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Clinical Investigation

Prospective Study Delivering Simultaneous Integrated High-dose Tumor Boost (≤70 Gy) With Image Guided Adaptive Radiation Therapy for Radical Treatment of Localized Muscle-Invasive Bladder Cancer

Shaista Hafeez, MSc, FRCR,[*,†] Karole Warren-Oseni, DCR(T),[†] Helen A. McNair, PhD,[*,†] Vibeke N. Hansen, PhD,[*,†] Kelly Jones, BSc,[*,†] Melissa Tan, BSc, FRCR,[*,†] Attia Khan, BSc, FRCR,[*,†] Victoria Harris, MD, FRCR,[†] Fiona McDonald, MD, FRCR,[†] Susan Lalondrelle, MD, FRCR,[†] Kabir Mohammed, MSc,[†] Karen Thomas, MSc,[†] Alan Thompson, FRCS,[†] Pardeep Kumar, PhD, FRCS,[†] David Dearnaley, MD, FRCR,[*,†] Alan Horwich, MD, FRCR,[*,†] and Robert Huddart, PhD, FRCR[*,†]

The Institute of Cancer Research; and †The Royal Marsden National Health Service Foundation Trust, London, United Kingdom

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Summary

The present prospective study has demonstrated the first experience of tumor dose escalation ≤70 Gy with intensity modulated radiation therapy delivered with a plan of the day approach. It achieves appropriate tumor boost coverage and provides an opportunity for normal

Purpose: Image guided adaptive radiation therapy offers individualized solutions to improve target coverage and reduce normal tissue irradiation, allowing the opportunity to increase the radiation tumor dose and spare normal bladder tissue.

Methods and Materials: A library of 3 intensity modulated radiation therapy plans were created (small, medium, and large) from planning computed tomography (CT) scans performed at 30 and 60 minutes; treating the whole bladder to 52 Gy and the tumor to 70 Gy in 32 fractions. A "plan of the day" approach was used for treatment delivery. A post-treatment cone beam CT (CBCT) scan was acquired weekly to assess intrafraction filling and coverage.

Results: A total of 18 patients completed treatment to 70 Gy. The plan and treatment for 1 patient was to 68 Gy. Also, 1 patient's plan was to 70 Gy but the patient was treated to a total dose of 65.6 Gy because dose-limiting toxicity occurred before dose

Reprint requests to: Shaista Hafeez, MSc, FRCR, Royal Marsden Hospital, Downs Rd, Sutton, Surrey SM2 5PT, United Kingdom. Tel: (20) 8661-3457; E-mail: Shaista.Hafeez@icr.ac.uk

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bladder sparing with acceptable toxicity.

escalation. A total of 734 CBCT scans were evaluated. Small, medium, and large plans were used in 36%, 48%, and 16% of cases, respectively. The mean ± standard deviation rate of intrafraction filling at the start of treatment (ie, week 1) was 4.0 ± 4.8 mL/min (range 0.1-19.4) and at end of radiation therapy (ie, week 5 or 6) was 1.1 ± 1.6 mL/min (range 0.01-7.5; $P = .002$). The mean D_{98} (dose received by 98% volume) of the tumor boost and bladder as assessed on the post-treatment CBCT scan was 97.07% ± 2.10% (range 89.0%-104%) and 99.97% ± 2.62% (range 96.4%-112.0%). At a median follow-up period of 19 months (range 4-33), no muscle-invasive recurrences had developed. Two patients experienced late toxicity (both grade 3 cystitis) at 5.3 months (now resolved) and 18 months after radiation therapy.

Conclusions: Image guided adaptive radiation therapy using intensity modulated radiation therapy to deliver a simultaneous integrated tumor boost to 70 Gy is feasible, with acceptable toxicity, and will be evaluated in a randomized trial.

Introduction

Radical radiation therapy (RT) is an alternative to cystectomy in appropriately selected patients with localized muscle-invasive bladder cancer as a part of a multimodality strategy (1, 2). Traditionally, the whole bladder has been treated as the target, even in the presence of unifocal disease, to a standard dose of 60 to 64 Gy in 1.8- to 2-Gy fractions to minimize the risk of significant late urinary toxicity (3-5). However, most local recurrences after RT develop at the original bladder tumor site, suggesting this dose insufficiently addresses occult disease in some patients (6). A higher dose could improve local control; however, safely achieving this has been limited by the uncertainties in target coverage (7-10).

The "plan of the day" image guided adaptive RT strategy using kilovoltage computed tomography (CT; cone beam CT [CBCT]) has mitigated the need for large population-based margins to capture the known bladder variability during RT (9-12). Several institutions have reported improved target coverage and normal tissue sparing with this approach (13-17). It therefore offers opportunity for dose escalation to >64 Gy.

Partial bladder RT focused on delivering the dose to the tumor alone rather than to the whole organ would further spare the normal tissues (12). In randomized control studies, tumor-focused 3-dimensional conformal RT techniques have demonstrated no compromise to local control compared with whole bladder treatment (18, 19). These studies predated the routine use of CBCT and failed to demonstrate improvement in urinary toxicity with partial bladder RT. One reason for this might have been treatment to an empty bladder with an isotropic margin of 1.5 cm around the tumor, which increased the proportion of normal bladder exposed to the high-dose region (18-20). Tumor-focused treatment to a full bladder can improve normal bladder sparing, but it is associated with difficulties in filling reproducibility (21-24).

Recent studies with intensity modulated RT (IMRT) using the "plan of the day" approach have shown that tumor-focused dose escalation to 68 Gy can achieve local control with minimal additional toxicity (22, 25). No reports have been published of dose escalation beyond 68 Gy. Studies of a bladder brachytherapy boost, treating focally up to a combined total physical dose of ~70 Gy, have provided evidence that external beam RT can be safely escalated to greater than current levels (8, 26-28). We report the first clinical experience of delivering a simultaneous integrated tumor boost, escalating the dose to 70 Gy in 32 fractions to a partially filled bladder with radiographer led plan of the day RT approach.

Methods and Materials

The patients were recruited prospectively to an institutional clinical research and ethics committee–approved RT dose escalation protocol (NCT01124682), conducted in accordance with European Union guidelines for good clinical practice. The primary study endpoint of the maximum tolerated dose will be reported separately after maturation of the follow-up data. In the present report, we describe the technical aspects of delivery.

Patient eligibility and selection

All eligible patients had pathologic evidence of muscle-invasive bladder cancer of any histologic subtype and were suitable to receive daily radical RT for stage T2-T4aN0M0 disease. Those with multifocal invasive disease or carcinoma in situ remote from the tumor were excluded.

Treatment

The patients were treated with initial transurethral resection of the bladder tumor. Those suitable received 3 to 4 cycles of neoadjuvant chemotherapy (gemcitabine with cisplatin). At cystoscopy, patients with no history of contrast medium sensitivity or active thyroid disease

received subepithelial ethiodized oil (Lipiodol) injected into the bladder wall (3-6 spots) to demarcate the maximum extent of visible tumor or tumor bed (29). RT was delivered with concomitant chemotherapy where appropriate (5-fluorouracil and mitomycin or weekly gemcitabine) (30, 31).

RT planning

After voiding, the patients drank 350 mL of water, 30 minutes after which a noncontrast-enhanced planning CT scan was performed (CT30), with scanning at 2.5-mm intervals from the fourth lumbar vertebrae to below the ischial tuberosities, 30 minutes after which a second planning CT scan (CT60) was acquired. No bladder emptying or drinking was permitted between the 2 scans.

The images were exported in Digital Imaging and Communications in Medicine format to the treatment planning system (Pinnacle, version 9.6, Philips Medical Systems). The CT30 and CT60 scans were fused. The gross tumor volume (GTV) was defined as the visible tumor (or tumor bed) and was delineated using the position of Lipiodol (where available), diagnostic imaging studies, and the surgical bladder map. It was as outlined the maximal extent of tumor seen on the pretreatment imaging study. The clinical target volume (CTV) was contoured to encompass the GTV, whole bladder, and any areas of extravesical spread.

The planning target volumes (PTVs) were produced by application of variable margins to the specified structures to create small, medium, and large PTV_{boost} and $PTV_{bladder}$. To model patient-specific filling, the large PTVs were informed by the magnitude of bladder filling between the CT30 and CT60 scans (Table 1).

Three plans were produced (small, medium, and large) using 5 static field IMRT plans, ensuring in accordance with International Commission on Radiation Units and Measurements 83 recommendation that the PTV D_{98} (dose received by 98% volume) achieve 90% (mandatory) to 95% (optimal) of the prescription dose (32). The $PTV_{bladder}$ was prescribed to 52 Gy in 32 fractions. The PTV_{boost} prescription dose was assigned as 64, 68, or 70 Gy.

The rectum (including the anus), other bowel (including the small and large bowel as a single structure), and femoral heads were contoured as solid structures by defining their outer wall on the CT30 scan. Constraint was also specified for the normal bladder outside the PTV_{boost} (to quantify normal bladder sparing). The dose constraints (Table E1; available online at www.redjournal.org) were derived from previous phase 3 studies (CHHIP and BC2001) (8, 30, 33, 34). In circumstances in which small or medium plans failed to meet mandatory normal tissue constraints, consideration was given to treat at a lower dose level, which allowed the constraints to be met or if this was not possible at the standard dose (64 Gy).

RT delivery

Before set up, the patients were asked to void their bladder and then to drink 350 mL of water. The pretreatment CBCT scan was acquired at 30 minutes and coregistered with the reference image (CT30) using an automated bone match.

Two adaptive plan of the day—trained radiographers selected the smallest PTV and corresponding plan that provided appropriate coverage of the bladder and tumor boost, with a 3-mm margin to account for intrafraction filling. Soft tissue matching was permitted to optimize bladder coverage and minimize normal tissue irradiation. The details have been previously presented (15, 35). In the event that no PTV covered the bladder, the patients were removed from the couch. Necessary interventions considered before reimaging are outlined in Figure E1 (available online at www.redjournal.org). Post-treatment CBCT scans were performed and reviewed on a weekly basis to assess intrafraction filling.

Table 1 PTV expansion details

CT data set	PTV	Laterally	Anteriorly	Posteriorly	Superiorly	Inferiorly
		GTV to PTV_{boost} expansion (cm)				
CT30	PTV_{boost} small	0.5	0.5	0.5	0.5	0.5
CT30	PTV_{boost} medium	0.5	0.5	0.5	0.5	0.5
CT30 if CTV difference on CT60 and CT30 <50 cm^3	PTV_{boost} large	0.75	2.0	1.2	2.5	0.75
CT60 if CTV difference on CT60 and CT30 >50 cm^3	PTV_{boost} large	0.5	1.5	1.0	1.5	0.5
		CTV to $PTV_{bladder}$ expansion (cm)				
CT30	$PTV_{bladder}$ small	0.5	0.5	0.5	0.5	0.5
CT30	$PTV_{bladder}$ medium	0.5	1.5	1.0	1.5	0.5
CT30 if CTV difference on CT60 and CT30 <50 cm^3	$PTV_{bladder}$ large	0.75	2.0	1.2	2.5	0.75
CT60 if CTV difference on CT60 and CT30 >50 cm^3	$PTV_{bladder}$ large	0.5	1.5	1.0	1.5	0.5

The margins were informed by previous work (13, 15).

Toxicity and response assessment

The patients were assessed at baseline, weekly during RT, and at 4 and 8 weeks after treatment completion. Data regarding acute toxicity were prospectively collected using the Common Terminology Criteria for Adverse Events, version 3.0.

The patients were then followed up at 3-month intervals for 18 months, 6-month interval for $\leq$3 years, and annually thereafter. Late toxicity was scored at these time points using the Radiation Therapy Oncology Group (RTOG) late radiation morbidity scoring schema.

Local control was assessed initially at 3 months using rigid cystoscopy. Repeat cystoscopy was performed every 3 months for 2 years and annually thereafter. CT scans of the chest, abdomen, and pelvis were performed at 1 and 2 years after treatment, with chest radiographs performed at the interval time points.

Statistical considerations and evaluation of RT

Recruitment to the PTV_{boost} dose level of 68 Gy or 70 Gy was determined using the time-to-event continual reassessment method. After treatment, the CBCT images were imported into the planning system (Pinnacle, version 9.6). Off line, a radiation oncologist (S.H.) assessed all plan selections. The time between the pretreatment and post-treatment CBCT scans was used as a surrogate for the on-line plan selection time.

The tumor boost (GTV), whole bladder (CTV), and normal bladder (excluding the tumor boost) were contoured by a single observer (S.H.) on each CBCT scan. If the GTV was not visible on the CBCT scan, it was reconstructed by creating a mesh structure from the planning CT scan and propagating it to the CBCT scan with adaptation to the corresponding anatomy. The isodoses were overlaid to determine the $D_{98\%}$ to the target. The cumulative dose received during the course of RT was determined (summation of the dose per fraction), accepting uncertainties compared with actual treatment (36-41).

The conformity index (CI_{RTOG}) was used as a surrogate for normal non−bladder tissue RT. The CI_{RTOG} was defined by the proportion of the volume within the reference isodose (95% and 98%) line of the selected plan for treatment delivery compared with the target on that day (42). A value close to 1 represents high conformity and implies less normal tissue irradiation.

Comparisons of the delivered and planned treatment were made using nonparametric statistics (Wilcoxon signed ranked and independent sample Kruskal-Wallis analysis), corrected for multiple testing (Bonferroni adjustment). All analyses were performed using SPSS, version 22 (IBM, Armonk, NY).

Results

From June 2012 to May 2014, 20 patients were recruited. The median age was 73 years (range 50-90). All patients had stage T2-T3N0M0 transitional cell carcinoma. The patient characteristics are listed in Table E2 (available online at www.redjournal.org).

RT planning

The mean $\pm$ standard deviation GTV was 22.37 $\pm$ 16.3 cm^3 (range 3.2-65.6). The mean CTV at 30 minutes and 60 minutes was 173.4 $\pm$ 129.9 cm^3 (range 89.6-696.9) and 229.7 $\pm$ 162.3 cm^3 (range 110-844.5), respectively. The mean bladder filling was 53.4 $\pm$ 61.2 cm^3 (range 1.9-252.4). The CT60 scan was used to inform the large plan for 6 patients. One patient (patient 19) was unable to hold her urine for the CT30 scan because of pre-existing grade 3 urinary symptoms and underwent imaging at 20 minutes.

All patients' treatment was planned to their allocated PTV_{boost} prescription dose. Low-dose mandatory bowel constraints (medium plan) were exceeded in 2 patients (patients 4 and 10) allocated to 70 Gy. However, no reduction of the allocated PTV_{boost} prescription dose was undertaken because de-escalation would not have improved this.

Two patients underwent repeat planning at their allocated PTV_{boost} dose after the start of RT. Patient 4 demonstrated a change in bladder shape and filling during week 1. A repeat CT30 scan was performed, and the new small and medium plan was used from fraction 7. Patient 9 demonstrated a change in rectal filling, and a large plan was re-created (without repeat scanning) and used from fraction 14.

A total of 18 patients completed treatment to 70 Gy. The plan and treatment for 1 patient was to 68 Gy, and 1 patient was treated to 30 fractions (estimated total dose of 65.6 Gy PTV_{boost}) because dose-limiting toxicity occurred before dose escalation.

CBCT acquisition

A total of 734 CBCT scans were evaluated (638 before RT and 96 after RT). Of the 638 pre-RT CBCT scans, 22 (3%) identified a significant bladder shape change with no plan deemed suitable for treatment delivery. This necessitated intervention (eg, bladder voiding) before repeat CBCT scanning to ensure target coverage for treatment was possible with the pre-existing library of plans. The total number of CBCT exposures for each patient is shown in Figure E2 (available online at www.redjournal.org).

Plan selection

Treatment was delivered using small, medium, and large plans for 36.1%, 47.8%, and 16.1% cases, respectively. Individual on-line plan selections are presented in Figure 1. The off-line plan sections demonstrated concordance with the radiographer plan selection of 94% (598 of 638). A small, medium, large, and no plan was chosen for 36.4%,

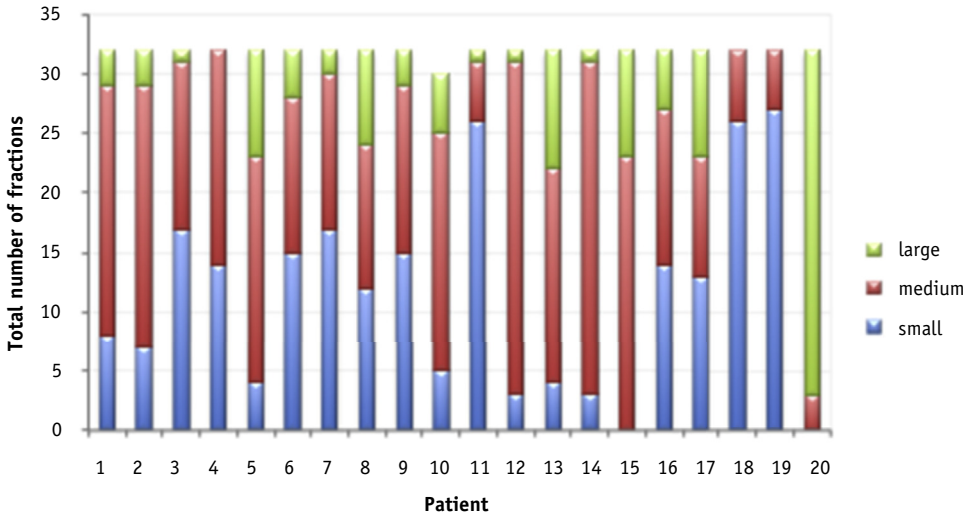

Fig. 1. On-line plan selection.

46.2%, 17.1%, and 0.3% of fractions, respectively. Of the 40 fractions that were nonconcordant, the on-line choice was smaller than the off-line selection on 21 occasions and larger than the off-line selection on 17 occasions. For 2 fractions, no plan was deemed suitable for treatment.

Target volume evaluation

The individual daily variation in tumor boost and bladder volume during the course of RT compared with treatment planning is presented in Figure 2. The mean bladder volume at the start of treatment was 164.1 ± 77.7 cm^3 (range 80.3-364.37) and as assessed on the final fraction was 138.0 ± 54.3 cm^3 (range 60.2-249.1; $P = .057$).

The mean time between the pre- and post-CBCT scan was 12:51 ± 2.0 minutes (range 9-18). The mean intrafraction filling during this time was 12.2 ± 14.4 cm^3 (range −5.6 to 97.3). A significant decrease was seen in the individual intrafraction filling during the treatment course. The mean intrafraction filling at the start of treatment was 50.7 ± 60.6 cm^3 (range 1.9-252.4) and as assessed toward the end of RT was 14.3 ± 21.8 cm^3 (range 0.1-97.3; $P = .001$). The mean rate of intrafraction filling at the start of treatment (ie, week 1) was 4.0 ± 4.8 mL/min (range 0.1-19.4) and as assessed toward the end of RT (ie, week 5 or 6) was 1.1 ± 1.6 mL/min (range 0.01-7.5; $P = .002$).

The mean D_{98} of the tumor boost and bladder for each on-line plan selection was 97.14% ± 2.83% (range 82.4%-100.5%) and 100% ± 2.77% (range 77.0%-111.6%), respectively. The individual cumulative dose delivered to the target volume during the treatment course is shown in Figure E3 (available online at www.redjournal.org). Intrafraction filling and nonconcordant plan selection did not adversely effect on-target coverage (Table E3; available online at www.redjournal.org).

Normal tissue sparing

All patients met the predefined dose constraints for normal bladder sparing at RT planning. The mean cumulative normal bladder volume to 60 Gy and 65 Gy was 43.1% ± 14.9% (range 19.9%-76.9%) and 28.1% ± 12.3% (range 11.7%-59.2%), respectively, for actual treatment (Fig. 3).

Significant improvements in the other low-dose bowel constraints were seen with summated plan assessment compared with the initial medium plan (Fig. E4; available online at www.redjournal.org). The mean percentage of target volume receiving 45% and 50% of the prescribed dose was 85.2 ± 54.7 cm^3 (range 14.7-243.3) and 58.6 ± 38.1 cm^3 (range 8.4-179.8) as evaluated on the medium plan compared with 67.6 ± 45.6 cm^3 (range 4.2-165.4; $P = .02$) and 42.9 ± 29.4 cm^3 (range 1.6-122.3; $P = .04$) for actual treatment delivery, respectively.

The mean CI_{RTOG} of the 95% and 98% reference isodose of the selected plan for treatment delivery to the tumor as seen on CBCT was 5.0 ± 2.2 (range 2.1-21.4) and 3.7 ± 1.6 (range 1.5-16.5) and to the whole bladder was 3.5 ± 1.0 (range 1.7-8.9) and 3.0 ± 0.8 (range 1.5-7.0), respectively. The mean CI_{RTOG} for plan selection and individual patients is listed in Table E4 and shown in Figure E5 (available online at www.redjournal.org).

Toxicity and response outcomes

At a median follow-up of 19 months (range 4-33), 17 patients were alive and disease free. No muscle-invasive recurrences developed within this cohort. Two patients developed non−muscle-invasive recurrence and 3 patients died of metastatic bladder cancer.

This technique was well tolerated (Fig. E6; available online at www.redjournal.org). No late grade 3

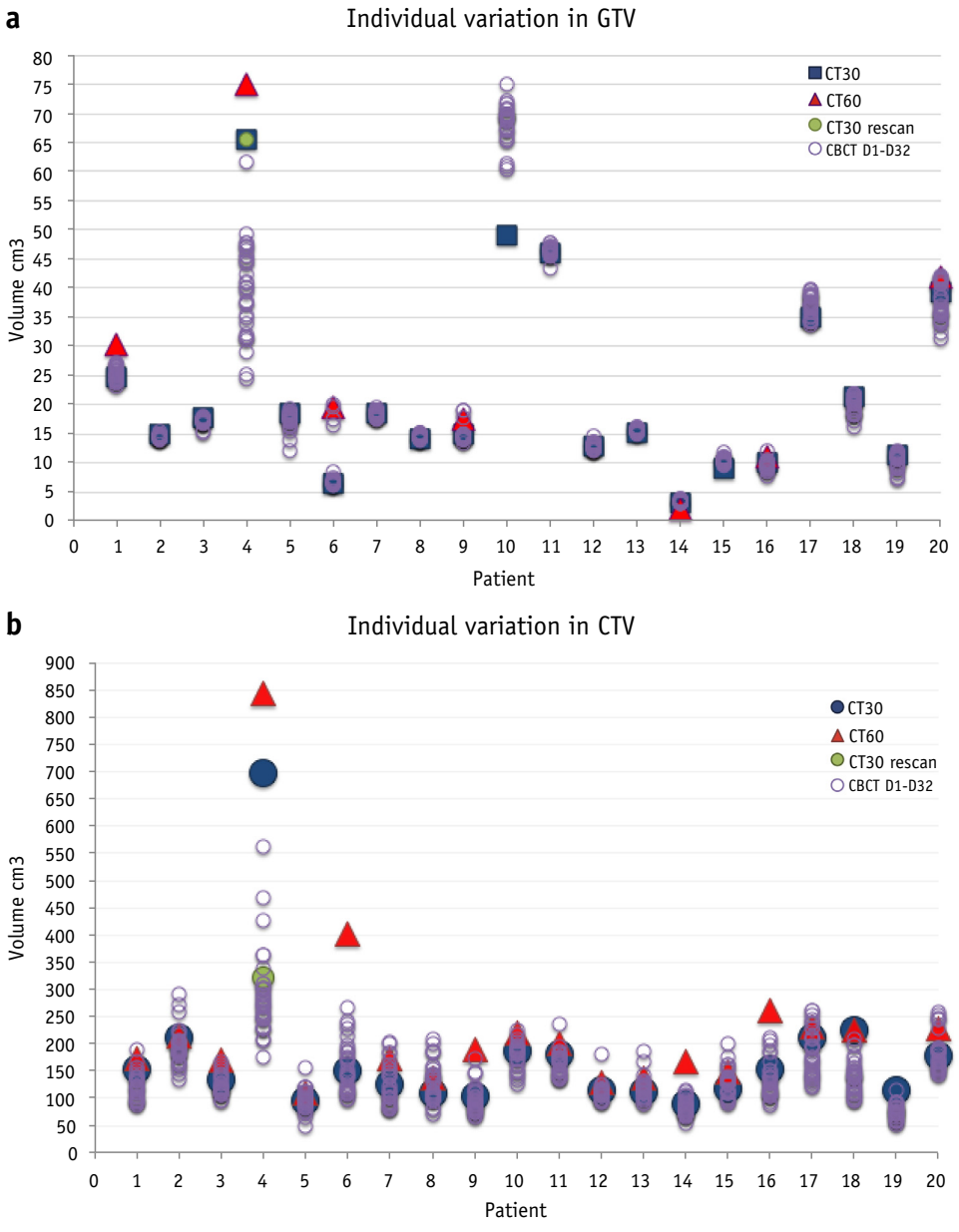

Fig. 2. (a) Individual variation in gross tumor volume (GTV). (b) Individual variation in clinical target volume (CTV). *Abbreviations:* CBCT = cone beam computed tomography; CT30 = noncontrast-enhanced planning computed tomography scan 30 minutes after patient drank 350 mL of water; CT60 = second planning computed tomography scan 60 minutes after patient drank 350 mL of water; D1-D32 = days 1 to 32 of radiotherapy.

gastrointestinal events had been observed in this cohort at the latest follow-up examination. Two patients experienced late urinary toxicity (grade 3 cystitis) at 5.3 months (now resolved) and at 18 months (grade 3 cystitis managed medically at the last follow-up visit) after RT.

Discussion

Successful partial bladder RT is dependent on the reliability of tumor definition on both the planning CT and the CBCT scans. This is subject to interobserver variation and can also be hampered after transurethral resection of the bladder tumor and neoadjuvant chemotherapy (43). Radiopaque markers inserted at cystoscopy can help inform target delineation, particularly in these circumstances (25, 29, 44).

Seven patients had neither visible disease at planning nor ethiodized oil inserted. GTV reconstruction by mesh manipulation on the CBCT scans in these patients arguably is open to systematic error. The initial GTV delineation at planning as the maximal extent of tumor seen on the pre-treatment imaging study should have offset this by erring toward a worst-case scenario. Even with careful adjustments, in the absence of visible macroscopic disease to

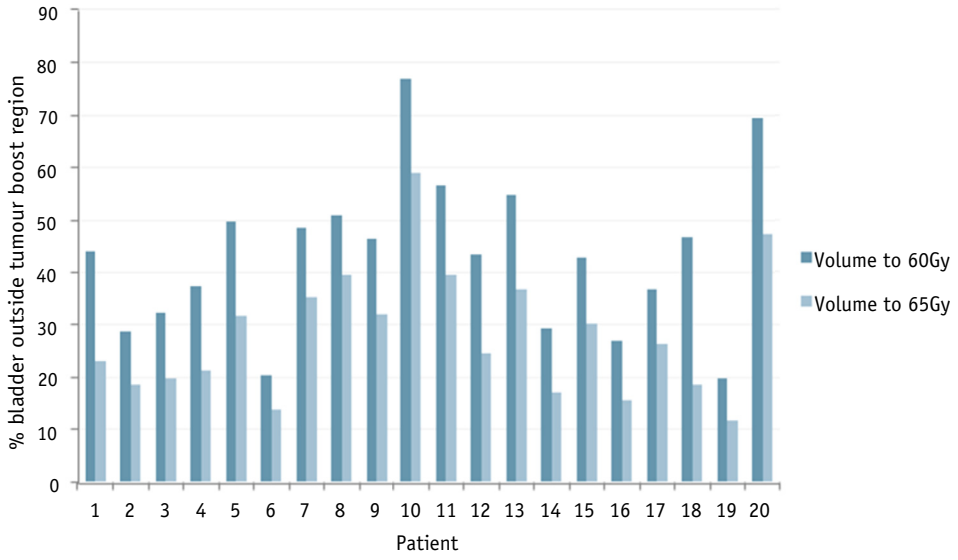

Fig. 3. Normal bladder sparing (summation dose to normal bladder outside tumor boost) with on-line plan selection.

provide guidance, the challenge of this method is reflected in the GTV variation on the CBCT scans. Target coverage of the tumor boost should therefore be interpreted within this context.

The tumor boost position relative to the bladder wall remains stable; therefore, it can be assumed that in most circumstances if the selected PTV appropriately covered the bladder, the boost would also be covered. This is reassuringly reflected clinically by the absence of muscle-invasive recurrence. Future tumor boost delineation ambiguity might be overcome by the development of magnetic resonance imaging-fused or guided approaches (45).

Although we achieved excellent target coverage and maintain normal bladder and bowel constraints, the high mean CI suggests scope to improve conformity of the current adaptive strategy. One approach would be to have a greater range of plans. Other groups have produced more extensive libraries for plan of the day approaches. Murthy et al (22) reported that of their library of 6 IMRT plans, the largest was not used at all and their second largest was used for $<1\%$ of treatments. The balance therefore between creating an extensive library of plans must be considered against the effect on resources and clinical usefulness. These larger libraries have also been associated with increased time for plan selection, which has implications for intrafraction filling and potentially a greater risk of error (22, 25).

Appropriate plan selection in a timely fashion from the choice of 3 plans was reflected in both our high off-line concordance rate (94%) and our target coverage evaluation on the post-treatment CBCT scan. Even in circumstances of nonconcordant plan selections, the instances of dosimetric compromise in which the D_{98} was $<90\%$ to either the bladder or boost was seen in only 0.03% of fractions. It reflects previous work that nonconcordance among trained individuals is a "close call" (15).

An alternative adaptive solution would be the development of on-line autosegmentation and deformable registration, allowing individualized RT plans to be created in real time (37). Pilot work has demonstrated potential dosimetric advantages compared with plan of the day solutions (40).

Margin selection for intrafraction filling will be more critical with increased conformity. Studies have shown that post-RT CBCT scans reveal that 5.5% and 16.1% of fractions will have bladder outside the selected plan when smaller uniform margins are used (22, 46). Application of anisotropic margins with larger superior and anterior expansions appears to best capture intrafraction filling (9, 13, 47-51). This is likely to have maintained the apparent robustness of our library to both inter- and intrafraction changes.

In some circumstances, intrafraction margin reduction during the treatment course should be contemplated with caution, because a significant reduction in the mean rate of intrafraction filling occurs over time. This might be a reflection of patients moderating hydration to manage their urinary symptoms. Any future margin reduction would require implementation of volumetric modulated arc therapy, given the faster treatment delivery times compared with static field IMRT (52).

A trend suggesting a reduction in bladder filling with time was seen, but no significant differences in bladder volume at the start of RT compared with at the final fraction were seen. This is in contrast to the findings from Foroudi et al (16), who showed an estimated 27% ($P<.0001$) decrease in median volume at the end of treatment. Decreasing bladder filling during the treatment course, presumably as a result of deteriorating urinary symptoms, increases the normal bladder tissue exposed to the high-dose region and the development of urinary toxicity. Bladder volume consistency was maintained during our

treatment because the drinking protocol and image acquisition time were actively managed. It also ensured that for most patients their initial library of 3 plans remained relevant.

Conclusions

The absence of local muscle invasive recurrence and low rates of late toxicity are encouraging and supports delivery of a simultaneous integrated 70-Gy tumor boost to a partially filled bladder. A library of 3 plans with the current margins successfully covered the spectrum of individual patient target volume change and maintained the normal tissue constraints. Whether this treatment approach is deliverable in other centers and translates into clinically meaningful outcomes for patients will be evaluated in an international randomized phase 2 trial (RAIDER; A randomised phase II trial of adaptive image guided standard or dose escalated tumour boost radiotherapy in the treatment of transitional cell carcinoma of the bladder) (53).

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