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ORIGINAL RESEARCH ARTICLE

# Radical radiotherapy using volumetric-modulated arc therapy for treating bladder and pelvic lymph nodes in locally advanced bladder cancer: A retrospective single-center study

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## Abstract

The prognosis of patients with muscle-invasive bladder cancer (MIBC) and pelvic nodes remains poor. We developed a novel radiotherapy (RT) protocol using volumetric-modulated arc therapy (VMAT) to treat bladder and locoregional nodes in MIBC. This study explores the safety, efficacy, and development of the VMAT protocol. Between June 2020 and August 2024, a total of 17 patients were treated using the novel VMAT protocol. The treatment regimen consisted of 57.5 Gy in 23 fractions to the bladder and 46 Gy in 23 fractions to the pelvic nodes. The present study reports on various parameters, including patient-related, disease-related, and treatment-related characteristics, along with toxicity profiles and long-term outcomes (response rates, nature of progression, and survival). The RT protocol was well tolerated, with 15 patients (88%) completing treatment as planned. Most acute toxicities were grade 1 or 2. One patient (6%) experienced a grade 3 acute toxicity (pain and local discomfort), while two patients (12%) experienced grade 3 late toxicity (colovesical fistula and severe radiation-induced cystitis). Following treatment, 12 patients (71%) had a response or a stable disease. Two patients (12%) developed local recurrence, six (35%) developed metastatic relapse, and nine patients (53%) showed no progression. The median progression-free survival was 15.8 months (95% confidence interval [CI]: 12.4 – 64.6), while the median overall survival was 23.1 months (95% CI: 13.6 – 64.6). This study has several limitations, primarily due to its retrospective design and small patient cohort. Furthermore, there was considerable variability in histology, fitness scores, and concomitant chemotherapy treatment. Nonetheless, the findings demonstrate the safety and feasibility of the VMAT protocol for treating the bladder and pelvic nodes in locally advanced MIBC, and they provide a rationale for future prospective studies to further evaluate the role of pelvic RT in this population.

***Keywords:*** Bladder cancer; Radiation therapy; Chemotherapy

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## 1. Introduction

Bladder cancer is the seventh most common cancer in the United Kingdom (UK), accounting for 3% of all cancers, with over 10,000 new cases diagnosed each year.[1,2]

Radical cystectomy (with or without neoadjuvant chemotherapy [NAC]) is the standard of care for patients with localized muscle-invasive bladder cancer (MIBC).[3,4] Trimodality therapy (TMT) is a bladder preservation strategy that combines radiotherapy (RT) with concurrent radiosensitizers after maximal transurethral resection of the bladder tumor (TURBT). The historical view of radical cystectomy being the gold standard of care in MIBC has been challenged by more recent data that have shown TMT to be equivalent, if not superior, in terms of disease control.[5]

Radical RT protocols in the UK usually employ a conventionally fractionated dose of 64 Gy in 32 fractions or a hypofractionated dose of 55 Gy in 20 fractions delivered to the entire bladder using a three-dimensional conformal technique or intensity-modulated RT (IMRT).[1] Supporters of conventional fractionation argue that a lower dose per fraction should result in a superior therapeutic index – characterized by a higher probability of tumor control and reduced rates of late toxicity – due to the presumed high $\alpha/\beta$ ratio of bladder cancer. However, a recent meta-analysis of individual patient data from the BCON and BC2001 trials, which allowed both dosing regimens, demonstrated similar toxicity rates and better locoregional control with hypofractionation.[6]

The survival outcomes of localized MIBC have significantly improved over the years. In a propensity-matched score analysis of MIBC treated with cystectomy or TMT, the 5-year disease-specific survival rate was 73.2% and 76.6% in the cystectomy and TMT groups, respectively.[7] However, there is limited data regarding the optimal management of patients with pelvic node-positive, non-metastatic bladder cancer, and the prognosis of these patients remains uncertain and poorly defined. A growing body of evidence indicates that this is a unique clinical entity with an intermediate prognosis that falls between advanced metastatic bladder cancer and bladder-confined MIBC.

The clinical management of bladder cancer, whether clinically or pathologically node-positive, has seen significant variation as practice patterns have continued to change. A palliative approach that involves systemic therapy alone, with local therapy saved for symptom control, is preferred by certain multidisciplinary teams. Others advocate for a curative-intent strategy that includes NAC with either cystectomy or TMT.[8,9]

Although several studies have shown that neoadjuvant and adjuvant chemotherapy reduces the rate of distant metastases, individuals with node-positive illness are also at a considerable risk of locoregional recurrence.[3,4,10]

There is a lack of good-quality evidence on the role of TMT in treating patients with node-positive disease. Delivering the prescribed dose to the target volume without raising the risk of acute and long-term toxicity is one of the primary challenges when using RT to treat patients with node-positive bladder cancer. However, the complex and dynamic manipulation of radiation beams has been made possible by advances in RT planning conformal approaches such as IMRT, enabling proper target coverage while sparing nearby organs at risk (OAR). In a study conducted by Sondergaard *et al.*,[11] 16 patients were treated with IMRT, delivering 60 Gy to the bladder and 48 Gy to the pelvic lymph nodes. The dose-volume histogram parameters for relevant normal tissues (e.g., bowel, bowel cavity, rectum, and femoral heads) for the IMRT plans were compared with the corresponding dose-volume histogram from the conformal sequential boost technique. IMRT demonstrated statistically significant sparing of normal tissue. For the bowel, a significant reduction was observed at all dose levels between 20 and 50 Gy ($p<0.05$), such as from 180 to 121 $cm^3$ at 50 Gy. Similar patterns were observed for the bowel cavity, rectum, and femoral head. The acute gastrointestinal (GI) toxicity was 38%. IMRT to the urinary bladder and elective lymph nodes resulted in considerable sparing of normal tissue compared to the conformal sequential boost technique.

To explore the use of TMT for treating patients with node-positive bladder cancer post-surgery, we developed a unique RT protocol utilizing volumetric modulated arc therapy (VMAT). The purpose of this study is to examine the evolution of the VMAT protocol and to assess the efficacy of RT in managing patients with primary bladder cancer and potentially involved locoregional pelvic lymph nodes.

## 2. Materials and methods

### 2.1. Study population

The novel VMAT-RT protocol was implemented in 2020, involving the delivery of 57.5 Gy in 23 fractions to the bladder and 46 Gy in 23 fractions to the nodes. We reviewed the RT planning systems (Varian Eclipse, US) to identify patients who received treatment with this protocol between June 2020 and August 2024. A total of 17 patients who were treated with this protocol were identified. All patients were discussed at the urology multi-disciplinary team meeting, had a histological confirmation of malignancy, and underwent computed tomography (CT) scans for staging of their disease. Based on the CT scan, all patients had disease limited to the pelvis, with no lymphadenopathy observed above the aortic bifurcation. As none of the patients were deemed appropriate for surgery, radical RT (with or without concurrent chemotherapy)

was recommended. Due to the retrospective nature of the study, obtaining consent for participation from the study subjects was not feasible.

The following parameters were identified and assessed through a review of the patients' clinical records:

i. Patient characteristics, including age, sex, comorbidities, and the reason for not proceeding with surgery
ii. Features of the disease – histology, stage (tumor [T] and node [N]), and date of diagnosis
iii. Treatment characteristics and toxicity – information about concomitant chemotherapy, early toxicity (less than 3 months), late toxicity (more than 3 months), and RT (number of completed fractions)
iv. Treatment response following chemoradiotherapy (CRT) completion – complete response was defined as complete tumor response on both CT scan and cystoscopy performed 3 months after treatment completion; stable disease was characterized by persistent tumor at cystoscopy, but no progression evident on staging CT scan; progressive disease was defined as unequivocal evidence of progression on cystoscopy or CT scan
v. Survival outcomes – overall survival (OS) and progression-free survival (PFS) estimated from the date of diagnosis, as well as the type (local vs. metastatic) and site of progression.

### 2.2. Development of VMAT clinical protocol

The standard RT dose is 55 Gy in 20 fractions for localized bladder cancer and 46 Gy in 23 fractions for pelvic nodes. The dose to the nodes was predefined at 46 Gy in 23 fractions. Radiobiological modeling was employed to estimate the biologically effective dose (BED) – equivalent to 55 Gy in 20 fractions delivered over 23 fractions as a synchronous integrated boost to the bladder. The BED was calculated using an $\alpha/\beta$ value of 10 for the tumor, and the aim was to keep BED for the primary tumor similar to the bladder-only clinical protocol (i.e., equivalent to 55 Gy in 20 fractions), without increasing the dose or the dose per fraction to the pelvic nodes, which was maintained at 46 Gy in 23 fractions.

The BED calculations were performed to calculate the dose per fraction to the primary tumor (i.e., bladder planning target volume [PTV]) for 23 fractions using Equation 1.

$$BED = nd[1 + \frac{d}{(\alpha/\beta)}] \quad (1)$$

Note: $d$ is the dose per fraction, and $n$ is the number of fractions.

The above dose modeling generated a dose fractionation of 57.5 Gy in 23 fractions with $BED_{10}$ of 71.88 Gy, which was similar to $BED_{10}$ of 70.13 Gy observed with 55 Gy in 20 fractions.

### 2.3. Treatment simulation

All patients were scanned supine with an empty bladder and rectum. Ankle and knee support were used to immobilize and achieve set-up reproducibility. A 100 mL Omnipaque intravenous contrast was administered with a 70 sec delay. No oral contrast was used for these patients.

### 2.4. Target delineation

The primary clinical target volume (CTVp) included the bladder and any extravesical extension, with a 5 mm margin applied mainly at the tumor site. The inclusion of prostatic urethra in the volume was at a clinician's discretion, and the whole prostate was included in patients with tumors located at the base or invading the prostate. In addition, the clinical target volume for the elective nodes (CTVn) started at the lower border of L5, using a 7 mm margin around the vessels, including common iliac, internal and external iliac, pre-sacral (from S1 to S3), and pelvic lymph nodes down to the level of obturators (top of pubic symphysis). The bowel, bladder, bone, and muscle were excluded from the CTVn. The primary PTV (PTVp) was produced using a 15 – 20 mm superiorly and 15 mm posteriorly, anteriorly, inferiorly, and laterally from the CTVp. The node PTV was produced using 10 mm in all directions from the CTVn.

### 2.5. Treatment planning

All patients were treated with VMAT using either Halcyon (Varian, United States) or TrueBeam (Varian, US) linear accelerators. The doses were calculated using the Acuros (dose to medium) algorithm (version 16, Varian, US). The treatment plans were optimized to achieve PTV coverage of V95% ≥99% (i.e., the volume of PTV receiving 95% of the prescription dose should be ≥99%) and V105% ≤2%. In addition to the target and OAR volumes, optimization structures were produced around the PTVp and node PTVs using an inner margin of 0.5 cm and outer margin of 1.5 cm to enhance target conformity. Upper objectives were used on these structures during optimization (Figure 1).

### 2.6. Treatment delivery

Before treatment delivery, all patients underwent daily cone beam CT imaging, and the setup differences were corrected for all fractions.

### 2.7. Statistical analysis

Descriptive statistics, such as the frequency (percentage) for categorical variables, were used to summarize the

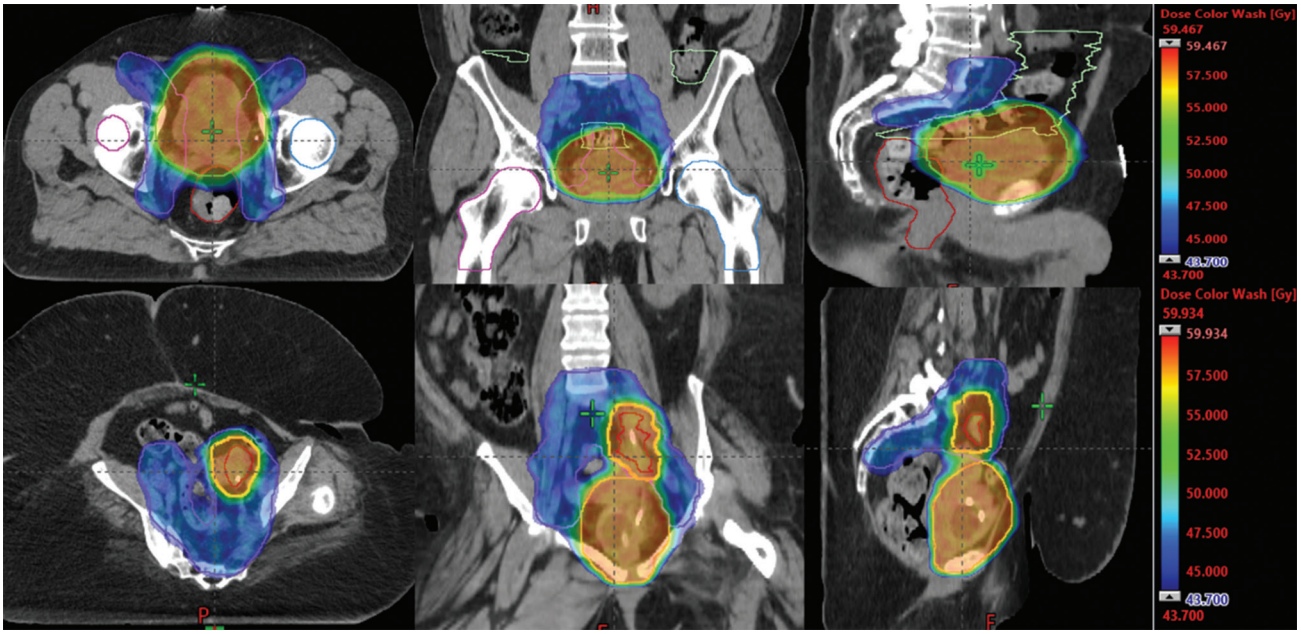


**Figure 1.** Dose distribution achieved with volumetric-modulated arc therapy (the dose color wash scale between 43.7 Gy [95% of the 46 Gy, node planning target volume prescription] and the max dose). The images at the top show the primary and prophylactic node volumes, as well as organs-at-risk structures, with dose distribution. The bottom images show the dose distribution for a node-positive patient, where the positive nodes received the same dose as the primary (i.e., 57.5 Gy), and the elective nodes received 46 Gy in 23 fractions.

distribution of various patient-, tumor-, and treatment-related variables. For the analysis of OS, disease-specific death was considered the sole event, while patients who were alive or had died from unrelated causes were censored at the time of their last visit. For PFS analysis, an event was defined as disease progression or recurrence, as indicated by radiological imaging and/or clinical deterioration. The durations of PFS and OS were calculated from the date of diagnosis. Survival probabilities were estimated using the Kaplan–Meier method. All statistical analyses were performed using the StatsDirect software system (StatsDirect Ltd, Version 4, UK).

## 3. Results

### 3.1. Patient characteristics and disease features

A total of 17 patients received RT to the bladder and pelvic nodes using VMAT protocol, with a male predominance (male, $n$ = 12; female, $n$ = 5). The median age was 66 years (range: 30 – 83 years). The reasons for not proceeding to surgery included locally advanced disease ($n$ = 8), concomitant comorbidities ($n$ = 6), unfavorable histology such as neuroendocrine transformation ($n$ = 2), and patient choice ($n$ = 1). The comorbidities, according to the American Society of Anesthesiologist status (ASA), were ASA1 ($n$ = 6), ASA2 ($n$ = 4), ASA3 ($n$ = 5), and ASA4 ($n$ = 2). The following comorbidities were frequently noted: pulmonary hypertension with Eisenmenger syndrome ($n$ = 1), cerebrovascular disease ($n$ = 1), peripheral vascular disease ($n$ = 1), sleep apnea ($n$ = 1), chromic paraplegia ($n$ = 1), ischemic heart disease ($n$ = 3), hypertension ($n$ = 4), and type II diabetes ($n$ = 3). The majority of patients ($n$ = 10) had transitional cell carcinoma (TCC), followed by TCC with divergent squamous ($n$ = 4), TCC with neuroendocrine differentiation ($n$ = 2), and pure poorly differentiated neuroendocrine (small cell phenotype) carcinoma ($n$ = 1). The distribution of T stages was T2 ($n$ = 5), T3 ($n$ = 10), and T4 ($n$ = 2). Two patients had N0 stage disease, and 15 patients had N1 stage disease, with positive pelvic nodes on cross-sectional imaging (Table 1).

### 3.2. Treatment characteristics and toxicity (Tables 2 and 3)

#### *3.2.1. Upfront (induction) chemotherapy*

Ten patients (59%) received an upfront (induction) systemic anti-cancer therapy (SACT) before proceeding to RT. The commonly employed regimens included gemcitabine/cisplatin ($n$ = 5), carboplatin/gemcitabine ($n$ = 1), atezolizumab ($n$ = 1), cisplatin/etoposide ($n$ = 1), carboplatin and etoposide ($n$ = 1), and cisplatin/gemcitabine followed by pembrolizumab ($n$ = 1). Seven patients (41%) proceeded to RT without any induction chemotherapy.

The median number of cycles was three; however, at least two patients (12%) received a prolonged duration of

**Table 1. Patient demographics and disease-related characteristics**

| Parameter | Value |
|---|---|
| Sex (number of patients, *n*=17) | |
| Male | 12 |
| Female | 5 |
| Age (years) | |
| Median (range) | 66 (30 – 83) |
| Comorbid status | |
| ASA1 | 6 |
| ASA2 | 4 |
| ASA3 | 5 |
| ASA4 | 2 |
| Histology | |
| Transitional cell cancer | 10 |
| TCC with squamous differentiation | 4 |
| Neuroendocrine differentiation | 3 |
| Reason for not proceeding to surgery | |
| Locally advanced disease | 8 |
| Comorbidities | 6 |
| Histology | 2 |
| Patient's choice | 1 |
| Staging (T stage) | |
| T2 | 5 |
| T3 | 10 |
| T4 | 2 |
| Staging (N stage) | |
| N0 | 2 |
| N1 | 15 |

Abbreviations: ASA: American Society of Anesthesiologists; N: Node; T: Tumor; TCC: Transitional cell carcinoma.

**Table 2. Treatment characteristics and toxicity**

| Parameter | Value |
|---|---|
| Induction systemic therapy | |
| Gemcitabine/cisplatin | 5 |
| Carboplatin/gemcitabine | 1 |
| Cisplatin/etoposide | 1 |
| Carboplatin and etoposide | 1 |
| Atezolizumab | 1 |
| Gemcitabine and cisplatin followed by pembrolizumab | 1 |
| No induction treatment | 7 |
| Radiotherapy (57.5 Gy in 23 fractions) | |
| Completed | 15 |
| Stopped early | 2 |
| Concurrent chemotherapy | |
| Gemcitabine | 9 |
| Cisplatin | 4 |
| Cisplatin/etoposide | 1 |
| Mitomycin/fluorouracil | 1 |
| No concurrent chemotherapy | 2 |
| Toxicity | |
| Early (<3 months) | |
| Fatigue | 14 |
| Nausea | 4 |
| Diarrhea | 9 |
| Pain/local discomfort | 9 |
| Increased frequency micturition | 8 |
| Dysuria | 6 |
| Hematuria | 2 |
| Constipation | 2 |
| Skin erythema | 1 |
| ≥Grade 3 toxicity | 1 |
| Late (>3 months) | |
| Gastrointestinal toxicity | 3 |
| Genitourinary toxicity | 2 |
| ≥Grade 3 toxicity | 2 |

systemic therapy before proceeding to CRT. One patient (6%) was treated with three cycles of gemcitabine/cisplatin followed by ten 3 weekly cycles of pembrolizumab. A second patient received atezolizumab for 2 years before proceeding to CRT (Table 2).

#### *3.2.2. RT (with or without concurrent chemotherapy)*

A total of 15 patients (88%) received concurrent chemotherapy (gemcitabine, $n$ = 9; cisplatin, $n$ = 4; cisplatin/etoposide, $n$ = 1; and mitomycin/fluorouracil, $n$ = 1), and two patients (12%) received only RT.

All treatments were planned using VMAT and delivered through either Halcyon or TrueBeam linear accelerators. Treatment plans were optimized to achieve the clinical goals (Table 3). Two full arcs were used for patients treated on TrueBeam, and three arcs were used for patients treated on Halcyon. The desired PTV coverage – specifically, 99% of the PTV covered by at least 95% of the prescription dose – was achieved in all patients. OAR doses were also achieved for most patients; however, the bowel bag constraint (V45 Gy < 195 cc) could only be achieved for two out of 17 patients. The rectum constraints (V40 Gy < 60%, V50 Gy < 50%, and V57.5 Gy < 5%) were exceeded in three, one, and four patients, respectively. No correlation was observed between OAR doses and the linear accelerator used for the treatment. Two out of

**Table 3. Clinical constraints and achieved doses for the planning target volume and organs at risk**

| Structure | Clinical constraints | Achieved clinical goals | Standard deviation |
|---|---|---|---|
| PTVnDVH[a] | V76% > 99% | 99.74 | 0.17 |
| PTVp | V95% > 99% | 99.79 | 0.32 |
| | V105% < 2.0% | 0.02 | 0.03 |
| Left femoral head | V50 Gy <25% | 0.00 | 0.00 |
| Right femoral head | V50% < 25% | 0.01 | 0.04 |
| Rectum | V40 Gy <60% | 46.49 | 16.08 |
| | V50 Gy <50% | 23.00 | 13.98 |
| | V57.5 Gy <5% | 6.47 | 8.80 |
| Small bowel[b] | V45 Gy <195 cc | 378.01 | 118.16 |

Notes: [a]PTVnDVH refers to the PTVn excluding PTVp; [b]Small bowel refers to the bowel bag.
Abbreviations: PTVn: Node planning target volume; PTVnDVH: Planning target volume normalized dose volume histogram; PTVp: Primary planning target volume.

17 patients had a nodal boost and were treated to 57.5 Gy in 23 factions (same as the PTVp) due to node-positive disease (Table 3).

All patients underwent cone-beam CT imaging before treatment delivery. Patient setup, bladder volume, and OAR volumes were reviewed, and setup corrections were applied before treatment delivery. None of the patients had any issues with the setup.

#### *3.2.3. Toxicity*

All patients were interviewed by the staff before the treatment, with toxicities recorded in the encounter workspace within the Aria radiation oncology radiation software system (Varian, US) The data indicate that all patients generally tolerated the treatment well, with acute toxicities predominantly rated as grade 1 or lower. There were 58 adverse events observed within 3 months of RT (early toxicity), with most graded as grade 1 or 2, and only one event was graded as clinically significant grade 3 toxicity. The most common toxicity observed was fatigue ($n$ = 14), followed by diarrhea ($n$ = 9), pain or local discomfort ($n$ = 9), increased frequency of micturition ($n$ = 8), dysuria ($n$ = 6), nausea ($n$ = 4), hematuria ($n$ = 2), constipation ($n$ = 3), proctitis ($n$ = 2), and skin erythema ($n$ = 1).

There were five adverse events observed after 3 months of treatment completion, with three events observed for GI, and two events observed for genitourinary. Two of these events were rated as grade 3, with one patient developing a colovesical fistula, and another patient experiencing significant morbidity due to poor bladder filling caused by radiation-inducing fibrosis, warranting surgical intervention.

### 3.3. Outcomes and survival analysis

#### *3.3.1. Initial assessment of response (3 months after completion of CRT)*

Three patients (18%) had no available assessment records. During treatment, two patients (12%) developed progression, with one (6%) developing liver metastases while the other patient (6%) developing liver and lung metastases. A total of 12 patients (71%) had post-treatment staging CT scans after 3 months of treatment completion, and eight (47%) of them had a cystoscopy performed at that time. Seven patients (41%) achieved a complete response, with no evidence of tumor progression on staging CT and no visible/residual tumor on cystoscopy. Five patients (29%) had a stable disease, with no progression on staging CT scans. However, four (23%) of these patients did not undergo a cystoscopy to confirm the completeness of the response, and one (6%) had a residual tumor visible on the cystoscopy (Figure 2A).

#### *3.3.2. Long-term outcomes (progression-free and OS)*

Following CRT, eight patients (47%) developed progression, with two patients (12%) experiencing local progression, and six patients (35%) experiencing metastatic progression. The isolated metastatic relapses most frequently occurred in the liver (n = 3), liver and lungs (n = 1), bone (n = 1), as well as the brain and nodes (n = 1). Following treatment, nine patients (53%) showed no signs of progression or relapse. Ten patients (59%) had passed away at the last follow-up (FU) visit (median FU: 15 months), with three patients (18%) dying due to unrelated causes and seven patients (41%) dying due to progressive disease (Figure 2B). Seven (41%) patients were alive and well, with no signs of recurrence. The median PFS was 15.8 months (95% confidence interval [CI]: 12.4 – 64.6). The median OS was 23.1 months (95% CI: 13.6 – 64.6), and the mean OS was 32.04 months (95% CI: 16.6 – 47.4) (Figure 3).

We investigated the effects of induction SACT, histology, and comorbidity status on OS. Patients who received induction SACT had a significantly improved OS compared to those who did not receive induction SACT (median OS: 40.1 vs. 13.6 months; hazard ratio [HR]: 0.16; 95% CI: 0.02 – 1.12; $p$=0.002). Patients with pure TCC had a non-significant trend toward improved OS (median OS not reached) compared to those with divergent squamous or neuroendocrine differentiation (median OS: 17.93 months; HR: 0.60; 95% CI: 0.13 – 2.68; $p$=0.49). Patients with ASA1 or ASA2 had a non-significant trend toward improved OS (median OS: 40.1 months) compared to those with ASA3 or ASA4 (median OS: 23.1 months; HR: 0.50; 95% CI: 0.09 – 2.64, $p$=0.32) (Figure 4).

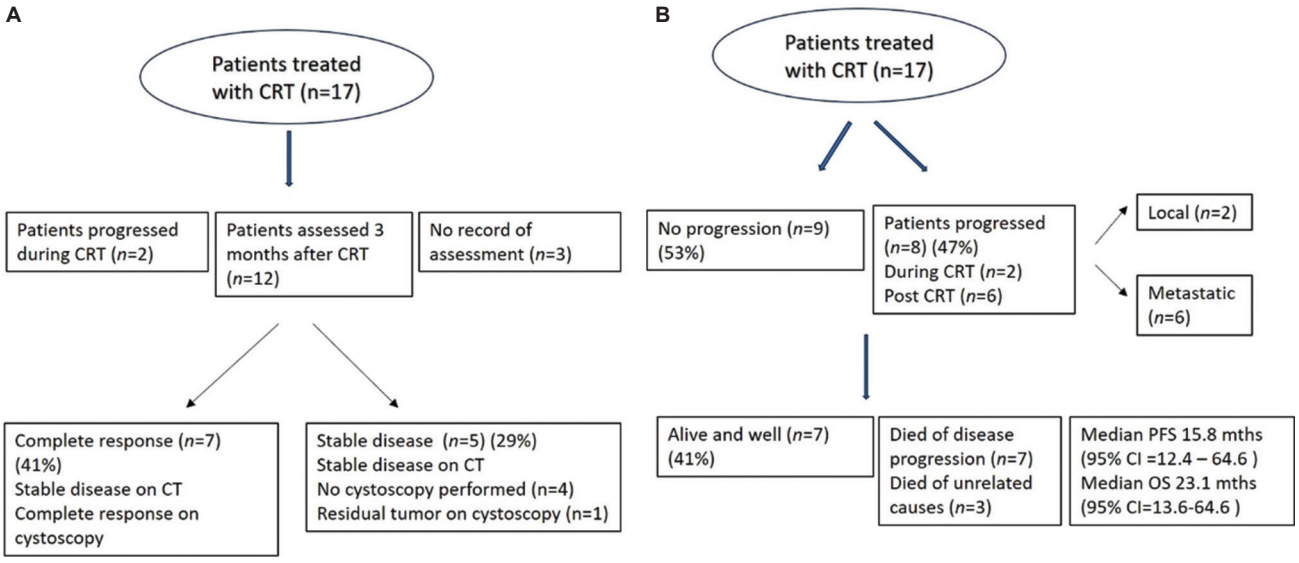


**Figure 2.** Schematic illustration of assessment of response post-radiotherapy and long-term outcomes. (A) Two patients showed disease progression during RT. The initial response was assessed 3 months after RT in 12 patients. Seven (41%) patients had a complete response, and five (29%) patients had stable disease post-RT; (B) Eight patients progressed post-RT, with six patients developing metastatic relapse and only two patients developing local recurrence. Nine (53%) patients developed no progression.
Abbreviations: CRT: Chemoradiotherapy; CT: Computed tomography; OS: Overall survival; PFS: Progression-free survival; RT: Radiotherapy.

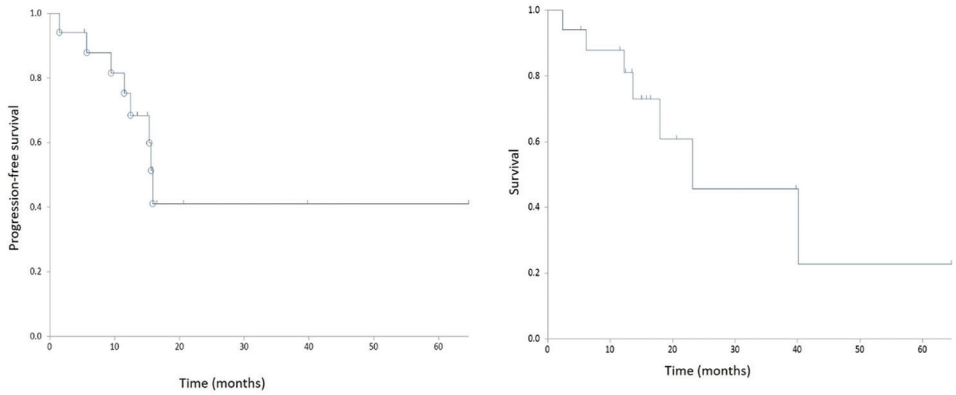


**Figure 3.** Kaplan–Meier survival analysis. After median follow-up of 15 months, ten patients had died: seven due to progressive disease, and three due to unrelated causes. Seven (41%) patients were alive and well. The median progression-free survival was 15.8 months (95% CI: 12.4 – 64.6). The median overall survival (OS) was 23.1 months (95% CI: 13.6 – 64.6) and the mean OS was 32.04 months (95% CI: 16.6 – 47.4).
Abbreviation: CI: Confidence interval.

## 4. Discussion

This study provides a retrospective analysis of bladder cancer patients who underwent RT (with or without concurrent chemotherapy) using a novel VMAT protocol. The protocol delivered 57.5 Gy in 23 fractions to the bladder and primary tumor, as well as 46 Gy in 23 fractions to the pelvic lymph nodes. Due to the comorbidities, low fitness scores (ASA3 or ASA4, $n$ = 7), adverse histology, or personal choice, radical cystectomy was not considered appropriate. Thus, these patients were treated with TMT, which involved TURBT followed by RT, and most patients also received concurrent chemotherapy.

Technological developments in RT delivery, from the four-field box approach to three-dimensional conformal RT (3D-CRT), IMRT, and VMAT, have made it possible to modulate the radiation dose, concentrating the high-dose regions around the tumor while minimizing the dose to adjacent OARs. When it comes to the definitive treatment of bladder cancer, IMRT using the VMAT technique may provide dosimetric and therapeutic advantages over 3D-CRT. A study by Sherry *et al.*[12] reported the dosimetric advantages of VMAT, observing over 50% reduction in the rectum and bowel (V40, V45, V50, V55, and V60) doses in the VMAT group compared to 3D-CRT. Daily

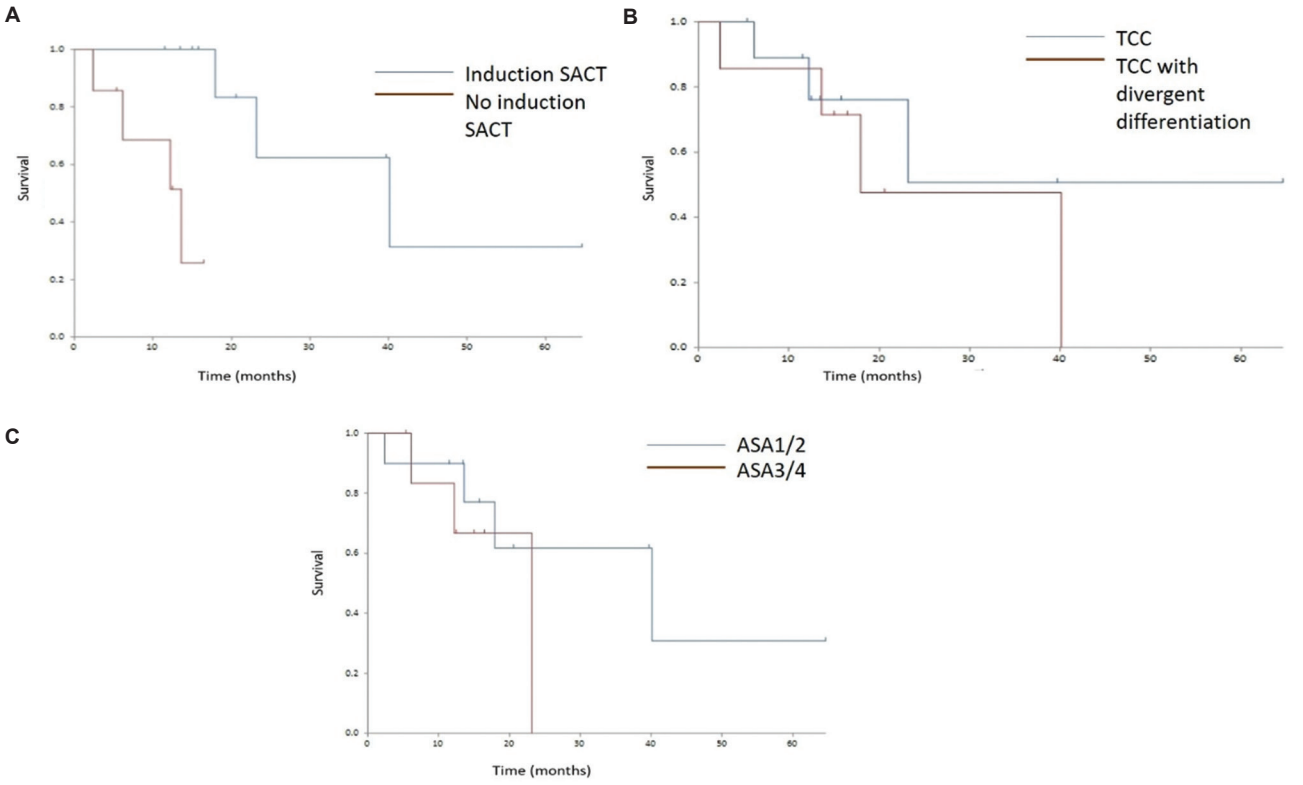


**Figure 4.** Effects of different variables on survival. (A) Effect of induction SACT: Patients who received induction SACT had a significantly improved OS compared to those who did not (median OS: 40.1 months vs. 13.6 months; HR: 0.16; 95% CI: 0.02 – 1.12; $p$=0.002); (B) Effect of histology: Patients with pure TCCs had a non-significant trend toward improved OS (median OS not reached), compared to those with divergent squamous or neuroendocrine differentiation (median OS: 17.93 months; HR: 0.60; 95% CI: 13 – 2.68; $p$=0.49); (C) Effect of co-morbidity: Patients with ASA1 or ASA2 had a non-significant trend toward improved OS (median OS: 40.1 months), compared to those with ASA3 or ASA4 (median OS: 23.1 months; HR: 0.50; 95% CI: 0.09 – 2.64; $p$=0.32).
Abbreviations: ASA: American Society of Anesthesiologists; HR: Hazard ratio; OS: Overall survival; SACT: Systemic anti-cancer therapy; TCC: Transitional cell carcinoma.

imaging with imaging-guided RT detects variations in the size, shape, and location of organs between fractions. Smaller radiation volumes can be used with image-guided RT without running the risk of geographical miss as it can detect differences in organ movements and bladder filling across fractions.[13]

The key prospective studies that investigated the role of radical RT in localized MIBC using conformal techniques are summarized in Table 4.[14-17] In a multicenter phase 3 trial reported by James *et al.*,[12] 360 patients with MIBC were randomized to receive RT, with or without concurrent chemotherapy. The chemotherapeutic protocol included mitomycin C (12 mg/m$^2$) on day 1 and fluorouracil (500 mg/m$^2$ of body-surface area per day), during fractions 1 – 5 and 16 – 20 of RT. The locoregional disease-free survival (DFS) rates after 2 years were 54% (95% CI: 46 – 62) in the radiation group and 67% (95% CI: 59 – 74) in the CRT group. The HR for the CRT group was 0.68 (95% CI: 0.48 – 0.96, $p$=0.03), with a median FU of 69.9 months. During treatment, the CRT group experienced slightly more grade 3 or 4 adverse events than the RT group (36.0% vs. 27.5%, $p$=0.07), but not during FU (8.3% vs. 15.7%, $p$=0.07).

In a study by Hoskin *et al.*,[16] 333 patients with MIBC were randomly assigned to either RT alone or RT with concurrent hypoxia adjustment using carbogen and nicotinamide (CON) in a phase 3 randomized trial. The patients were treated with either 64 Gy in 32 fractions over 6.5 weeks or 55 Gy in 20 fractions over 4 weeks. After 6 months, the complete cystoscopy response rate was 76% for RT alone and 81% for RT+CON ($p$=0.3). The 3-year OS were 46% and 59% ($p$=0.04) for RT alone and RT+CON arms, respectively. RT+CON significantly decreased the probability of death ($p$=0.03) and relapse ($p$=0.05) in the multivariate comparison. The therapy groups did not differ significantly in terms of GI or late urinary morbidity.

In a prospective phase 2 study, 50 MIBC patients received concurrent gemcitabine at 100 mg/m$^2$ on days 1,

**Table 4. Prospective studies of conformal radiotherapy with concurrent chemotherapy in muscle-invasive bladder cancer using conformal techniques**

| Study, patient number (*n*), and study type | RT dose | Chemotherapy/ radiosensitizing regime | Toxicity | Survival |
|---|---|---|---|---|
| James *et al.*,[12] *n*=360, phase 3 RCT of RT compared to CRT | 64 Gy in 32 fractions for 6.5 weeks or 52.5 Gy in 20 fractions for 4 weeks | Mitomycin/ fluorouracil | Grade 3 – 4 adverse events for RT (27.5%) and CRT (36.0%) | 2-year survival rate of 67% for CRT, compared to 54% for RT HR: 0.68; 95% CI: 0.48 – 0.96; *P*=0.03 |
| Hoskin *et al.*[16] *n*=333, phase 3 RCT of RT compared to RT+CON | 64 Gy in 32 fractions for 6.5 weeks or 52.5 Gy in 20 fractions for 4 weeks | Carbogen/ nicotinamide | No difference in grade 3 – 4 of GI or GU toxicity | 3-year survival rate of 59% for RT+CON, compared to 46% for RT (*p*=0.04) |
| Choudhury *et al.*,[17] *n*=50, phase 2 prospective single-arm study | 55 Gy in 20 fractions for 4 weeks | Gemcitabine | Four patients could not complete chemotherapy due to bowel toxicity | 3-year survival rate of 75% |
| Sabaa *et al.*,[15] *n*=104, phase 2 prospective single-arm study | Conventional fractionation 64 Gy in 32 fractions | Gemcitabine/ cisplatin | No significant grade 3 – 4 toxicity was observed and all patients completed treatment as planned | 5-year survival rate of 59.4% |

Abbreviations: CI: Confidence interval; CON: Carbogen and nicotinamide; CRT: Chemoradiotherapy; GI: Gastrointestinal; GU: Genitourinary; HR: Hazard ratio; RCT: Randomized controlled trial; RT: Radiotherapy.

8, 15, and 22, along with a 28-day RT regimen consisting of 55 Gy in 20 fractions. All patients completed RT, and 46 (92%) of them were able to complete all four gemcitabine cycles. Two patients (4%) stopped their treatment after two cycles, while two (4%) stopped after three cycles. Out of 47 patients who had a post-treatment cystoscopy, 44 (88%) of them had a full endoscopic response. Out of 36 patients who were still alive at the median FU of 36 months (range: 15 – 62 months), 32 (64%) of them had a functional and intact bladder. Two (4%) patients died as a result of treatment-associated complications, five patients (10%) died due to intercurrent disease, and seven patients (14%) died due to metastatic MIBC. Cystectomy was performed on three patients (6%) due to recurrent illness and one (2%) due to toxicity. The OS was 75%, and cancer-specific survival was 82% after 3 years.[15]

Multiple single-arm prospective studies in RT oncology have evaluated the role of radical RT in conjunction with concurrent cisplatin-based chemotherapy and reported a 3-year survival rate ranging from 60% to 80%. Based on this evidence, concurrent CRT is currently considered the gold standard of care for patients undergoing TMT as part of a bladder preservation strategy.

Few studies have investigated the role of RT for patients with advanced bladder cancer and node-positive disease. A multicenter retrospective study looking at survival outcomes in patients with node-positive MIBC was reported by Swinton *et al.*[18] Participating UK oncology centers that offered both TMT and radical cystectomy provided data on patients (*n* = 287) with clinically node-positive, non-metastatic MIBC. All patients had a median OS of 1.55 years (95% CI: 1.35 – 1.82 years). When compared to palliative care, undergoing radical treatments was associated with an enhanced OS rate (HR: 0.32; 95% CI: 0.23 – 0.44; $p<0.001$). Patients who had radical treatment (*n* = 163) either underwent radical cystectomy (*n* = 76) or received a radical dose of RT (*n* = 87). The multivariate analysis revealed no correlation between the choice of radical treatment and OS (HR: 0.94; 95% CI: 0.63 – 1.41; $p=0.76$) or PFS (HR: 0.74; 95% CI: 0.50 – 1.08; $p=0.12$). Swinton *et al.* recommended that all patients with node-positive MIBC should have access to bladder-sparing TMT treatment due to limited prognosis and the recognized morbidities associated with radical cystectomy. Tan *et al.*[9] reported on a phase 2 prospective study of intensity-modulated pelvic node and bladder RT, conducted to assess the feasibility of delivering IMRT to treat the bladder and pelvic nodes in patients with node-positive or high-risk node-negative bladder cancer. In this study, they delivered 64 Gy in 32 fractions to the tumor bed, 60 Gy in 32 fractions to the positive nodes, and 52 Gy in 32 fractions to the bladder, excluding the tumor bed and elective nodes. The trial reported acute grade 1 and 2 GI and genitourinary toxicities in 81.1% and 70.6% of patients, respectively, and grade 3 toxicities of 5.4% and 20.6%, respectively. Grade 3 late toxicities were 5%, with one patient reporting grade 3 cystitis and hematuria. No grade 3 or 4 toxicities were reported in year 2. The median 1-, 2-, and 5-year pelvic relapse-free survival rates were 55%, 37%, and 26%, respectively. The median OS was 1.9 years (95% CI: 1.1 – 3.8), with 1-, 2-, and 5-year OS rates of 68%, 50%, and 34%, respectively. Sondergaard *et al.*[11] treated 16 patients with 60 Gy to the bladder and

48 Gy to nodes and reported that six (38%) of the patients had grade 1 and 2 lower toxicities after IMRT, while no grade 3 and 4 toxicities were reported in this study.

The role of pelvic RT in MIBC has also been evaluated in the adjuvant (post-operative) setting. In a multicenter phase 2 trial by Fonteyne *et al*.,[19] 17 patients received IMRT, delivering 50 Gy in 25 fractions to the tumor bed and pelvic nodes. Acute grade 2 GI toxicity was observed in 62% of patients, while 4% developed acute grade 3 GI toxicity. One patient had grade 5 diarrhea and vomiting due to obstruction after 1 month. In a trial by Murthy *et al*.,[20] 18 patients were treated to the tumor bed and pelvic node to 50.4 Gy in 28 fractions, and they reported that RT to the lymph nodes increased DFS from 70% to 85%.

The present study describes a novel hypofractionated RT dose-fractionation schedule (57.5 Gy to the primary tumor and 46 Gy in 23 fractions to the nodes) using VMAT for treating bladder and pelvic nodes in patients with MIBC. To our knowledge, this protocol has not been reported previously. The development of the protocol was based on sound radiobiological modeling with a BED equivalent to a hypofractionated schedule of 55 Gy in 20 fractions ($\alpha/\beta$ value of 10), with similar probabilities of tumor control. The $BED_{2Gy}$ for late toxicity in the new protocol (with an $\alpha/\beta$ value of 2 for late-responding tissues) was 64.68 Gy, compared to 65.3 Gy for the hypofractionated schedule of 55 Gy in 20 fractions. Therefore, it was hypothesized that the use of the new protocol of 57.5 Gy in 23 fractions would be associated with similar levels of tumor control and toxicity as the hypofractionated schedule of 55 Gy in 20 fractions. In MIBC, pelvic RT is often administered using conventional fractionation, which uses 46 – 48 Gy to target the nodes and 60 – 64 Gy to target the primary tumor. A recent meta-analysis of patients with localized MIBC found that hypofractionated RT was linked to improved locoregional control as compared to conventional fractionation. Therefore, a hypofractionated pelvic RT technique may offer benefits in terms of promoting effective local control.

Six patients (35%) in the study cohort had major comorbidities, and two patients (12%) had adverse histology with neuroendocrine transformation, making them a prognostically unfavorable group of patients. A total of 15 patients (88%) had evidence of clinically node-positive disease, and two patients (12%) received elective nodal irradiation in the presence of high-risk MIBC. Ten patients (59%) received SACT with platinum-based doublet combination chemotherapy – the most commonly employed regime ($n$ = 8). One patient (6%) received cisplatin/gemcitabine chemotherapy followed by maintenance pembrolizumab, and another (3%) patient received upfront atezolizumab. The median number of cycles administered was three, and patients were reviewed after the completion of chemotherapy to ensure they had no significant residual toxicity before commencing RT. NAC targets micrometastatic disease and may reduce primary tumor volume after incomplete TURBT, while also improving the OS and DFS rates. In the BA06 study, NAC with cisplatin, methotrexate, and vinblastine was administered, followed by either cystectomy or RT. The trial reported a 16% reduction in the risk of death, with the 3-year survival rate increasing from 50% to 56% in favor of NAC.[10] Before cystectomy or RT, platinum-based neoadjuvant combination chemotherapy has demonstrated the potential to deliver a 5% absolute OS benefit and a 9% DFS benefit at 5 years.[21]

The use of induction SACT was associated with a significant prolongation of OS rate in patients (median OS: 40.1 vs. 13.6 months; HR: 0.16; 95% CI: 0.02 – 1.12; $p$=0.002). The survival benefit was much higher than those reported in previous studies. However, the results may be skewed in favor of SACT due to two patients (6%) who had a prolonged duration of immunotherapy before proceeding with RT.

Most patients in our study cohort also received concurrent chemotherapy with a single agent, either gemcitabine or cisplatin – the most commonly employed regimens. Most of the acute toxicities reported were grade 1 or 2, including fatigue, diarrhea, pain or local discomfort, increased frequency of micturition, and dysuria. One patient (6%) had a grade 3 acute toxicity event (pain and local discomfort), and two patients (17%) experienced grade 3 late toxicity events (colovesical fistula and severe radiation-induced cystitis). The retrospective nature of the study limits the accurate assessment of toxicities. Nonetheless, the toxicity rates reported in our study are consistent with those reported by other studies. In our study, 70% of patients ($n$ = 12) had a complete response or stable disease after CRT completion. More than 50% of patients ($n$ = 9) remained disease-free at the last FU, with 47% ($n$ = 8) developing disease progression (local progression, $n$ = 2; metastatic progression, $n$ = 6). The median PFS was 15.8 months. Seven patients (41%) were alive and well, with no signs of recurrence, and the median OS was 23.1 months (95% CI: 13.6 – 64.6).[9]

Our results indicate that the VMAT protocol of 57.5 Gy in 23 fractions prescribed to the bladder and primary tumor, as well as 46 Gy in 23 fractions to the pelvic lymph nodes, can be safely delivered along with concurrent chemotherapy. This protocol resulted in minimal clinically significant grade 3 toxicity and an approximately 70% response rate, including a 41% complete clinical response

rate. Moreover, the treatment was extremely effective in achieving good local control, with only two patients developing local progression. Approximately 75% ($n$ = 6) of relapses were metastatic in nature. The above results contradict those reported by Tan *et al*.,[9] in which 70% of patients relapsed, and 52.6% developed locoregional recurrence. In comparison, 52.9% of our patients remained disease-free, and most of the relapses (35%) were metastatic in nature. The lower rates of overall relapse and local recurrence observed in our study could be explained by the shorter FU period or the potentially higher therapeutic effectiveness of hypofractionated RT compared to conventional RT. These results are encouraging, especially as they come from a subgroup of patients with a poor prognosis.

The current study has a number of limitations, most of which are associated with its retrospective design and small patient population. Furthermore, there was a notable variation within the research cohort in terms of histology, fitness ratings, and concomitant chemotherapy treatment. Moreover, in the absence of a direct comparison, the study cannot evaluate the dosimetric advantages of VMAT over standard conformal RT techniques. Thus, these results should be interpreted with caution. However, the findings contribute significant information to the expanding body of evidence, supporting the probable role of RT in treating patients with MIBC and node-positive disease. The report emphasizes the need for further research and the planning of larger prospective studies to explore the potential role of RT in patients with MIBC and locoregional pelvic lymph nodes.

Future research should explore the intriguing effects of combining immunotherapy with RT. By targeting the programmed cell death 1 receptor, its ligand, or the cytotoxic T lymphocyte antigen 4, immune checkpoint inhibitors (ICIs) alter the immune response to cancer cells.[22] Current phase 2 and phase 3 clinical trials are investigating the addition of ICIs as the "fourth modality" to trimodality treatment for localized MIBC.[23] Preclinical data suggest that ICIs and RT may synergize, with radiation stimulating an immune response by releasing antigens from the tumor, which has been hypothesized to account for the sporadic "abscopal" effects of radiation.[24] The potential for dose-limiting GI toxicity (e.g., colitis) is one of the primary concerns when combining immunotherapy and RT, and this becomes particularly relevant once the pelvic lymph nodes are included in the irradiated volumes.[25] The presence of cancer cells induces a systemic response, leading to metabolic and immunological changes, which can be assessed using biomarkers. These changes may help identify patients with high-risk diseases who could benefit from more aggressive (multimodality) therapies. The inclusion of biomarkers in future research is imperative to evaluate the treatment effects and outcomes.[26]

## 5. Conclusion

The prognosis for patients with bladder cancer and pelvic nodes remains poor, and in the absence of surgery, most of these patients are treated with the best supportive care or palliative systemic therapy options. We successfully implemented a novel pelvic RT protocol for MIBC treatment, which was well tolerated with low levels of clinically significant acute or late toxicities. The OAR constraints were met using both TrueBeam and Halcyon VMAT, with plans consisting of two arcs or three arcs. The present study demonstrates the safety and feasibility of using this VMAT protocol in a fragile and prognostically unfavorable group of patients, with approximately 70% response rate and more than 90% local control rate. Most relapses were metastatic in nature, with a median OS of 23.1 months. The results from the study support the design of larger prospective studies to further evaluate the role of RT in patients with MIBC and pelvic nodes.

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## Conflict of interest

The authors declare that they have no competing interests.

## Author contributions

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## Ethics approval and consent to participate

The study was reported to the Trust clinical governance team and the Audit Management and Tracking (AMaT) online portal. Due to the retrospective nature of the study, obtaining consent for participation from the study subjects was not feasible.

## Consent for publication

This is a retrospective analysis of patients who provided informed consent for the treatment. No patient-identifiable information has been used in the manuscript.

## Availability of data

The data for this study can be obtained by submitting a request to the lead or corresponding author.

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