Efficiency and toxicity of hypofractionated radiotherapy with concurrent gemcitabine in the treatment of muscle-invasive bladder cancer (retrospective study)

Mohamed RF[1], ElZahir EM[2], Mostafa HG[1]

[1] Department of Clinical Oncology, Faculty of Medicine, Assiut University, Egypt.
[2] Radiotherapy Department, South Egypt Cancer Institute, Assiut University, Egypt.

Abstract:

Objectives: The objective was to calculate the toxicity of modified hypofractionated radiation combined with gemcitabine as well as local control, disease free survival (DFS), overall survival (OS), and bladder preservation rate in patient with muscle invasive bladder cancer (MIBC).

Methods: Weekly 100 mg/m2 doses of gemcitabine were utilized as a radio-sensitizer. 30-minute intravenous infusion two to four hours before radiation treatment. Patients were treated with a hypo-fractionated radiation schedule utilizing a SIEMENS Linear accelerator over the course of four weeks and twenty-eight days, delivering 5250 cGy/20 fractions at 262.5 cGy per fraction.

Results: In the 82 cases of bladder cancer that were examined, we observed a significantly lower frequency of patients who suffered frequent urination (p=0.002), urgency (p=0.001), and proctitis (p=0.031) when comparing early and late toxicities. An overall bladder preservation rate of 87.8% is achieved in the majority of the analyzed cases (87.7%), with a regressive course in 59.8%, a stationary course in 28.0%, and a progressive course in ten cases (12.2%). Patients had a median follow-up time of 56 months after a 5-year observation period. (Range, 1 month to 8 years). At 94 months, the OS rate was 84.3% and at 93 months, the DFS rate was 82.8%.

Conclusion: Good efficacy and acceptable tolerability for a weekly, low-dose gemcitabine with hypofractionated radiation regimen in MIBC patients.

Keywords: gemcitabine, radio-sensitizer, hypofractionated radiotherapy, MIBC, TCRH.

Received: 19 June 2023
Accepted: 9 July 2023

Authors Information:
Rehab Farouk Mohamed
Department of Clinical Oncology, Faculty of Medicine, Assiut University, Egypt.
email: foroukrehab@aun.edu.eg

Esraa Mostafa Abd-ElZahir
Radiotherapy Department, South Egypt Cancer Institute, Assiut University, Egypt
email: essra.mostafa93@gmail.com

Hanan Gamal-Eldeen Mostafa
Department of Clinical Oncology, Faculty of Medicine, Assiut University, Egypt
email: h.mostafa@aun.edu.eg

Corresponding Author:
Rehab Farouk Mohamed
Department of Clinical Oncology, Faculty of Medicine, Assiut University, Egypt.
email: foroukrehab@aun.edu.eg

Introduction:

The most frequent cancer of the urinary system, with over 80,000 new cases and over 17,000 deaths per year in the US, is bladder cancer. Over 200,000 people die from bladder cancer yearly and 600,000 new cases are reported globally. These bladder malignancies are mostly urothelial in developed regions of the world like North America and Western Europe. Almost 70% of newly discovered cases of bladder cancer are in their early stages and have not yet spread to the muscular layer of the bladder wall. The remaining 30% of patients have bladder cancer with muscular invasion. [1].

The incidence of bladder cancer in Egypt at 2020 was 10,655 (7.9%) of all cancers. Over the past 50 years, bladder cancer has been the most prevalent disease in Egypt. According to international standards, the incidence of bladder cancer in Egypt in 2002 was around 30,000 new cases annually. It's interesting to note that squamous cell carcinoma (SCC), which made up between 59% and 81% of reported bladder cancers between 1960 and 1980, has been the most prevalent histological type of bladder cancer in Egypt. In Egypt, chronic bladder infection with Schistosoma haematobium, has been the most significant risk factor for bladder cancer, in contrast to the major etiologies of smoking and occupational exposures in Western countries [2-10].

In order to satisfy the needs of two patient groups—those with minor diseases who want to avoid invasive surgery and those with significant medical co-morbidities for whom radical cystectomy would be too risky—bladder preservation therapies for MIBC have been developed. There are a number of bladder preservation techniques, with the trimodal technique (TMT) of maximum transurethral resection (MTUR) plus chemotherapy (CTH) receiving the greatest support. Although the results are worse for individuals

who cannot have surgery than for those who can, bladder preservation procedures nevertheless have the potential to be therapeutic [11].

MTUR is combined with concurrent radiation therapy (RT) and a sensitizing chemotherapeutic induction regimen in modern bladder-sparing procedures. Early treatment response is evaluated via cystoscopy and re-biopsy. Adjuvant CTH is used in patients who experience a clinical complete response (CR). Patients who didn't fully respond should get a cystectomy soon away [12].

Although chemo-radiotherapy (CRT) is now usually chosen over RT alone, it is critical to understand that most people have access to a choice of sensitizing CTH. As a result, only a small percentage of patients will be unable to get CRT. If RT is deemed required, a recent study demonstrates that it is realizable with satisfactory results. CRT is superior to RT alone, but they have also provided evidence that RT has therapeutic potential on its own. The loco-regional disease-free survival (DFS) rate at 2 years was 54%, whereas the 5-year overall survival (OS) rate was 35%. [13].

Gemcitabine in combination with platinum has shown activity in both neoadjuvant and metastatic urothelial cancers. As demonstrated in the Phase II GemX project, this can also be employed as a radio-sensitizer in the form of weekly infusions at 100 mg/m2 [14]. The 5-year OS, DFS, and cystectomy-free survival rates for patients receiving gemcitabine-based CRT were 59 percent, 80.9 percent, and 93.3 percent, respectively. The therapy was also well tolerated [15].

Up until now, a large portion of the world has been exposed to bladder radiation at a normal fractionation of 1.8–2 Gy [16]. Two radiation schedules are frequently utilized in the UK: the hypofractionated regimen of 55 Gy in 20 settings over 4 weeks and the 64 Gy in 32 settings over 6.5 weeks schedule. The hypofractionated regimen is anticipated to become the gold standard of care following the publication of a meta-analysis comparing the two regimens by merging two large Phase III trials, BC2001 and BCON. Hypofractionated radiation was found to be superior to 64 Gy in 32 fractions and non-inferior for OS and late bladder and rectum toxicity regardless of radio-sensitizer choice when compared to invasive loco-regional therapy [17].

Although it was predicted that bladder cancer would progress quickly, it was also predicted that it would have a high α/β ratio, which raised the prospect that mild hypofractionation could be less effective and more likely to cause late damage. Therefore, it was unexpected to find that moderate hypofractionation is safer and more efficient than conventional fractionation. This would suggest that the α/β ratio is less than expected and/or that the impact of repopulation is more than anticipated. After about 5 weeks of dosage restrictions for hypofractionation, tumor repopulation may cause radiation effectiveness to decline. The hypofractionated regimen should be utilized as the gold standard of therapy because shorter fractionations are also more convenient for patients and less expensive [18].

Patients and Methods:

Population study:

A study on 82 patients was conducted in the radiotherapy department at the South Egypt Cancer Institute, Assiut University, from January 2012 to December 2017. Retrospective analysis was done on the medical records of the participants who received maximum TUR and had transitional cell carcinoma (TCC) of the bladder that was histologically confirmed. The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification was used to stage the patients. (T1-T3, N0, and M0). Patients having node-positive disease, evidence of distant metastasis (M1) prior to chemo-radiotherapy, abnormal biochemistry, evidence of tumor-related hydronephrosis, prior pelvic RT, or previous chemotherapy administration were excluded from the study.

Ethical approval:

Before any data were collected, the review board of the Assiut University Faculty of Medicine's ethics committee authorized the research protocol. (IRB No 17101562).

Study design:

MTUR was performed under general anesthesia, cystoscopy with bladder biopsies were typically carried out. Within three weeks of their initial cystoscopy, individuals had a second look to check for any residual tumor. A thorough physical examination, routine hematologic laboratory evaluations, an MRI of the abdomen and pelvis or a CT scan, as well as chest imaging, should all be done prior to RT, at least 4 weeks after the patient's diagnostic TUR of the bladder tumor. Before beginning CRT, as a radio-sensitizer, gemcitabine was administered weekly at a rate of 100 mg/m2. Two to four hours prior to radiation treatment, a 30-minute intravenous infusion. Patients were treated with a hypo-fractionated radiation schedule utilizing a SIEMENS Linear accelerator over the course of four weeks and twenty-eight days, delivering 5250 cGy/20 fractions at 262.5 cGy per fraction.

Follow up:

Three months following the end of the treatment, a cystoscopy was performed. Biopsies were taken of any observed anomalies. Abdominal and pelvic MRI scans were done either before or at least 4 weeks after any biopsy. The Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) were used to assess the tumor response as follows:

- CR: was defined as the absence of visible tumor endoscopically and the absence of histologic evidence of disease. Additional cystoscopies were done at 7, 12, and yearly after that. Repeat MRI scans were performed at the 12- and 24-months.
- Partial response (PR): was defined as presence of superficial non- MIBC (NMIBC) in form of residual tumor in cystoscopy and confirmed by histological evidence of disease. Patients had TUR as a result,

and were then treated with second-look cystoscopy and conventional intravesical instillation. Patient underwent cystectomy if disease was persistent.

- Stable disease (SD): was defined either as persistent superficial tumor as PR after instillation or persistent MIBC after end of CRT. Cystectomy was recommended as salvage treatment of these patients.
- Progressive disease (PD): was defined as increase size of persistent MIBC or distant metastasis.

Endpoint of study:

- DFS: was calculated from the date of starting the protocol up to date of recurrence or distant metastasis or death from any cause.
- OS: was calculated from the date of diagnosis up to date of death or the last follow up.

Toxicities evaluation:

On the first and last days of treatment, toxicity was evaluated weekly. The Radiation Therapy Oncology Group (RTOG) for Research and Treatment of Cancer was used to score acute toxicity for an additional 6 weeks following the end of treatment. After one year, it was evaluated every six months with time for a cystoscopy and imaging examination.

Statistical analysis:

Version 22 of the statistical software for the social sciences (SPSS) Inc., Chicago, Illinois, USA, was used for all statistical calculations. When quantitative data were not frequently distributed, they were statistically reported in terms of mean, standard deviation (SD), and median (range). When appropriate, qualitative data were statistically described using frequencies (the number of occurrences) and relative frequencies (percentages). For the purposes of calculating OS and DFS, Kaplan-Meier's technique with log rank test was employed. To identify relevant factors connected to mortality, hazard ratio (HR) with a 95% Confidence Interval (CI) and COX regression analysis were calculated. P-value set to 0.05 levels of significance.

Results:

The current study was a retrospective study that attempted to estimate the response to modified hypofractionated RT concurrent with gemcitabine in 82 patients with MIBC in addition to estimating local control, DFS, OS, bladder preservation rate, and toxicity of this protocol among patients attending to South Egypt Cancer Institute, Assiut University.

Table 1 provides an overview of the patients and tumor characteristics. They ranged in age from 34 to 85 years old, with a mean age of 59.07 + 8.81 years. Six patients (7.3%) were under the age of 50, while 76 patients (92.7%) were above the age of 50. One case (1.2%) was female, while nearly all of the investigated cases (98.8%) were men. A third (32.9%) of the patients under study had comorbid conditions; the most prevalent of these was hypertension, which was present in 18 cases (22.0%), followed by cardiac conditions in eight instances (9.8%), and diabetes mellitus in seven cases (8.5%). In contrast, 3.7% and 1.2%, respectively, of the population had chronic obstructive pulmonary disease (COPD) and deep venous thrombosis (DVT). The performance status (PS) of the patients under study was also determined, and it revealed that PS (0 + 1) was present in 52 instances (63.4%) and PS (2 + 3) in 30 cases.

Table 1 patients and tumor characteristics (n=82)

Patients characteristics	No.	**%**
Age (years)		
• Mean± SD	59.07 ± 8.81	
• Median (range)	60 (34-85)	
Age groups		
• < 50 years	6	(7.3)
• ≥ 50 years	76	(92.7)
Gender		
• Male	81	(98.8)
• Female	1	(1.2)
Associated comorbidity	27	(32.9)
• Diabetes mellitus	7	(8.5)
• Hypertension	18	(22.0)
• Cardiac	8	(9.8)
• COPD	3	(3.7)
• DVT	1	(1.2)
Performance status		
• 0	24	(29.3)
• 1	28	(34.1)
• 2	23	(28.0)
• 3	7	(8.5)
Histological type		
• Invasive TCC	82	(100.0)
Tumor grade		
• G1	2	(2.4)
• G2	73	(89.0)
• G3	7	(8.5)
TNM staging		
• T1N0M0	3	(3.7)
• T2N0M0	73	(89.0)
• T3N0M0	6	(7.3)
Focality		
• Single	69	(84.1)
• Multifocal	13	(15.9)

SD: standard deviation; **COPD:** chronic obstructive pulmonary disease; **DVT:** deep venous thrombosis; **TCC:** transitional cell carcinoma; **G:** grade.

All of the cases in the study had invasive TCC bladder cancer, which was verified histologically. Regarding the tumor grade (G), there were two cases with G1 (2.4%), 73 cases with G2 (89.0%), and seven cases (8.5%) with G3. Three cases (3.7%) of tumor size (T) T1; 73 cases (89.0%) of T2; and six cases (7.3%) of T3. In the majority of the cases examined (84.1%), there is only one lesion, whereas 15.9% of the cases have multifocal lesions.

As shown in Table 2, more than half of the cases studied (62.2%) had possibly suspected risk factors for bladder cancer, including active smoking in 28 cases (34.1%), bilharzias in six cases (7.3%), hepatitis B virus (HBV) infection in seven cases (8.5%), hepatitis B virus (HCV) infection in one case (1.2%), and renal risk factors in four cases (one case had ureteric stones and hydronephrosis, and three cases had nephrectomy).

Table 2: Risk factors for development of bladder cancer among the studied patients (n=82)

Risk factors	No.	(%)
Risk factors	51	(62.2)
Smoking	28	(34.1)
Bilharzias	6	(7.3)
Hepatitis		
• HBV	7	(8.5)
• HCV	1	(1.2)
Renal		
• Ureteric stones and hydronephrosis	1	(1.2)
• Nephrectomy	3	(3.7)

HBV: hepatitis B infection; **HCV:** hepatitis C infection.

According to Table 3, there were 30 cases of early toxicities in the form of proctitis, urgency, and increased frequency of urination (11.0% grade 1, 15.9% grade 2, and 9.8% grade 3). Additionally, there was 22.0% grade 1, 3.7% grade 2, and 1.2 % of grade 3 proctitis. A total of 21 cases (25.6%) of haematological toxicity were observed, including thrombocytopenia in 12.2%, anemia in 6.1%, liver damage in 3.7%, neutropenia in 2.4%, and leukopenia in just one case (1.2%). For gastrointestinal toxicity, there were 15 cases (18.3%) that experienced diarrhea 7 cases (8.5%) and 8 cases (9.8%) with grade 1 and grade 2, respectively.

Table 3's analysis of the incidence of late toxicity reveals that there were 12 cases (14.6%) of increased frequency of urination (2.4% grade 1, and 12.2% grade 2), seven cases (8.5%) of urgency (4.9% grade 1, and 3.7% grade 2), and twelve cases (14.6%) of proctatis (7.3% grade 1, and 7.3% grade 2). When comparing early and late toxicities in the instances of bladder cancer that were analyzed, we saw a significantly lower number of patients who experienced frequent urination (p=0.002), urgency (p=0.001), and proctitis (p=0.031).

The majority of the cases analyzed (87.7%) achieve response (59.8% have regressive course, 28.0% have stationary course, and ten cases (12.2%) have progressive course), resulting in an overall bladder preservation rate of 87.8%. Regarding the recurrence status of our examined cases, ten patients (12.2%) experienced disease recurrence throughout the follow-up period. (five cases with loco-regional recurrence to the bladder and adjacent lymph nodes, and five cases developed distant metastasis mainly bone and brain metastasis). 11.0% of the cases we evaluated had overall mortality Table 4.

Regarding the five years OS and DFS (Table 5, Figure 1, 2). The patient's age, smoking status, bilharzia infection, G stage, and T stage all had no effect on the OS or DFS of the cases under research ($p > 0.05$ in each case). The 82 bladder cancer patients had a 56-month median follow-up period. (Range, 1 month to 8 years). 9 of them died (11.0%). The OS rate was 84.3% at 94 months, per Kaplan-Meier analysis. The disease returned in 10/82 patients, or 12.2% of the total. Approximately 55 months passed before the local disease reappeared. (Range, 1 month to 8 years). At 93 months, the DFS rate was 82.8%, as shown by Kaplan-Meier analysis.

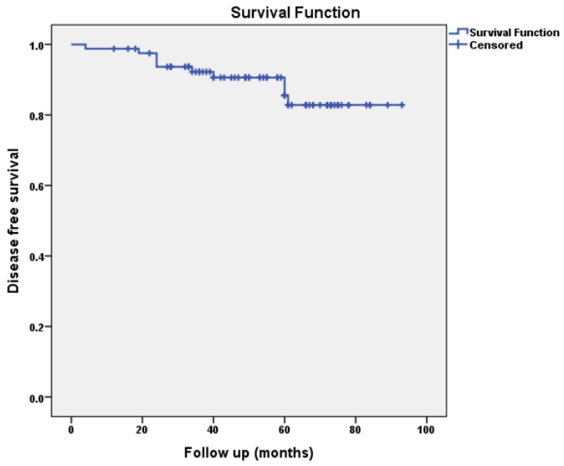

Fig. 1: Disease free survival of patients according to Kaplan-Meier analysis, the rate at 93 months was 82.8%

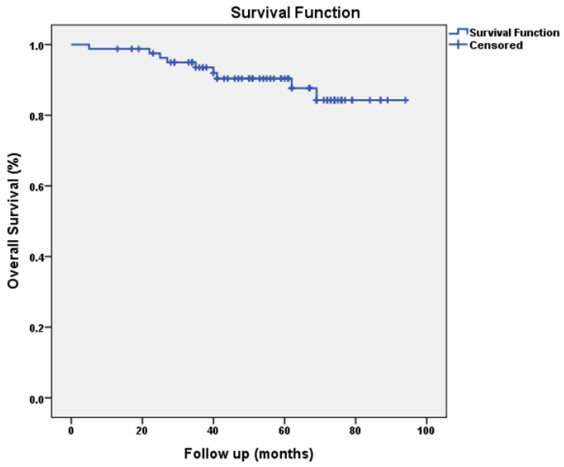

Fig. 2: Overall survival of patients according to Kaplan-Meier analysis, the rate at 94 months was 84.3%

Table 3 Incidence of early and late toxicities among the studied bladder cancer patients (n=82)

	Early toxicity		Late toxicity		*P* value
	No.	**%**	**No.**	**%**	
urological toxicity					
Frequency					
• No	52	(63.4)	70	(85.4)	
• Grade 1	9	(11.0)	2	(2.4)	**0.002**
• Grade 2	13	(15.9)	10	(12.2)	
• Grade 3	8	(9.8)	0	(0.0)	
Urgency					
• No	28	(34.1)	75	(91.5)	
• Grade 1	30	(36.6)	4	(4.9)	<**0.001**
• Grade 2	17	(20.7)	3	(3.7)	
• Grade 3	7	(8.5)	0	(0.0)	
Proctitis					
• No	60	(73.2)	70	(85.4)	
• Grade 1	18	(22.0)	6	(7.3)	**0.031**
• Grade 2	3	(3.7)	6	(7.3)	
• Grade 3	1	(1.2)	0	(0.0)	
Hematological toxicity					
• No	61	(74.4)			
• Thrombocytopenia	10	(12.2)			
• Anemia	5	(6.1)			
• Hepatic toxicity	3	(3.7)			
• Neutropenia	2	(2.4)			
• Leukopenia	1	(1.2)			
Gastrointestinal toxicity					
• No GIT toxicity	67	(81.7)			
• Diarrhea grade 1	7	(8.5)			
• Diarrhea grade 2	8	(9.8)			

Table 4 Outcome among the studied patients (n=82)

	No.	**%**
Response		
• Regressive	49	(59.8)
• Stationary	23	(28.0)
• Progressive	10	(12.2)
Bladder preservation rate	72	(87.8)
Recurrence status		
• No recurrence	72	(87.8)
• Recurrence	10	(12.2)
▪ Loco-regional	5	(6.1)
▪ Distant metastasis	5	(6.1)
o Bone	5	(100.0)
o Brain	4	(80.0)
Outcome		
• Alive	73	(89.0)
• Died	9	(11.0)

Table 5 Overall survival and disease free survival according to clinic- pathological details of the studied patients (n=82)

	OS (5 years) Estimate ± SD	*P* value	DFS (5 years) Estimate ±SD	*P* value
Age groups				
• < 50 years	100.0 %± 0.0	0.322	100.0 ± 0.0	0.305
• ≥ 50 years	89.5 ± 3.8		81.0 ± 5.8	
Smoking				
• No	87.8 ± 4.7	0.356	87.7 ± 4.7	0.661
• Yes	95.2 ± 4.6		83.5 ± 9.0	
Performance status				
• 0 +1	94.0 ± 3.3	0.197	90.3 ± 4.9	0.089
• 2+4	83.8 ± 7.5		77.0 ± 9.8	
Bilharzias				
• No	84.4 ± 5.6	0.644	82.9 ± 5.6	0.702
• Yes	83.3 ± 15.2		83.3 ± 15.2	
Tumor grade				
• G1				
• G2	90.5 ± 3.7	0.920	85.1 ± 5.1	0.919
• G3	85.7 ± 13.2		85.7 ± 13.2	
T stage				
• T1				
• T2	89.2 ± 3.9	0.564	83.9 ± 5.2	0.527
• T3	100.0 ± 0.0		100.0 ± 0.0	

OS: overall survival; **DFS:** disease free survival; **SD:** standard deviation; **G:** grade; **T:** tumor

Discussion:

With more than 500,000 new cases and 210,000 deaths worldwide in 2020, TCCs are the tenth most frequent malignancy [16]. In Egypt, bladder cancer is the second most frequent cancer in men (10.7%), especially in Upper Egypt (12.60%), where it affects men at an age-adjusted prevalence of 21.1% [19]. An estimated 30% of patients had bladder cancer that had MIBC. The gold standard treatment option historically included radical cystectomy and extensive pelvic lymph-node dissection. However, this can be linked to morbidity, high rates of postoperative complications, and frequently necessitates a permanent stoma, which might impair the patient's quality of life [20].

The National Comprehensive Cancer Network (NCCN) guideline published in 2019 ranked TMT, a representative bladder preservation therapy (BPT) that uses concurrent CRT after MTUR, as category 1 in the treatment of locally advanced MIBC [21].

According to Mustaq et al in accordance with the current study, patients aged 60 to 70 years represented 35.73% of bladder cancer patients, while patients aged at least 70 years represented approximately 21.26% of bladder cancer patients in the Egyptian population. In fact, about 80% of bladder cancer cases are diagnosed in adults aged 65 or older [22, 23]. Age-related increases in bladder cancer incidence suggest that the disease takes decades after exposure to mutagens in order to overcome cellular tumor-suppressor mechanisms and lead to carcinogenesis [24].

Men are almost four times as likely as women to be diagnosed with bladder cancer worldwide. In the present study, we found that 98.8% of the cases were men. This disparity can be explained by variations in tobacco smoking rates; men continue to have a larger relative risk of dying from bladder cancer than women do. (3.0 vs. 2.4). Other potential risk factors for men include exposure to chemicals at work, alcohol consumption, and red meat consumption [24, 25].

The safety and activity profile of concurrent CRT based on gemcitabine for the treatment of MIBC have been reported in the final reports of eight phase I-II trials [14, 26-32]. Each participant in the current trial received a hypofractionation treatment consisting of weekly doses of 100 mg/m2 of gemcitabine and 5250 cGy/20 fractions for a period of 4 weeks which is used in our study.

In terms of urological toxicity, it's interesting that we saw no long-term toxicity at grades 3-4. The earlier phase II study by Choudhury et al which used weekly gemcitabine 100 mg/m2 and 52.5 Gy over 4 weeks, provided support for our research. They stated that this regimen showed encouraging outcomes with a 64%

local control rate (bladder in situ) and extremely low long-term toxicity [14]. The same holds true for the long-term toxicity findings identified by Oh et al while employing concurrent RT and twice-weekly gemcitabine [33]. In agreement with the current study, several additional phase I or II bladder cancer trials showed that gemcitabine was used as a radio-sensitizer once per week without significant liver harm [14, 27, 32].

It's interesting to note that in numerous other phase I/II trials, although involving different tumor types, biweekly gemcitabine with concurrent radiation did not result in liver toxicity [34]. During the initial TUR assessment after therapy, 72 patients had a complete radiological and pathological response, with an OS rate of 87.8%. Ten patients experienced recurrence, however (five with loco-regional recurrence and five with distant metastasis). These findings are supported by a phase II study that used conformal hypofractionated RT with gemcitabine, which had lower 3-year OS (75%), DFS (82%), and CR rates (88%) than the current study. While a different published study by Cowan and colleges, who looked at the treatment of 60 chosen patients with hypofractination radiation alone, showed a 75% CR rate and 61% OS [35].

The patient's result may vary based on the radiation dose, technique, and the number of prior TUR treatments, in addition to the tumor G [36]. As opposed to the present study, a recent prospective phase II Egyptian trial by Mohamed et al evaluated the efficacy of hypofractionated radiation in combination with gemcitabine for bladder preservation in elderly bladder cancer patients. The OS rate was reported to be 94.4%, while the DFS rate was reported to be 72.6% by the author. Among the 25 patients who experienced CR, four underwent cystectomy due to local recurrence, one had metastases, and one developed both local recurrence and distant metastasis [37].

The last study by Mohamed et al only included older patients (65 years old), and age does affect patient outcome, which may be the cause of this disparity. Finding prognostic variables that can forecast the progression of cancer is a significant challenge for urologists. More accurate predictions of the likelihood of survival at each follow-up and the capacity to calculate cancer-specific survival (CSS) could result in more informative prognostic data used in patient monitoring [38].

The objective of the current study was to identify valid prognostic markers for bladder cancer patients' survival; however, the COX regression analysis showed that none of the clinic-pathological information about the patients could be regarded as a significant predictor of mortality. This finding may be due to the study's retrospective design, which may have an impact on the viability and quality of the data collected, as well as the fact that the sample size was small and this was a single institution study. This result emphasizes the necessity of a bigger prospective multicenter trial to investigate the role of modified hypofractionated radiation in patients with invasive bladder cancer who are also receiving gemcitabine.

In accordance with the findings of the current study, Kucuk et al prior investigation found that, despite the fact that the odds of survival significantly decreased with increasing tumor stage, there was no statistically significant association between tumor stage and OS. The authors attribute this finding to the small sample size of the patients under investigation (p=0.15) [39]. In contrast, the BC2001 trial's predetermined prognostic criteria for invasive loco-regional control included age, sex, tumor stage, use of neoadjuvant chemotherapy, and degree of resection; and for OS, these factors included age and sex [40, 41].

Conclusion:

TMT demonstrated good efficacy and tolerable toxicity in the treatment of MIBC when hypofractionated radiation is combined with weekly low-dose gemcitabine.

List of abbreviations:

AJCC: American Joint Committee on Cancer
BPT: bladder preservation therapy
CI: Confidence Interval
COPD: chronic obstructive pulmonary disease
CR: complete response
CRT: chemo-radiotherapy
CSS: cancer-specific survival
CTH: chemotherapy
DFS: disease free survival
DVT: deep venous thrombosis
G: grade
HBV: hepatitis B virus
HCV: hepatitis C virus
MIBC: muscle invasive bladder cancer
MTUR: maximum transurethral resection
NCCN: National Comprehensive Cancer Network
NMIBC: non- muscle invasive bladder cancer
OS: overall survival
PD: Progressive disease
PR: Partial response
PS: performance status
RECIST: Response Evaluation Criteria in Solid Tumors
RT: radiation therapy
RTOG: Radiation Therapy Oncology Group
SCC: squamous cell carcinoma
SD: Stable disease
SD: standard deviation
SPSS: statistical package for the social sciences
TCC: transitional cell carcinoma
TMT: trimodal technique
TNM: tumor-node-metastasis

Financial support:

No financial support for this article.

Availability of data and materials:

The data underlying this article will be shared on reasonable request to the corresponding author. foroukrehab@aun,edu,eg. All data generated or analyzed during this study are included in this published article.

Conflict of interests:

The authors declare that they have no competing interests.

Funding:

No funding is declared for this article.

Author contributions:

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

References:

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin. 2023 Jan;73(1):17-48.
2. Global Cancer Observatory (Globocan), Egypt fact sheet. https://gco.iarc.fr/today/data/factsheets/populations/818-egypt-fact-sheets.pdf (2020).
3. El-Sebai I, El-Bolkainy MN, Hussein MH. Cancer institute registry. Med J Cairo Univ 1973;41:175.
4. El-Bolkainy MN, Mokhtar NM, Ghoneim MA, et al. The impact of schistosomiasis on the pathology of bladder carcinoma. Cancer. 1981 Dec 15;48(12):2643-8.
5. Mohkatar N, editor. 1st ed. Cairo: The National Cancer Institute at Cairo University; Cancer pathology registry (1985–1989), 1991.
6. Soliman AS, Brody ML, Raouf AA, et al. Cancer mortality in Menofeia, Egypt: comparison with U.S. mortality rates. Cancer Causes Control. 1999 Oct;10(5):349-54..
7. el-Mawla NG, el-Bolkainy MN, Khaled HM. Bladder cancer in Africa: update. Semin Oncol. 2001 Apr;28(2):174-8.
8. Parkin MD, Bray F, Ferlay J, et al. Global cancer statistics 2002, CA Cancer J Clin. 2005 Mar-Apr;55(2):74-108.
9. El-Bolkainy MN. Topographic pathology of cancer. 1st edn. Cairo: The National Cancer Institute, Cairo University; 1998.
10. Mostafa MH, Sheweita SA, O'Connor PJ. Relationship between Schistosomiasis and Bladder Cancer. Clin Microbiol Rev. 1999 Jan;12(1):97-111.
11. Mirza A, Choudhury A. Bladder preservation for muscle invasive bladder cancer. Bladder Cancer. 2016 Apr 27;2(2):151-163.
12. Jiang DM, Jiang H, Chung PWM, et al. Neoadjuvant chemotherapy before bladder- sparing chemoradiotherapy in patients with non-metastatic muscle- invasive bladder cancer. Clin Genitourin Cancer. 2019 Feb;17(1):38-45.
13. James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med. 2012 Apr 19;366(16):1477-88.
14. Choudhury A, Swindell R, Logue JP, et al. Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. J Clin Oncol. 2011 Feb 20;29(6):733-8.
15. Caffo O, Thompson C, De Santis M, et al. Concurrent gemcitabine and radiotherapy for the treatment of muscle-invasive bladder cancer: A pooled individual data analysis of eight phase I–II trials. Radiother Oncol. 2016 Nov;121(2):193-198.
16. Portner R, Bajaj A, Elumalai T, et al. A practical approach to bladder preservation with hypofractionated radiotherapy for localised muscle-invasive bladder cancer. Clin Transl Radiat Oncol. 2021 Aug 8;31:1-7.
17. Choudhury A, Porta N, Hall E, et al. Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials. Lancet Oncol. 2021 Feb;22(2):246-255.
18. Yan M, Gouveia AG, Cury FL, et al. Practical considerations for prostate hypofractionation in the developing world. Nat Rev Urol. 2021 Nov;18(11):669-685.
19. Ibrahim AS, Khaled HM, Mikhail NN, et al. Cancer incidence in Egypt: results of the national population-based cancer registry program. J Cancer Epidemiol. 2014;2014:437971.
20. Novara G, Catto JW, Wilson T, et al. Systematic review and cumulative analysis of perioperative outcomes and complications after robot-assisted radical cystectomy. Eur Urol. 2015 Mar;67(3):376-401.
21. Kimura T, Ishikawa H, Kojima T, et al. Bladder preservation therapy for muscle invasive bladder cancer: the past, present and future. Jpn J Clin Oncol. 2020 Sep 28;50(10):1097-1107.
22. Mushtaq J, Thurairaja R, Nair R. Bladder cancer. Surgery (Oxford) 2019;37(9), 529-537.
23. Fedewa SA, Soliman AS, Ismail K, et al. Incidence analyses of bladder cancer in the Nile delta region of Egypt. Cancer Epidemiol. 2009 Oct;33(3-4):176-81.
24. Saginala K, Barsouk A, Aluru JS, et al. Epidemiology of bladder cancer. Med Sci (Basel). 2020 Mar 13;8(1):15.
25. Bellmunt J, Orsola A, Leow JJ, et al. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014 Sep;25 Suppl 3:iii40-8..
26. Azria D, Riou O, Rebillard X, et al. Combined chemoradiation therapy with twice-weekly gemcitabine and cisplatin for organ preservation in muscle-invasive bladder cancer: long-term results of a phase 1 trial. Int J Radiat Oncol Biol Phys. 2014 Mar 15;88(4):853-9.
27. Borut K, Lijana ZK. Phase I study of radiochemotherapy with gemcitabine in invasive bladder cancer. Radiother Oncol. 2012 Mar;102(3):412-5.
28. Caffo O, Fellin G, Graffer U, et al. Gemcitabine and radiotherapy plus cisplatin after transurethral resection as conservative treatment for infiltrating bladder cancer: Long-term cumulative results of 2 prospective single-institution studies. Cancer. 2011 Mar 15;117(6):1190-6.
29. Caffo O, Fellin G, Graffer U, et al. Phase I study of gemcitabine and radiotherapy plus cisplatin after

transurethral resection as conservative treatment for infiltrating bladder cancer. Int J Radiat Oncol Biol Phys. 2003 Dec 1;57(5):1310-6.
30. De Santis M, Bachner M, Cerveny M, et al. Combined chemotherapy with gemcitabine in patients with locally advanced inoperable transitional cell carcinoma of urinary bladder and/or in patients ineligible for surgery: a phase I trial. Ann Oncol. 2014 Sep;25(9):1789-1794.
31. Kent E, Sandler H, Montie J, et al. Combined-modality therapy with gemcitabine and radiotherapy as a bladder preservation strategy: results of a phase I trial. J Clin Oncol. 2004 Jul 1;22(13):2540-5.
32. Sangar VK, McBain CA, Lyons J, et al. Phase I study of conformal radiotherapy with concurrent gemcitabine in locally advanced bladder cancer. Int J Radiat Oncol Biol Phys. 2005 Feb 1;61(2):420-5.
33. Oh KS, Soto DE, Smith DC, et al. 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 Biol Phys. 2009 Jun 1;74(2):511-7.
34. Pauwels B, Korst AE, Lardon F, et al. Combined modality therapy of gemcitabine and radiation. Oncologist. 2005 Jan;10(1):34-51.
35. Cowan RA, McBain CA, Ryder WD, et al. Radiotherapy for muscle-invasive carcinoma of the bladder: results of a randomized trial comparing conventional whole bladder with dose-escalated partial bladder radiotherapy. Int J Radiat Oncol Biol Phys. 2004 May 1;59(1):197-207.
36. Rödel C, Weiss C, Sauer R. Trimodality treatment and selective organ preservation for bladder cancer. J Clin Oncol. 2006 Dec 10;24(35):5536-44.
37. Mohamed HAH, Salem MA, Elnaggar MS, et al. Trimodalities for bladder cancer in elderly: Transurethral resection, hypofractionated radiotherapy and gemcitabine. Cancer Radiother. 2018 May;22(3):236-240.
38. Zhang L, Wu B, Zha Z, et al. Clinicopathological factors in bladder cancer for cancer-specific survival outcomes following radical cystectomy: a systematic review and meta-analysis. BMC Cancer. 2019 Jul 19;19(1):716.
39. Kucuk U, Pala EE, Cakır E, et al. Clinical, demographic and histopathological prognostic factors for urothelial carcinoma of the bladder. Cent European J Urol. 2015;68(1):30-6.
40. Huddart RA, Porta N, Lewis R, et al. 2507 Prognostic factors in muscle invasive bladder cancer patients receiving radiotherapy with or without chemotherapy in the BC2001 trial (CRUK/01/004). European J cancer, 2015;3(51), S475-S476.
41. Otto W, May M, Fritsche HM, et al. Analysis of sex differences in cancer-specific survival and perioperative mortality following radical cystectomy: results of a large German multicenter study of nearly 2500 patients with urothelial carcinoma of the bladder. Gend Med. 2012 Dec;9(6):481-9.