The Egyptian Journal of Hospital Medicine (January 2024) Vol. 94, Page 427-435

Whole Pelvis versus Bladder Only Radiotherapy in Trimodality Therapy for Negative Lymph Node Muscle Invasive Bladder Cancer

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ABSTRACT

Background: Trimodality therapy has been recommended as a valid treatment option for well-selected patients of muscle invasive bladder cancer (MIBC). The benefit of elective nodal irradiation during bladder radiotherapy (RT) remains a controversial topic.

Objectives: Our study comparing bladder only (BO) versus whole pelvis (WP) radiotherapy, concurrent with cisplatin to evaluate BO radiotherapy outcome and toxicity.

Patients and methods: A randomized prospective study comparing BO versus WP radiotherapy using 3D conformal radiotherapy concurrent with cisplatin followed by 4 cycles gemcitabine/cisplatin in nonmetastatic negative lymph node MIBC.

Results: Our cohort included 28 and 30 patients in BO and WP group, respectively. No statistically significant difference (P =0.59) was detected between 2 groups as regard disease free survival (DFS)rate at 3 years, which was 81% and 85 % in BO and WP group, respectively. At 3 years the reported bladder cancer specific survival and overall survival(OS) rate in BO group was 83% and 75 %, respectively while for WP group the results were 80 % and 73%, respectively with no statistically significant difference between the 2 groups. Regarding RT toxicity, acute small bowel (P=0.03) and acute rectal toxicity (P=0.007) showed statistically significant difference favouring BO radiotherapy while acute genitourinary toxicity (P=0.91), late genitourinary (P =0.33) and late GIT toxicity (P=0.4) showed no statistically significant difference between the 2 groups.

Conclusion: BO radiotherapy concurrent with chemotherapy is an effective treatment option in patients with lymph node-negative MIBC with comparable oncologic outcomes and less RT toxicity when compared with WP radiotherapy.

Keywords: Bladder only radiotherapy, Whole pelvis radiotherapy, Bladder radiotherapy.

INTRODUCTION

In 2020, an estimated 573,000 new cases diagnosed with bladder cancer and 213,000 deaths. Therefore, bladder cancer ranked as the 10th most commonly cancer worldwide. In Egypt, bladder cancer remains as a serious health concern as it is the 3rd most prevalent cancer according to GLOBACAN 2020 [(1)].

Management of MIBC, which constitute 25% of bladder cancer diagnosis is challenging with neoadjuvant chemotherapy followed by radical cystectomy with bilateral pelvic lymphadenectomy, is considered the standard of care for treatment by international guidelines. Although there is progress in surgical techniques and perioperative care, radical cystectomy causes significant postoperative morbidity and complication even in the most experienced hands at high volume centers. Additionally, the majority of bladder cancer patients are elderly, and many of them may not be good candidates for surgery because of co-morbidities that could raise the risk of complications after surgery [(2,3)].

So, trimodality therapy has emerged as an alternative treatment of MIBC that would provide non-inferior oncological outcomes to radical cystectomy and maintain quality of life. Unfortunately, there are no completed head-to-head randomized comparisons between the trimodality therapy and radical cystectomy.

However, data from matched comparisons and meta-analysis demonstrate that trimodality therapy yield similar long-term survival rates and comparable clinical oncologic outcomes when compared to radical cystectomy. Based on these data, the current NCCN Guidelines and the American Society of Clinical Oncology have recommended trimodality therapy as a valid treatment option for appropriate-selected patients of MIBC who refuse to undergo radical cystectomy, as well as those who are not candidates for neoadjuvant chemotherapy and surgery [(4,5)].

Trimodality therapy consists of maximum transurethral resection of bladder tumor (TURBT) followed by chemotherapy concurrently with radiotherapy. The radiation volume in trimodality therapy needs further investigations particularly the unresolved issue of benefit of elective pelvic lymph node (LN) irradiation in negative lymph node MIBC. Consequently, for bladder preservation, elective nodal irradiation is a matter of debate in practice worldwide [(6)].

RTOG protocols include irradiation to WP then the bladder and gross tumor received radiotherapy (RT) boost while the UK BC 2001 trial using whole bladder radiotherapy showed that regional nodal failure was similar to that reported in the studies utilizing WP radiotherapy[(7)].

Received: 02/08/2023
Accepted: 01/10/2023

Our study examines trimodality therapy in negative lymph node MIBC comparing BO radiotherapy versus WP radiotherapy, concurrent with cisplatin, aiming to evaluate outcomes, feasibility and safety of BO radiotherapy when compared with WP radiotherapy.

PATIENTS AND METHODS

A randomized phase II prospective study comparing BO radiotherapy versus WP radiotherapy using 3D conformal radiotherapy concurrent with cisplatin followed by 4 cycles gemcitabine/cisplatin. This study was conducted in Sohag University Hospital and Sohag Cancer Institute between 2020 and 2023.

Eligibility criteria: Inclusion criteria included age ≥18 years, patients with proved invasive urothelial carcinoma of the bladder, operable localized MIBC by imaging (cT2-T3), GFR≥60 ml/min and ECOG performance status ≤ 2 at the start of treatment. Exclusion criteria included evidence of distant metastasis or lymph node metastasis, uncontrolled systemic disease which would exclude the patient from the study, history of other malignancy within the previous 2 years (other than adequately treated BCC of the skin or adequately treated in situ carcinoma of the cervix), inflammatory bowel disease, and history of previous pelvic radiotherapy.

All patients underwent evaluation with cystoscopy and tumour biopsy, physical examination and ECOG performance status assessment, CBC, KFTs including creatinine and urea, estimation of GFR, MRI or CT Pelvis (MRI was preferable), CT chest and abdomen and bone scan if bone pain. Patients were randomized using simple randomization method as the first eligible patient was included either in BO or WP group after coin toss then second patient was included in the other group then continued in the same way.

Treatment protocol

- All patients underwent maximum TURBT before the initiation of radiotherapy. Complete TURBT was defined as no gross residual disease on cystoscopy. Radiotherapy began within 6 weeks following maximum TURBT.

Radiotherapy treatment

CT simulation was from L1 to mid-thigh at 3-5 mm slice thickness. Patients were CT simulated in supine position using knee and feet support for immobilization with an empty bladder and rectum. Patients were simulated and treated with empty bladder and rectum. IV contrast was administrated when WP radiotherapy was planned to be given.

1-Target volume and radiotherapy dose

I. Patients in BO radiotherapy group: clinical target volume (CTV) included the whole bladder and prostatic urethra then expansion of CTV with 1.5 cm to create planning target volume (PTV) except at superior and anterior wall as the margin is 2 cm. The total dose was 64 Gy in 32 fractions; one fraction per day and five fractions per week.

II. Patients in WP radiotherapy group received RT to whole pelvis with 44 Gy in 22 fractions. Nodal volumes included:

• **Presacral nodes**: extend from L5-S1 to the top of S3 and included 1-1.5 cm of tissue anterior to the sacrum and between the vessel contours.

• **Iliac nodes**: contoured by expanding the iliac vessel contours by 7 mm in all dimensions except the superior and inferior dimensions. Contour the common iliac and external and internal iliac vessels starting superiorly at L5-S1.

External iliac nodes: extend inferiorly to the top of the femoral heads

Internal iliac nodes: extend inferiorly until they are not visible on CT scan or exit via the greater sciatic notch.

• **Obturator nodes**: include 1 cm width of tissue medial to the obturator internus muscle extending from the anterior border of the ilium to its posterior border and starting superiorly at the inferior border of the iliac vessel contours to the top of the pubic symphysis.

Expansion of previous CTV nodal volumes with 7 mm create nodal PTV.

The bladder boost included the whole bladder and prostatic urethra plus 1.5 cm to create PTV except at superior and anterior wall as the margin is 2 cm to a dose of 20 Gy in 10 fractions. One fraction per day and five fractions per week.

- Organs at risk contouring included:
- Bowel: include the entire bowel in one bag contour starting 1.5 cm above the superior extent of the nodal PTV.
- Rectum: from the recto-sigmoid junction to the level of the ischial tuberosities.
- Bilateral femoral head and neck.

Chemotherapy included the following

A. Concurrent chemotherapy: Cisplatin 40 mg/m^2 administered weekly.

B. 4 cycles adjuvant gemcitabine (1000 mg/m^2)/ cisplatin (70 mg/m^2) repeated every 3 weeks starting 4 weeks post concurrent chemoradiotherapy.

Complications of RT that occurred during and within 90 days after end of concurrent chemoradiotherapy were classified as acute toxicity, while those occurring later were considered late RT toxicity. Acute and late RT toxicities were assessed based on acute and late RTOG radiotherapy toxicity grading. Chemotherapy toxicity was assessed based on CTCAE v 5. Toxicity was assessed

weekly during chemoradiotherapy and every cycle during adjuvant chemotherapy. Complete response to concurrent chemoradiotherapy has been defined as no visible tumor and negative biopsies at cystoscopy done 3 months post concurrent chemoradiotherapy.

Regular assessment was performed every 3 months at first 2 years then every 6 months thereafter or as clinically indicated by physical examination, toxicity assessment by RTOG and CTCAE v 5, CT chest, abdomen and pelvis or MRI pelvis when available and cystoscopy.

Ethical consideration

The Ethics Committee of Faculty of Medicine, Sohag University, approved this study and patient's informed written consent was obtained to participate in the study. This work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Survival outcomes

- **Disease free survival (DFS)** was defined as time from end of concurrent chemoradiotherapy in patients achieving complete response to death or last follow up or date of progression.
- **Bladder cancer specific survival** was defined as time from diagnosis to death due to bladder cancer or last follow up.
- **Overall survival (OS)** was defined as time from diagnosis to death or last follow up.

Statistical analysis

STATA version 17.0 was used for data analysis. Qualitative data were presented as frequency and percentage and were compared using either Chi square test or Fisher exact test. Quantitative data were presented as mean, standard deviation (SD), median, and range. The Kaplan–Meier survival method with the log rank test was used to assess different categories on survival. P value was considered significant if it was < 0.05.

RESULTS

The preliminary cohort included 61 patients, unfortunately 3 patients were excluded as they didn't complete the prescribed course of radiotherapy due to patients' negligence. Our final cohort included 58 patients with non-metastatic negative lymph node MIBC enrolled between May 2020 till January 2021 of whom 28 patients were included in BO radiotherapy group and WP radiotherapy group included 30 patients.

Patients' age ranged between 49-67 years with mean age 62 years old and 65.5% of our patients were older than 60 years. Male patients represented the majority of our patients (84.5%) with male to female ratio was 5:1. Thirty one percent of our patients had history of bilharziasis and 72.4% were current smoker or stopped smoking within last 3 months. Performance status assessment revealed that 62% of patients had performance status of 1. Patients who had tumor that was more than 3 cm in greatest dimension were 58.6%. At initial diagnosis, T2 was detected in 55% of patients while the remainder 45% had T3. Grade 2 was the most common grade representing 69% of our cohort. Mild to moderate hydronephrosis was detected in 13 patients with only 2 patients underwent percutaneous nephrostomy insertion. All patients underwent maximum TURBT prior to starting radiation therapy with 72.4% had complete TURBT before radiotherapy. Fifty-three patients (91.4%) received concurrent cisplatin weekly with radiotherapy with the remaining 5 patients didn't complete concurrent cisplatin due to hematological toxicity. The majority of our patients (74%) received the prescribed course of 4 cycles gemcitabine/cisplatin.

No significant differences were detected between 2 groups as regard patients, tumor characteristics and receiving chemotherapy as shown in Table 1. Therefore, the 2 groups were well balanced as regard patients' characteristics, tumor characteristics and receiving chemotherapy.

Table 1. Comparison between bladder only radiotherapy and whole pelvis radiotherapy group as regards patients, tumor characteristics and receiving chemotherapy

	Variable	Bladder only radiotherapy N=28	Whole pelvis radiotherapy N=30	P value
Age/year	Mean ± SD Median (range)	61.71±4.81 63 (49:67)	62.23±3.28 63 (55:67)	0.91
Age/year	≤60 year >60 year	10 (35.7%) 18 (64.3%)	10 (33.3%) 20 (66.7%)	0.85
Gender	Female Male	4 (14.3%) 24 (85.7%)	5 (16.7%) 25 (83.3%)	1.00
Performance status	0 1	10 (35.7%) 18 (64.3%)	12 (40 %) 18 (60 %)	0.74
History of bilharziasis	Absent Present	18 (64.3%) 10 (35.7%)	22 (73.3%) 8 (26.7%)	0.46
Smoking	Non-smoker or ex-smoker Current smoker	7 (25 %) 21 (75 %)	9 (30 %) 21 (70 %)	0.67
Site of tumors	Posterior wall lateral wall Dome Trigone Anterior wall More than one site	5 (17.9%) 14 (50%) 5 (17.9%) 1 (3.6%) 1 (3.6%) 2 (7%)	9 (30 %) 8 (26.7%) 3 (10%) 4 (13.3%) 1 (3.3%) 5 (16.7%)	0.16
Multiplicity	Solitary Multiple	25 (89%) 3 (11%)	28 (93%) 2 (7%)	0.57
Growth pattern	Papillary Solid	4 (14%) 24 (86%)	6 (20%) 24 (80%)	0.58
Tumor size (largest diameter)	≤ 3cm > 3cm	12 (43%) 16 (57%)	12 (40%) 18 (60%)	0.83
Pathology	Urothelial Urothelial (squamous differentiation) Urothelial (glandular differentiation) Urothelial (signet ring variant)	23 (82.1%) 4 (14.2%) 1 (3.7%) 0	22 (73.3%) 5 (16.7%) 1 (3.3%) 2 (6.7%)	0.56
Grade	Grade 1 Grade 2 Grade 3	4 (14.3%) 20 (71.4%) 4 (14.3%)	3 (10%) 20 (66.7%) 7 (23.3%)	0.64
Associated CIS	No Yes Not known	15 (53.5%) 1 (3.5%) 12 (43%)	15 (50%) 2 (6.7%) 13 (43.3%)	0.86
LVI	No Yes Not known	11 (39.3%) 1 (3.6%) 16 (57.1%)	14 (46.7%) 0 16 (53.3%)	0.52
T stage	T 2 T 3	16 (57%) 12 (43%)	16 (53.3%) 14 (46.7%)	0.77
TURBT completeness	Complete Incomplete	21 (75%) 7 (25%)	21 (70%) 9 (30%)	0.67
Hydronephrosis	No Present	24 (85.7%) 4 (14.3%)	21 (70%) 9 (30%)	0.15
Concurrent chemotherapy	Complete Incomplete	25 (89%) 3 (11%)	28 (93 %) 2 (7 %)	0.46
Adjuvant chemotherapy	Complete Incomplete	22 (78.6%) 6 (21.4%)	21 (70%) 9 (30%)	0.11

Man Whitney U test used to compare mean and median of age.Abbrevations CIS: carcinoma in situ, LVI: lymphovascular invasion, TURBT:transurethral resction of bladder tumor.

Treatment outcomes

On imaging and cystoscopy assessment at 3 months post concurrent chemoradiotherapy, complete response was achieved in 75% and 73.4% of patients in BO group and WP group, respectively with no statistically significant difference was detected between the 2 groups. Fifteen patients didn't achieve CR, 7 patients in BO group and 8 patients in WP group. They were offered salvage cystectomy, 10 patients refused and insisted on continuation of chemotherapy. The remaining 5 patients who accept salvage cystectomy unfortunately didn't undergo surgery, four of them due to medical comorbidities and one patient delayed surgery due to patient factors then refused surgery. Later on, 9 patients developed either locoregional or distant metastasis.

With median follow up of 36 months (range 11-40 months). Locoregional relapse was detected in 4 patients proved by cystoscopic biopsy to be muscle invasive and by imaging to be non-metastatic. The two patients in WP group who had local relapse underwent salvage cystectomy and pelvic LN dissection with ileal conduit. The histopathology result showed T3 N0 in both patients then patients received chemotherapy. The other 2 patients were in BO group, one of them underwent salvage cystectomy and pelvic LN dissection with ileal conduit with histopathology result showed T2 N0. The other patient, which is the only patient who had pelvic LN relapse in our study refused surgery then missed follow up. Distant metastases were detected in 5 and 7 patients in BO and WP group, respectively.

Bone and lung were the most common sites of distant metastasis in BO group while in WP group, bone was the most common site. These patients received 2nd line chemotherapy and palliative radiotherapy to bone in case of bone metastasis and bisphosphonates. No significant differences were detected between the 2 groups as regard locoregional relapse, distant metastasis and sites of distant metastasis.Unfortunately, at the end of our study 17 patients died. Bladder cancer was the cause of death in 11 patients while the other 6 patients died of other causes such as complication of liver cirrhosis and development of 2nd primary cancer with no significant difference was detected between the 2 groups.

DFS rate at 3 years was 81% and 85 % in BO group and WP group, respectively with no statistically significant difference was detected between 2 groups (P =0.59) as shown in figure 1.

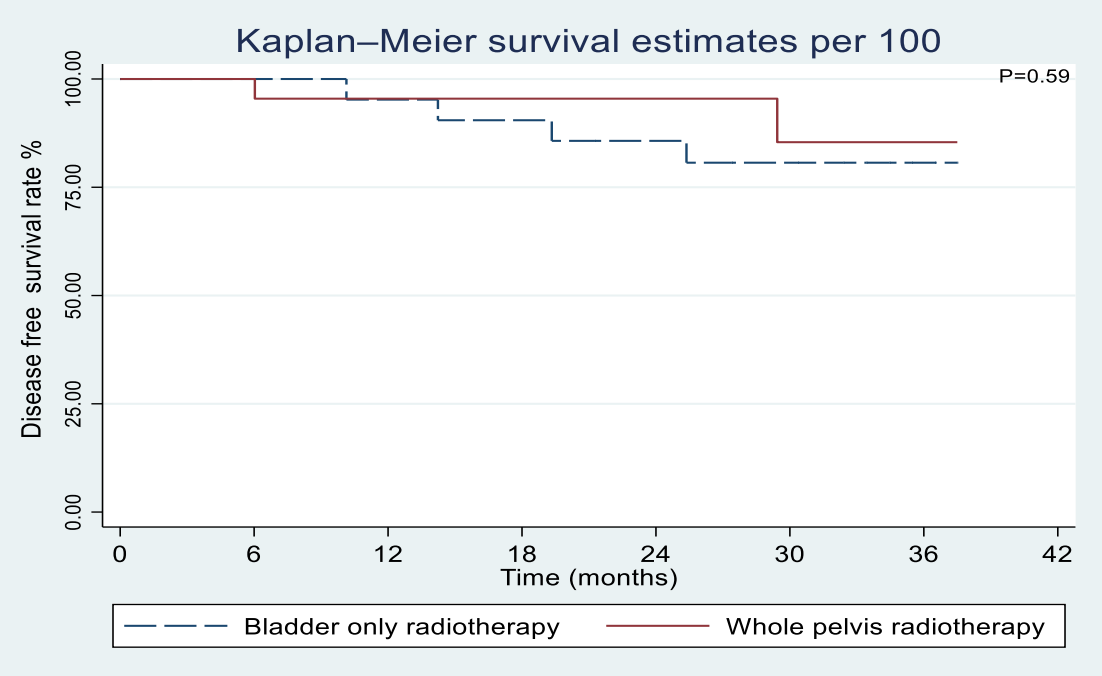

Figure 1. Disease free survival rate.

For BO group the reported bladder cancer specific survival rate was 83% and OS rate was 75 % at 3 years. For WP group the reported bladder cancer specific survival rate was 80 % and OS rate was 73% at 3 years with no statistically significant difference between the 2 groups was reported for bladder cancer specific survival and OS, as shown in figures 2 and 3.

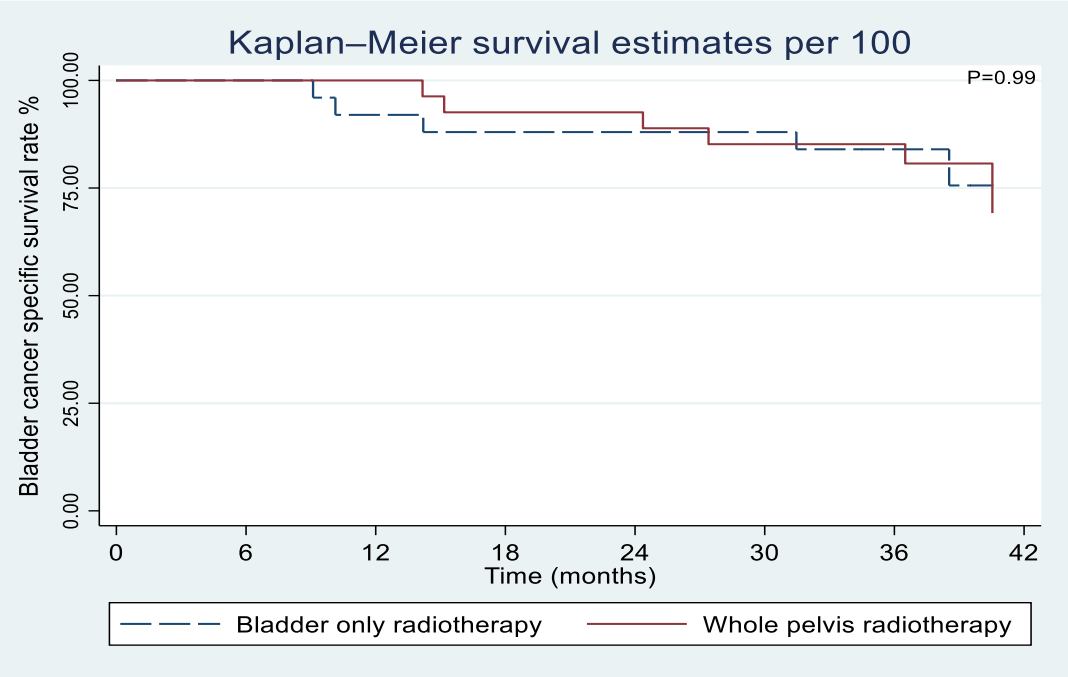

Figure 2. Bladder cancer specific survival rate

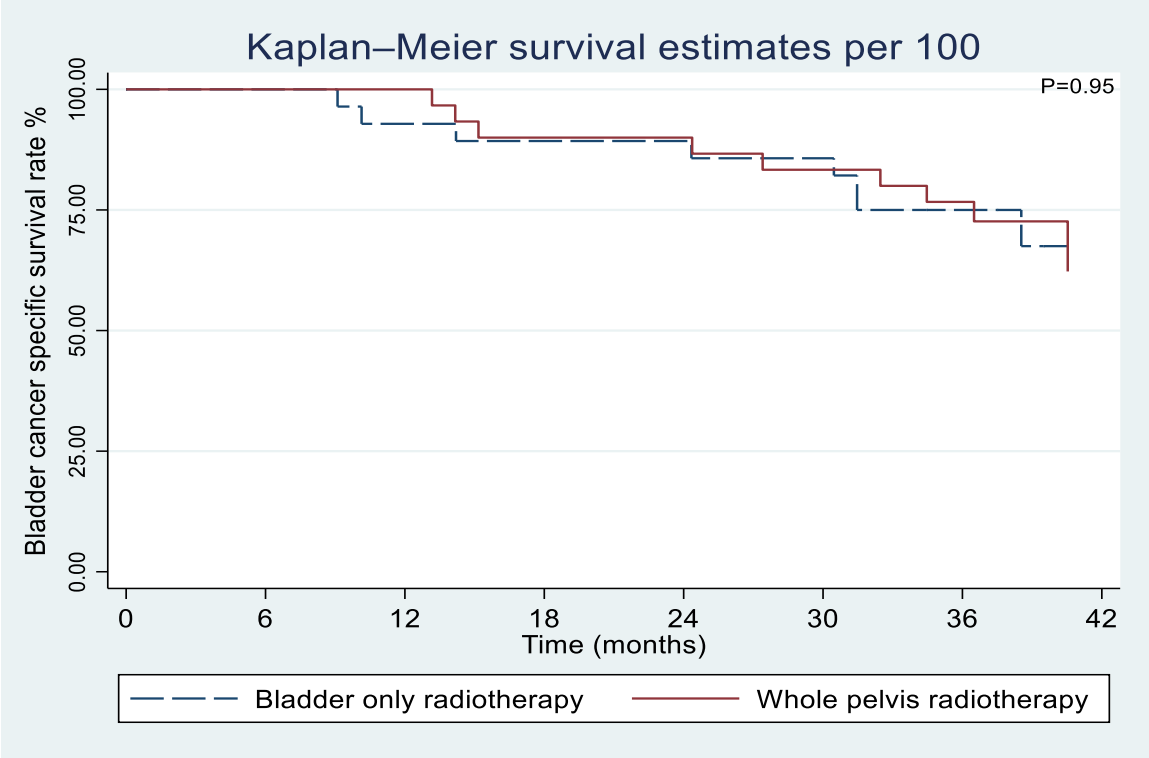

Figure 3. Overall survival rate

Treatment toxicity

Comparison between the 2 groups as regard RT toxicity was summarized in table 2. There was statistically significant difference between the 2 groups as regard acute small bowel(p=0.03) and rectal(p=0.007) toxicity favouring BO radiotherapy but no statistical differences were detected as regard acute genitourinary(p=0.91) toxicity, late genitourinary(p=0.33) toxicity and late GIT(p=0.59) toxicity.

56.9% of patients reported grade 2 acute genitourinary toxicity in the form of cystitis and/or frequency, with 10% complaining from grade 3 toxicity.

The acute bowel (abdominal pain, diarrhea) and rectal (proctitis) toxicities reported by 15.5% and 17.3% of patients, respectively, were of grade 1 or 2 and improved on supportive treatment. As regard late toxicity, no grade 3 genitourinary or GIT toxicity was detected. Grade 1 and/or 2 genitourinary toxicity reported in 13.8% and only 5% complained from grade 1 and/or 2 GIT toxicity.

Table 2. Comparison between bladder only radiotherapy and whole pelvis radiotherapy group as regards radiotherapy toxicity

Variable	Bladder only radiotherapy N=28	Whole pelvis radiotherapy N=30	P value
Acute radiotherapy toxicity			
Bowel (abdominal pain and diarrhea)			
Absent	27 (96.4%)	22 (73.3%)	**0.03**
Grade 1	1 (3.6%)	2 (6.7%)	
Grade 2	0	6 (20%)	
Rectum (proctitis)			
Absent	25 (89.3%)	23 (76.7%)	**0.007**
Grade 1	3 (10.7%)	1 (3.3%)	
Grade 2	0	6 (20%)	
Genitourinary			
Absent	2 (7.1%)	1 (3.3%)	**0.91**
Grade 1	8 (28.6%)	8 (26.7%)	
Grade 2	15 (53.6%)	18 (60%)	
Grade 3	3 (10.7%)	3 (10%)	
Late radiotherapy toxicity			
Genitourinary			
Absent	25 (89.3%)	25 (83.3%)	**0.33**
Grade 1	1 (3.6%)	0	
Grade 2	2 (7.1%)	5 (16.7%)	
GIT toxicity			
Absent	27 (96.5%)	28 (93.3%)	**0.59**
Grade 1/2	1 (3.5%)	2 (6.6%)	

As regard chemotherapy toxicity, neutropenia was the most common hematologic toxicity during concurrent chemotherapy reported in 32.8% of patients. During adjuvant chemotherapy, most patients (93%) developed neutropenia of grade 1/2. Thrombocytopenia was reported in 22.2% of patients. Unfortunately, 2 patients developed renal failure and required dialysis but none of our patients report ototoxicity. No grade 3/4 hematologic toxicity was detected during course of treatment. Table 3 illustrates that no statistically significant difference was detected between the 2 groups as regard chemotherapy toxicity, either during concurrent or adjuvant chemotherapy.

Table 3. Comparison between bladder only radiotherapy and whole pelvis radiotherapy group as regards chemotherapy toxicity

Variable	Bladder only radiotherapy N=28	Whole pelvis radiotherapy N=30	P value
Concurrent chemotherapy toxicity			
Neutropenia			
No	19 (68%)	20 (66.7%)	0.92
Grade 1/2	9 (32%)	10 (33.3%)	
Thrombocytopenia			
No	27 (96.4%)	29 (96.7%)	1.00
Grade 1/2	1 (3.6%)	1 (3.3%)	
Anemia			
No	26 (93%)	28 (93.3%)	1.00
Grade 1/2	2 (7%)	2 (6.7%)	
Vomiting			
No	24 (85.7%)	25 (83.3%)	1.00
Grade 1/2	4 (14.3%)	5 (16.7%)	
Adjuvant chemotherapy toxicity			
Neutropenia			
No	2 (7%)	2(7%)	1
Grade 1/2	26 (93%)	28 (93%)	
Thrombocytopenia			
No	21 (75%)	24 (80%)	0.57
Grade 1/2	7 (25%)	6 (20%)	
Anemia			
No	24 (85.7%)	25 (83.3%)	1.00
Grade 1/2	4 (14.3%)	5 (16.7%)	
Vomiting			
No	19 (68%)	20 (66.7%)	0.92
Grade 1/2	9 (32%)	10 (33.3%)	
Renal failure			
No	27 (96.4%)	29 (96.7%)	1.00
Yes	1 (3.6%)	1 (3.3%)	

DISCUSSION

Whether to irradiate pelvic LN or not during curative bladder RT in node-negative MIBC is still a matter of controversy. Elective radiation for regional LNs is supported by data from cystectomy series showing that micrometastasis in pelvic LN were detected in up to 30% of patients with radiologically negative LN, with incidence varying from 15% to 60% depending on tumor stage. In addition, pelvic LN dissection is associated with survival benefit in MIBC patients [3,6].

Supporting this a study included 599 patients with urothelial MIBC (cT2-4aN0-2M0) who received RT at 10 academic centers across Canada comparing BO radiotherapy versus WP radiotherapy. This study demonstrated that WP radiotherapy did not affect CR rates (p=0.526) but was associated with significant improvement in cancer-specific survival (p=0.016) and OS (p=0.002). This study was retrospective study with various treatment protocols, toxicity that was not evaluated in this cohort and patients in WP group were younger, and more commonly received neoadjuvant chemotherapy and concurrent chemotherapy, compared to BO radiotherapy [8].

Based on these data, there is biological rationale to electively irradiate pelvic nodes during bladder RT. However, the benefit of elective nodal radiotherapy has not been established in clinically negative lymph node MIBC. In addition, because of the bowel's close proximity to the bladder and the pelvic nodal volumes, the acute and late GIT toxicity rates are particularly noteworthy with reported grade 1 and/or 2 GIT toxicity of 75%. Therefore, pelvic LN may not be targeted in bladder RT to minimize bowel toxicity for patients with

cN0 disease but without oncologic outcome compromise [9].

The large BC2001 trial including radiotherapy to whole bladder show LN relapse of <10%, which is not high as might have been expected from surgical pathological staging suggesting that not all patients may benefit from elective radiation to pelvic LN. Data show that in patients receiving curative bladder radiotherapy with or without inclusion of pelvic LN, the nodal relapse rate ranged between 4% and 14% [7,10].

The largest prospective randomized trial comparing BO versus WP concurrent chemoradiotherapy conducted by **Tunio *et al.*,** in which 102 patients with cT2–T4a N0 MIBC were randomized to receive WP radiotherapy versus 98 patients received BO radiotherapy. Cisplatin was given concurrently with RT in both groups. The reported 5-year DFS was (46.9% vs 47.1%; P=0.54) and OS was (51% vs 52.9%; P=0.8) in BO versus WP group, respectively with no statistically significant difference were detected between the 2 groups. Regional lymphadenopathy relapse reported was 15.7 % of patients in WP group versus 17.5 % in BO group. Significant difference in acute GIT radiotherapy toxicity (P=0.05) was detected favouring BO radiotherapy. The overall incidence of acute grade 3/4 GIT toxicity was 3.9% versus 2% in WP versus BO group, respectively with no difference as regard acute genitourinary toxicity (P=0.5). No late GIT toxicity was documented in BO while one patient developed subacute intestinal obstruction [11].

Another Egyptian randomized trial included 60 patients with cT2–T3 N0 MIBC. After maximum TURBT, patients were randomized to receive BO versus WP radiotherapy with concurrent cisplatin/paclitaxel then 4 cycles adjuvant paclitaxel/cisplatin for both groups. Again, BO group showed similar 2-year DFS (63 versus 60%, P=0.79), DSS (83 versus 79%, P=0.68) and OS (79 versus 75%, P=0.76) in comparison to WP group, respectively. Acute GIT toxicity was experienced by 93% of patients in WP group and only 17% of patients in BO group with a statistical significance (P < 0.0001). No significant difference was found between the 2 groups as regard acute genitourinary (P = 1.0), late genitourinary (P = 0.792) and late GIT toxicity (P = 0.609)[12].

Use of pelvic LN radiation may not affect long-term survival outcomes for patients with node-negative MIBC as shown in a study of concurrent chemoradiotherapy with BO versus WP radiotherapy. There was no survival difference between groups: 5- and 10-year OS was 27.4 and 13 % in the BO group vs. 32% and 13 % in the WP group, respectively. On multivariable analysis, there was no significant association between pelvic lymph node RT and OS [13].

Our results are consistent with these results with no statistically significant difference (P =0.59) was detected between the 2 groups as regard DFS rate at 3 years, which was 81% and 85 % in BO group and WP group, respectively. For BO group the reported bladder cancer specific survival rate was 83% and OS rate was 75 % at 3 years. For WP group the reported bladder cancer specific survival rate was 80 % and OS rate was 73% at 3 years with no statistically significant difference between the 2 groups was reported (P=0.99) and (P=0.95) for bladder cancer specific survival and OS, respectively.

Regarding toxicity, acute small bowel (P=0.03) and acute rectal toxicity (P=0.007) showed statistically significant difference in favour of BO radiotherapy while acute genitourinary toxicity (P=0.91), late genitourinary (P =0.33) and late GIT toxicity (P=0.59) showed no statistical difference between the 2 groups.

Pelvic LN received incidental dose during whole bladder irradiation, which may be enough for micrometastatic disease eradication. The obturator, external iliac, and internal iliac LNs received mean dose of 59, 45, and 36 Gy, respectively. This may explain why elective pelvic LNs irradiation may have no clear benefit in patients with cN0 bladder cancer [7].

Additionally, concurrent cisplatin with RT and adjuvant 4 cycles gemcitabine/cisplatin received in our study may play a role in eradication of micrometastasis resulting in lower rate of distant recurrence and improved local control.

An updated results of the BC2001 trial concluded that chemoradiotherapy resulted in improvement of locoregional control. However, this resulted in nonsignificant improvement of DFS (*P*=0.069), metastasis free survival (*P* = 0.089), OS from 2 year onwards (*P*=0.3), and bladder cancer specific survival (*P* = 0.11) [14].

Recently, meta-analysis of ten randomized controlled trials showed that cisplatin-based adjuvant chemotherapy in MIBC patients improved survival by 6% at 5 year indicating that adjuvant chemotherapy containing cisplatin is an effective option to improve outcomes for MIBC [15].

CONCLUSION

In conclusion, our study results show that bladder only radiotherapy concurrent with chemotherapy is a feasible treatment in patients with negative lymph node MIBC with comparable oncologic outcomes and less radiotherapy toxicity when compared with whole pelvis radiotherapy. Further large, randomized trials are needed to prove our findings especially in the era of modern RT techniques, which deliver a more conformal dose to target and reduce dose to the surrounding areas. Novel imaging modalities are needed to improve clinical staging, for

appropriate selection of radiotherapy volume for trimodality therapy.

LIMITATIONS

- Small sample size is one of the most limitation of our study, unfortunately T4a patients and patients with non-urothelial bladder cancer were not represented in our study.

- **Funding**: The study was fully funded by the Sohag University Hospital and Sohag Faculty of Medicine.
- **Conflict of interest**: The author(s) had nothing to declare.

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