RESEARCH ARTICLE

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Superiority of Adjuvant Hyperfractionated Radiotherapy Over Chemotherapy Following Radical Cystectomy

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Abstract

Background: Bladder cancer (LABC) after radical cystectomy (RC) is common, even with chemotherapy, and is associated with high morbidity and mortality. Therefore, this work aimed to investigate the effect and efficacy of adjuvant sandwich chemotherapy plus radiotherapy versus adjuvant chemotherapy alone for LABC after RC. **Methodology:** This phase III trial was conducted in 125 patients with bladder cancer who underwent RC and were randomized to one of the following two adjuvant treatments. The chemotherapy plus RT arm received 2 cycles of gemcitabine and cisplatin before and after RT, with a 1-week break between chemotherapy and RT. The second arm, receiving chemotherapy alone, had 4 cycles of gemcitabine and cisplatin. **Results:** LRF was significantly reduced in the combined group ($P < 0.001$); however, DM was comparable between groups ($p = 0.3$). Furthermore, 64.9% of patients in the combined group were still alive, compared with only 5.9% in the chemotherapy group. Moreover, the mean time to local failure was not significantly different between the two groups (24.0 ± 0.1 vs. 26.5 ± 9.8, $p = 0.08$, respectively, for the combined group compared with the chemotherapy arm), but the mean time to DM was significantly prolonged in the combined group compared with the chemotherapy group (51.2 ± 14.9 vs. 29.7 ± 12.1, $p < 0.001$, respectively). **Conclusion:** Adjuvant chemotherapy plus RT was associated with significant improvements in LRFS and improvements in OS compared with chemotherapy alone in LABC.

Keywords: Bladder cancer- Chemotherapy- Radiotherapy- Radical cystectomy

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Introduction

The 5-year overall survival percentage for muscle-invasive urothelial bladder cancer (MIBC) (cT2-T4) is 50% [1-3]. This illness is very aggressive. The prevailing best therapeutic options are radical cystectomy (RC) and pelvic lymph node dissection (LND), often accompanied by preoperative cisplatin-based chemotherapy [4]. Loco-regional recurrence (LRR) is an early occurrence that affects 4 to 25% of patients [5, 6], notwithstanding the optimism surrounding treatment. Besides its possible impact on metastasis-free survival (MFS) and overall survival (OS), locoregional recurrence (LRR) is responsible for the poor prognosis [7].

Adjuvant chemotherapy (AC) is very efficacious in managing locally advanced bladder cancer post-RC; nonetheless, the recurrence of the illness is considerable. Postoperative radiation (PORT) has resurfaced as a focal point in enhancing outcomes for locally advanced bladder cancer. Zaghloul et al. first established that postoperative radiotherapy (PORT) given to patients with ≥pT3 BC after radical cystectomy (RC) resulted in a 49% five-year disease-free survival (DFS) and an 87% local control rate, in contrast to 25% and 50%, respectively, for those who did not get supplementary treatment [8].

Additionally, we discovered that PORT serves as an independent predictor of both local free recurrence survival and disease-free survival (DFS) [9]. Nonetheless, the generalizability and safety of PORT were considered uncertain as over half of the patients in the Zaghloul trial had squamous cell predominant histology, and later research indicated detrimental effects linked to the now-obsolete radiation procedures [10]. The innovations in radiation delivery techniques have led to an increase in PORT use in MIBC. A new phase III study will evaluate the impact of PORT compared with sandwiched chemotherapy plus PORT on local recurrence-free survival (LRFS) in patients with MIBC, stage ≥pT3b, at the time of radical cystectomy (RC). The outcomes of a phase II trial comparing interleaved adjuvant chemotherapy with PORT to adjuvant chemotherapy alone have not been reported. The trial documented a 96% vs 69% (HR, 0.08; $P < .01$) for 2 year LRFS favoring the sandwich protocol and a non-significant trend towards favorable outcomes

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in disease-free survival (DFS) (68% vs 56%, p = 0.07) and OS 71% vs 60% (HR, 0.61;P = .11) with adjuvant combined regimen (adjuvant chemotherapy + PORT) (8).

The first prospective study in this inquiry assessed the efficacy of adjuvant chemotherapy combined with PORT versus adjuvant chemotherapy alone. While the addition of PORT to adjuvant chemotherapy in locally advanced bladder cancer may enhance oncologic results, the existing data are limited. PORT is now under investigation in many ongoing studies to assess its effectiveness in locally advanced bladder cancer [11, 12].

Consequently, we chose to investigate the effectiveness and influence of adjuvant sandwich chemotherapy combined with radiation compared to adjuvant chemotherapy alone for locally advanced bladder cancer after radical treatment.

Materials and Methods

Study design and participants

It is a randomized, prospective, phase 3 clinical trial conducted at the Clinical Oncology Department at Assiut University Hospital and the South Egypt Cancer Institute. Recruitment of patients began in February 2020 and ended in March 2024. The study was done with the agreement of the South Egypt Cancer Institute and Assiut University ethical committee, having an ethical approval number 486. The study included the following risk variables: stage ≥ pT3 (as per the American Joint Committee on Cancer's Cancer Staging Manual, Fourth Edition), or positive pathological lymph nodes, treated at South Egypt Cancer Institute and Assiut University. One hundred twenty-five patients aged 70 years or younger with bladder cancer had a radical cystectomy. The research compared adjuvant chemotherapy only with adjuvant sandwich chemotherapy in conjunction with radiation.

Non-muscle invasive bladder cancer, receiving neoadjuvant chemotherapy, and individuals with additional malignancies were deemed exclusion criteria.

All bladder cancer patients had comprehensive laboratory testing (coagulation profile, liver enzymes, renal function tests, and complete blood count) and radiographic assessments (bone scan, computed tomography, or magnetic resonance imaging) to evaluate local and distant metastasis. This included history-taking (both clinical and familial), clinical examinations, tumor staging, and radiological assessments.

Randomization

A computer-generated random number was used to allocate patients to one of the two adjuvant therapies using the closed-envelope approach as outlined below. The chemotherapy and radiotherapy group got two regimens of gemcitabine and cisplatin, administered one week apart, immediately before and after radiotherapy. A four-cycle protocol of gemcitabine and cisplatin was delivered to the limb undergoing sole chemotherapy treatment.

Procedures

Adjuvant chemotherapy

All patients received AC regimens including gemcitabine and cisplatin. Gemcitabine (1000 mg/m2 intravenously over 30 minutes) was provided on days 1, 8, and 15 of the 28-day chemotherapy treatment, while cisplatin (70 mg/m2 intravenously over 30 minutes) was administered on day 2. In reaction to adverse effects, chemotherapy dosages were modified.

Adjuvant radiotherapy

To streamline the organization of radiation treatment, all patients in the chemotherapy plus RT cohort received CT scan simulation. Intravenous contrast was provided unless prohibited. The patient was supine while receiving radiation to the cystectomy site and bilateral pelvic lymph nodes, using 3-D conformal techniques with 6-mV or 15-mV photons on linear accelerator Elekta synergy. The three-field beam arrangement, including one anterior beam and two posterior oblique beams, was used to provide therapy to most patients. Following radical cystectomy for bladder cancer, the clinical target volume (CTV) for adjuvant radiation therapy typically includes the pelvic lymph nodes and the cystectomy bed, especially in cases with positive surgical margins. The CTV encompasses the area where microscopic cancer cells may remain after surgery.

In most individuals, the field extended to the superior aspect of S1, whereas those assessed to be at increased risk for nodal involvement had it extended to the superior aspect of S2. The inferior boundary extended laterally 1 to 1.5 cm beyond the pelvic brim, reaching the pubic symphysis anteriorly, the anterior one-third of the rectal wall posteriorly, and the lower two-thirds of the obturator foramen inferiorly. A total dose of 4500 cGy was delivered to patients by 150 cGy per fraction bid, 6 hours apart, over a duration of three weeks.

Follow-up

During the first two years of the research, evaluation of all patients was done every 3 months, then a bi-annual assessment by pelviabdomen CT scans or MRI was done throughout the latter three years, with metastatic workup on demand. Consequently, they were performed yearly, unless clinically warranted differently.

Locoregional recurrence-free survival is defined as the duration from radical cystectomy to any recurrence in the pelvic lymph nodes or soft tissues occurring before or within three months after the manifestation of distal failure. Recurrences that manifested inside the inguinal nodes or superior to the iliac bifurcation were classified as distant metastases. In all cohorts, the European Organization for Research and Treatment of Cancer (EORTC) version 3.0 was used to evaluate late gastrointestinal tract adverse events likely linked to radiotherapy, identified more than 90 days post-therapy completion. The reported pelvic recurrence, including a putative late gastrointestinal tract adverse impact, was linked to the illness recurrence.

Results

One hundred twenty-five patients with bladder carcinoma after radical cystectomy were randomly allocated between 2 cycles of chemotherapy followed by

Table 1. Demographic Differences between Study Groups

Characteristics	combined group (n= 74)	Chemotherapy group (n=51)	p-value
Age (mean± SD)[1]	67.35 ± 7.5	65.22± 7.2	0.055
Median	70	65	
Range	65-80	50-78	
Sex[2]			
Male (n=98)	59 (79.7%)	39 (76.5%)	0.4
Female (n=27)	15 (20.3%)	12 (23.5%)	

Data expressed as mean± SD, median, number, percentages, and analyzed by [1]; independent sample t-test and [2]; Fisher's exact test.

radiotherapy then another 2 cycles of chemotherapy and 4 cycles of systemic chemotherapy alone, the mean age was slightly younger for those received chemotherapy than combined therapy (p=0.003), but the distribution of sex was comparable in both groups (p=0.4), Table 1.

TCC was the predominant pathologic type encountered in both groups, other pathologies (small cell carcinoma, sarcomatoid carcinoma, adenocarcinoma) were accumulated mainly in those receiving chemotherapy alone, most tumors in combined group were considered differentiated compared with chemotherapy group with significant impact, also radical cystectomy with ileocecal conduit took the major share in combined group compared with Ureterocutaneous shunt in chemotherapy group followed by rectal bladder and ileal conduit in the former and later groups respectively (<0.001), the median number of dissected LNs was significantly higher (<0.001) while tumor size was lower in combined group compared with chemotherapy group, Table (2), Figure (1).

As expected, LRF was significantly reduced in combined group (P<0.001) than chemotherapy arm as only 11 patients developed local failure versus 49 patients in the chemotherapy arm however the duration of local failure to occur showing no statistical significance despite of the obvious numerical difference between the 2 arms as only one patient developed local failure in first 2 years while 10 patients developed local failure in chemotherapy arm, DM was comparable in both groups (p=0.3), furthermore 64.9% of patients in combined group were still alive compared to only 5.9% of patients in chemotherapy group, Table (3).

Moreover, the mean time for local failure was not

Table 2. Differences in Clinicopathologic Characteristics between Study Groups

Characteristics	Combined (n=74)	Chemotherapy (n=51)	p-value
Pathologic type			
TCC	62 (83.8%)	33 (66%)	0.001
SCC	10 (13.5%)	6 (11.8%)	
Others	2 (2.7%)	12 (23.5%)	
Grade			
G1	11 (14.9%)	0 (0%)	<0.001
G2	55 (74.3%)	19 (37.3%)	
G3	8 (10.8%)	32 (62.7%)	
T-stage			
T2	2 (2.7%)	1 (2%)	0.06
T3	41 (55.4%)	38 (74.5%)	
T4a	31 (41.9%)	12 (23.5%)	
Surgical intervention			
Ileal conduit	9 (12.2%)	12 (23.5%)	
Ureterocolic shunt	10 (13.5%)	20 (39.2%)	
Ureterocutaneous	2 (2.7%)	9 (17.6%)	
Rectal bladder	17 (23%)	4 (7.8%)	<0.001
Ileocecal conduit	36 (48.6%)	6 (11.8%)	
Number of LN dissected[b]	15 (6-20)	12 (5-20)	0.013
Tumor size[a]	4.7± 1.2 cm	5.5± 1.8 cm	0.005
N staging			
N0	34 (45.9%)	30 (58.8%)	0.07
N1	28 (37.8%)	12 (23.5%)	
N2	12 (16.2%)	9 (17.6%)	

Data expressed as number, percentages, median (range), mean± SD, and analyzed by likelihood ratio, Mann Whitney u-test[a], independent sample median test[b].

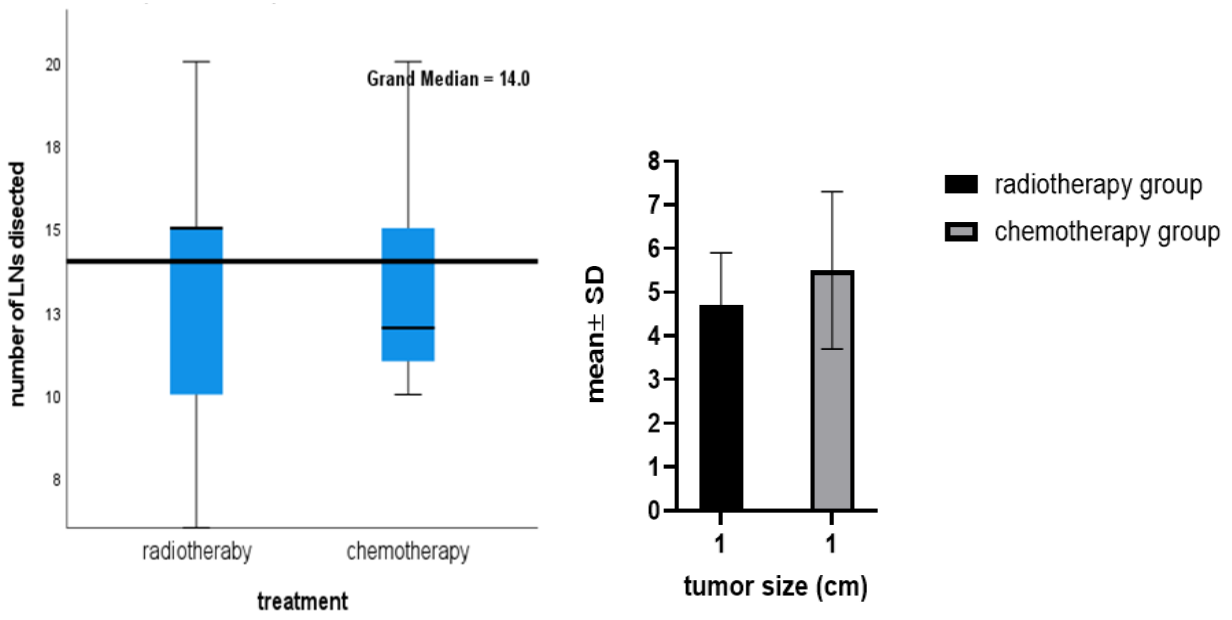

Figure 1. Differences in Tumor Size and Number of LN Dissected between Study Groups. P value <0.001 regarding number of dissected lymph nodes

significantly different between both groups (24.0± 0.1 vs. 26.5± 9.8, p=0.08 respectively for combined group compared with chemotherapy arm, but the mean time for DM was significantly prolonged in combined group compared with chemotherapy group (51.2± 14.9 vs. 29.7± 12.1, p<0.001 respectively), Figure (2).

Survival outcomes among study groups

The mean OS was 68.1± 2.8 (95%CI= 62.6-73.5) vs. 43.9± 2.0 (95%CI= 40-47.8) months, while the median OS were 60 months vs 40 months for combined arm and chemotherapy arm respectively with log rank=40.9 and p<0.001. The mean distant metastasis free survivals were 59.3± 2.5 (95%CI=54.5-64.2) vs. 38.5± 2.0 (95%CI=34.6-42.4) months, while the median DMFS were 60 months vs 36 months for combined arm and chemotherapy arm respectively with log rank=37.6 and p<0.001.

The mean LRF survival was 67.04± 3.3 (95%CI= 60.6-73.5) vs. 27.2± 1.5 (95%CI= 24.2-30.1) months, while the median LRF were 60 months vs 24 months for combined arm and chemotherapy arm respectively with log rank=76.7 and p<0.001, Figures (3a-3b-3c). Intuitively, being of male gender was associated with significantly better LRFS, DMFS, and OS, also patients with TCC and grade 1 had improved survival, having radical cystectomy with rectal bladder or ileocecal bladder were associated with better LRFS, DMFS, and OS.

Consistently, patients treated with combined chemotherapy and radiotherapy had significantly higher LRFS, DMFS, and OS compared with those treated with only chemotherapy.

The independent predictors for improved LRFS, DMFS, and OS in multivariate analysis consistently associated with reduced hazard ratios for death and relapse were tumor pathology (TCC) and treatment with combined radiotherapy and chemotherapy, for LRFS, HR=0.3,

Table 3. Treatment Outcomes and Patients' Fates

Outcome	Combined (n=74)	Chemotherapy (n=51)	p-value
Locoregional failure			
Yes	11 (14.9%)	49 (96.1%)	<0.001
No	63 (85.1%)	2 (3.9%)	
2-year LRF			
<24 months	1 (1.4%)	10 (19.6%)	0.7
≥24 months	10 (13.5%)	39 (76.5%)	
Distant metastasis			
Yes	24 (32.4%)	21 (41.2%)	0.3
No	50 (67.6%)	30 (58.8%)	
Fate			
Dead	26 (35.1%)	48 (94.1%)	<0.001
Alive	48 (64.9%)	3 (5.9%)	

Data expressed as number, percentages and analyzed by Fisher's exact, Chi^2 with continuity correction.

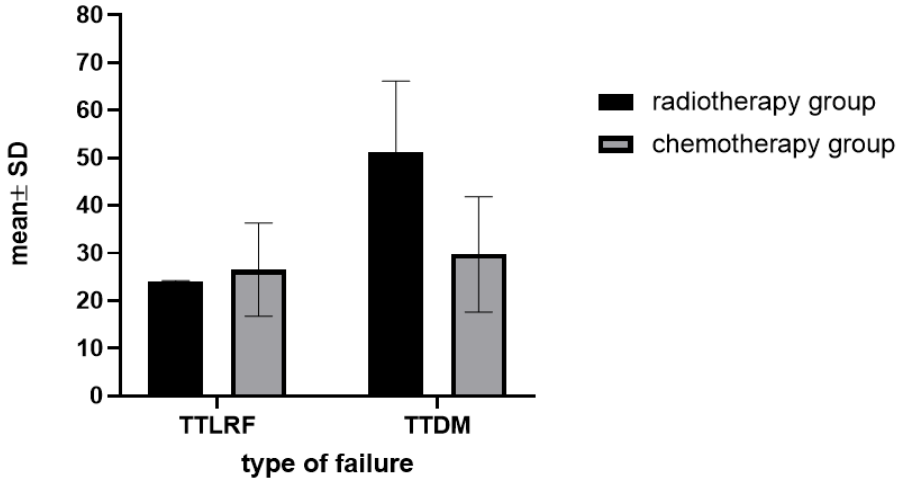

Figure 2. Differences in Time to Local Failure p=0.08 and Time to Distant Failure p<0.001, Mann Whitney U-test.

p<0.001, and HR=6.9, p<0.001. for DMFS, HR=0.2, p<0.001, and HR=10.1, p<0.001. For OS, HR=0.14 and 0.3, p<0.001 and 0.012 for TCC and SCC, HR=2.9, p=0.002, Tables (4-5-6).

patients received systemic chemotherapy alone experienced higher grades of nausea and vomiting where >50% of patients developed grades 2-3 nausea and vomiting compared with only 10-12% in patients received combined modality treatment, furthermore diarrhea grades 1-2 developed in 98% compared with

Table 4. Univariate and Multivariate Analysis of Factors Predictive for LR Failure Free Survival

LRFS	Univariate analysis		Multivariate cox analysis	
Characteristics	Mean ± SD	p-value	HR (95% CI)	p-value
Age	-0.02	0.8	-----	
Sex				
Male	40.2± 16.8	0.04	------	
Female	34.9± 17.8			
No of dissected LNs	-0.04	0.7	1.13 (1.1-1.2)	0.001
Tumor size	-0.2	0.045	----	---
Tumor pathology				<0.001
TCC	44.1± 15.5	<0.001	0.3 (0.12-0.51)	<0.001
SCC	23.9± 0.3		1.4 (0.6-3.1)	0.4
Others	21.6± 15.7		Reference	----
Tumor grade				0.046
G1	57.1± 15.9	<0.001	0.1 (0.1-0.6)	0.02
G2	40.6± 18.2		0.7 (0.4-1.2)	0.19
G3	31.2± 9.2		References	------
T-stage				
T2	24.0± 0.0	0.1	-------	-------
T3	37.8± 17.9			
T4a	42.3± 15.3			
Surgical intervention				
Ileal conduit	31.9± 20.9		-------	
Ureterocolic shunt	31.2± 9.7	0.001		---------
Ureterocutaneous	38.5± 13.6			
Rectal bladder	38.0± 15.1			
Ileocecal conduit	48.8± 16.6			
Treatment				
Chemotherapy alone	26.8± 9.7	<0.001	6.9 (3.6-13.6)	<0.001
Combined Protocol	47.5± 15.9			

Data expressed mean± SD, r; Spearman rho coefficient, analyzed by cox regression model with forward conditional method for predictor analysis.

Table 5. Univariate and Multivariate Analysis for Factors Predictive of Distant Metastasis Free Survival

DM-FS	Univariate analysis		Multivariate cox analysis	
Characteristics	Mean ± SD	p-value	HR (95% CI)	p-value
Age	r=0.02	0.6	-----	
Sex				
Male	47.6± 14.5	0.001	------	
Female	37.1± 15.1			
No of dissected LNs	-0.1	0.3	1.2 (1.1-1.3)	<0.001
Tumor size	0.12	0.2	----	---
Tumor pathology				<0.001
TCC	48.4± 13.5	<0.001	0.2 (0.05-0.4)	<0.001
SCC	42.1± 16.7		0.4 (0.13-1.4)	0.1
Others	28.0± 12.9		Reference	----
Tumor grade				
G1	53.8± 17.3	0.06	-------	-------
G2	45.9± 15.7			
G3	41.9± 12.8			
T-stage				<0.001
T2	24.0± 0.0	0.045	19.4 (3.3-113.4)	<0.001
T3	46.2± 15.7		0.5 (0.3-1.04)	0.06
T4a	45.3± 13.9		Reference	
Surgical intervention				<0.001
Ileal conduit	36.0± 17.3		2.7 (1.3-5.7)	0.008
Ureterocolic shunt	44.2± 13.2	0.003	0.5 (0.24-1.2)	0.12
Ureterocutaneous	41.4± 13.5		2.6 (0.9-7.7)	0.08
Rectal bladder	52.4± 9.03		0.8 (0.4-1.8)	0.6
Ileocecal conduit	48.4± 16.1		Reference	
Treatment				
Chemotherapy alone	37.9± 13.7	<0.001	10.1 (5.1-19.7)	<0.001
Combined Protocol	50.4± 14.1			

Data expressed mean± SD, r; Spearman rho coefficient, analyzed by cox regression model with forward conditional method for predictor analysis.

77% of patients respectively, conversely, >92% of patients received systemic chemotherapy did not express tenesmus compared to 29% of patients received combined modality, Table (7).

Ninety-eight percent of patients receiving chemotherapy expressed variable degrees of anemia,

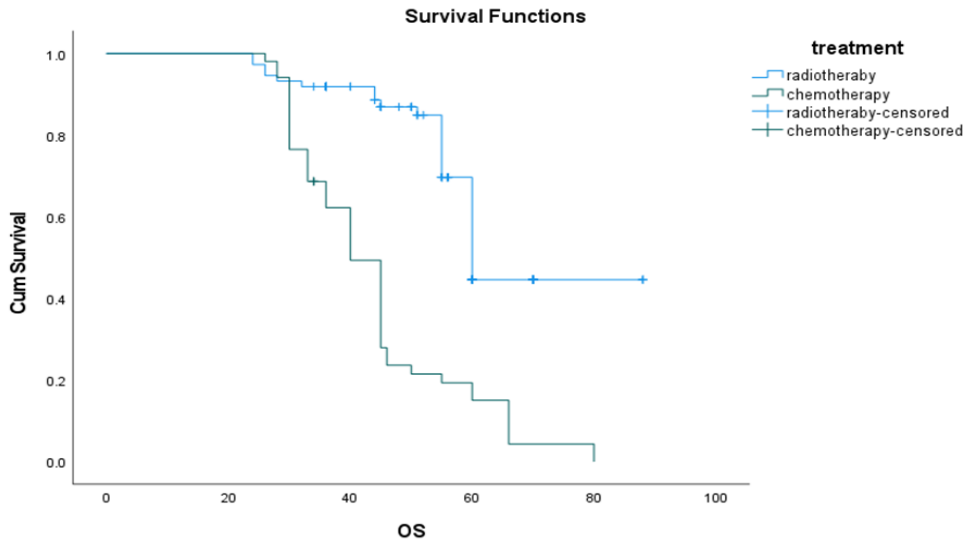

Figure 3a. Differences in OS between Treatment Groups. p<0.001

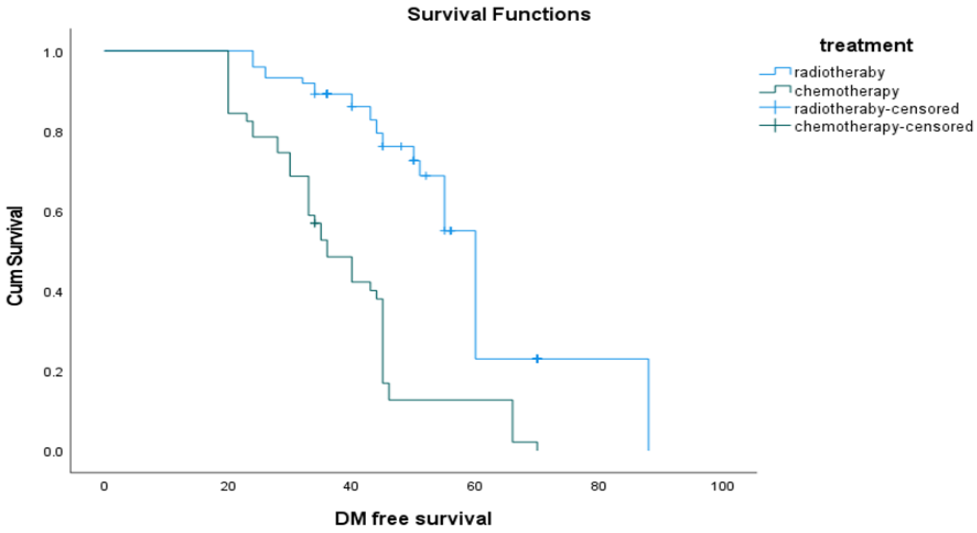

Figure 3b. Differences in Distant Metastasis Free Survival between Treatment Groups. p<0.001

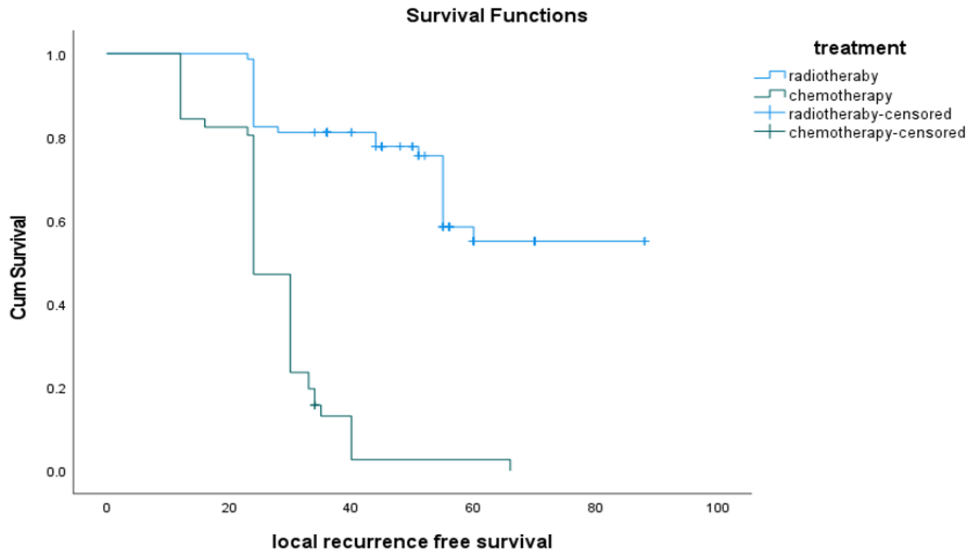

Figure 3c. Differences in Locoregional Recurrence Free Survival. p<0.001

neutropenia, and thrombocytopenia compared with 44.6%, 39.2%, and 13.5% of patients treated with combined modality, and expressed only grade 1 toxicities, Table (8).

Discussion

Patients with locally advanced disease (pT3–4) have high rates of pelvic recurrence and poor OS after radical cystectomy, PLND, and perioperative chemotherapy, with pelvic failure 20%–45% and 5-year survival 10%– 50% depending on risk factors. There is limited data regarding the use of adjuvant radiation to improve these outcomes, and further prospective studies are needed to confirm its benefits [13].

Our study was done on 125 urinary bladder cancer patients who underwent radical cystectomy and were randomly allocated to one of the two arms. One arm received adjuvant 2 cycles of cisplatin and gemcitabine, followed by hyperfractionated radiotherapy 4500 cGY, followed by another 2 cycles of chemotherapy. The other arm was receiving 4 cycles of adjuvant cisplatin and gemcitabine without radiotherapy. The majority of patients were TCC, T3-4, and there was a significant difference regarding the type of surgery, as most patients in the combined arm had an Ileocecal conduit versus uretrocoloic shunt in the chemotherapy arm. Patients in the combined arm group demonstrated less tumor size with a larger number of dissected lymph nodes and showed better locoregional control than the chemotherapy arm as local recurrence within 2 years was 1.4% in the combined arm compared with 19.6% in the chemotherapy arm, which was clinically evident. Distant metastasis free time was significantly longer in the combined arm. The median locoregional free survival reached 60 months and 24 months in the combined arm and chemotherapy arm, respectively. The data showed a significantly distant metastasis-free survival in the combined arm rather than the chemotherapy arm; this was reflected by significantly

Table 6. Univariate and Multivariate Analysis of Predictors for Overall Survival

OS	Univariate analysis		Multivariate cox analysis	
Characteristics	Mean ± SD	p-value	HR (95% CI)	p-value
Age	r=0.004	0.9	0.93 (0.88-0.98)	0.009
Sex				
Male	49.6± 14.01	0.016	------	
Female	42.2± 13.8			
No of dissected LNs	-0.1	0.3	1.2 (1.1-1.3)	<0.001
Tumor size	0.2	0.034	----	---
Tumor pathology				<0.001
TCC	50.3± 13.3	<0.001	0.14 (0.1-0.3)	<0.001
SCC	45.8± 16.8		0.3 (0.1-0.8)	0.012
Others	35.1± 9.3		Reference	----
Tumor grade				0.027
G1	57.1± 15.9	0.039	0.04 (0.004-0.44)	0.008
G2	48.4± 13.7		0.9 (0.4-1.9)	0.7
G3	44.9± 14.0		Reference	
T-stage				<0.001
T2	24.0± 3.5	0.007	12.5 (2.4-65.1)	0.003
T3	50.0± 14.2		0.42 (0.21-0.84)	0.014
T4a	45.0± 13.4		Reference	
Surgical intervention				
Ileal conduit	40.4± 13.5			
Ureterocolic shunt	44.5± 12.7	<0.001		
Ureterocutaneous	49.3± 18.0		---------	--------
Rectal bladder	55.7± 6.4			
Ileocecal conduit	50.2± 15.4			
Treatment				
Chemotherapy alone	43.0± 13.7	<0.001	2.9 (1.5-5.6)	0.002
Combined protocol	51.5± 13.8			

Data expressed mean± SD, r; Spearman rho coefficient, analyzed by cox regression model with forward conditional method for predictor analysis.

Table 7. GIT Toxicity Differences between the Study Groups

Toxicity	Combined	Chemotherapy	
Nausea			
No nausea	10 (13.5%)	1 (2%)	
Grade 1	56 (75.7%)	17 (33.3%)	<0.001
Grade 2	8 (10.8%)	31 (60.8%)	
Grade 3	0 (0%)	2 (3.9%)	
Vomiting			
No vomiting	58 (78.4%)	1 (2%)	
Grade 1	7 (9.5%)	10 (19.6%)	<0.001
Grade 2	9 (12.2%)	39 (76.5%)	
Grade 3	0 (0%)	1 (2%)	
Diarrhea			
No diarrhea	17 (23%)	1 (2%)	<0.001
Grade 1	37 (50%)	39 (76.5%)	
Grade 2	20 (27%)	11 (21.6%)	
Tenesmus			
No	22 (29.7%)	47 (92.2%)	
Grade 1	37 (50%)	4 (7.8%)	<0.001
Grade 2	15 (20.3%)	0 (0%)	

Data expressed as numbers and percentages, analyzed by chi^2 with likelihood ratio.

better overall survival in the combined arm. Patients with more differentiated pathology, female gender, more lymph node dissection, rectal bladder or ileocecal bladder, and those who received the combined protocol demonstrated

Table 8. Hematologic Toxicity between Study Groups

Toxicity	Combined (n=74)	Chemotherapy (n=51)	p-value
Anemia			
No	41 (55.4%)	1 (2%)	
Grade 1	33 (44.6%)	20 (39.2%)	<0.001
Grade 2	0 (0%)	20 (39.2%)	
Grade 3	0 (0%)	10 (19.6%)	
Neutropenia			
No	45 (60.8%)	1 (2%)	<0.001
Grade 1	29 (39.2%)	32 (62.7%)	
Grade 2	0 (0%)	18 (35.3%)	
Thrombocytopenia			
No	64 (86.5%)	1 (2%)	<0.001
Grade 1	10 (13.5%)	29 (56.9%)	
Grade 2	0 (0%)	21 (41.1%)	

Data expressed as numbers and percentages, analyzed by chi^2 with likelihood ratio.

better prognosis, LRFS, DMFS, and OS. Regarding toxicity, there was more significant nausea and vomiting and diarrhea in the chemotherapy group, but tenesmus was expressed in the combined arm, reaching 29%.

Mathieu etal (4) did a retrospective study that included patients with MIUBC treated with RC followed by adjuvant radiotherapy, where the majority of patients were T3-4, N+, and received 61 GY conventional radiotherapy. The study found that only 9% GIT and genitourinary acute toxicities occurred even in patients with neobladder,3-year LRRFS 45%, DMFS 37%, OS 49%, and LRR reached 14%, which is nearly the same as our study regarding LRR in patients who received adjuvant combined chemotherapy and radiotherapy. Zaghloul et al. [14] detected less local control with adjuvant hyperfractionated 10-13% than conventional radiotherapy, whereas in our study, we demonstrated better local control in the combined arm, which may be due to the chemotherapy given. EL Moniem [15] etal studied preoperative radiotherapy compared to postoperative radiation after RC and demonstrated improved 3-year OS, DFS, and LRRFS but with significant toxicities.

Stein et al. [16] reported reduced OS with more positive lymph nodes, and Herr etal found that the number of dissected lymph nodes affects OS, where 17% decrease in OS was observed when fewer than 10 lymph nodes were dissected, and this is in line with our study. Also, Baumann et al. [17] and Skinner etal (2) demonstrated that staging and the number of lymph nodes dissected were the most important factors affecting LRRFS and OS.

John Ernandez et al. [10] had studied adding adjuvant radiotherapy to chemotherapy after RC compared to adjuvant chemotherapy alone. The study did not report any OS improvement with adding radiotherapy in the adjuvant setting, and this may be due to the group of patients who chose to receive radiotherapy being a high-risk group that all had T4 and positive surgical margins.

Zaghloul et al. [8] studied adjuvant sandwich combined chemotherapy plus radiotherapy after RC versus chemotherapy alone, and a significant improvement in LRFS was favored toward the combined arm, as the 2-year LRFS was 96% in the combined arm compared to 69% in the chemotherapy arm, with good improvement subsequently in DFS and OS, this is in line with our results, where LRFS was significantly improved with the combined arm, as median LRFS reached 60 months in the combined arm versus 24 months in the chemotherapy arm.

Moreover, Orré et al. [4] studied fifty-seven patients with MIBC who underwent radical cystectomy (RC) followed by adjuvant radiotherapy (RT). During the median follow-up period of 40.4 months (14%) had locoregional recurrence (LRR). The three-year LRRFS, MFS, and OS rates were 45%, 37%, and 49%, respectively. (9%) suffered acute grade ≥3 toxicity related to gastrointestinal, genitourinary, and physiologic parameters.

Fonteyne et al. [18] reported that 15% of patients who received adjuvant radiotherapy after (RC) developed local recurrences, leading to a 2-year local recurrence-free rate (LRFR) of 83%. This Figure is inferior to the documented 2-year LRFR of 96% for the combination arm as reported by Zaghloul et al. The integration of radiation and chemotherapy has benefits that warrant further exploration.

In conclusion, in radical cystectomy instances, adjuvant chemotherapy plus radiation treatment showed significant improvements in LRFS, OS, and DMFS compared to chemotherapy alone in LABC. Adjuvant radiotherapy should be considered for inclusion in locally advanced bladder cancer.

Author Contribution Statement

AS 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, AS, AH and AH provided support regarding the statistical analysis and discussion. DA performed all methodological procedure and AS was responsible for data analysis and manuscript revision. All authors have reviewed and approved the final version of the manuscript.

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Availability of data and material

All data analyzed were included within the manuscript

Competing Interests

The authors indicated no potential conflicts of interest.

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