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Bladder only Versus Standard Whole Pelvis Chemo-Irradiation In Clinically Node Negative Muscle Invasive Bladder Cancer

Mohammed A Refaat[1], Mai Mahmoud M. Abdel-Rahman[*1], Abbas M Sarhan[1], Ahmad M AlHosainy[1], Nabila Hefzi[1], Khaled Abdelwahab[2], Safa A Balata[1]

[1]Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Zagazig University, Egypt

[2]Urology Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding Author:**

Mai Mahmoud M. Abdel-Rahman

Email ID: mairefaat1986@gmail.com

ABSTRACT

Background: Bladder-preserving chemo-radiation has become a viable substitute for radical cystectomy for individuals suffering from muscle-invasive bladder cancer (MIBC). But in clinically node-negative (cN0) patients, the necessity of elective pelvic nodal irradiation remains controversial. The incidental dose delivered to pelvic lymphatics during bladder-only radiotherapy (BORT) may be sufficient for microscopic nodal disease control, potentially reducing unnecessary toxicity. So, we aimed to determine the dose of radiotherapy received by pelvic lymph nodes in bladder only radiotherapy technique and to compare toxicity, pelvic nodal relapse, systemic relapse of BORT vs standard technique.

Methods: This prospective comparative study enrolled patients with cT2-T3N0M0 MIBC who were randomized into two arms: Arm A (**WPRT**) receiving standard whole-pelvis fields followed by bladder boost and Arm B (**BORT**) receiving bladder-only chemo-radiation. Both groups received concurrent cisplatin-based chemotherapy. Acute and late toxicities were graded according to CTCAE version 5. Nodal and systemic relapse rates were analyzed alongside overall survival (OS), and dosimetric parameters for pelvic lymph node regions.

Results: Both treatment arms achieved comparable complete response (CR) rates, with no statistically significant difference in regional control or OS. The mean dose received incidentally by external, internal, obturator, and presacral lymph nodes during BORT reached therapeutic thresholds (>30 Gy) in most patients. Acute gastrointestinal and hematologic toxicities were significantly lower in the BORT group. No increase in nodal relapse was observed with bladder-only irradiation.

Conclusion: Bladder-only chemo-radiation provides equivalent tumor control and survival outcomes compared to whole-pelvis fields in cN0 MIBC while significantly reducing toxicity. Incidental nodal dose coverage during bladder-only irradiation may be sufficient to eradicate microscopic nodal disease, supporting its role as a safe and effective bladder-preserving strategy.

Keywords: *Muscle-invasive bladder cancer, bladder-only radiotherapy, chemo-radiation, pelvic lymph nodes, toxicity, survival.*

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1. INTRODUCTION

The most prevalent cancer affecting the urinary system is bladder cancer. Bladder cancer is the ninth most common cancer diagnosed globally [1]. In Egypt, bladder cancer is the third most frequent type of cancer. It ranks as the third most common cause of cancer-related deaths [1, 2].

Other than certain occupational exposure to chemicals and water contaminants, smoking cigarettes is the leading cause of bladder cancer development in the majority of countries, accounting for around 50% of all cases because tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons, which are excreted by the kidneys. [3].

The most prevalent histologic subtype in the US and Europe is urothelial (transitional cell) carcinomas, which can arise anywhere there is transitional epithelium, including the renal pelvis, ureter, bladder, and proximal two thirds of the urethra. Higher grades are frequently associated with variant histology [4].

For many years, radical cystectomy (RC) combined with pelvic node dissection has been regarded as the gold standard of care [5]. However, according to a recent study, surgical morbidity is still high [6].

In the last years, curative oncological approaches for various cancer types, from anal cancer to head and neck cancers, have shifted from invasive surgery to organ-preserving therapies [7]. As a new method with manageable toxicities and comparable oncologic outcomes to cystectomy for patients with MIBC, trimodality treatment—which includes TURBT, radiation, and chemotherapy—has gained appeal as an alternative to RC [8].

Depending on the pathological finding after radical cystectomy and pelvic lymphadenectomy showing that micro-metastases in pelvic lymph nodes range from 25% to 44% [9], most investigators recommended the inclusion of pelvic lymph nodes in the radiation portals.

Depending on the role of chemotherapy introduced in conjunction with radiotherapy and in the adjuvant setting and the incidental dose received by pelvic nodes in eradicating any micrometastases present, pelvic nodal irradiation can be skipped in clinically node negative muscle invasive bladder cancer [10]. However, there is variation in the use of elective nodal irradiation for bladder conservation around the globe [11]. Regional nodal involvement is not unusual in MIBC, hence in a series of Radiation Therapy Oncology Group (RTOG) trials, the radiation fields included a limited pelvic portal treated to 40 to 45 Gy followed by a boost to the bladder [12]. Among other consensus, the UK-based BC 2001 trial that compared radiation with CRT did not employ elective nodal radiotherapy (RT) and found that the nodal relapse rate was less than 5%, which is comparable to the failure patterns found in studies that used pelvic RT [13, 28].

The incidental dose received by the pelvic nodal regions, especially the nodes located along the external iliac, obturator, and internal iliac vessels, may account for this discrepancy between the biological justification and the apparent lack of clinical benefit with prophylactic pelvic irradiation [14]. Additionally, the growing incorporation of systemic chemotherapy into radiation protocols may be sufficient to treat micro metastatic disease in pelvic lymph nodes and negate any potential benefit of elective pelvic nodal irradiation. The choice to include or exclude the pelvic lymph nodes in radiation therapy for bladder cancer differs based on clinical procedures and is still up for debate. The pelvic field should be optional, according to the National Comprehensive Cancer Network (NCCN) recommendations, and should be chosen depending on the patient's comorbidities and the risk of radiation-related damage [15].

2. METHODS

This prospective, comparative study was carried out at Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Zagazig University on Patients with histologically verified muscle-invasive bladder urothelial cancer (cT2–T3N0M0) who were clinically and radiologically node-negative on CT or MRI imaging. Written informed consent was given by each patient. The Zagazig University institutional ethics committee gave its approval to the project. (IRB No.: 5581-12-9-2019).

Inclusion criteria:

- Age ≥ 18 years
- ECOG performance status 0–2
- Adequate bone marrow, renal, and hepatic functions
- No evidence of regional or distant metastasis

Exclusion criteria:

- Prior pelvic radiotherapy or chemotherapy
- Extensive carcinoma in situ (CIS)
- Poor bladder capacity or function
- Inflammatory bowel disease

Treatment Arms

Two treatment groups were randomly assigned to the patients:

Arm A – Whole-Pelvis Radiotherapy (WPRT): Patients received standard pelvic field irradiation encompassing the obturator, internal, external, and presacral lymph nodes, followed by a sequential boost to the bladder.

Arm B – Bladder-Only Radiotherapy (BORT): The entire bladder was treated using 3D-conformal technique, with no

elective pelvic nodal coverage.

Radiotherapy Planning and Delivery

All patients underwent CT simulation in the supine position with an empty bladder and empty rectum. Planning target volumes (PTVs) were delineated according to the RTOG bladder cancer contouring atlas. For the BORT group, The PTV was created by expanding the 1.5–2 cm isotropic margin of the clinical target volume (CTV), which comprised the whole bladder and gross tumor volume (GTV). The obturator, external, internal, and presacral chains—the bladder and pelvic lymphatic regions were included in the initial CTV for the WPRT group. Using 3DCRT 15 MV photon beams was applied to administer the treatment.

Dose prescription:

- *Arm A (WPRT):* 44 Gy in 22 fractions to the whole pelvis, followed by 20 Gy bladder boost (total 64 Gy)
- *Arm B (BORT):* 64 Gy in 32 fractions to bladder only (2 Gy/fraction)
- Dose constraints to organs at risk (OARs) were applied per QUANTEC guidelines.
- Verification images were acquired to ensure reproducibility.

Concurrent Chemotherapy

All patients received concurrent cisplatin-based chemotherapy as a radio-sensitizer.

Cisplatin was administered at a dose of 40 mg/m² weekly during radiotherapy.

Assessment and Follow-up

Hematologic and biochemical profiles were tracked, and patients had weekly clinical evaluations for acute toxicity during treatment. CTCAE v5.0 scales were used to grade the toxicity.

Response assessment was done 12 weeks after completion of therapy using cystoscopy and contrast-enhanced CT/MRI abdomen and pelvis.

- **Complete response (CR):** no residual tumor
- **Partial response (PR):** ≥50% regression
- **Stable disease (SD):** <50% regression
- **Progressive disease (PD):** appearance of new lesions

Follow-up was conducted every 3 months for the first 2 years, then every 6 months thereafter. Recurrence patterns were classified as **nodal**, or **distant**.

Dosimetric Analysis

To assess the incidental dose received by pelvic nodal groups (external, internal, obturator, and presacral), dose–volume histograms (DVHs) were created for each patient in both arms. Mean, maximum (Dmax), and minimum (Dmin) doses were compared between arms.

Bladder volume was correlated with dosimetric parameters using Pearson's correlation test.

3. STATISTICAL ANALYSIS

Microsoft Office Excel 2010 for Windows (Microsoft Corp., Redmond, WA, USA), SPSS 22.0 for Windows (IBM Inc., Chicago, IL, USA), and MedCalc 13 for Windows (MedCalc Software bvba, Ostend, Belgium) were used to gather, tabulate, and statistically analyze all of the data. Fisher's exact test, chi-squared test, and Mann-Whitney U test were employed. The period between a patient's diagnosis and their most recent follow-up contact, or the date of their regional relapse, was used to calculate their regional relapse free survival, or RRFS. The period between the patient's diagnosis and the date of their most recent follow-up contact, or the date of their distant recurrence, was used to determine the distant relapse free survival, or DRFS. The time between the date of diagnosis and the date of death or the most recent follow-up contact was used to compute overall survival. The Kaplan-Meier plot method was used to estimate these time-to-event distributions, and the two-sided exact log-rank test was used for comparison. The relationship between bladder volume and lymph node dosimetric parameters was examined using Spearman's correlation coefficient (r).

4. RESULT

Table (1): Comparison between group A and group B regarding demographic and clinical data.

Demographic data	Group A (N=19) No.	%	Group B (N=19) No.	%	Test	p-value (Sig.)
Gender						
Male	14	73.7%	17	89.5%	1.576[a]	0.405
Female	5	26.3%	2	10.5%		(NS)
Age (years)						
Mean±SD	64.57±5.31		66.94±6.82		-1.553[b]	0.120
Median (Range)	63 (56 – 80)		68 (52 – 80)			(NS)
ECOG PS						
ECOG 1	3	15.8%	5	26.3%	0.633	0.693
ECOG 2	16	84.2%	14	73.7%		(NS)
cT stage						
cT2	8	42.1%	9	47.4%	0.106	0.744
cT3	11	57.9%	10	52.6%		(NS)
Grade						
Grade II	0	0%	0	0%	0.000	1.000
Grade III	19	100%	19	100%		(NS)
Extent of resection						
Complete resection	9	47.4%	11	57.9%	0.422	0.516
Incomplete resection	10	52.6%	8	42.1%		(NS)
Gap of RTH interruption						
≤7 days	15	78.9%	16	84.2%	0.175	1.000
>7 days	4	21.1%	3	15.8%		(NS)

Categorical variables were expressed as number (percentage); Continuous variables were expressed as mean ± SD & median (range); a: Chi-square test; b: Mann Whitney U test; p-value<0.05 is significant; Sig.: Significance.

No statistically significant differences (NS) were found between Group A and Group B in all demographic and clinical parameters. Both groups are comparable in terms of age, gender, ECOG status, tumor stage, tumor grade, extent of resection, and radiotherapy interruption duration (Table 1).

Table (2): Comparison between group A and group B regarding toxicity of treatment.

Toxicity of treatment	Group A (N=19) No.	%	Group B (N=19) No.	%	Test[a]	p-value (Sig.)
Genitourinary toxicity						
Grade 1	3	15.8%	3	15.8%	0.000	1.000
Grade 2	16	84.2%	16	84.2%		(NS)

Frequency						
Grade 0	2	10.5%	1	5.3%	0.870	0.647
Grade 1	3	15.8%	5	26.3%		(NS)
Grade 2	14	73.7%	13	68.4%		
Dysuria						
Grade 0	2	10.5%	3	15.8%	1.200	0.549
Grade 1	16	84.2%	16	84.2%		(NS)
Grade 2	1	5.3%	0	0%		
Urgency						
Grade 0	7	36.8%	4	21.1%	2.634	0.268
Grade 1	7	36.8%	12	63.2%		(NS)
Grade 2	5	26.3%	3	15.8%		
Gastrointestinal toxicity						
Grade 0	0	0%	10	52.6%		**<0.001**
Grade 1	5	26.3%	5	26.3%		(HS)
Grade 2	8	42.1%	3	15.8%		
Grade 3	5	26.3%	1	5.3%		
Grade 4	1	5.3%	0	0%		
Diarrhea						
Grade 0	0	0%	11	57.9%	18.305	**0.001**
Grade 1	7	36.8%	4	21.1%		(S)
Grade 2	8	42.1%	3	15.8%		
Grade 3	3	15.8%	1	5.3%		
Grade 4	1	5.3%	0	0%		
Rectal pain						
Grade 0	4	21.1%	13	68.4%	14.127	**0.003**
Grade 1	5	26.3%	4	21.1%		(S)
Grade 2	7	36.8%	2	10.5%		
Grade 3	3	15.8%	0	0%		

Categorical variables were expressed as number (percentage); a: Chi-square test; p-value<0.05 is significant; Sig.: Significance.

Regarding gastrointestinal toxicity: Highly significant difference (HS) was observed favoring Group B, with Group A experiencing higher toxicity grades (Grades 2–4). Regarding diarrhea: a statistically significant difference (S) was observed favoring Group B; more severe symptoms were reported in Group A. regarding rectal pain: a statistically significant difference (S) also favoring Group B; higher pain grades were seen in Group A. Other toxicity parameters showed no significant differences between the groups (Table 2).

Table (3): Comparison between group A and group B regarding outcome of treatment.

Outcome of treatment	Group A (N=19)		Group B (N=19)		Test[a]	p-value (Sig.)
	No.	%	No.	%		
Radiological response						
Complete response	6	31.6%	6	31.6%	0.730	0.866
Partial response	8	42.1%	6	31.6%		(NS)
Stable disease	1	5.3%	2	10.5%		
Progressive disease	4	21.1%	5	26.3%		
Regional relapse	(N=15)		(N=14)			
Absent	13	86.7%	13	92.9%	0.299	1.000
Present	2	13.3%	1	7.1%		(NS)
Distant relapse						
Absent	13	86.7%	13	92.9%	0.299	1.000
Present	2	13.3%	1	7.1%		(NS)
Mortality						
Alive	7	46.7%	8	57.1%	0.318	0.573
Died	8	53.3%	6	42.9%		(NS)

Categorical variables were expressed as number (percentage); a: Chi-square test; p-value<0.05 is significant; Sig.: Significance.

The two groups did not vary significantly (NS) in terms of mortality, regional or distant relapse, or radiological response. Both groups' rates of full and partial responses were comparable (Table 3).

Table (4): Comparison between group A and group B regarding survival.

Survival	Group A (N=15)	Group B (N=14)	Test[c]	p-value (Sig.)
Regional Relapse Free Survival (RRFS)				
Mean RRFS (months)	34 months	36 months	0.724	0.395
(95%CI)	(28,692 – 39.308)	(36 – 36)		(NS)
6-month RRFS	100%	100%		
12-month RRFS	91.7%	100%		
24-month RRFS	91.7%	100%		
36-month RRFS	68.8%	83.3%		
Distant Relapse Free Survival (DRFS)				
Mean DRFS (months)	32.15 months	36 months	0.530	0.466
(95%CI)	(27.404 – 36.904)	(36 – 36)		(NS)
6-month DRFS	100%	100%		

12-month DRFS	92.3%	100%		
24-month DRFS	92.3%	100%		
36-month DRFS	73.8%	83.3%		
Overall Survival (OS)				
Mean OS (months)	21.63 months	25.214 months	0.395	0.530
(95%CI)	(15.141 – 28.134)	(18.650 – 31.778)		(NS)
6-month OS	93.3%	100%		
12-month OS	65%	64.3%		
24-month OS	40.6%	57.1%		
36-month OS	40.6%	57.1%		

Continuous variables were expressed as mean (95%CI), 95%CI: 95% confidence interval; c: Log rank test; p<0.05 indicates significant; and categorical variables were expressed as number (percentage).

No statistically significant differences were observed in Regional Relapse-Free Survival (RRFS), Distant Relapse-Free Survival (DRFS), or Overall Survival (OS). Group B showed numerically higher survival rates at 24 and 36 months compared to Group A, but these differences were not statistically significant (Table 4).

Table (5): Comparison between group A and group B regarding dosimetric parameters of Lower Common Iliac (LCI) lymph nodes.

Dosimetric parameters	Group A (N=19)	Group B (N=19)	Test[b]	p-value (Sig.)
Bladder volume (cc)				
Mean±SD	169.05±95.27	205.73±118.91	-0.967	0.334
Median (Range)	146 (51 – 360)	242 (51 – 360)		(NS)
LCI volume (cc)				
Mean±SD	51.10±27.10	52.94±31.82	-0.088	0.930
Median (Range)	44 (16 – 102)	35 (23 – 109)		(NS)
LCI Dmax (cGy)				
Mean±SD	3839.89±866.27	176.05±66.06	-5.271	**<0.001**
Median (Range)	4382 (2382 – 4707)	163 (0 – 323)		(HS)
LCI Dmean (cGy)				
Mean±SD	2560.57±1335.85	119.21±78.15	-5.274	**<0.001**
Median (Range)	2455 (613 – 4586)	86 (25 – 246)		(HS)
LCI V40 (%)				
Mean±SD	38.78±38.48	0±0	-4.264	**<0.001**
Median (Range)	30 (0 – 100)	0 (0 – 0)		(HS)
LCI V50 (%)				
Mean±SD	18.94±37.87	0±0	-2.082	**<0.001**
Median (Range)	0 (0 – 98)	0 (0 – 0)		(HS)

Continuous variables were expressed as mean ± SD & median (range); b: Mann Whitney U test; p-value<0.05 is significant; Sig.: Significance.

All parameters (LCI Dmax, LCI Dmean, LCI V40, LCI V50) showed highly significant differences (HS), with Group A was higher than Group B (Table 5).

Table (6): Comparison between group A and group B regarding dosimetric parameters of External Iliac (EI) lymph nodes.

Dosimetric parameters	Group A (N=19)	Group B (N=19)	Test[b]	p-value (Sig.)
EI volume (cc)				
Mean±SD	100.78±30.13	71.10±30.36	-2.554	**0.011**
Median (Range)	100 (49 – 143)	67 (18 – 120)		(S)
EI Dmax (cGy)				
Mean±SD	6540.31±135.43	6537.89±179.69	-0.219	0.826
Median (Range)	6552 (6174 – 6675)	6600 (6267 – 6784)		(NS)
EI Dmean (cGy)				
Mean±SD	5268.47±465.93	3064.36±1374.83	-4.578	**<0.001**
Median (Range)	5194 (4217 – 6026)	2523 (746 – 5323)		(HS)
EI V40 (%)				
Mean±SD	97.26±4.94	36.57±23.17	-5.275	**<0.001**
Median (Range)	99 (80 – 100)	32 (13 – 80)		(HS)
EI V50 (%)				
Mean±SD	54.36±24.91	29.36±23.61	-2.797	**0.005**
Median (Range)	53 (11 – 87)	27 (8 – 76)		(S)

Continuous variables were expressed as mean ± SD & median (range); b: Mann Whitney U test; p-value<0.05 is significant; Sig.: Significance.

EI volume, Dmean, V40 and V50 were significantly higher in Group A than group B (Table 6).

Table (7): Comparison between group A and group B regarding dosimetric parameters of Internal Iliac (InI) lymph nodes.

Dosimetric parameters	Group A (N=19)	Group B (N=19)	Test[b]	p-value (Sig.)
InI volume (cc)				
Mean±SD	121.57±23.08	92.05±32.29	-2.671	**0.008**
Median (Range)	119 (74 – 146)	110 (38 – 143)		(S)
InI Dmax (cGy)				
Mean±SD	6325.31±321.43	6168.47±373.87	-1.331	0.183
Median (Range)	6437 (5210 – 6564)	6268 (5359 – 6609)		(NS)
InI Dmean (cGy)				
Mean±SD	5150.05±432.42	2917.36±1289.77	-5.159	**<0.001**
Median (Range)	5037 (4180 – 5772)	3538 (813 – 4400)		(HS)
InI V40 (%)				

Mean±SD	97.05±4.71	21.05±20.45	-5.292	**<0.001**
Median (Range)	99 (80 – 100)	12 (2 – 59)		(HS)
InI V50 (%)				
Mean±SD	52.89±24.76	14±15.57	-4.431	**<0.001**
Median (Range)	47 (10 – 90)	8 (0 – 42)		(HS)

Continuous variables were expressed as mean ± SD & median (range); b: Mann Whitney U test; p-value<0.05 is significant; Sig.: Significance.

InI Volume, InI Dmean, InI V40, and InI V50 were significantly higher in Group A than group B (Table 7).

Table (8): Comparison between group A and group B regarding dosimetric parameters of Obturator (Obt) lymph nodes.

Dosimetric parameters	Group A (N=19)	Group B (N=19)	Test[b]	p-value (Sig.)
Obt volume (cc)				
Mean±SD	36.31±12.03	33.21±10.39	-0.527	0.598
Median (Range)	39 (15 – 54)	36 (15 – 46)		(NS)
Obt Dmax (cGy)				
Mean±SD	6469.15±125.19	6408.84±146.14	-1.654	0.098
Median (Range)	6463 (6203 – 6636)	6425 (6209 – 6636)		(NS)
Obt Dmean (cGy)				
Mean±SD	6037.94±314.78	5344.94±596.10	-3.788	**<0.001**
Median (Range)	6101 (5283 – 6381)	5200 (4187 – 6204)		(HS)
Obt V40 (%)				
Mean±SD	99.26±1.62	78±19.68	-5.028	**<0.001**
Median (Range)	100 (95 – 100)	80 (32 – 99)		(HS)
Obt V50 (%)				
Mean±SD	97.73±4.74	65.52±22.82	-5.005	**<0.001**
Median (Range)	100 (85 – 100)	60 (19 – 98)		(HS)

Continuous variables were expressed as mean ± SD & median (range); b: Mann Whitney U test; p-value<0.05 is significant; Sig.: Significance.

Obt Dmean, Obt V40, and Obt V50 were significantly higher in Group A than group B (Table 8).

Table (9): Comparison between group A and group B regarding dosimetric parameters of Presacral (Ps) lymph nodes.

Dosimetric parameters	Group A (N=19)	Group B (N=19)	Test[b]	p-value (Sig.)
Ps volume (cc)				
Mean±SD	15.94±3.65	14.05±4.35	-1.427	0.141
Median (Range)	15 (9 – 22)	14 (8 – 23)		(NS)
Ps Dmax (cGy)				

Mean±SD	5047.89±696.50	2507.47±1987.41	-3.759	**<0.001**
Median (Range)	4722 (4009 – 6066)	1708 (193 – 5492)		(HS)
Ps Dmean (cGy)				
Mean±SD	4712±418.52	1059.05±1007.52	-5.282	**<0.001**
Median (Range)	4624 (3930 – 5333)	606 (168 – 3114)		(HS)
Ps V40 (%)				
Mean±SD	99.84±0.37	4.94±9.02	-5.602	**<0.001**
Median (Range)	100 (99 – 100)	0 (0 – 25)		(HS)
Ps V50 (%)				
Mean±SD	23.10±35.41	1.15±2.11	-1.053	0.292
Median (Range)	0 (0 – 83)	0 (0 – 6)		(NS)

Continuous variables were expressed as mean ± SD & median (range); b: Mann Whitney U test; p-value<0.05 is significant; Sig.: Significance.

Ps Dmax, Ps Dmean, and Ps V40 showed highly significant differences (HS), with Group A receiving higher than group B. No significant difference was observed in Ps volume and Ps V50 (Table 9).

Table (10): Correlation between bladder volume (cc) and dosimetric parameters of lymph nodes among the studied patients.

Dosimetric parameters	Bladder volume (cc)					
	Group A (N=19)		Group B (N=19)		All patients (N=38)	
	r	p-value (Sig.)	r	p-value (Sig.)	r	p-value (Sig.)
LCI Dmax (cGy)	+0.374	0.115 (NS)	-0.611	**0.005 (S)**	-0.219	0.186 (NS)
LCI Dmean (cGy)	+0.419	0.075 (NS)	+0.132	0.591 (NS)	-0.008	0.963 (NS)
LCI V40 (%)	+0.154	0.530 (NS)			-0.013	0.940 (NS)
LCI V50 (%)	+0.428	0.067 (NS)			+0.237	0.152 (NS)
EI Dmax (cGy)	+0.708	**0.001 (S)**	+0.292	0.225 (NS)	+0.483	**0.002 (S)**
EI Dmean (cGy)	+0.428	0.067 (NS)	+0.466	**0.044 (S)**	+0.164	0.325 (NS)
EI V40 (%)	+0.309	0.198 (NS)	+0.024	0.922 (NS)	-0.055	0.742 (NS)
EI V50 (%)	+0.321	0.180 (NS)	+0.011	0.965 (NS)	+0.100	0.550 (NS)
InI Dmax (cGy)	+0.738	**<0.001 (HS)**	+0.425	0.070 (NS)	+0.444	**0.005 (S)**
InI Dmean (cGy)	+0.398	0.091 (NS)	-0.200	0.413 (NS)	-0.074	0.659 (NS)
InI V40 (%)	+0.189	0.439 (NS)	+0.268	0.267 (NS)	-0.028	0.867 (NS)
InI V50 (%)	+0.257	0.289 (NS)	+0.336	0.160 (NS)	+0.105	0.529 (NS)
Obt Dmax (cGy)	+0.380	0.108 (NS)	+0.329	0.169 (NS)	+0.200	0.203 (NS)
Obt Dmean (cGy)	+0.547	**0.015 (S)**	+0.602	**0.006 (S)**	+0.331	**0.043 (S)**
Obt V40 (%)	+0.190	0.435 (NS)	+0.482	**0.037 (S)**	+0.064	0.701 (NS)
Obt V50 (%)	-0.049	0.841 (NS)	+0.672	**0.002 (S)**	+0.073	0.663 (NS)
Ps Dmax (cGy)	+0.484	**0.036 (S)**	+0.778	**<0.001 (HS)**	+0.386	**0.017 (S)**

Ps Dmean (cGy)	+0.530	**0.020 (S)**	+0.531	**0.019 (S)**	+0.134	0.422 (NS)
Ps V40 (%)	-0.435	0.063 (NS)	+0.536	**0.018 (S)**	-0.075	0.653 (NS)
Ps V50 (%)	+0.326	0.173 (NS)	+0.536	**0.018 (S)**	+0.351	**0.031 (S)**

r: Spearman's correleation coefficient; p-value<0.05 is significant; Sig.: Significance.

In Group A, bladder volume showed significant positive correlations with EI Dmax, InI Dmax, Obt Dmean, Ps Dmax and Ps Dmean. In Group B, more significant correlations were observed, including strong positive associations with LCI Dmax, EI Dmean, Obt Dmean, Obt V40, Obt V50, Ps Dmax, Ps Dmean, Ps V40 and Ps V50. Overall, Group B appears to have a stronger dose dependency on bladder volume than Group A (Table 10).

5. DISCUSSION

Bladder cancer is the ninth most common cancer diagnosed globally and the most prevalent disease affecting the urinary system [1]. In Egypt, bladder cancer is the third most frequent type of cancer. It ranks as the third most common cause of cancer-related deaths [1, 2]. Muscle-invasive bladder cancer is seen in about 30% of bladder cancer patients [16].

Organ preservation with multimodality therapy is utilized in modern oncology to treat a variety of cancers, such as head and neck malignancies, prostate, anal, and breast cancers. As an alternative to radical cystectomy (RC), bladder preservation (trimodality therapy TMT) is typically saved for patients with smaller solitary tumors, negative nodes, no multifocal or widespread CIS, no tumor-related hydronephrosis, and satisfactory bladder function prior to treatment [17].

TMT includes maximal transurethral resection of bladder tumor (TURBT) as safely as feasible followed by external beam radiation therapy (EBRT) with concurrent [18]. The majority of TMT patients achieve a clinical complete response (cCR) (70–80%), avoiding salvage radical cystectomy while offering long-term survival rates similar to those in current radical cystectomy series, [19].

Numerous studies showed that a total dosage greater than 55–60 Gy was linked to better local control, indicating the significance of dose escalation in bladder cancer outcomes [20].

Patients with invasive bladder cancer have been advised to receive 60–66 Gy of radiation in 2 Gy portions since 1999. [21]. This total prescription dose to the whole bladder is still commonly used in prospective trimodal treatment trials that use standard fractionation without dose escalation. Majewski et al. imply that higher doses may produce better results. They postulated that a 6% increase in local control and a 7.5% rise in 5-year overall survival would follow each 1 Gy increase in the total dose over 60 Gy. Interest in raising the dose to the complete bladder above 66 Gy has so far been halted by fear of toxicity [22].

There is still debate on the inclusion of the pelvis in the EBRT field for patients with node-negative MIBC [23].

Surgical studies showing that the extent of lymph node dissection improves survival chances, even in node-negative patients [24], perhaps due to the high occurrence of clinically undetected pelvic micrometastases [25], providing support for nodal irradiation. Data from surgical series that indicate micro-metastases could be shown in about one-third of cases with clinically and radiologically negative nodes lend credence to the justification for irradiating pelvic lymph nodes. [26]

However, patients randomly assigned to receive whole-pelvis or bladder-only RT did not vary in bladder preservation, disease-free survival, or OS rates, according to Tunio et al and Patel et al. [23,27]. Furthermore, in the Bladder Cancer 2001 (BC2001), the largest bladder preservation trial to date to be published [13], all patients received just bladder-directed radiation therapy without pelvic nodal coverage. Only around 5% of patients experienced pelvic nodal failure [28], and bladder preservation rates and long-term survival outcomes were similar to those in US-based trials where most radiation oncologists included at least some pelvic lymph nodes in the target volume [29].

As a question about volume of irradiation in treating MIBC as an essential part of TMT, we searched volume descalation by comparing standard whole pelvis radiotherapy versus bladder only irradiation.

The mean age (range) of the patients in our study was 64.5 (56–80) years for group A and 66.9 (52–80) years for group B. This was similar to the mean age of 61.95 in both groups reported by Tunio et al. [27].

Male patients presented 73.7% of group A, while in group B were 89.5% in our study. This was nearly matched with Tunio et al. [27] study which included 85.8% and 85.5% of group A and group B respectively% male patients and Arafat W et al. [30] study that reported to include male patients 86.7% of group A and 93.3% of group B.

All patients in our study had performance status of ≤ 2 compatible with studies of Tunio et al. [27] and Arafat W et al. [30].

Clinical stage in current study ranged between T2 and T3 representing 42.1% and 57.9% respectively in group A and 47.4% and 52.6% respectively in group B. This is nearly similar to that found in Tunio et al study, where T2 represented 45.8% and T3 represented 50% of their study in group A and represented 45.5% and 50% respectively in group B. Moreover, they

included 4.2% and 4.5% of their patients with T4 in group A and B [27].

However, there is significant difference between our study and that of Arafat W et al. [30] where they included 80% T2 and 20% T3 disease in group A and 83.3% T2 and 16.7% T3 disease in group B.

All patients in our study had high grade (grade III) urothelial carcinoma coping with the concept stated by Mahul B Amin that invasive urothelial carcinoma should be graded as high grade, irrespective of the depth of invasion [31]. All detrusor muscle-invasive urothelial carcinomas are considered to be high grade tumors [32].

Only 47.4% and 57.9% of our patients in both groups underwent complete TURBT. This can be explained by most of our patients were of T3, multifocal disease so TURBT was cautious for fear of perforation.

In Arafat W et al. [30] study, percentage of complete TURBT was 76.7% and 83.3% in both groups respectively. The same in Tunio et al. [27] study, complete TURBT was 76.7% and 76.4% in group A and B.

During our radiotherapy treatment course, there was interruption either due to intolerable toxicity or due to machine malfunction or poor patient compliance. However, this interruption has no impact on our results being supported by two large retrospective studies from Holland and Belgium that showed no significant effect of prolonging treatment time on outcome [33, 34].

However, there is growing evidence that unscheduled breaks in the treatment of radical radiotherapy that result in an extension of the total treatment duration negatively impact local control and cure rates for patients with specific tumors, such as cervical carcinoma, small and non-small cell lung cancer, and head and neck squamous cell carcinoma, however, regarding bladder transitional cancer, there is greater uncertainty [35, 36]. Longer treatment times for bladder cancer patients may have an impact on their outcomes, according to two small publications [37, 38], but two larger retrospective studies from Holland and Belgium found no evidence of a substantial impact. [33, 34].

Complete response achieved after finishing course of chemoradiation was documented in 31.6% in both groups. This percentage is significantly less than what was achieved in Tunio et al. [27] study where CR was achieved in 93.1% and 92.8% in both groups. Similarly, complete response was noted in 73.3% and 76.7% in both groups in Arafat W et al. [30] study.

This may be explained by that nearly half of our patients did not have complete TURBT and of course because small number of sample.

Acute genitourinary toxicity in both groups was mostly in the form of frequency, dysuria and urgency. Grade 2 frequency was 73.7% vs 68.4% in both groups. Grade 1 dysuria was 84.2% in both groups; with no significant variation between both arms of study.

This is comparable with acute genitourinary toxicity, presented by grade I-II symptoms; frequency, nocturia and dysuria, in Arafat W et al study 93.3% and 86.7% in both groups.

Our results showed higher incidence of acute genitourinary toxicity compared with Tunio et al results which showed overall incidence of GU toxicity presented in cystitis being only 14.7% and 12.2% in both groups.

About acute gastrointestinal toxicity, there was significant difference between both groups being diarrhea and rectal pain the most presenting symptoms. In group A, grade 1, 2, 3, 4 diarrhea was 36.8%, 42.1%, 15.8% and 5.3% respectively. This is significantly high compared with the incidence of diarrhea in group B; as 57.9% of our patients showed no diarrhea while grade 1, 2, 3, 4 was 21.1%, 15.8%, 5.3% and 0% respectively.

Our results are comparable with those of Arafat W et al. study where in group A grade 1-2 recorded 86.7% and grade 3-4 recorded 6.7% and in group B grade 0 65%, grade 1-2 was 51.7% and grade 3-4 was 3.3%.

However, our results also showed higher incidence of acute gastrointestinal toxicity compared with Tunio et al. study; where diarrhea grade 1-2 affected only 4.7% of their patients in group A and grade 3-4 affected 3.9% and in group B, grade 1-2 diarrhea was 3.1% and grade 3-4 was 2%.

Regarding treatment outcome, 31.6% of our patients achieved complete response in both groups, while partial response was 42.1% and 31.6% in group A and B respectively with no significant difference.

Progressive course was noted in 4 patients (21%) and 5 patients (26.3%) in both groups respectively. Those patients were advised to go for radical cystectomy and in case of refusal of surgery, palliative chemotherapy was recommended.

Our findings regarding assessment of response are quite different from those of Arafat W et al. [30] study as they used split course of chemoradiotherapy and initially assessed their patients after induction chemotherapy. Complete response was noted in 22 patients (73.3%) and 23 patients (76.6%) in both arms respectively and were referred for consolidation chemoradiation. Those who did not achieve complete response were excluded and referred for either of radical cystectomy or palliative treatment.

Also, our results are different from those of Tunio et al. [27] results where complete response was recorded in 95 patients

(93.1%) in group A and 91 patients (92.8%) in group B. This is definitely attributed to high percentage of patients who had initial complete TURBT. Those with progressive course were referred to salvage cystectomy.

Regional relapse was recorded in 13.3% of our patients in group A and 7.1% of those in group B within a 36 month- period of follow up with no significant difference between both groups.

That is matched with findings of Arafat W et al. [30] study; as regional relapse occurred in 2 patients (7.1%)and 3 patients (10.3%) in both arms of their study and quite similar to regional relapse found in Tunio et al. [27] study where 15 patients (15.8%) in group A and 16 patients (17.6%) in group B.

Two patients in group A and B of our study developed distant metastasis which is significantly less than observed in Arafat W et al. [30] study and Tunio et al. [27] study where distant metastasis occurred in 5 and 4 patients in group A and B in the former study and 36 and 37 patients in both groups in the latter study.

At the time of analysis, 3- year overall survival was 46.7% and 57.1% in both groups of our study respectively with no significant difference. This is very consistent with Petal et al. [23] study where estimated 3-year OS between bladder-only vs. bladder plus PLN radiation groups was 40.9% vs. 46.2% and likely corresponding to 5- year overall survival detected in Tunio et al. study being 52.9% and 51% in both groups.

Arafat W et al. [30] study showed better 2- year survival; achieving 75% and 79.3% in both groups.

Comparing dosimertic parameters between group A where lymphatics were irradiated electively and group B where lymphatics received incidental dose by bladder only irradiation, mean dose of lower common iliac lymph nodes was significantly higher in group A vs group B (2560 cGY vs 119.2 cGY); lower than the incidental dose of 10 GY in Lewis et al study **[14].**

The volume of lower common iliac lymph nodes receiving 40 GY (V40) in our study is 38.7% vs 0% in both groups compared with 7% in Lewis et al. [14] study.

Regarding external iliac lymph nodes, Dmax was not different between both arms of our study 65.4 GY vs 65.3 GY respectively resembling that in Lewis et al. [14] study (64 GY). Dmean recorded 52.6% vs 30.6GY respectively with high significant difference and the latter is less than that in Lewis et al study (45 GY).

V40 is significantly higher in group A vs B covering 97.2% vs 36.5% of external iliac lymph nodes volume, which is also lower than that of Lewis et al study (61%).

V50 is also achieving significant difference between both groups 54.3% vs 29.3% which is much lower than Lewis et al study 54% [14].

Concerning internal iliac lymph nodes Dmax, both groups recorded no significant difference 63.2 GY vs 61.6 GY which is similar to Lewis et al study (63 GY), while mean dose showed high significant difference 51.5GY vs 29 GY which is relatively lower than Lewis et al finding (36 GY).

V40 and V50 varied significantly between both groups; 97% vs 21% and 52.8% vs 14% respectively and again our incidental dose is much less than that in Lewis et al study 46% and 40%.

Obturator lymph nodes did not differ in Dmax achieving about 64 GY in both arms of our study which was not different from Lewis et al finding (68 GY). Mean dose showed high significant difference 60.3 GY vs 53.4 GY respectively while Lewis et al recorded high incidental dose of 59 GY. V40 and V50 in our study covered 99% vs 78% and 97.7% vs 65.5% in both groups respectively, which is lower than volume covered by the incidental dose in Lewis study 88% and 84%.

Presacral lymph nodes exhibited significant difference between both groups regarding Dmax, mean dose and V40. Dmax was 50.4GY vs 25 GY which is lower than that in Lewis et al study (42 GY). Mean dose was 47 GY vs 10.6 GY which is again lower than that recorded in Lewis et al study (29 GY). V40 covered 99.8% vs 5% of presacral lymph nodes volume while in Lewis et al study covered 26%.

The difference between the dosimetric parameters of our study and that of Lewis et al study is attributed to the bladder volume. In group B of our study, mean bladder volume was 205 cc (range 51-360 cc) and only 32% of our patients had bladder volume exceeding 300 cc, while most patients 70% in the latter study showed bladder volume exceeding 300 cc.

This drawback in our study can be explained by irritable bladder symptoms of our patients and patient were instructed for bladder emptying protocol.

When comparing our results based on 3D planning technique to IMRT, we found relative increase in the dosimetric parameters of lymphatics in the arm based on incidental dose delivery.

In our study, median Dmean values of lower common iliac, external iliac, internal iliac, obturator and presacral lymph nodes were 86 cGY (25-246), 2523 cGY (746-5323), 3538 cGY (813-4400), 5200 cGY (4187-6204) and 606 cGY (168-3114) respectively. In Ozyigit G et al. [39] study, the same findings were 100 (0-1500), 9500 (300-4100), 750 (200-1400), 3300 (400-5000) and 300 (100-2800).

Median V40s in our study were 0% of lower common iliac, 32% (13-80) of external iliac, 12% (2-59) of internal iliac, 80% (32-99) 0f obturator and 0% of presacral lymph nodes. Our results are significantly higher than Ozyigit G et al. [39] study; where V40 is13% (5-63) of external iliac, 9% (0-43) of internal iliac and 47% (13-88) of obturator lymph nodes.

There is currently no data comparing bladder-only irradiation using IMRT or VMAT versus bladder-plus-ENI techniques. To the best of our knowledge, in the age of IMRT and VMAT, that work is the first to examine accidental nodal doses with bladder-only irradiation. The study's findings demonstrated that incidental nodal doses from bladder-only irradiation using contemporary methods are less than those from the 3DCRT series [39].

6. CONCLUSION

This study demonstrated that bladder-only radiotherapy (BORT), when delivered concurrently with weekly cisplatin in clinically node-negative muscle-invasive bladder cancer, results in significantly lower gastrointestinal toxicities in grade 2-4, particularly diarrhea and rectal pain compared to the standard whole pelvis radiotherapy technique. Moreover, both techniques achieved comparable outcomes in terms of genitourinary toxicity, radiological response, regional and distant relapses and survival outcomes. These findings suggest that omitting elective pelvic nodal irradiation may be a safe and effective option for selected patients. Additionally, dosimetric analysis revealed that pelvic lymph nodes received considerable incidental doses even in the bladder-only technique. Notably, bladder filling plays a crucial role in enhancing incidental nodal irradiation and potentially supporting nodal control in bladder only radiotherapy.

7. RECOMMENDATIONS

Larger multicenter randomized controlled trials are warranted to validate the oncologic safety of bladder-only radiotherapy.

Longer follow-up is necessary to evaluate long-term survival, late toxicities, and local/regional control.

Future studies should integrate patient-reported outcomes and QoL assessments to capture the full impact of reduced toxicity.

If confirmed in larger cohorts, BORT may become a preferred standard in selected MIBC patients to reduce GI toxicity while maintaining efficacy.

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