Comparison of 3 image-guided adaptive strategies for bladder locoregional radiotherapy

KONG, Vickie C., TAYLOR, Amy <http://orcid.org/0000-0002-7720-6651>, CHUNG, Peter, CRAIG, Tim and ROSEWALL, Tara

Published version

KONG, Vickie C., TAYLOR, Amy, CHUNG, Peter, CRAIG, Tim and ROSEWALL, Tara (2018). Comparison of 3 image-guided adaptive strategies for bladder locoregional radiotherapy. Medical Dosimetry. (In Press)

Medical Dosimetry ■■ (2018) ■■–■■

Medical Dosimetry

journal homepage: www.meddos.org

Dosimetry Contribution:

Comparison of 3 image-guided adaptive strategies for bladder locoregional radiotherapy

Vickie C. Kong, MSc,[*,†] Amy Taylor, MSc,[‡] Peter Chung, MD,[*,†] Tim Craig, PhD,[*,†] and Tara Rosewall, PhD[*,†]

[*]*Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, Canada;* [†]*Department of Radiation Oncology, University of Toronto, Toronto, Canada; and* [‡]*Department of Allied Health Professions, Sheffield Hallam University, Sheffield, United Kingdom*

ARTICLE INFO

Article history:
Received 10 October 2017
Received in revised form 28 February 2018
Accepted 1 March 2018

Keywords:
Bladder cancer
Adaptive radiotherapy
Dose accumulation

ABSTRACT

The objective of this study was to compare the dosimetric differences of a population-based planning target volume (PTV) approach and 3 proposed adaptive strategies: plan of the day (POD), patient-specific PTV (PS-PTV), and daily reoptimization (ReOpt). Bladder patients ($n = 10$) were planned and treated to 46 Gy in 23 fractions with a full bladder in supine position by the standard strategy using a population-based PTV. For each patient, the adaptive strategy was executed retrospectively as follows: (1) POD—multiple distributions of various PTV sizes were generated, and the appropriate distribution based on the bladder of the day was selected for each fraction; (2) PS-PTV—population-based PTV was used for the first 5 fractions and a new PTV derived using information from these fractions was used to deliver the remaining 18 fractions; and (3) ReOpt—distribution was reoptimized for each fraction based on the bladder of the day. Daily dose was computed on all cone beam computed tomographies (CBCTs) and deformed back to the planning computed tomography (CT) for dose summation afterward. V_{95_Accu}, the volume receiving an accumulated delivered dose of 43.7 Gy (95% prescription dose), was measured for comparison. Mean V_{95_Accu} (cm^3) values were 1410 (standard deviation [SD]: 227), 1212 (SD: 186), 1236 (SD: 199), and 1101 (SD: 180) for standard, POD, PS-PTV, and ReOpt, respectively. All adaptive strategies significantly reduced the irradiated volume, with ReOpt demonstrating the greatest reduction compared with the standard (– 25%), followed by PS-PTV (– 16%) and POD (– 12%). The difference in the magnitude of reduction between ReOpt and the other 2 strategies reached statistical significance ($p = 0.0006$). ReOpt is the best adaptive strategy at reducing the irradiated volume because of its frequent adaptation based on the daily geometry of the bladder. The need to adapt only once renders PS-PTV to be the best alternative adaptive strategy.

Introduction

The standard treatment for muscle-invasive bladder cancer is radical cystectomy with bilateral pelvic lymphadenectomy, reporting a 5-year overall survival of 40% to 60%.[1] However, for patients who are not suitable for surgery or

---

Reprint requests to Vickie C. Kong, MSc, MRT (T), Radiation Medicine Program, Princess Margaret Cancer Centre, 610 University Avenue, Toronto, ON, Canada.

E-mail: Vickie.kong@rmp.uhn.on.ca

https://doi.org/10.1016/j.meddos.2018.03.004

those who prefer to preserve the bladder, radiotherapy has been offered as part of a multimodality approach, reporting a 5-year overall survival rate of 45% to 52%.[2-5] The clinical target volume (CTV) consists of the pelvic lymph nodes (PLNs), the entire bladder, and the primary tumor.[3] A multiphase treatment regimen is frequently adopted, delivering a prescription dose of 40 to 50 Gy to the PLN and the entire bladder in the first phase, followed by a boost of 10 to 20 Gy to the primary tumor alone to minimize the volume of small bowel being irradiated to high dose.[6]

Despite the use of cone beam computed tomography (CBCT) to localize the bladder during radiotherapy, there are barriers to delivering precision locoregional irradiation due to the presence of 2 independent moving targets: the PLN, which is relatively immobile with respect to the bony anatomy, and the highly distensible bladder, whose volume and position may vary substantially during a course of radiotherapy. In the presence of 2 independently moving targets, adaptive radiotherapy has been demonstrated to be the most efficacious when compared with various image guidance strategies.[7,8]

Different adaptive strategies, such as "plan of the day" (POD),[9-19] "patient-specific planning target volume (PTV)" (PS-PTV), [20-22] and daily reoptimization (ReOpt)[23] have been proposed and investigated for bladder radiotherapy to compensate for the large interfraction and interpatient variations observed. However, most studies have evaluated the efficacy based on geometric coverage,[9,12,15,17-21,24] per-fraction comparison,[13,22] or direct summation of dose-volume histogram.[10,11] Moreover, previous studies have primarily compared the different methods of generating the multiple PTVs for the POD strategy[10,15,19] or between 2 adaptive strategies.[23] Because deformable image registration (DIR) enables the accumulation of delivered dose to the target and the normal tissue onto a reference image by tracking the corresponding voxels between multiple image datasets,[25-27] it was applied in the present study to conduct a dosimetric comparison of 3 adaptive strategies against a standard population margin-based PTV in assessing their efficacy in reducing the irradiated volume for locoregional radiotherapy for bladder cancer.

Methods and Materials

Upon local research ethics board approval, patients with bladder cancer who were prescribed with image-guided radiotherapy to the PLN and the whole bladder between May 2013 and December 2014 were retrospectively identified. Any patient who has metallic prosthesis was excluded because of inferior CBCT image quality induced by the artifact. This resulted in a total of 10 patients (7 men and 3 women).

All were treated in the supine position with a full bladder using the standard strategy, in which the PLN and the whole-bladder CTV contours were used to generate 2 PTVs: the PTV_{PLN}, by applying a 5-mm expansion on the PLN, and the standard PTV_{WB}, by applying a 15-mm expansion on the whole bladder. A 7-field IMRT distribution using 6 MV was generated to deliver 46 Gy in 23 fractions to meet the following evaluation criteria: (1) 99% of PTV_{PLN} and PTV_{WB} receiving ≥ 43.7 Gy (95% of prescription dose) and (2) 1% of PTV_{PLN} and PTV_{WB} receiving ≤ 48.3 Gy. The same distribution was used to deliver all 23 fractions using Synergy XVI (Elekta Ltd, Crawley, UK). Daily CBCT was acquired for treatment verification purposes (M20 collimator, full scan, 120 kV, 40 mA, 40 ms).

To simulate the execution of each adaptive strategy and to calculate the accumulated delivered dose for comparison, the planning computed tomography (CT) and 23 daily CBCTs were imported into RayStation v.4.5.2 (RaySearch Laboratories, Stockholm, Sweden) and registered using bony anatomy to reproduce the treatment position. PLN and whole-bladder contours were delineated by a single observer (V.K.) on each of the 230 CBCTs by manually modifying the contour propagated from the planning CT.[28]

Adaptive strategies

PTV_{PLN} remained the same, whereas PTV_{WB} was modified for each adaptive strategy as follows:

(1) POD[18]: Four PTV_{WB} ($PTV_{WB}0$, $PTV_{WB}5$, $PTV_{WB}10$, and $PTV_{WB}15$) were constructed by uniformly expanding the whole-bladder CTV by 0, 5, 10, and 15 mm. This method resulted in a total of 4 IMRT distributions in the POD library for each patient. Selection of the "treatment PTV" was simulated by choosing the smallest PTV_{WB} that encompassed the bladder visualized on each of the 23 CBCTs. The dose for each fraction was computed on the CBCT based on the PTV_{WB} distribution selected.

(2) PS-PTV[21]: PS-PTV_{WB} was derived by applying a 5-mm expansion on a combination of the whole-bladder CTV contours from the planning CT and the first 5 CBCTs (Fig. 1). The dose for the first 5 fractions was computed on the first 5 CBCTs using the PTV_{PLN} + standard PTV_{WB} distribution, and then a new distribution was created based on PTV_{PLN} and PS-PTV_{WB} and was calculated on the remaining 18 CBCTs.

(3) Daily ReOpt[23]: The whole-bladder CTV contour on each of the 23 CBCTs was expanded by 5 mm to generate 23 PTV_{WB}. The PTV_{PLN} was propagated from the planning CT onto the CBCT and combined with each PTV_{WB} to construct a daily ReOpt-PTV. The beam configuration and optimization objectives used for generating the initial standard dose distribution were used to reoptimize the dose distribution and to deliver a daily fractional dose of 2 Gy to the ReOpt-PTV on each of the 23 CBCTs.

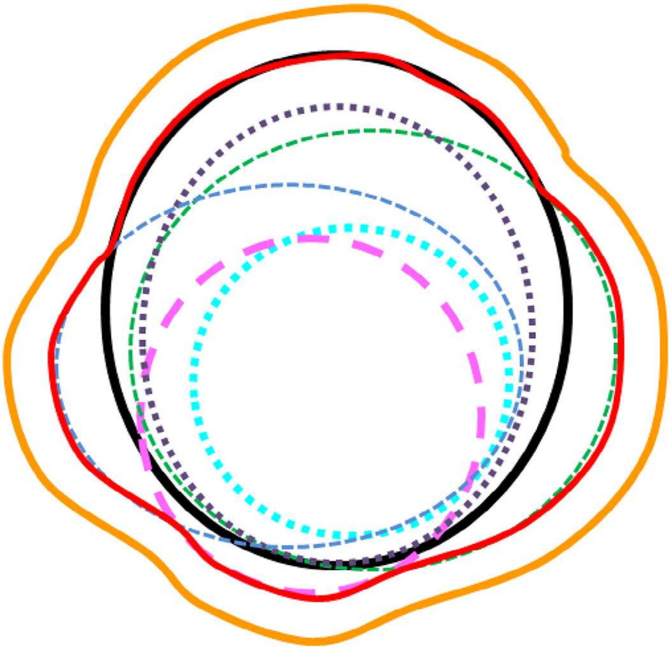

Fig. 1. Schematic representation of PS-PTV generation. The planning bladder (black solid line) and the 5 CBCT bladders (dashed lines) were combined to form the occupancy volume (red). Five millimeters was added to generate the PS-PTV. (Color version of figure is available online.)

Dose accumulation

CT-CBCT DIR was performed using the Anatomically Constrained Deformation Algorithm (ANACONDA),[29] creating a deformation map for each CBCT. Bladder and the PLN were used as the guiding structures for the registration to improve the quality of the output.[30] After assigning the CBCT density number using the auto setting in the treatment planning system (Fig. 2), the fractional dose computed on each CBCT was then mapped onto the planning CT, based on the DIR output. These mapped daily doses were then summed for each adaptive strategy.

Data collection and statistical analysis

The V_{95_Accu} (volume irradiated to an accumulated dose of 43.7 Gy [95% of prescription dose]) were obtained for each patient. The ratio of normal tissue encompassed by V_{95_Accu} ($NTinV_{95\_Accu}$) to V_{95_Accu} was calculated as another metric to evaluate the efficacy of the adaptive strategies in reducing normal tissue irradiation. One-way analysis of variance was used to determine the difference between the standard PTV and the adaptive strategies, and paired t-test was used when comparing 2 strategies. $p < 0.05$ was considered statistically significant. The percentage difference from the standard V_{95_Accu} to each adaptive strategy was calculated to evaluate its efficacy in reducing the treatment volume. In addition, pairwise analysis on individual patients was conducted to facilitate comparison.

Results

A total of 10 planning CTs and 230 CBCTs from 10 patients with bladder cancer were included in the present study, resulting in 40 V_{95_Accu} volumes for comparison. Overall, the treatment bladder volume was smaller than the planning scan volume, with a median treatment/planning volume ratio of 0.51 (range: 0.43 to 0.87). Nevertheless, an equivalent or larger bladder volume was achieved for 27% of the fractions. There was large variation among patients in the magnitude of interfraction volume changes (Fig. 3). However, no correlation was observed between the initial planning bladder volume and the magnitude of daily variation.

The dose from each fraction was deformed back to the reference CT for total dose accumulation. Without any adaptation, V_{95_Accu} of the standard was 1472 cm^3 (standard deviation [SD]: 227 cm^3). This value was significantly reduced to a mean volume (cm^3) of 1294 (SD: 186), 1234 (SD: 199), and 1102 (SD: 180) by POD, PS-PTV, and ReOpt, respectively, translating to a median reduction of 13%, 14%, and 29%

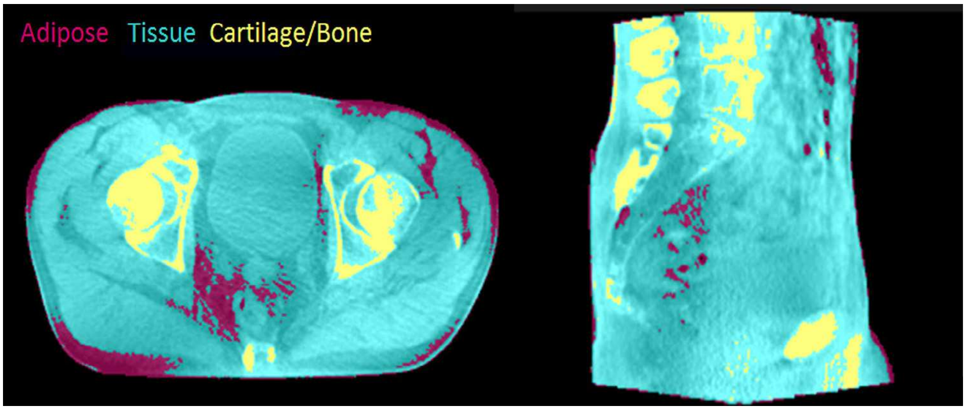

Fig. 2. Axial and sagittal views displaying the assignment of CBCT density. The mass density of adipose tissue and cartilage and bone were (g/cm^3) 0.95, 1.05, and 1.6, respectively. (Color version of figure is available online.)

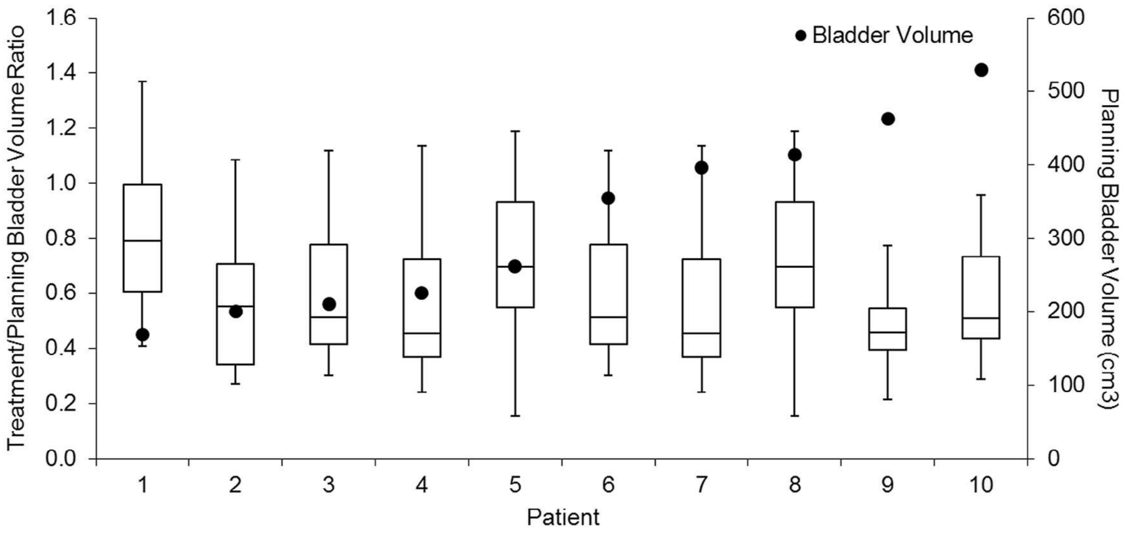

Fig. 3. The planning bladder volume (cm^3) of the individual patients (black dots), along with the corresponding median, interquartile range, and full range of treatment/planning bladder volume ratios (box and whisker).

from the standard V_{95_Accu} ($p = 0.002$) (Fig. 4). The reduction by ReOpt was significantly greater than the other 2 strategies ($p = 0.0006$), and the V_{95_Accu} reduction by PS-PTV was greater than that by POD ($p < 0.05$).

The proportion of normal tissue in V_{95_Accu} was the highest for standard, with a mean $NTinV_{95\_Accu}/V_{95\_Accu}$ ratio of 0.63 (SD: 0.05). All 3 adaptive strategies significantly reduced the ratio to a mean of 0.50 to 0.58, with ReOpt being the most superior ($p < 0.05$). Using the standard as the reference, the $NTinV_{95\_Accu}$ was reduced by a median of 43%, 21%, and 20% by ReOpt, POD, and PS-PTV, respectively. The magnitude of improvement among adaptive strategies were significantly different ($p = 0.0003$).

The relative V_{95_Accu} reduction from the standard by each of the adaptive strategies for patient no. 6 is shown in Fig. 5. The greatest improvement was in the inferior portion, which was common for all patients. Dose reduction was also frequently seen in the superior-anterior aspect, particularly with the ReOpt strategy.

Interpatient comparison

ReOpt was able to achieve the smallest V_{95_Accu} for all patients except for patient no. 7 and patient no. 5 (Fig. 6). The per-patient magnitude of reduction from the standard ranged from 8% to 35% (Table 1). Patient nos. 4, 6, and 9 benefited most from ReOpt in this cohort with a magnitude of reduction greater than the upper quartile of 32%. These 3 individuals all had a treatment/planning bladder volume ratio smaller than the median of 0.51. PS-PTV was the second best adaptive strategy for 7 of 10 patients.

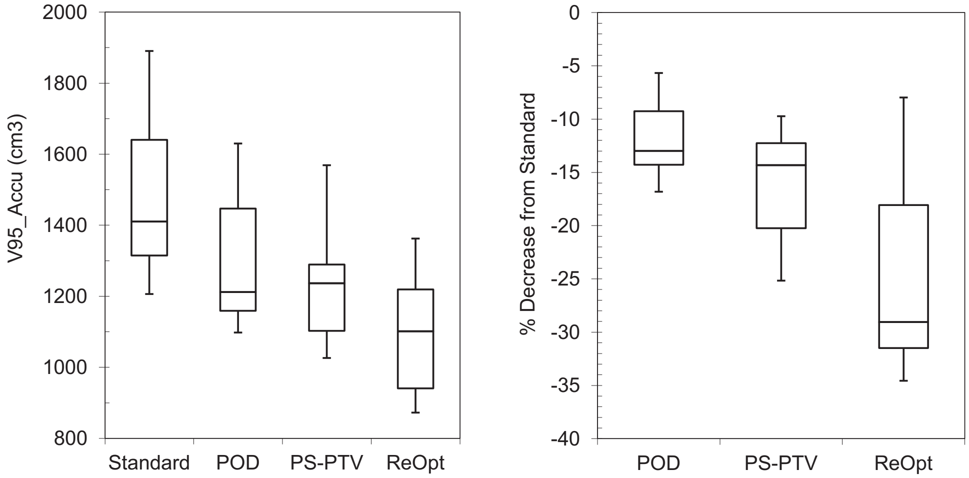

Fig. 4. Mean and range of V_{95_accu} (left); % decrease in V_{95_accu} by the adaptive strategies compared with standard (right).

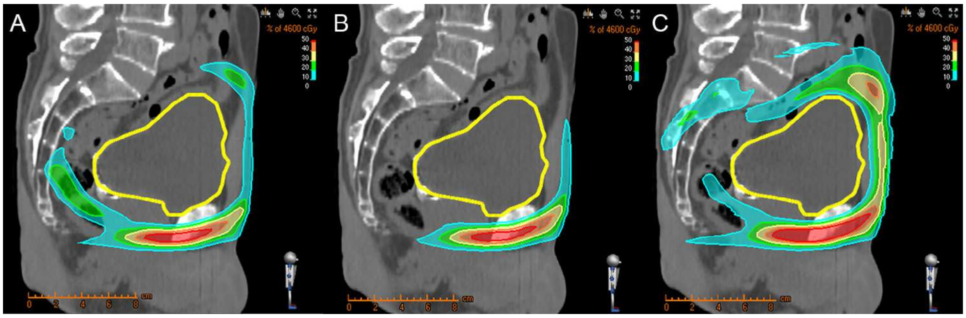

Fig. 5. Sagittal view of patient no. 6 displaying the bladder (yellow line) and the distribution of the dose reduction (color wash) from the standard by (A) POD, (B) PS-PTV, and (C) ReOpt. Magnitude of reduction represented by color wash—red (50%), orange (40%), yellow (30%), green (20%), and blue (10%). (Color version of figure is available online.)

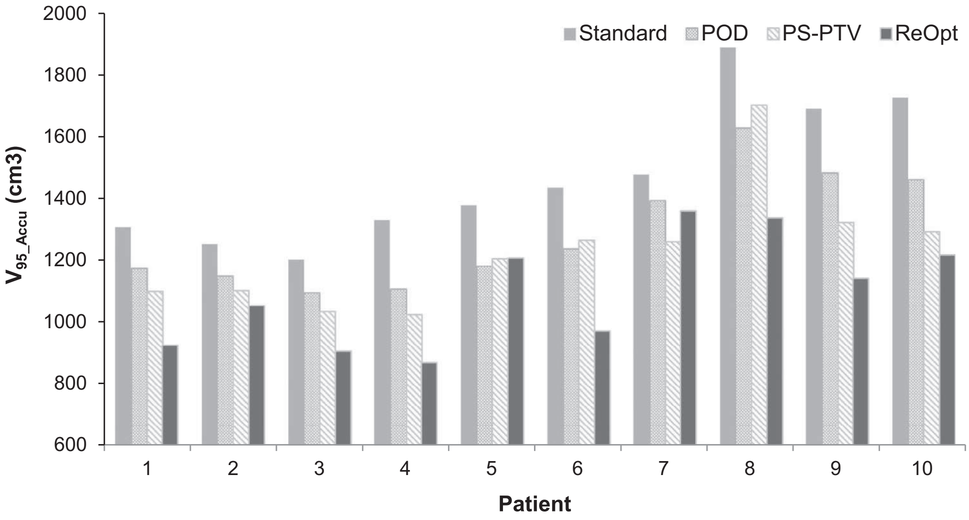

Fig. 6. Comparison of V_{95_Accu} among the standard and the 3 adaptive strategies.

Table 1

Treatment/planning bladder volume ratio of individual patients along with the corresponding percentage decrease from the standard V_{95_Accu} for each adaptive strategy

Patient	Treatment/planning bladder volume ratio	% Decrease from standard V_{95_Accu}		
		ReOpt	PS-PTV	POD
8	0.43	29	10	14
4	0.46	35	23	17
6	0.46	32	12	14
9	0.47	32	22	12
3	0.51	25	14	9
7	0.51	8	15	6
2	0.55	16	12	8
5	0.70	12	13	14
1	0.79	29	16	10
10	0.87	29	25	15

Discussion

Using the subject as their own control, 3 adaptive strategies were applied to 10 patients with bladder cancer to calculate the delivered dose for comparison against a nonadaptive approach. This is the first study to evaluate the efficacy of 3 different adaptive strategies for the treatment of the PLN and the bladder.

All 3 proposed adaptive strategies significantly reduced the irradiated volume compared with the standard, with ReOpt being the most efficacious among the strategies. The magnitude of V_{95_Accu} reduction with ReOpt was significantly greater than both the PS-PTV and the POD because of its ability to adjust to the changes in the position and the volume of the bladder. This finding is consistent with that of the only study published to date that compared the efficacy of ReOpt with the POD strategy. Using 7 patients in the study, Vestergaard *et al.* reported a mean reduction of 59% with ReOpt compared with the nonadaptive approach and this rate was noted to be significantly greater than the 34% attained by POD.[23] The improvement by either the ReOpt or the POD in Vestergaard *et al.* was much greater than the results presented in this study, in which the median reductions were 29% and 12%. This result could be due to the inclusion of PLN, along with the bladder, as the treatment volume in this study, as the magnitude of improvement by

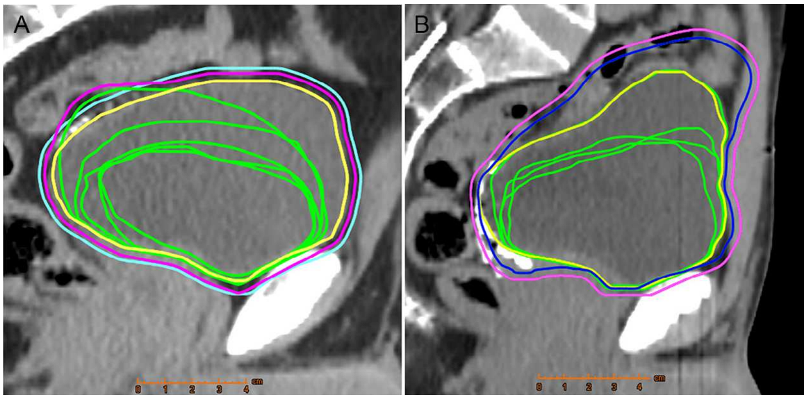

Fig. 7. (A) Sagittal view of patient no. 8. Despite a small bladder volume on CBCT 1 to 5 (green), PS-PTV (pink) was expanded in the anterior-superior direction because of the inclusion of the planning bladder (yellow). The resultant shape and volume were comparable with $\text{PTV}_{\text{WB}}5$ (blue). (B) Sagittal view of patient no. 6. Fx 4 bladder (blue) was much larger than the planning (yellow) and the bladder from Fx 1 to 3 and 5 (blue), resulting in a large PS-PTV (pink). (Color version of figure is available online.)

any adaptive strategy had been reported to be smaller when PLN was included.[11,14] Unlike the bladder, in which modification of the PTV_{WB} is required to account for the significant geometric variations, the PTV_{PLN} remains the same, hence reducing the effect of the adaptive strategies. The smaller margin used to construct the standard PTV for the bladder in this study (15 mm *vs* 20 mm in Vestergaard's study) also may have contributed to a smaller magnitude of improvement reported herein.

The present study found large interpatient variation in the magnitude of V_{95_Accu} volume reduction, with the largest reduction seen for ReOpt, followed by PS-PTV and POD. In Vestergaard's study, however, POD exhibited a greater degree of interpatient variation than ReOpt.[23] This finding could be due to the different bladder filling protocol used for planning and treatment. Full bladder was adopted for planning and treatment in the present study, and despite specific instructions, large interfraction variation in bladder filling was reported. By creating a new distribution based on the bladder filling of the day, ReOpt achieved a greater V_{95} reduction for patients exhibiting larger bladder filling changes than those who could achieve a more consistent bladder volume. This finding may explain the differences between the present study and Vestergaard *et al.*, who used an empty bladder protocol, and reported a more consistent bladder volume and shape. Alternatively, the differences in the findings could be attributed to the different methods used in generating the POD library between the 2 studies. In this study, a uniform expansion in 5-mm increments was applied to the planning bladder to construct various PTV_{WB} for the POD library, whereas these volumes were derived based on patient-specific information from the first few treatment fractions in Vestergaard *et al.* The latter method would account for additional variation and therefore would result in a larger range of interpatient variations.

Despite adapting only once after the fifth fraction, PS-PTV was able to achieve a greater reduction in V_{95} than POD. There were 3 patients[5,6,8] in which PS-PTV was noted to be comparable or inferior to POD, which could be attributed to a similar shape and volume between the PS-PTV and the PTVs in the POD. Figure 5A displays the sagittal view of patient no. 8. Despite a smaller bladder in the first 5 fractions, the PS-PTV was enlarged by the inclusion of the planning bladder in its construction. With $\text{PTV}_{\text{WB}}5$ being selected for 91% of the fraction for this patient, the outcome between the 2 strategies was therefore comparable. Similarly, the volume of PS-PTV of patient no. 6 was augmented by the inclusion of a much larger bladder from the fourth fraction, weakening its volume sparing effect in subsequent fractions (Fig. 7B). As the inclusion of an "outlier" volume was shown to affect the efficacy of PS-PTV, exclusion of these volumes should be considered to derive a PS-PTV that is more reflective of the bladder geometry for the remaining fractions.

There are several strengths and limitations in the present study. Although there were only 10 patients included, it can be considered a good representation of the anatomical variation of the population through the inclusion of both male and female patients. In addition, the sample size was one of the largest among studies in which dose accumulation had been performed for evaluation.[14,16,23] Patients were instructed to have a comfortably full bladder for planning and treatment in the present study, and hence, the magnitude of improvement observed in this study may vary if patients were planned and treated with an empty bladder. Many institutions adopt the empty bladder protocol for better reproducibility, patient comfort, and minimizing the irradiated volume.[9,12,15,17,22,23] There are several reasons for supporting the use of full bladder. First, studies have indicated that there were no significant differences in motion of the bladder wall using full or empty preparation, and therefore, the same margin could be applied.[21,31] Second, there is a substantial dosimetric benefit to using full bladder preparation to maximize sparing of a normal bladder wall when partial bladder irradiation is prescribed for some cases.[14] Third, smaller bladder volumes have demonstrated greater intrafraction motion due to filling, necessitating a larger margin to account for the changes.[32] Patients would also experience difficulty achieving an empty bladder toward the end of treatment because of swelling, toxicity, and administration of concurrent chemotherapy. This finding was demonstrated in Webster's study, in which PS-PTV derived based on an empty bladder resulted in poor target coverage because of a larger treatment bladder in later fractions.[24] The isotropic margin and the method used to generate the POD library in the present study are also recognized as a limitation in generalizing the findings. Many methods of generating the POD library have been reported,[9-19,22] and the efficacy of each method against the other 2 adaptive strategies needs to be further investigated.

Conclusions

The large and random variation in bladder volumes observed in this cohort of patients benefited from the use of any of the proposed adaptive strategies, especially when the treatment bladder volumes were predominantly smaller than the planning bladder volume. Dosimetric improvements using ReOpt were the most significant, because of the method's ability to provide adequate target coverage with maximum sparing of normal tissue. However, the resource burden associated with this strategy was substantial, limiting its application in a clinical environment with the current technology. On the other hand, the need to adapt only once renders PS-PTV to be the best alternative adaptive strategy and has been implemented at our institution to improve treatment quality.

References

1. Gakis, G.; Efstathiou, J.; Lerner, S.P.; *et al.* ICUD-EAU International Consultation on Bladder Cancer 2012: Radical cystectomy and bladder preservation for muscle-invasive urothelial carcinoma of the bladder. *Eur. Urol.* **63**(1):45–57; 2013. [Epub 2012/08/25].
2. Kotwal, S.; Choudhury, A.; Johnston, C.; *et al.* Similar treatment outcomes for radical cystectomy and radical radiotherapy in invasive bladder cancer treated at a United Kingdom specialist treatment center. *Int. J. Radiat. Oncol. Biol. Phys.* **70**(2):456–63; 2008. [Epub 2007/10/02].
3. Milosevic, M.; Gospodarowicz, M.; Zietman, A.; *et al.* Radiotherapy for bladder cancer. *Urology* **69**(1 suppl.):80–92; 2007. [Epub 2007/02/07].
4. Bellmunt, J.; Orsola, A.; Wiegel, T.; *et al.* Bladder cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **22**(suppl. 6):vi45–9; 2011. [Epub 2011/10/20].
5. Mak, R.H.; Hunt, D.; Shipley, W.U.; *et al.* Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: a pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. *J. Clin. Oncol.* **32**(34):3801–9; 2014. [Epub 2014/11/05].
6. Kavanagh, B.D.; Pan, C.C.; Dawson, L.A.; *et al.* Radiation dose-volume effects in the stomach and small bowel. *Int. J. Radiat. Oncol. Biol. Phys.* **76**(3 suppl.):S101–7; 2010. [Epub 2010/03/05].
7. Qi, P.; Pouliot, J.; Roach, M. 3rd; *et al.* Offline multiple adaptive planning strategy for concurrent irradiation of the prostate and pelvic lymph nodes. *Med. Phys.* **41**(2):021704; 2014. [Epub 2014/02/11].
8. Ferjani, S.; Huang, G.; Shang, Q.; *et al.* Alignment focus of daily image guidance for concurrent treatment of prostate and pelvic lymph nodes. *Int. J. Radiat. Oncol. Biol. Phys.* **87**(2):383–9; 2013. [Epub 2013/08/03].
9. Burridge, N.; Amer, A.; Marchant, T.; *et al.* Online adaptive radiotherapy of the bladder: small bowel irradiated-volume reduction. *Int. J. Radiat. Oncol. Biol. Phys.* **66**(3):892–7; 2006.
10. Vestergaard, A.; Sondergaard, J.; Petersen, J.B.; *et al.* A comparison of three different adaptive strategies in image-guided radiotherapy of bladder cancer. *Acta Oncol. (Madr)* **49**(7):1069–76; 2010. [Epub 2010/09/14].
11. Tuomikoski, L.; Collan, J.; Keyrilainen, J.; *et al.* Adaptive radiotherapy in muscle invasive urinary bladder cancer–an effective method to reduce the irradiated bowel volume. *Radiother. Oncol.* **99**(1):61–6; 2011. [Epub 2011/03/25].
12. Lalondrelle, S.; Huddart, R.; Warren-Oseni, K.; *et al.* Adaptive-predictive organ localization using cone-beam computed tomography for improved accuracy in external beam radiotherapy for bladder cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **79**(3):705–12; 2011. [Epub 2010/05/18].
13. Foroudi, F.; Wong, J.; Kron, T.; *et al.* Online adaptive radiotherapy for muscle-invasive bladder cancer: Results of a pilot study. *Int. J. Radiat. Oncol. Biol. Phys.* **81**(3):765–71; 2011. [Epub 2010/10/12].
14. Lutkenhaus, L.J.; Visser, J.; de Jong, R.; *et al.* Evaluation of delivered dose for a clinical daily adaptive plan selection strategy for bladder cancer radiotherapy. *Radiother. Oncol.* **116**(1):51–6; 2015. [Epub 2015/06/23].
15. Tuomikoski, L.; Valli, A.; Tenhunen, M.; *et al.* A comparison between two clinically applied plan library strategies in adaptive radiotherapy of bladder cancer. *Radiother. Oncol.* **117**(3):448–52; 2015.
16. Meijer, G.J.; van der Toorn, P.P.; Bal, M.; *et al.* High precision bladder cancer irradiation by integrating a library planning procedure of 6 prospectively generated SIB IMRT plans with image guidance using lipiodol markers. *Radiother. Oncol.* **105**(2):174–9; 2012. [Epub 2012/10/02].
17. Kuyumcian, A.; Pham, D.; Thomas, J.M.; *et al.* Adaptive radiotherapy for muscle-invasive bladder cancer: Optimisation of plan sizes. *J. Med. Imaging Radiat. Oncol.* **56**(6):661–7; 2012. [Epub 2012/12/06].
18. Murthy, V.; Master, Z.; Adurkar, P.; *et al.* "Plan of the day" adaptive radiotherapy for bladder cancer using helical tomotherapy. *Radiother. Oncol.* **99**(1):55–60; 2011. [Epub 2011/03/15].
19. Vestergaard, A.; Kallehauge, J.F.; Petersen, J.B.; *et al.* An adaptive radiotherapy planning strategy for bladder cancer using deformation vector fields. *Radiother. Oncol.* **112**(3):371–5; 2014. [Epub 2014/08/26].
20. Pos, F.J.; Hulshof, M.; Lebesque, J.; *et al.* Adaptive radiotherapy for invasive bladder cancer: a feasibility study. *Int. J. Radiat. Oncol. Biol. Phys.* **64**(3):862–8; 2006. [Epub 2006/02/07].
21. Tolan, S.; Kong, V.; Rosewall, T.; *et al.* Patient-specific PTV margins in radiotherapy for bladder cancer—A feasibility study using cone beam CT. *Radiother. Oncol.* **99**(2):131–6; 2011. [Epub 2011/05/31].
22. Foroudi, F.; Wong, J.; Haworth, A.; *et al.* Offline adaptive radiotherapy for bladder cancer using cone beam computed tomography. *J. Med. Imaging Radiat. Oncol.* **53**(2):226–33; 2009. [Epub 2009/06/17].

23. Vestergaard, A.; Muren, L.P.; Sondergaard, J.; *et al*. Adaptive plan selection vs. re-optimisation in radiotherapy for bladder cancer: A dose accumulation comparison. *Radiother. Oncol.* **109**(3):457–62; 2013. [Epub 2013/10/09].
24. Webster, G.J.; Stratford, J.; Rodgers, J.; *et al*. Comparison of adaptive radiotherapy techniques for the treatment of bladder cancer. *Br. J. Radiol.* **86**(1021):2013. [Epub 2012/12/21]; 20120433.
25. Velec, M.; Moseley, J.L.; Eccles, C.L.; *et al*. Effect of breathing motion on radiotherapy dose accumulation in the abdomen using deformable registration. *Int. J. Radiat. Oncol. Biol. Phys.* **80**(1):265–72; 2011. [Epub 2010/08/25].
26. Jaffray, D.A.; Lindsay, P.E.; Brock, K.K.; *et al*. Accurate accumulation of dose for improved understanding of radiation effects in normal tissue. *Int. J. Radiat. Oncol. Biol. Phys.* **76**(3 suppl.):S135–9; 2010. [Epub 2010/03/05].
27. Yu, J.; Hardcastle, N.; Jeong, K.; *et al*. On voxel-by-voxel accumulated dose for prostate radiation therapy using deformable image registration. *Technol. Cancer. Res Treat.* **14**(1):37–47; 2015. [Epub 2013/12/21].
28. Rosewall, T.; Xie, J.; Kong, V.; *et al*. Automated delineation of the normal urinary bladder on planning CT and cone beam CT. *J. Med. Imaging. Radiat. Sci.* **47**(1):21–9; 2016.
29. Weistrand, O.; Svensson, S. The ANACONDA algorithm for deformable image registration in radiotherapy. *Med. Phys.* **42**(1):40–53; 2015.
30. Gu, X.; Dong, B.; Wang, J.; *et al*. A contour-guided deformable image registration algorithm for adaptive radiotherapy. *Phys. Med. Biol.* **58**(6):1889–901; 2013. [Epub 2013/02/28].
31. Dees-Ribbers, H.M.; Betgen, A.; Pos, F.J.; *et al*. Inter- and intrafractional bladder motion during radiotherapy for bladder cancer: A comparison of full and empty bladders. *Radiother. Oncol.* **113**(2):254–9; 2014. [Epub 2014/12/09].
32. Foroudi, F.; Pham, D.; Bressel, M.; *et al*. Intrafraction bladder motion in radiation therapy estimated from pretreatment and posttreatment volumetric imaging. *Int. J. Radiat. Oncol. Biol. Phys.* **86**(1):77–82; 2013.