean loco-regional relapse free survival (LRRFS) was 31.6±1.8, 95% CI=28.1-35.1, and the median was 26.5±1.4, the one-year loco-regional RFS was 92.9%, and 2-year (LRRFS) was 66.7%.Acute and late genitourinary toxicity was grade 2 in most of patients and also acute and late toxicity of gastrointestinal was equal or less than grade 1. **Conclusion:** In external radiotherapy for muscle invasive bladder cancer a concomitant boost technique of invasive bladder cancer with shortening of the overall treatment time provides a high probability of local control and overall survival with acceptable toxicity.

**Keywords:** Concomitant boost- bladder cancer- trimodality therapy

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## Introduction

Bladder cancer is the most common genitourinary tract malignancy among Egyptian males (16%), Bladder cancer is the 10th most common cancer worldwide. It is the 6th most common cancer in men and the 17th most common cancer in women globally.There were more than 573,000 new cases of bladder cancer in 2020. Bladder cancer deaths in 2020 in Egypt was 7.8/100000 (World cancer research fund international, bladder statistics, 2020) (Khaled, 2005). Most of bladder cancer patients are diagnosed around the age of 70 years. So we must consider the performance state of these patients and the presence of comorbidities before choice the suitable management strategies (DeLancey et al., 2008). In muscle invasive bladder cancer, radical cystectomy is considered the standard treatment line (Chan et al., 2017). But bladder sparing therapy can be considered an alternative for patients refusing surgery or are not candidates for surgery (Sengelov et al., 1999). Trimodality treatment show a very favorable outcome in those patients (Zhong et al., 2019). Trimodality treatment include complete transurethral resection, chemotherapy and radiotherapy (Zhong et al., 2019). Massachusetts General Hospital Program utilizing trimodality treatment depicted encouraging results with 5-year overall survival (OS) of 57%, and disease specific

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survival (DSS) of 66% (Giacalone et al., 2017). Also, the pooled analysis of six multicenter prospective RTOG trials evaluating this combined modality therapy showed similar outcomes with 5-year OS of 57% and 5-year DSS of 71% (Mak, 2014). However, omitting chemotherapy from trimodality regimens was associated with worse outcomes compared to trimodality with 5-year OS and 5-year DSS of only 20-40%, and 31-56.8% respectively (Langsenlehner et al., 2010). Therefore, through our work, we tried to improve the outcomes of the trimodality treatment in patients who were not candidate for surgery by practicing concomitant radiotherapy bladder boost.

## Materials and Methods

Between October 2019 and November 2021, we enrolled 42 patients in Prospective, one arm trial carried out at radiotherapy department in South Egypt Cancer Institute (SECI), clinical oncology department in Assiut University Hospital and medical oncology department in South Egypt Cancer Institute. The study was approved by SECI ethics committee (approval number: 479) and informed written consent was taken from all participating patients.

Eligible patients had pathologically confirmed transitional cell carcinoma of the bladder cT2-4aN0M0 (TNM staging system for bladder cancer 8th ed.,2017), who refused surgery or had contraindications to surgery, and treated conservatively with radiotherapy. All patients underwent maximal TUBRT before beginning of chemoradiation therapy which was delivered in all patients. All patients had KPS equal or more than 60%.

After maximum TUBRT, two cycles of chemotherapy were administrated as gemcitabine intravenous infusion at a dose of 1,000 mg/m$^2$ on days 1, 8 and 15 plus cisplatin 70mg/m$^2$ on day 2 of each cycle. In Patients with impaired renal function and/or heart disease, cisplatin was replaced by carboplatin with area under the curve 5 (AUC5) on day 2. Concurrent chemotherapy was delivered on Days 1, 8, 15, 16, 29, 30 of the radiation therapy, in the form of cisplatin 20mg/m$^2$ as a 30-min infusion, 3–4h before radiotherapy section. Three-dimensional conformal Radiotherapy (3D-CRT) technique with individual.

CT- based simulation was generated for all patients with bladder empty protocol after completion of transurethral resection of bladder tumor (TURBT), 4–6 weeks after chemotherapy, or 4–8 weeks after maximum TURT in the case of local radiotherapy alone, with patients in the supine position using upper and lower alpha cradles custom immobilization.

Three-dimensional treatment planning with 6- 15 megavoltage (MV) photons using linear accelerators Elekta synergy plateform was applied in all patients with designed portals by multi-leaf collimators. Gross target volume (GTV) included the gross tumor, clinical target volume (CTV) included the whole urinary bladder and finally adding a 2-3cm margin to the empty bladder generated the planning target volume (PTV1), and was treated to a dose of 45 Gy in 25 daily fractions of 1.8 Gy, and concomitant boost phase (PTV2) which was an isotropic 1-1.5 cm expansion of the whole bladder, and was covered by the 95% isodose line, the concomitant Boost field was added in the last two weeks of the course, with 1.5 Gy per fraction, at least as 6-h apart between the two fractions, to a cumulative dose of 60 Gy, with an overall treatment time of 5 weeks was applied.

Acute toxicities were examined weekly according to the Common Toxicity Criteria for Adverse Events v.3.0 (CTCAE). The Radiation Therapy Oncology Group/ The European Organization for Research and Treatment of Cancer (RTOG/EORTC). Late Radiation Morbidity Scoring Scheme was used to define the late toxicity. The response (assessed by Recist criteria V1.1) to treatment was first examined 6 to 8 weeks after end of therapy with cystoscopy and biopsy of the tumor bed and normal bladder, or repeated TURT if residual macroscopic disease was detected. Computed tomography of the abdomen and the pelvis was also performed. Follow up CT chest, pelvis, and abdomen with or without cystoscopy were done every 3-months' time interval to detect the recurrence, also bone scan was done every 6-months.

*Statistics*

The association between categorical variables was analyzed by Chi square test with likelihood or Pearson according to whether >20% of cells contained <5 observations or not. For association between categorical (three or more categories) variables and numerical ones, Kruskal-Wallis test was used.

Ordinal logistic regression was run to assess the probability of having poor response to 3DCRT with concomitant boost due to different predictors, odds ratio =Ln (probability of non CR) = $a+B_1X_1+\ldots\ldots+B_pX_p$, survival curves were analyzed by Kaplan-Meier test and compared by log-Rank test which compares the whole survival experience between response categories, overall survival (OS) was calculated from time of diagnosis until time of death or last follow up, while loco-regional relapse free survival (LRRFS) calculated as the time elapsed between diagnosis and evidence of an event which was either death, bladder, or lymph node relapses, bladder intact RFS measured as the time between diagnosis and only bladder relapse or death of patients, other patients who did not experience an event were considered censored. All data were analyzed using IBM SPSS version 26 and considered significant at p-value $\leq 0.05$.

## Results

Table 1; summarized baseline characteristics of 42 recruited patients, although most patients had T2 and T3 diseases but 4 patients with T4a which might partly explained lower complete response rate, in addition the study involved 8 patients with hydronephrosis, and 18 patients with incomplete TURT, and 10 patients with multifocal bladder lesions, radiotherapy alone without platinum sensitizer was delivered to 5 patients attributed to hydronephrosis.

The overall response rate was 73.8% with complete response observed in 22 patients, local relapse occurred in 8 patients after a median time of 15 months, while only lymph node relapse occurred in 3 patients as tabulated in

Table 1. Baseline Patients' Characteristics

| Characteristic | Description (percentage) |
|---|---|
| Age (mean ±SD) | 76±5.04 |
| Median (range) | 75 ys (61-85) |
| Sex m/f | 27/15 (1.8: 1) |
| KPS | |
| >70% | 21 (50) |
| <70% | 21 (50) |
| TNM Stage | |
| T2N0M0 | 25 (59.5) |
| T3N0M0 | 13 (31) |
| T4aN0M0 | 4 (9.5) |
| Grade | |
| Intermediate grade TCC | 26 (61.9) |
| High grade TCC | 16 (38.1) |
| Hydronephrosis | 8 (19) |
| TURT | |
| Median number of previous TURT | 2 |
| Duration since last one TURT | Median 2 months |
| One month | 6 (14.3) |
| Two months | 23 (54.8) |
| Three months | 13 (31) |
| Completeness of last TURT | |
| Yes | 24 (57.1) |
| No | 18 (42.9) |
| Multifocality | |
| Yes | 10 (23.8) |
| No | 32 (76.2) |
| Treatment | |
| Chemoradiation | 37 (88.1) |
| Radiotherapy alone | 5 (11.9) |
| Follow up time (mean ±SD) | 26.9 ±6.8 |
| Median (range) | 25 months (11-37) |

Data expressed as number, percentages, mean±SD, and median, KPS; Karnofsky performance status

Table 2. Responses to 3DCRT with Concomitant Boost in 42 Patients with TCC

| Variable | Description (percentage) |
|---|---|
| Response | |
| CR | 22 (52.4) |
| PR | 9 (21.4) |
| SD | 11 (26.2) |
| ORR | 73.80% |
| Local relapse | 8 (19) |
| Time to local relapse (mean ±SD) | 15.2±5.6 ms |
| Median (range) | 15 ms (6-25) |
| Only LN relapse | 3 (7.14) |
| Distant relapse | 10 (23.8) |
| Time to distant relapse | 16.4±6.8 |
| Median (range) | 18.5 ms (6-27) |
| Metastatic sites | |
| Pulmonary metastases | 7 (16.7) |
| Peritoneal metastases | 1 (2.4) |
| Bone metastases | 3 (7.14) |
| Outcome | |
| Dead | 8 (19) |
| Alive | 34 (81) |

Data expressed as mean ±SD, median, number, percentages, CR, complete response; PR, partial response; SD, stable disease; ORR, overall response rate

Table 2.

Intuitively, patients with good KPS, T2N0M0, intermediate grade, and complete TURT had significantly higher CR rates than their counterparts, grabbed the attention was the effect of hydronephrosis where 5 patients achieved CR, and the insignificant effect of hydronephrosis on the type of response as mentioned in Table 3.

Ordinal logistic regression: In order to find real effect of different independent predictors on response to 3DCRT

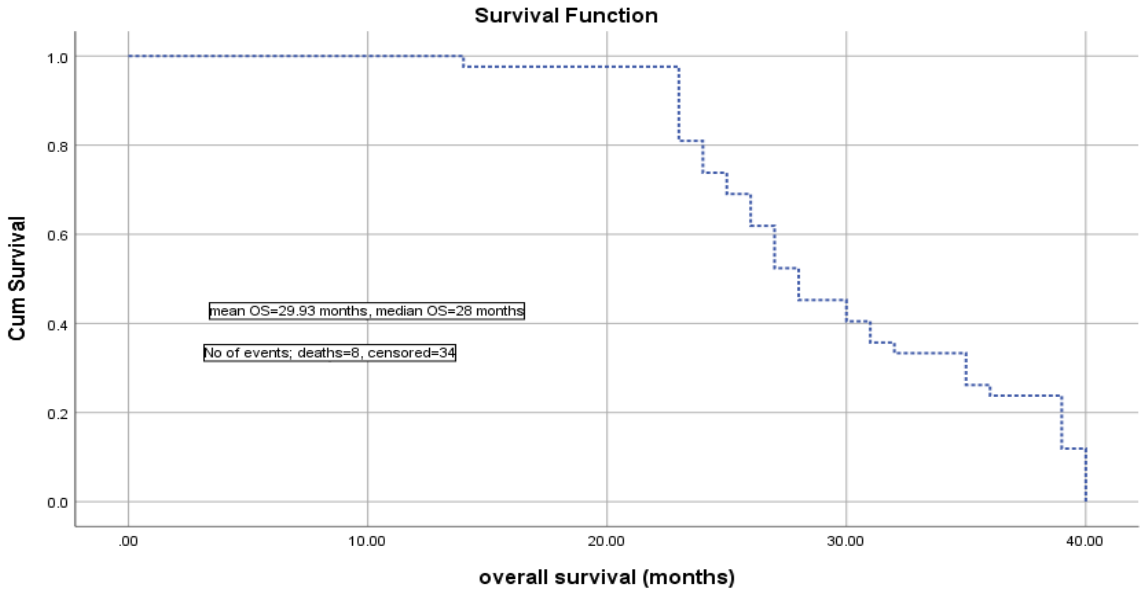


Figure 1. Overall Survival Curve of 42 Patients with Bladder TCC

Table 3. Relations between Response and Patients' Characteristics

| Variable | Response (percentage) | | | P-value |
|---|---|---|---|---|
| | CR | PR | SD | |
| Age1 | 75 (70-85) | 78 (61-82) | 76 (70-85) | 0.7 |
| Sex (m/f) | 12/10 | 7/2 | 8/3 | 0.4 |
| KPS | | | | LR=6.6 |
| >70 | 13 (59.1) | 6 (66.7) | 2 (18.2) | P=0.037 |
| <70 | 9 (40.9) | 3 (33.3) | 9 (81.8) | |
| TNM | | | | |
| T2N0M0 | 16 (72.7) | 7 (77.8) | 2 (18.2) | LR=11.8 |
| T3N0M0 | 5 (22.7) | 1 (11.1) | 7 (63.6) | P=0.019 |
| T4aN0M0 | 1 (4.5) | 1 (11.1) | 2 (18.2) | |
| Grade | | | | |
| Intermediate | 17 (77.3) | 6 (66.7) | 3 (27.3) | LR=7.9 |
| High | 5 (22.7) | 3 (33.3) | 8 (72.7) | P=0.02 |
| TURT | | | | |
| Complete | 16 (72.7) | 6 (16.7) | 2 (18.2) | LR=9.7 |
| Incomplete | 6 (27.3) | 3 (33.3) | 9 (81.8) | P=0.008 |
| Focality2 | | | | |
| Unifocal | 17 (77.3) | 9 (100) | 6 (54.5) | P=0.06 |
| Multifocal | 5 (22.7) | 0 (0) | 5 (45.5) | |
| Hydronephrosis | | | | |
| Yes | 5 (22.7) | 0 (0) | 3 (27.3) | P=0.1 |
| No | 17 (77.3) | 9 (100) | 8 (72.7) | |

All data were expressed as number and percentages, and analyzed by likelihood ratio of $\chi^2$ test except Focality2 analyzed by Pearson $\chi^2$ test, age1 analyzed by Kruskal-Wallis test and expressed as median (range), KPS; Karnofsky performance status.

with concomitant boost in comparison between different categories of predictors, ordinal logistic regression was performed, the final model gave a significant improvement over baseline intercept only (so gave better prediction of odds ratio) with Chi square =12.61, p=0.05, however the model integrated only KPS, stage, grade, TURT, and focality (which gave significant associations with responses) that could explain about 29.8% of the observed responses. The probability of having PR and SD compared to CR was nearly twice lower in those with KPS >70% compared with <70%, stages T2N0M0 and T3N0M0 each with a probability nearly three times lower than

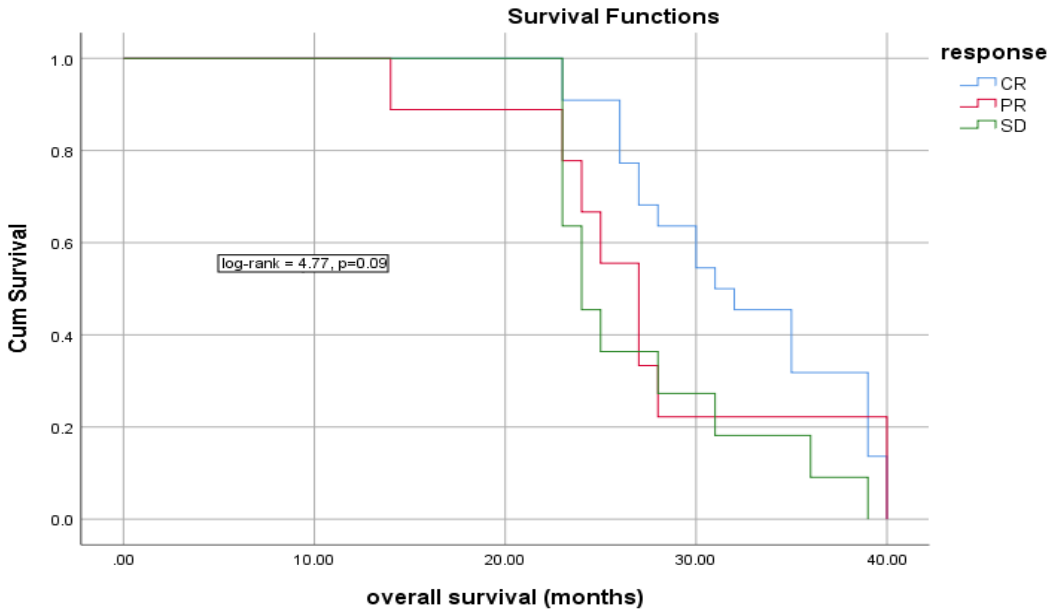


Figure 2. Overall Survivals of Different Response Types

Table 4. Ordinal Logistic Regression of Different Predictors on Response

| Predictors | Estimate | Wald | p-value | Odds ratio | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| KPS | | | | | | |
| >70% | -0.296 | 0.152 | 0.6 | 2.13 | -1.78 | 1.19 |
| Stage | | | | | | |
| T2N0M0 | -0.993 | 0.691 | 0.4 | 3.303 | -3.34 | 1.35 |
| T3N0M0 | -0.06 | 0.003 | 0.9 | 3.05 | -2.25 | 2.13 |
| Grade | | | | | | |
| Intermediate | -1.067 | 1.261 | 0.2 | 2.585 | -2.93 | 0.79 |
| Complete TURT | -1.089 | 1.947 | 0.1 | 2.175 | -2.61 | 0.44 |
| Unifocal lesion | -1.019 | 1.095 | 0.2 | 2.649 | -0.89 | 2.93 |

Wald test≈ t-test; CI, confidence interval; KPS, Karnofsky performance status

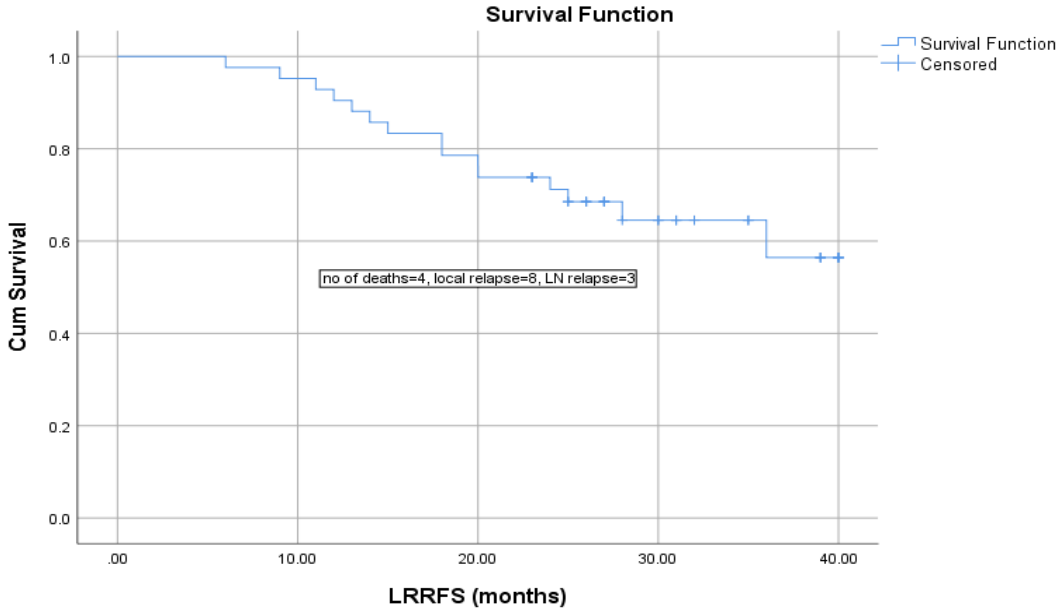


Figure 3. Loco-Regional RFS in 42 Patients with Bladder TCC

T4aN0M0 of having the previously mentioned responses and so on, all predictors did not give significant effects on odds ratio to indicate that they had equal strength on the type of response in spite of different odds ratios as shown in Table 4.

*Survival curves*

The median OS for 42 patients with TCC of bladder treated with 3DCRT and concomitant boost was 28 months, the mean OS was 29.9±1.04, and (95% confidence interval=27.9-32), Figure 1. The one-year OS was 100%, 2-year OS was 81%, and 3-year OS was 26.2%. Mean and Median overall survival according to response. There were no significant differences in the mean OS according to response along the three curves as a whole (Figure 2), although significant early separation of these curves was observed with Breslow test =6.6, p=0.038. but all curves

Table 5. Overall Survival According to the Response

| Response | Mean | SE | 95% CI | | Median |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| CR | 32.3 | 1.3 | 29.8 | 34.8 | 31 ms |
| PR | 27.6 | 2.7 | 22.2 | 32.9 | 27 ms |
| SD | 27.2 | 1.7 | 23.8 | 30.6 | 24 ms |
| Log Rank=4.77, p=0.09 | | | | | |

Analyzed by Kaplan-Meier test

Table 6. Toxicity Pattern of 42 Patients with TCC

| Acute toxicity | Descriptive (percentage) | Late toxicity | Descriptive (percentage) |
|---|---|---|---|
| Acute GU toxicity | | Late GU toxicity | |
| ≤grade 1 | 11 (26.2) | ≤ grade 1 | 15 (35.7) |
| Grade 2 | 28 (66.7) | Grade 2 | 25 (59.5) |
| Grade 3 | 3 (7.1) | Grade 3 | 2 (4.8) |
| Acute GIT toxicity | | Late GIT toxicity | |
| ≤ grade 1 | 32 (76.2) | ≤grade 1 | 37 (92.9) |
| Grade 2 | 10 (23.8) | Grade 2 | 5 (7.1) |

Data expressed as number and percentages

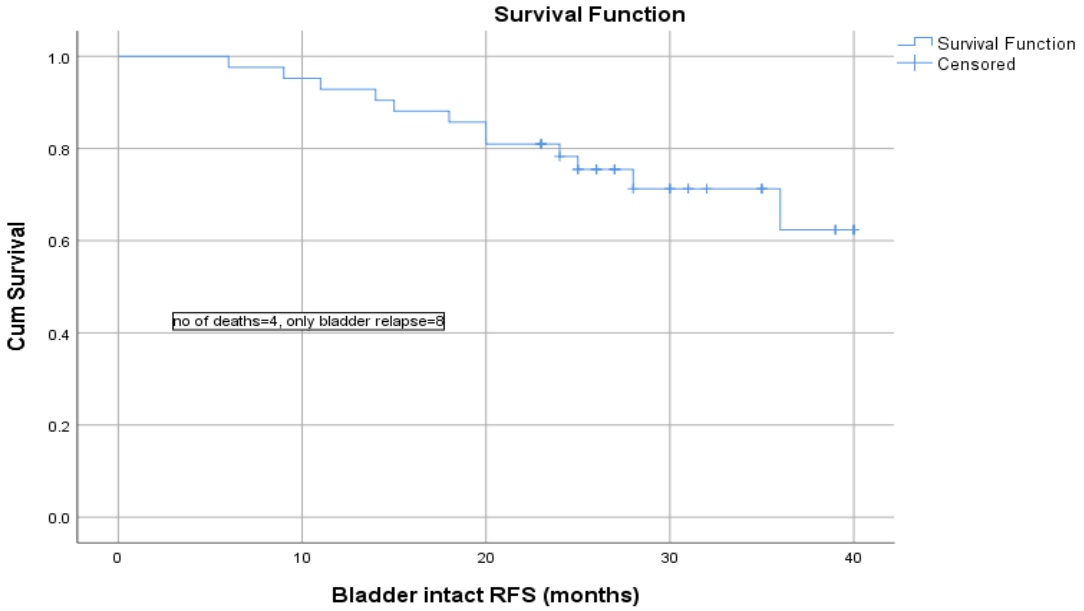


Figure 4. Showed the Bladder Intact Relapse Free Survival

converged at the end with Tarone-ware =5.8, p=0.06, the corresponding mean and median survival according to the response was tabulated in Table 5.

*loco-regional relapse free survival*

The mean LRRFS was 31.6±1.8, 95% CI=28.1-35.1, and the median was 26.5±1.4, the one-year loco-regional RFS was 92.9%, and 2-year LRRFS was 66.7%, Figure 3.

*Bladder intact RFS*

The mean bladder intact RFS was 33.4±1.7 months with 95% CI=30.1-36.6, and the median was 27±1.3 months as shown in Figure 4.

*Toxicity of treatment*

All patients completed their course of treatment with concurrent chemoradiation and concomitant boost, with the exception of 5 patients who were planned from the start to receive radiotherapy alone, acute toxicities were considered mild to moderate with only grade 3 GU toxicity found in 3 patients while late grade 3 GU toxicity was observed in 2 patients as illustrated in table 6. 66.7% of patients had G2 acute GU toxicity and 59.5% had G2 GU late toxicity, while 76.2% had equal and less than G1 acute GIT toxicity and 92.9% had equal or less than G1 late GIT toxicity. So this radiotherapy dose and technique given in this study has accepted toxicity profile.

## Discussion

Muscle invasive urinary bladder cancer treatment is a problematic issue as tumor showed a high rate of proliferation and repopulation with short survival, even with radical cystectomy 5 year-OS is only 27-55% with poor impact on quality of life (QOL) (Zaghloul, 2010). Alternatively, bladder preservation protocols and trimodality therapy are practiced right now with a recurrence rate of 28-60% and OS 39-63%. Many studies tried to find out the optimal radiotherapy dose and fractionation schemes (Zaghloul and Mousa, 2010).

The radio-resistance associated with cellular repopulation is supposed to be overcomed by accelerated radiotherapy where the same total dose can be delivered in shorter time compared to conventionally fractionated radiotherapy. A dose increment of 0.36 Gy per day is required to compensate for this repopulation.

In the current study, the rate of complete response (CR) was unsatisfactory (52.4%), that could be attributed to the significant percentage of incomplete TURT, high clinical stages as well as high histological grades included, in contrast to previous reports (Pos et al., 2003; Yavuz et al., 2003; Rodel et al., 2002) where the CR rate reached 74–84% by similar concomitant boost radiotherapy schedules.

Furthermore, the 2-year loco-regional RFS and mean bladder intact RFS in our results were 66.7% and 33.4 months respectively and these findings were comparable to what reported by Pos et al (Pos et al., 2003). The use of reduced radiation fields allowed dose increment with increased tolerance, without impairment of local control or increased toxicity as evidenced in many studies (Yavuz et al., 2003; Cowan et al., 2004).

Moreover, the synchronous combination of chemotherapy with radiation significantly improved loco-regional control in MIBC patients in a multicenter phase 3 trial compared with radiotherapy alone (James et al., 2012). In literature, the 5-year OS for trimodality treatment strategies ranged from 50%-60% (Ding et al., 2020), however in our results, we merely achieved 3-year OS of 26% that could be explained by more elderly patients recruited (median age 76 years), poor performance status with KPS<70% in half of patients in addition to the associated hydronephrosis irrespective of treatment protocol in 19% of them, also high percentage of patients

had high grade with incomplete TURBT, the later was confirmed to be a significant predictor of OS in a previous meta-analysis (Yavuz et al., 2003), and finally 23.8% of patients developed distant metastasis after a median time of 18.5 months which significantly impaired OS among studied patients.

In the current study, 2 cycles of neoadjuvant chemotherapy were only tolerated by 60% of our patients that might explain in part, poor survival although the true benefit of neoadjuvat chemotherapy was not confirmed in bladder preservation protocols in a previous phase III study (Rodel et al., 2002). Moreover, ORR among study patients was 73.8% with >50% achieved CR, poor PS, T3-4a, high grade, and incomplete TURBT were significant prognostic factors for response in bivariate analysis, in spite, the current results were not comparable to Sham Eldin et al, where ORR was 85% with 70% CR rate with also T stage, high grade, and TURBT, in addition to multifocality and hydronephrosis were considered significant prognostic factors, but our results revealed comparable acute and late toxicities to the previously mentioned study in spite of recruitment of elderly patients (Ashraf et al., 2019).

Concurrent chemoradiation with concomitant boost was considered tolerable alternative treatment modality especially in elderly to radical cystectomy, grade III acute radiation induced cystitis and enteritis were developed in 7.1% and 10% of patients respectively, while grade III late urinary toxicities were developed in 4.8% and with no >grade III toxicity developed and no >grade II late intestinal toxicity also developed, these findings were comparable to most of adverse effects in previously mentioned studies of concomitant boost (Pos et al., 2003; Yavuz et al., 2003; Ashraf et al., 2019).

The rate of late toxicity in our study was low, we recorded GI and II toxicities in all patients except 2 patients developed GIII genitourinary (reduced bladder capacity) and 5 patients (7.1%) suffered from GII gastrointestinal toxicity. Our results are consistent with other studies (Yavuz et al., 2003; Cowan et al., 2004; Chen et al., 2003). The low incidence of severely impaired bladder capacity seems to be a well-balanced compromise between tumor control and toxicity.

In Lutkenhaus et al., (2016) who compared conformal box technique versus IMRT with simultaneous boost in elderly surgically unfit patients and demonstrated a CR rate of 87%, 3-year OS and loco-regional control rate of 44% and 73%, acute grade ≥2 urinary and intestinal toxicities developed in 26% and 19%, and late grade ≥ 2 urinary and intestinal toxicities were reported in 14% and 5% respectively for all patients, although we were not in alignment with Lutkenhaus study regarding the response but we approached their survival rates and achieved comparable toxicities by our protocol as bladder injury increases for doses over 50Gy (Khosravi –Shahi and Cabezon-Gutierrez, 2012).

*Abbreviation*

CRT, Chemoradiation; CR, Complete response; CTV, Clinical target volume; DFS, Disease free survival; GTV, Gross tumor volume; IMRT, intensity modulated radiotherapy; TRUBT, Transurethral resection of bladder tumor; PTV, Planning target volume; OS, Over all survival; 3DCRT, 3 dimentional conformal radiotherapy; CI, Confidence interval; LRRFS, Locoregional recurrence free survival; DSS, Disease specific survival; LRDFS, Locoregional disease free survival; GU, Genitourinary; GI, Gastrointestinal; QOL,Quality of life.

## Author Contribution Statement

AA is the first author of the manuscript and made contributions to the protocol design. DA analyzed and interpreted the data, and all authors drafted the manuscript. DA and RA provided support regarding the statistical analysis and discussion. AH 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.

## Acknowledgements

Not applicable.

*Availability of data and material*

All data analyzed were included within the manuscript.

*Ethical approval*

The study was approved by South Egypt Cancer Institute (SECI) ethics committee (approval number: 479) and informed written consent was taken from all participating patients.

*Limitation of the study*

Small sample size, inhomogeneity of patients, and lack of molecular profiling, like the apoptotic index or Ki-67 index, which recorded to be strong predictive factors for local control and may be helpful in selecting patients for concomitant boost strategy, were considered crucial limitations in the current work hindered many statistical relationships.

*Competing Interests*

The authors indicated no potential conflicts of interest.

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