Clinical Oncology 31 (2019) 646–652

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Adaptive Radiotherapy for Carcinoma of the Urinary Bladder: Long-term Outcomes With Dose Escalation

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Received 1 March 2019; received in revised form 23 April 2019; accepted 2 May 2019

Abstract

Aims: To report long-term outcomes with dose-escalated, image-guided adaptive radiotherapy (ART) for bladder preservation in muscle-invasive bladder cancer (MIBC).
Materials and methods: All MIBC patients receiving bladder-preserving ART at our institute from 2009 to 2018 were analysed. For ART, three anisotropic planning target volumes (PTV) were concentrically grown around the simulation bladder volume. A library of intensity-modulated radiotherapy plans was created for each patient. A total dose of 64 Gy in 32 fractions to the entire bladder and 55 Gy to pelvic nodes was planned, with 68 Gy to the tumour bed (2 Gy equivalent dose = 68.7 Gy, $\alpha/\beta = 10$) as simultaneous integrated boost for solitary tumours. The most appropriate PTV encompassing the bladder ('plan-of-the-day') was chosen daily using on-board megavoltage imaging. Neoadjuvant and concurrent chemotherapy was prescribed for medically fit patients.
Results: Of a total of 106 patients, most had T2 (68%) or T3 (19%) disease. Ninety-two patients (87%) completed 64 Gy to the whole bladder. Sixty-three patients (59%) received 68 Gy as tumour bed boost. Seventy-six per cent received concurrent weekly chemotherapy. At a median follow-up of 26 months, 3-year locoregional control, disease-free survival and overall survival were 74.3, 62.9 and 67.7%, respectively. Eighty-two per cent of patients retained disease-free bladder. Radiation Therapy Oncology Group grade III/IV acute genitourinary and gastrointestinal toxicities were 7.5% and 0%, respectively, and late genitourinary/gastrointestinal toxicities were 6.5% and 3.8%, respectively. Overall survival, disease-free survival, locoregional control and grade III/IV genitourinary/gastrointestinal toxicities did not differ significantly with dose escalation.
Conclusion: Plan-of-the-day ART is clinically safe and effective for bladder preservation and can be implemented in routine clinical practice. A high bladder preservation rate is achievable without compromising on survival or toxicities. Dose escalation does not seem to affect outcomes.

Key words: Adaptive radiotherapy; bladder cancer; dose escalation; plan-of-the-day; tomotherapy

Introduction

Adaptive radiotherapy (ART) techniques have emerged as a feasible practical solution to improve the accuracy of dose delivery in bladder-preserving radiotherapy [1,2]. A large range of intra- and interfraction motion of the bladder during radiotherapy delivery increases the risk of missing the target volume when using conformal techniques such as intensity-modulated radiotherapy (IMRT). Large planning margins can mitigate this risk at the cost of higher dose to the normal bowel. ART techniques incorporate such patient-specific heterogeneity to ensure accurate target coverage while sparing the healthy tissues. The 'plan-of-

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https://doi.org/10.1016/j.clon.2019.06.005
0936-6555/

the-day' (POD) approach of ART utilises daily imaging to select the best fit plan from a library of plans. It has been shown to be effective, well-tolerated and feasible [2–4]. Most of these studies have reported their results in small patient groups, treated under well-defined study protocols. Long-term outcomes in muscle-invasive bladder cancer (MIBC) with POD-based bladder-preserving ART are yet to be reported from routine clinical practice.

The use of daily image-guided radiotherapy can also potentially allow accurate dose escalation to the gross tumour volume to improve local control [5]. However, accurate delivery of a bladder dose in excess of 60 Gy while sparing the surrounding normal tissues can be challenging. Here we report the long-term clinical outcomes in patients with MIBC treated using POD ART with dose escalation, as a part of the trimodality approach of bladder preservation.

Materials and Methods

Patients diagnosed with bladder cancer, who were suitable for bladder preservation were treated with trimodality therapy (TMT) at our institute from 2009 to 2018. The baseline diagnostic and staging evaluation consisted of clinical history and examination; blood tests; computed tomography of the chest, abdomen and pelvis; a bone scan and/or 18-fluorodeoxyglucose positron emission tomography computed tomography. Cystoscopic biopsy and disease mapping using an institutional standardised bladder map were carried out for all patients. Patients with histologically proven transitional cell carcinoma, primary tumour stage T1 to T4 (American Joint Committee on Cancer TNM staging, seventh edition) with no or limited regional lymph nodal involvement, no distant metastasis, no tumour-attributable hydronephrosis, absence of extensive carcinoma *in situ* and reliable for regular follow-up were considered for bladder preservation. They were treated with TMT consisting of maximal safe transurethral resection of bladder tumour (TURBT), followed by chemoradiation. Patients with a large tumour volume were offered neoadjuvant chemotherapy with two to four cycles of gemcitabine (1000 mg/m^2, days 1 and 8) and carboplatin area under curve-5, day 1) given 3 weekly. Concurrent chemotherapy was advised for clinically fit patients, with either cisplatin (30 mg/m^2) if renal function was adequate, or carboplatin (area under curve-2) if mild renal derangement, or gemcitabine 200 mg/m^2 weekly with radiotherapy.

Radiotherapy planning and the treatment technique for the adaptive POD approach followed at our institution has been described previously [6]. In brief, computed tomography-based simulation for radiotherapy was carried out with patients in supine position, using a knee rest. Dose escalation using simultaneous integrated boost (SIB) was considered for selected patients with a solitary tumour or two closely located tumours in the absence of any carcinoma *in situ* and the tumour location being suitable to deliver the boost dose safely without the risk of overdose to the bowel. These patients were simulated and treated with a comfortably full bladder. For the remaining patients, simulation and treatment were carried out with an empty bladder. The primary clinical target volume (CTV) contour included the entire bladder and prostate. Three different planning target volumes (PTVs) were concentrically and anisotropically generated around the primary CTV, ranging from 0.5 to 2.5 cm (see Supplementary Table S1). These margins were intended to generate the smallest PTV that would cover the bladder wall in each direction 85, 90 and 95% of the time [6]. For the patients treated with full bladder, a zero margin PTV (PTV_zero) was also generated to be used when the bladder volume at treatment delivery was less than the simulation volume. For SIB-based dose escalation, CTV boost was delineated encompassing the visible tumour and any suspicious thickening of the bladder wall, considering the baseline pelvic computed tomography scan and cystoscopic disease map. A boost PTV was generated with a generous 1 cm margin to this CTV, to allow coverage of the boost volume irrespective of the size of the bladder PTV. The nodal CTV for patients with MIBC included pelvic lymph nodes delineated until the lower limit of the fifth lumbar vertebra, as per existing Radiation Therapy Oncology Group (RTOG) guidelines [7]. The nodal PTV was generated with a 5 mm margin to the nodal CTV. For each primary PTV (zero, small, medium and large), IMRT treatment plans were generated on theTomotherapy planning station (Accuray, Sunnyvale, CA, USA). Total doses of 64 Gy in 32 fractions to the bladder PTV; 68 Gy in 32 fractions to the boost PTV if applicable (2.12 Gy per fraction, equivalent dose for 2 Gy fractions $[EQD2]_{10} = 68.7$ Gy); and 55 Gy in 32 fractions to the nodal PTV (1.72 Gy per fraction, $EQD2_{10} = 54$ Gy) were prescribed using the SIB technique. In each plan, coverage of the target PTV by 95% of the prescribed dose was ensured. Sparing of the bowel was achieved by keeping the bowel volume receiving 45 Gy (V45) below 158 cm^2, V50 below 110 cm^2 and V55 below 28 cm^2 before approving the treatment plan.

Helical Tomotherapy-based image-guided IMRT was used for every patient, with daily on-board megavoltage computed tomography (MVCT) imaging before treatment. For every fraction, automatic pelvic bone match was followed by manual co-registration of MVCT and simulation CT, to fit the bladder into the most appropriate smallest PTV (Figure 1). Matching of the boost volume was prioritised in patients chosen for dose escalation. The patient was treated with the plan linked to the PTV selected for that day (POD

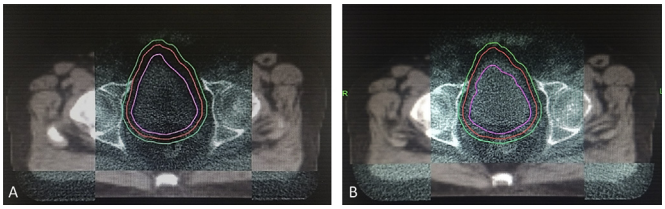

Fig 1. Axial view of on-board megavoltage computed tomography matched with planning computed tomography showing the three planning target volumes (PTVs), with the bladder fitting into the smallest PTV in the first fraction (A) but requiring a larger PTV in the second fraction (B).

approach) [6]. Acute genitourinary and gastrointestinal toxicities in each patient were assessed weekly by a radiation oncologist during the course of radiotherapy. Follow-up was carried out 3 monthly for the first 2 years and 6 monthly subsequently, with cystoscopy and urine cytology at each visit. Late genitourinary and gastrointestinal toxicities were recorded as per RTOG toxicity grading.

The clinical records of all patients treated with the above approach who completed at least 3 months of follow-up after radiotherapy were analysed for outcomes using SPSS® version 21 (IBM Inc). Demographic characteristics were analysed using descriptive statistics. Survival analysis was carried out using the Kaplan–Meier method, starting from the date of histopathological diagnosis. Overall survival (OS) was defined from the date of histopathological diagnosis until the date of death due to any cause or the date of last follow-up. Disease-free survival (DFS) was defined from the date of histopathological diagnosis until the date of recurrence of disease. Log-rank test was used for univariate analysis for prognostic factors and Cox proportional hazard was used for multivariate analysis (a P value of 0.05 was considered significant).

Results

From 2009 to 2018, 106 patients with bladder cancer were treated with ART. Patient characteristics and treatment details are shown in Table 1. As expected, about two-thirds of the patients (62.3%) had at least one pre-existing comorbid condition. Most (92%) had node-negative disease. Maximal TURBT was carried out in 96% of patients.

Neoadjuvant chemotherapy was given in 23 (21.7%) patients, most commonly gemcitabine combined with cisplatin or carboplatin. Concurrent chemotherapy was administered in 81 (76.4%) patients, 63 (78%) of whom received at least five cycles of planned chemotherapy. Most commonly, concurrent chemotherapy was platinum-based (63%), followed by gemcitabine (35%). Early termination of concurrent chemotherapy due to severe acute chemotherapy-related toxicity was required in 15 (18.5%) patients, 10 of whom had received gemcitabine and four had received cisplatin.

Bladder tumour boost by SIB technique was planned for 71 (67%) patients. Pelvic nodal boost was given in 96 (91%) patients. Median duration of radiotherapy was 47 days. Five patients received bladder dose <60 Gy (bladder partially treated = 1, distant progression during radiotherapy = 1, persistent severe haematuria during radiotherapy = 1, persistent symptomatic urinary tract infection during radiotherapy = 1, defaulted radiotherapy = 1). Five patients (4.7%) had a break during radiotherapy due to treatment-related toxicity. Radiotherapy was stopped at <50 Gy delivered dose in three patients due to severe acute toxicities.

With a median follow-up of 26 months, 2-year OS was 75.2% and 3-year OS was 67.7% using Kaplan–Meier statistics (Figure 2). Among the 31 (29.2%) deaths, 21 (67.7%) were due to disease and the 3-year DFS was 62.9%. There was no significant difference in terms of OS and DFS between groups receiving 64 or 68 Gy to the tumour (3-year OS 59.9% versus 70.4%, $P = 0.43$; 3-year DFS 63.8% versus 62%, $P = 0.57$). The influence of patient age at diagnosis, presence of comorbidities, use of neoadjuvant chemotherapy and concurrent chemotherapy on DFS and OS were analysed using log-rank test. None of these showed any statistical significance on DFS. Age <65 years ($P = 0.001$), neoadjuvant chemotherapy ($P = 0.01$) and concurrent chemotherapy ($P = 0.02$) showed a significant effect on OS in univariate analysis. On multivariate analysis, the effect of age at diagnosis (hazard ratio 1.05, 95% confidence interval 1.01–1.09, $P = 0.01$) and neoadjuvant chemotherapy (hazard ratio 2.08, 95% confidence interval 1.01–4.29, $P = 0.05$) remained significant.

Recurrence of disease was observed in 33 (31.1%) patients (Table 2). Isolated local recurrence was seen in 16 patients; of these, nine cases were non muscle-invasive and were managed with TURBT only. Isolated muscle-invasive recurrence within the bladder was seen in seven of 33 patients.

Table 1
Patient demographics and treatment details

Demographic	*n* (106)	%
Gender		
Male	96	90.6
Female	10	9.4
Age		
Median (range)	65.5 (21–86)	
Comorbidities		
Hypertension	49	46.2
Diabetes mellitus	32	30.1
Cardiac	10	9.4
Respiratory	9	8.5
Tumour group		
Recurrent NMIBC	6	5.7
MIBC	100	94.3
T stage		
T1	6	5.7
T2	72	67.9
T3	20	18.9
T4	8	7.5
N stage		
N0	97	91.6
N1	5	4.7
N2	2	1.9
N3	2	1.9
Neoadjuvant chemotherapy		
Received	23	21.7
Not received	83	78.3
Concurrent chemotherapy		
Received	81	76.4
Not received	25	23.6
Nodal irradiation		
Yes	96	91.6
No	10	9.4
Received dose (to tumour)		
≤64 Gy	43	40.5
68 Gy	63	59.5

MIBC, muscle-invasive bladder cancer; NMIBC, non muscle invasive bladder cancer.

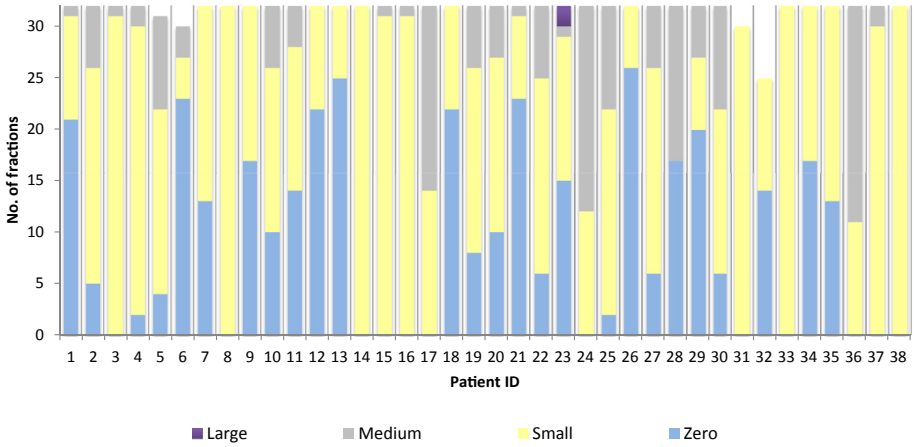

Fig 2. Choice of planning target volume in each fraction in a subset analysis of 38 patients.

Table 2
Patterns of disease recurrence

Site of recurrence	*n* (%)
Local NMIBC	9 (8.5)
Local MIBC	7 (6.6)
Local + distant	3 (2.8)
Nodal + distant	2 (1.9)
Distant only	12 (11.3)
Total	33 (31.1)

MIBC, muscle-invasive bladder cancer; NMIBC, non muscle invasive bladder cancer.

Surgical salvage for these was with radical cystectomy in five patients and TURBT in two patients who refused cystectomy. The overall bladder preservation rate at 3 years was 91.3% and the rate of retaining a disease-free bladder at 3 years was 77%. The 3-year locoregional control was 74.3% and was similar in the groups receiving 64 and 68 Gy (3-year locoregional control 73.5% versus 75.8%, $P = 0.46$). The bladder preservation rate and local control were also similar between these two groups.

The incidence of acute and late genitourinary and gastrointestinal adverse effects after radiotherapy is shown in Table 3. Grade III/IV acute genitourinary toxicity was seen in 7.5% of patients. Late grade III/IV genitourinary toxicity was 6.5% and gastrointestinal toxicity was 3.8%. Bladder dose of 68 Gy showed no significant correlation with acute or late grade III gastrointestinal/genitourinary toxicities ($P = 0.32$ and 0.50, respectively).

The choice of PTV was analysed in a subset of 38 patients (total 1207 MVCTs) from this study to understand the frequency of use of PTV margins (Figure 3). The best fit PTV had been chosen by the treating radiation oncologist on the first three fractions of radiotherapy and by the radiotherapy technologist for subsequent fractions. The most frequent PTV chosen for each individual patient throughout their course of radiotherapy was studied. PTV_small was the most common choice in most patients ($n = 22$), followed by PTV_zero in 13 and PTV_medium in only three patients. The frequency of choosing various PTVs was also analysed as a proportion of total fractions. Again, PTV_small was chosen the most frequently (56%), followed by PTV_zero (30%) and PTV_medium (13%). A large PTV was used in only two of 1207 fractions. This subset analysis indicates that bladder protocol compliance and daily imaging allowed the adoption of smaller margins in most patients.

Discussion

This is the largest report of long-term outcomes of bladder preservation using dose-escalated ART for definitive treatment of MIBC. Over the decades, radical radiotherapy for MIBC has evolved from a suboptimal alternative in patients unfit for radical cystectomy to an equally

Table 3
Acute and late toxicities post-radiotherapy

Toxicity grade	Acute gastrointestinal toxicity *n* (%)	Acute genitourinary toxicity *n* (%)	Late gastrointestinal toxicity (maximum) *n* (%)	Late genitourinary toxicity (maximum) *n* (%)
0	40 (37.7)	18 (17)	77 (72.6)	53 (50)
1	43 (40.6)	49 (46.2)	11 (10.4)	16 (15.1)
2	18 (17)	26 (24.5)	6 (5.7)	22 (20.7)
3	0 (0)	8 (7.5)	4 (3.8)	6 (5.6)
4	0 (0)	0 (0)	0 (0)	1 (0.9)
Unknown	5 (4.7)	5 (4.7)	8 (7.5)	8 (7.5)

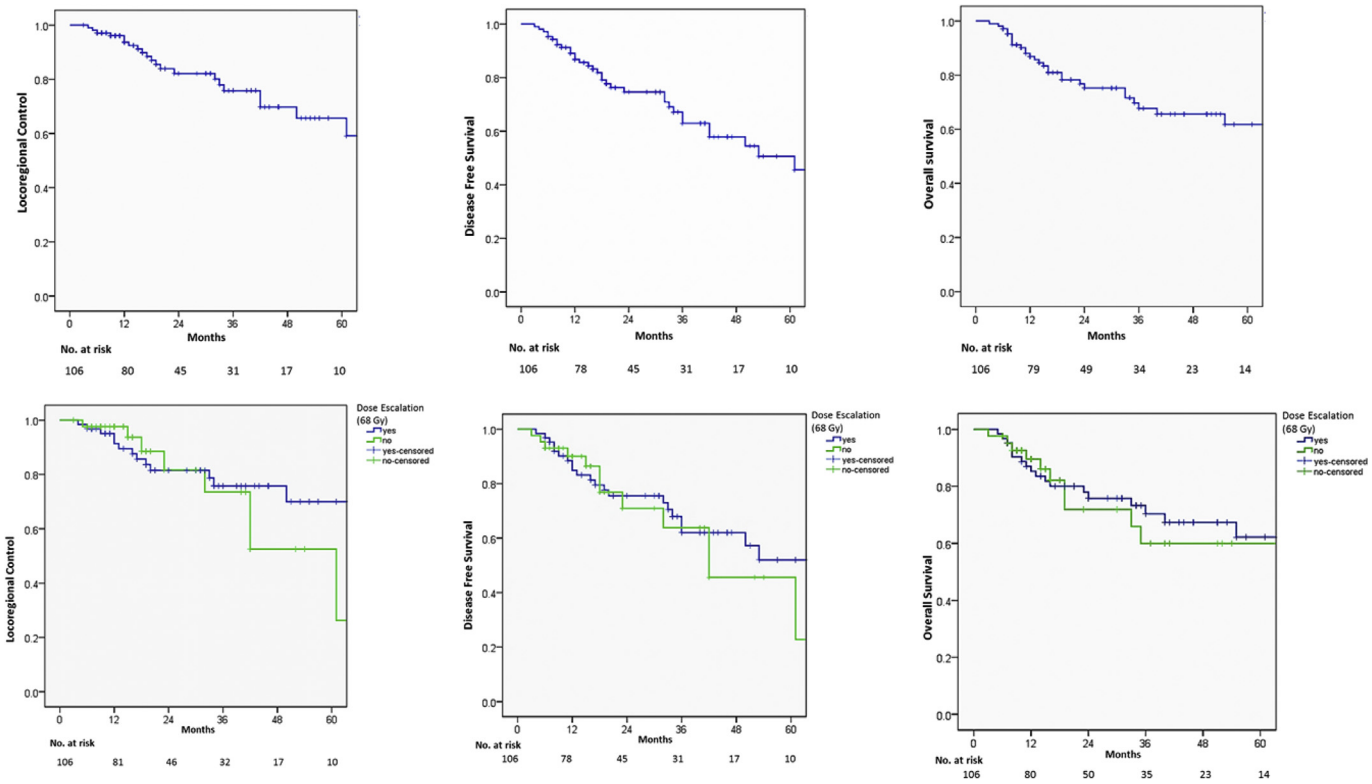

Fig 3. Kaplan–Meier estimates of overall survival, disease-free survival and locoregional control.

efficacious option for bladder preservation. This study shows the feasibility of adaptive IMRT for bladder preservation outside the clinical trials in routine clinical practice, with patient outcomes comparable with radical cystectomy cohorts.

Older studies comparing the outcomes in MIBC suggested inferior survival outcomes with radiotherapy compared with cystectomy, but a review of recent evidence shows results with modern radiotherapy techniques being comparable with the surgical series [8,9]. A population-based study from the National Cancer Data Base showed similar survival between TMT and radical cystectomy (40 months versus 43 months) but favoured surgery for longer term outcomes [10]. Another systematic review of 13 396 patients treated across various clinical trials favoured TMT over radical cystectomy for 5-year OS (57% versus 52%, $P = 0.04$) [11]. Raza *et al.* [12] reported outcomes with modern robot-assisted radical cystectomy from the International Robotic Cystectomy Consortium multi-institutional database, as 5-year OS of 50% and 5-year cancer-specific survival of 75%. Similarly, published long-term outcomes with TMT range from 5-year OS of 52–73% and 5-year cancer-specific survival of 64–82% [13,14]. Published evidence comparing outcomes of TMT versus radical cystectomy continues to derive greatly varied conclusions, favouring one modality over the other, depending on the sample population, patient selection, treatment protocols, quality of trials included and statistical techniques [10,11,15,16]. The clinical outcomes from BC2001 [17,18] and BCON [19] trials, the two largest randomised trials in bladder-preserving radiotherapy, are comparable with the results observed in this study. Overall survival and DFS at 3 years were observed to be 59 and 54%, respectively in the radiosensitiser arm of the BCON trial, compared with 67.7 and 63% in our cohort. The 3-year locoregional control in our study was 74.3%, compared with 67% at 2 years in the chemoradiotherapy arm of the BC2001 trial.

Conventional pelvic radiotherapy has been associated with significant genitourinary and gastrointestinal toxicity, which was often dose limiting. Evolution in radiotherapy techniques, a better understanding of dose-response principles in bladder radiotherapy, and the addition of chemotherapy have contributed to improvement of TMT protocols. Radiotherapy dose in excess of 60 Gy to the whole bladder has been associated with improved complete response rates [11]. Such a large dose can be delivered safely with modern conformal techniques that allow for significant sparing of the normal bowel tissue [20]. However, the risk of target miss is higher with smaller PTV margins of conformal radiotherapy due to variation in bladder filling. To ensure accurate coverage of the target volume, ART has emerged as an exciting solution. ART for bladder involves modification of the PTV margins to adapt to intra- and interfraction variation in the target volume. This ensures not only satisfactory target volume coverage, but also minimises normal tissue irradiation to reduce toxicity. A retrospective study using multiple PTVs variably expanded superiorly to create a library of plans showed the potential small bowel sparing with the POD approach [21]. Further research explored various methods of determining optimum margins to

balance target coverage with normal tissue sparing. A single planning CT image can be used to generate a standard PTV around the bladder using population-based margins, and expanded in isotropic or anisotropic 5 mm increments to create three to six PTVs [6,22]. Although simple, this approach does not completely account for individual variations in bladder filling. A more patient-specific approach is to use multiple planning CT scans with successive bladder filling to delineate PTVs, starting from either an empty bladder or a full bladder [4,23]. However, systematic error between radiotherapy planning and actual treatment may still be present. To compensate for this, the bladder can be delineated on multiple conebeam scans (CBCTs) taken during the first week of treatment in addition to the planning scan [1]. This accounts for real-time patient-specific variations in target volume, but is resource-intensive and the corresponding benefit of reduction in irradiated volume compared with improved target coverage is not well-established [1,20]. Creation of multiple plans should take into account the frequency of usage of each plan; a library of three plans seems to be sufficient for the implementation of the POD approach in routine clinical practice.

Advances in radiotherapy delivery techniques for bladder cancer have also opened up the possibilities of dose escalation to improve outcomes. Pos *et al.* [5] showed that 3-year local control could be increased by a factor of 1.44 by a 10 Gy increase in the total dose. The feasibility of delivering a higher dose to the involved bladder while simultaneously treating the remaining bladder with a lower dose was shown in the BC2001 cohort [18]. Using such a SIB technique, dose escalation of 68–70 Gy to the tumour volume was shown to be feasible with the POD approach without any significant increase in toxicity [3]. However, the benefit of dose escalation has not yet been unequivocally reported in clinical practice. In our cohort, patients receiving 68 Gy (69 Gy EQD2) to the tumour volume did not show a significant difference in terms of local control, DFS or OS. A higher dose also did not result in any significant increase in grade II/III genitourinary/gastrointestinal toxicities. The BC2001 trial reported an 8.3% incidence of late grade III/IV toxicities on long-term follow-up, whereas late genitourinary and gastrointestinal toxicity rates in our study were 6.5 and 3.8%, respectively [17]. Thus, dose escalation is practical, but its benefit needs to be evaluated in larger trials such as the ongoing RAIDER trial (NCT02447549).

About half the recurrences seen in this study were at distant sites (17 of 33, 51%) and isolated muscle-invasive recurrence within the bladder was seen in only 21% (seven of 33) of patients. Most of the recurrences confined to the bladder were managed with TURBT alone; radical cystectomy was used for surgical salvage in only five patients. The infrequent recurrence of invasive tumour within the bladder is important, not only in the resultant high 3-year bladder preservation rate of 91%, but also for the potential of systemic therapy in achieving distal control.

Among the factors contributing to OS, only age at diagnosis and neoadjuvant chemotherapy were observed to be statistically significant in multivariate analysis. Existing literature shows that distant failures account for up to a third of the recurrences after surgery or radiotherapy [24]. Hence, the addition of systemic therapy in the form of neoadjuvant chemotherapy may have a better potential to improve outcomes as compared with dose escalation for bladder cancer. Previous studies have reported the benefit of radiosensitising systemic therapy with radical radiotherapy. Mitomycin and 5-fluorouracil given with radiotherapy showed improved DFS in the BC2001 trial, whereas the BCON study reported improved DFS and OS by hypoxia modification using concurrent carbogen and nicotinamide with radiotherapy [17,19]. However, concurrent chemotherapy showed no difference in DFS or OS in our cohort.

The retrospective nature of this study and the small number of patients in subgroup analyses do not allow for definite interpretation of the impact of neoadjuvant or concurrent chemotherapy or dose escalation upon the clinical outcomes. Results from randomised trials are expected to answer this. Meanwhile, the potential of dose escalation to compensate for the absence of concurrent chemotherapy in medically unfit patients is an interesting avenue for further research.

Conclusion

POD ART-based bladder preservation is ready for the transition from clinical trials into daily clinical practice. It is a feasible and effective approach to implement bladder-preserving TMT as an alternative to radical cystectomy. Dose escalation to 69 Gy $EQD2_{10}$ to the tumour bed is well tolerated but may not have an effect on either locoregional control or survival.

Conflicts of Interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.06.005.

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