Radiotherapy and Oncology 99 (2011) 55–60

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Adaptive radiotherapy

'Plan of the day' adaptive radiotherapy for bladder cancer using helical tomotherapy

Vedang Murthy [a,*], Zubin Master [b], Pranjal Adurkar [b], Indranil Mallick [a], Umesh Mahantshetty [a], Ganesh Bakshi [c], Hemant Tongaonkar [c], Shyamkishore Shrivastava [a]

[a] Department of Radiation Oncology; [b] Department of Medical Physics, Tata Memorial Centre, Mumbai, India; [c] Department of Urology, Tata Memorial Hospital, Mumbai, India

ARTICLE INFO

Article history:
Received 1 October 2010
Received in revised form 31 January 2011
Accepted 31 January 2011

Keywords:
Tomotherapy
Adaptive radiotherapy
Bladder cancer
Dose escalation
Plan of the day

ABSTRACT

Background and purpose: This study assessed the potential of tomotherapy based Image Guided Radiotherapy (IGRT) to increase the accuracy of bladder irradiation using a 'plan of the day' adaptive radiotherapy (ART) technique.

Materials and methods: Ten patients with muscle invasive bladder cancer underwent bladder preservation with trimodality therapy in an ongoing trial. All patients received 64 Gy/32# to the whole bladder and seven of them received a boost of 68 Gy/32# to the tumour bed. The ART technique entailed the generation of six IMRT plans for each patient, using six isotropic PTVs of 5–30 mm applied to the bladder volume (CTV) to generate the PTVs. Megavoltage CT (MVCT) imaging was done to correct positioning errors and choose the 'plan of the day'.

Results: Post treatment MVCT scans (315 scans) were used to generate multiple anisotropic PTVs for three hypothetical scenarios. Overall, coverage of anterior and superior walls required larger margins than other walls. Maximum geographical miss, in spite of IGRT, was noted for the superior (13.8%) and anterior walls (10.3%).

Conclusions: Plan of the day ART is a feasible and promising technique for optimal treatment and dose escalation in bladder cancer.

Outcomes with radiotherapy for bladder cancer leave a large scope for improvement. Factors contributing to the suboptimal results include poor patient selection, under-staging of disease, failure to deliver an adequate radiation dose to the tumour, inadequate radiotherapy technique by today's standards and failure to treat patients within clearly defined bladder conservation protocols, which incorporate optimal surgery and chemotherapy [1,2].

The most commonly used technique in radiotherapy for invasive bladder cancer is still treating the entire bladder with a 15–30 mm margin to a dose of 60–66 Gy using 3–4 conformal fields. Intensity Modulated Radiotherapy (IMRT) has not benefitted bladder cancer radiotherapy due to the fact that the bladder is a mobile and hollow organ which changes in shape, size, and position during a course of irradiation (organ motion).

There is some evidence for dose response in bladder cancer [3,4] and a possible benefit with dose escalation. However, irradiation of the whole bladder to high doses with current techniques involves relatively large treatment margins with consequently large volumes of irradiated bowel causing clinically significant toxicity. One approach to dose escalation is to escalate the dose only to the bladder tumour. However organ motion, deformation and inter/intra fraction variability limit the feasibility of this approach with conventional techniques [5–7]. Image Guided Radiotherapy (IGRT), with soft tissue imaging, has the potential to improve the therapeutic ratio, particularly for a mobile target like the bladder.

This study was planned to assess the potential of IGRT delivered using helical tomotherapy to increase the accuracy of bladder cancer irradiation using an adaptive radiotherapy technique. The primary endpoint of this study was to determine the feasibility of the approach of using multiple PTVs, ensuring the best possible coverage of the bladder each day. This involved generating multiple treatment plans and treating patients with a 'plan of the day' based on daily pre-treatment MVCT imaging. The secondary end points were generation of (anisotropic) PTV margins especially in different resource based scenarios, determining geographical miss and ensuring acceptable toxicity with the modestly escalated dose.

Materials and methods

This is a pilot study to evaluate the feasibility of an adaptive technique to treat muscle invasive bladder cancer as a method of bladder conservation. The data collection and analysis were designed to be broad enough to apply to scenarios ranging from comprehensive adaptive IGRT to simple daily bone matching using electronic portal imaging devices (EPID). The study was approved

* Corresponding author. Address: Tata Memorial Hospital and Advanced Centre for Treatment Research and Education in Cancer (ACTREC), Tata Memorial Centre, Mumbai 410 210, India.
E-mail address: vmurthy@actrec.gov.in (V. Murthy).

0167-8140/$ - see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.radonc.2011.01.027

by the Institutional Review Board and all patients were consented before enrolment. From August 2008, 10 suitable patients (9 male 1 female) were enrolled and underwent treatment in the first phase of this ongoing protocol (www.ctri.in, CTRI/2009/091/000559). The anisotropic PTV margins generated from this study are being used in the next phase of the protocol, which also includes the treatment of the pelvic nodes.

Inclusion criteria were age >18 years, T_{2b}–T_4 (UICC 2002) histologically proven transitional cell carcinoma without nodal or distant metastasis, absence of hydronephrosis and suitability for bladder preservation. Patients had a maximal safe tumour resection and a cystoscopic bladder map was always available. Concurrent chemotherapy was given with weekly Cisplatin (30 mg/m^2) and one patient received 2 cycles of neoadjuvant chemotherapy (Gemcitabine and Carboplatin). Acute urinary and bowel toxicities were recorded in the RTOG scale. All patients underwent 3-monthly cystoscopy, chest X-ray and urine cytology on follow-up.

The adaptive radiotherapy (ART) technique

This technique entailed the generation of six isotropic PTVs for each patient at the time of planning and thus the generation of six separate IMRT plans for each patient. All patients were treated on helical tomotherapy and daily MVCT image guidance scans were used to correct for patient positioning errors and to choose the most appropriate PTV, depending on the shape, size and position of the bladder on that day.

Planning CT scan

Patients underwent a planning CT scan in the supine position with a knee rest and anterior and lateral fiducials. Non-contrast scans were taken from the umbilicus to 5 cm below the ischial tuberosity, with 3 mm slice thickness. The decision to treat on a full bladder or an empty bladder was based on the need for boosting the tumour bed. Patients with a solitary tumour or two tumours in close proximity were deemed suitable for a simultaneous integrated boost (SIB) and were treated with a full bladder. A full bladder would facilitate better identification of the tumour bed and minimise the volume of normal bladder receiving a higher dose. These patients followed a bladder filling protocol which involved voiding and then drinking 400 ml of water, 30 min before the planning CT scan. Patients not suitable for SIB, due to multiple tumours or presence of carcinoma in situ, underwent a planning CT scan with an empty bladder and were asked to void just before their treatment.

Contouring

The whole bladder was delineated as the CTV and six PTVs were grown by giving isotropic margins from 5 mm to 30 mm, in steps of 5 mm (Fig. 1). If the patient was eligible for an SIB, a CTV boost volume was contoured, consisting of the tumour bed, any visible tumour and suspicious areas based on its visibility in the planning CT scan, as well as information from the cystoscopy bladder map and diagnostic imaging. The CTV boost volume was given a uniform 10 mm margin to generate a PTV boost volume. The rectum, bowel and femoral heads were contoured as organs at risk (OAR). The pelvic nodes were not prophylactically irradiated for this phase of the study.

Treatment planning

Treatment planning was done on the proprietary Tomotherapy Planning Station (Ver.3.1.5.3). Six IMRT plans were generated for each patient (one for each PTV). The prescription dose planned for the bladder PTVs was 64 Gy/32# (2 Gy/#) and in cases with SIB, PTV boost was planned for 68 Gy/32# (2.13 Gy/#). The 2 Gy equivalent dose (EQD2) for the boost volume was 69.7 Gy for late effects ($\alpha/\beta = 3$) and 68.7 Gy for tumour kill ($\alpha/\beta = 10$). The OAR constraints defined by RTOG P-0126 were met.

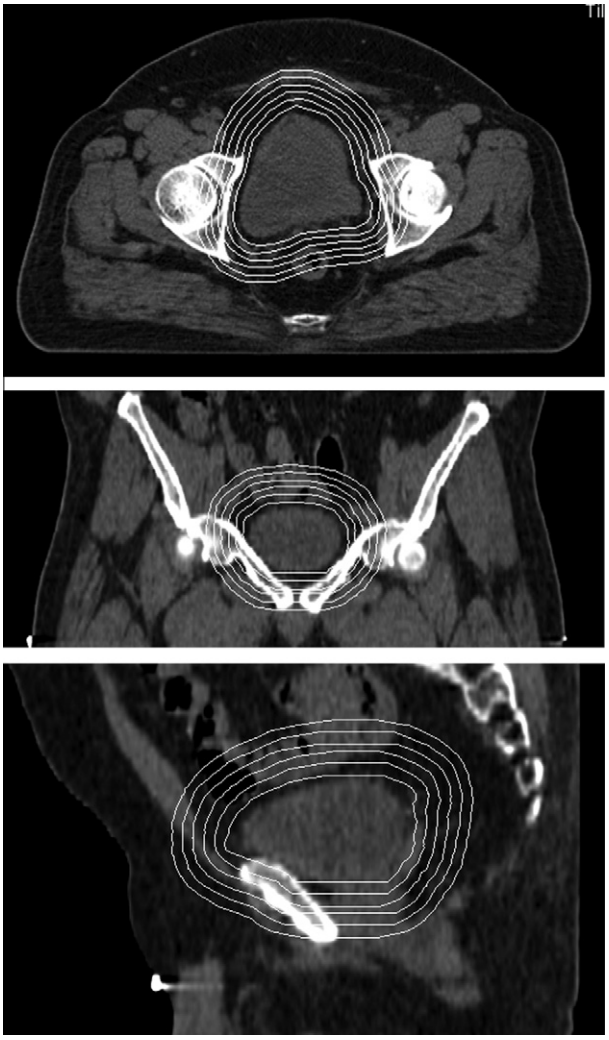

Fig. 1. Planning CT scan in axial, coronal and sagittal planes with six isotropic PTV margins.

MVCT scanning and registration

For each treatment fraction, a pre and a post treatment MVCT scan was taken. Pretreatment MVCT was co-registered with planning KVCT scan using automatic fusion of the bony anatomy (Fig. 2a). The translational shifts (lateral, longitudinal and vertical) and rotational variations (pitch, roll and yaw) were recorded. After the automatic 'bone-match', the co-registration was manually adjusted so that the bladder fit into the smallest of the six PTVs (plan of the day), depending on the bladder size, position and shape (Fig. 2b). This manual positioning ('bladder-match') accounted for the deformation and displacement of the bladder for that fraction. The selected 'plan of the day' and the final applied corrections were recorded.

It was ensured that the selected PTV encompassed the bladder with at least a clear, visible 2–3 mm margin to account for potential intra-fraction bladder filling and imaging uncertainty. Action levels were defined for pitch and yaw as >2°, as tomotherapy cannot correct for these rotations. Grossly abnormal bladder

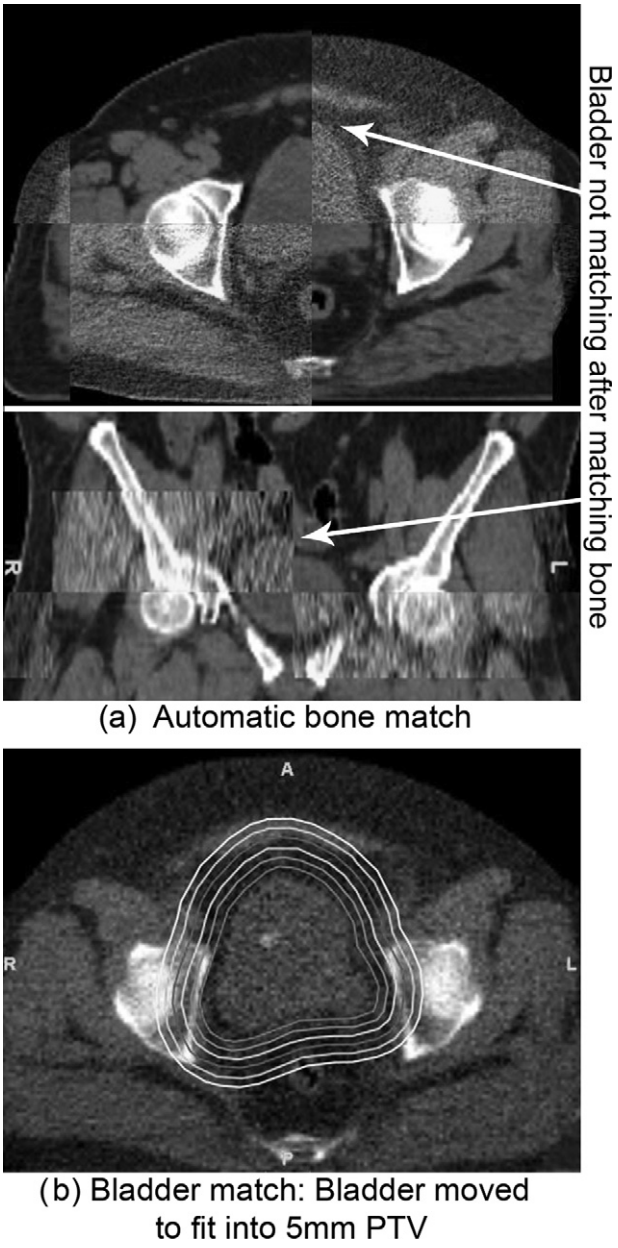

Fig. 2. Co-registration of planning KVCT and daily pre-treatment MVCT scans. (a) Automatic bone match showing mismatch of bladder in axial and coronal planes. (b) Selection of plan of the day by fitting the bladder into the most appropriate PTV margin (innermost PTV in this case).

shapes/sizes mandated a repetition of the entire patient setup and registration process. A post treatment MVCT scan was taken in the treated position for verification and margin estimation.

Data analysis: method of anisotropic PTV generation

All post treatment MVCT scans were individually analysed to determine anisotropic PTV margins. Data were collected in the Tomotherapy Plan Adaptive module (Ver.3.1.4.6) for the bladder wall in six directions. The six PTVs generated on the planning CT scan were overlaid on the post treatment MVCT scans. In each direction of measurement, the smallest of the six PTV margins that encompassed the bladder wall was identified and as a result, the measurements were quantised in steps of 5 mm. By this methodology, it is possible for the margin measured in a certain direction to be influenced by the adjacent bladder walls, leading to an overestimation of the anisotropic margin. However, measurements were made near the central region of the bladder structure, where the contribution of adjacent walls would be minimal. The margins for the anisotropic PTVs were calculated by determining the smallest margin that encompassed the bladder wall in each direction, to a pre-specified level (85th, 90th and 95th percentile) of certainty. For example, the 85th percentile PTV will cover the whole bladder 85% of the time or in 85% of the fractions. PTV margins for any certainty level could be generated, though we selected the 85th, 90th and 95th percentile as it covered an acceptable range to implement in practice. The above process was repeated with the image fusion re-adjusted to simulate a 'bone match' and the margins for each bladder wall were determined again. The entire process from patient selection to post-treatment processing of the data to determine anisotropic PTV margins is given in Fig. 3 as a flow chart.

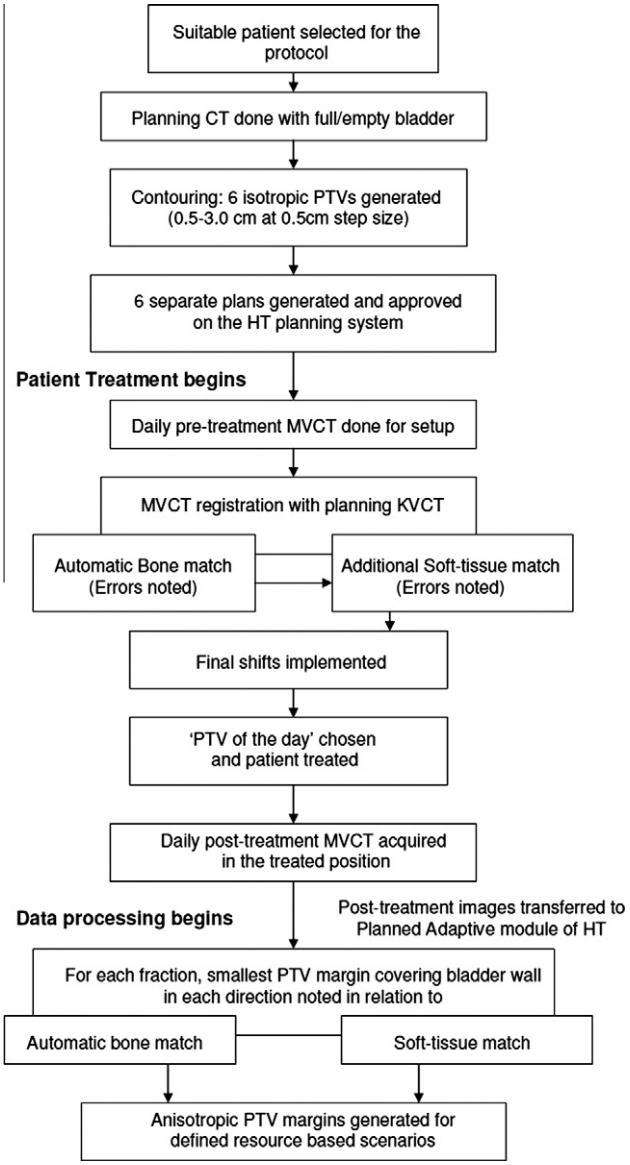

Fig. 3. Workflow of the entire process, from patient selection to post-treatment data analysis to determine anisotropic margins.

Results

A total of 315 MVCT scans of 10 patients were analysed, of which seven patients received a tumour bed boost up to 68 Gy in 32 fractions as an SIB. This cohort of 10 patients had a median

age of 62.5 years (range: 35–79 years) and nine patients were staged as T_{2b} while only 1 was T_4 (all patients were N_0).

Geographical miss

Data were collected for the instances where the bladder wall was outside the selected 'plan of the day' at the end of treatment. Table 1 shows the percentage geographical miss for the bladder wall in each direction.

'Plan of the day' selection

The PTV selected for each fraction depended on the bladder filling for that day and the relative position of the bladder. As seen in Table 2, 99.4% of the fractions were treated with 5–15 mm PTV plans and nearly 90% of the fractions were treated with 5 and 10 mm plans.

Anisotropic margins for PTV

The margins needed to encompass the bladder wall in each direction, 85–95% of the time, during a course of external beam radiotherapy, were determined. Using this data, multiple anisotropic PTVs can be generated and used for adaptive radiotherapy (Table 3).

Clinical outcome

At a median follow-up of 13.2 months (range 7.4–18.7 months), all patients had a complete response of the bladder tumour with no obvious radiotherapy sequelae on cystoscopy. One patient (T_4 N_0) had clinical evidence of pelvic nodal recurrence at 12 months post-RT, for which he received palliative re-irradiation on tomotherapy and is alive with the disease. Although late toxicity data will emerge with longer follow-up, all patients tolerated the treatment well with only one patient having gross haematuria (RTOG Grade 3 toxicity) at the end of radiotherapy, which on cystoscopy was due to a bladder stone and resolved completely at 6 weeks post RT. Grade 2 urinary and bowel/rectal toxicities were seen in two patients each. No patient had Grade 3 bowel toxicity.

Discussion

We have clinically implemented an adaptive radiotherapy technique of IGRT for bladder cancer and attempted to optimise margin generation for multiple anisotropic PTVs. The use of the plan of the day to actually treat the patients in a clinical situation is novel in this study. Local control and early toxicity results look promising in spite of dose escalation incorporated in the protocol. The concept of 'plan of the day' was initially described by Burridge et al. [8] who proposed the use of 3 PTVs grown around the bladder with a variable superior margin. Based on the pre treatment CBCT images, the most appropriate PTV that covered the shape of the bladder was chosen. This was a dosimetric study on CBCT scans acquired during conventional treatment using 4-field box technique. Using this system there was a reduction of small bowel volume irradiated and, there was the potential to reduce margins in the posterior–inferior, right, and left directions to 10 mm. The present study was designed to refine this concept further, and incorporate IMRT and dose escalation as a proof of principle. Moreover, the idea was to be able to validate the previous reports of generation of anisotropic PTVs with daily pretreatment MVCT images and relatively stringent bladder filling/emptying protocol [9].

We started with multiple (six) isotropic PTV margins around the bladder CTV. Although this required six separate IMRT plans for each patient, it was considered achievable in the research setting. Steps of 5 mm were used in all six directions for better flexibility in plan selection each day. Further, while daily pretreatment MVCT was used for plan selection, post treatment scans were used to generate anisotropic PTV as it accounts for intrafraction bladder filling and represents the 'worst case scenario' in terms of potential target miss, though it possibly overestimates the geographical miss reported above.

The need for anisotropic PTV margins has been discussed previously by several investigators [9–15]. However the methodology

Table 1
Percentage geographical miss of the bladder wall in each direction.

	Superior	Inferior	Anterior	Posterior	L Lateral	R Lateral
Treated with full bladder	16.1	0.00	12.1	0.5	4.5	8.0
Treated with empty bladder	11.5	0.00	7.3	3.1	4.2	4.2
All patients	13.8	0.00	10.3	1.3	4.4	6.9

Table 2
Frequencies of PTVs selected as 'plan of the day'.

	5 mm	10 mm	15 mm	20 mm	25–30 mm	Total
Treated with full bladder (n = 7)	92 (42.0%)	102 (46.6%)	24 (11.0%)	1 (0.5%)	0 (0.0%)	219 (100%)
Treated with empty bladder (n = 3)	20 (20.8%)	67 (69.8%)	8 (8.3%)	1 (1.0%)	0 (0.0%)	96 (100%)
All patients (n = 10)	112 (35.6%)	169 (53.7%)	32 (10.2%)	2 (0.6%)	0 (0.0%)	315 (100%)

Table 3
Margins (mm) for the bladder wall in all directions, based on coverage probability.

		Superior	Inferior	Anterior	Posterior	L Lateral	R Lateral
Final soft tissue (bladder) match	PTV1 (95th)	25	10	25	15	16.5	20
	PTV2 (90th)	25	10	20	10	15	15
	PTV3 (85th)	20	10	15	10	10	10
Automatic bone match	PTV1 (95th)	26.5	10	25	15	20	25
	PTV2 (90th)	25	10	20	13	15	23
	PTV3 (85th)	20	10	15	10	15	15

employed to arrive at the conclusion has varied, ranging from weekly diagnostic scans to offline CBCT corrections and one recent study that has looked at daily CBCT in 10 patients to assess bladder filling variability [9]. We tried to evaluate the daily interfraction bladder motion more comprehensively using volumetric imaging which would provide better insight into the most appropriate margins for the population. Most of these studies conclude that the largest variation occurs in the anterior and superior direction and there is a significant chance of geographical miss at these walls unless these margins are increased to 20–25 mm. The anisotropic PTVs derived from these data support this observation. It should however be noted that even with daily soft tissue imaging, there is a substantial risk of geographical miss due to the intrafraction bladder filling (Table 1). This risk could be minimised if the treatment time is reduced. The use of image guided IMRT in this study, especially on the helical tomotherapy platform, required 21 min for each fraction (median time on couch). This was calculated from the beginning of the pre treatment MVCT to the end of the post treatment MVCT. Using other technology platforms or non IMRT/IGRT modalities with fewer projections may reduce this time.

One of the secondary objectives of this study has been to define the appropriate PTV that needs to be generated based on the available resources at a radiotherapy centre. The centres have been broadly grouped into three categories and the proposed solutions for each of the centres are based on a combination of physiological motion patterns and setup errors generated from this data.

1. *Centres with access to daily ART:* These centres may use multiple anisotropic PTVs (up to 3–4) around the CTV bladder and perform ART by choosing the best 'plan of the day' (Table 3). These new anisotropic PTVs have been generated based on the extent of the bladder wall in each direction to cover the 85th, 90th and 95th percentile. Each successive PTV increases the percentage likelihood of coverage of the bladder wall and enables the operator to choose the most appropriate PTV. In a recent study from the Royal Marsden Hospital [11], 15 patients were treated with weekly hypofractionated radiotherapy for advanced bladder cancer. The anisotropic PTVs were generated based on patterns of bladder filling for individual patients by using multiple planning CT scans at different time points (0, 15 and 30 min). In the present study, percentiles of the bladder wall in each direction were used to identify patterns of bladder filling in the population. Using this method of daily adaptation, a smaller PTV margin may be appropriate for a large majority of fractions enabling a reduction of dose to surrounding normal tissues.

2. *Centres with access to soft tissue image guidance but no ART:* Centres with access to soft tissue image guidance, but with resource constraints in terms of physics/planning time, machine availability and manpower, may use a single anisotropic PTV to treat all the fractions and get CTV coverage of 95% or 90% as shown in Table 3. This would provide a balance between achieving acceptable CTV coverage, normal tissue toxicity and optimal resource utilisation. The margins would however be best determined by each centre performing a similar pilot study and estimate the errors for their respective infrastructure.

3. *Centres with access to only EPID as image guidance*: Centres without access to soft tissue imaging that use daily electronic portal imaging for set up would need to use margins that take into account the bladder filling and deformation. This margin has been derived in the present study from the automated bone match data without a soft tissue match i.e., simulating a scenario of using only an EPID (Table 3). It is assumed here that an EPI match is equivalent to a CT based bone match.

We have not documented the margins in a scenario where a patient is being treated on a treatment unit with no EPID. In such a case, the physiological motion of the bladder as well as the setup (systematic and random) errors for the pelvis would need to be taken into account by the margins, and these systematic and random errors would be machine and centre specific. Moreover, based on the method of data generation used in this study it is not appropriate to make statistically robust recommendations for this scenario.

The margins generated from this study indicate a larger margin needed for coverage of bladder wall in the right lateral direction (95% coverage with 20 mm) as compared to the left (95% coverage with 16.5 mm). A physiological basis of this difference is unlikely and a larger sample size would possibly even out the difference. It is worth noting that the right lateral wall data were particularly skewed due to two patients whose bladder showed asymmetric filling.

The data on geographical miss from this study need to be interpreted with caution. Data were collected for the instances where the bladder wall was outside the selected plan of the day at the end of treatment. The post treatment MVCT scans were used to estimate this and give us a worst case scenario. For the purpose of this study, a significant geographic miss was considered when the bladder wall was outside the selected PTV by more than 5 mm i.e., beyond the next overlaid PTV. This was done as all our measurements were quantised in steps of 5 mm and to account for imaging uncertainty, relatively long treatment times, the additional time for setting up the post treatment scan, etc. Also, based on the estimates of the dose distributions from the planning data, a wall which is outside the PTV by 10 mm and 15 mm would receive 73% and 63% of the prescribed dose, respectively. A 5 mm miss would still receive 86% of the prescribed dose.

Although calculating the doses to the normal tissue was beyond the scope of this study, clinical toxicity data are quite promising and are a proof of principle that adaptive radiotherapy can reduce normal tissue complications. Further dosimetric support for IGRT can be seen from Foroudi et al. who recently reported that 27 bladder cancer patients, who were treated with daily adaptive IGRT using cone-beam computed tomography, showed substantially reduced normal tissue doses both in the high dose (>45 Gy) and low dose (>5 Gy) regions [16].

For each fraction, the appropriate plan of the day was chosen by an oncologist or a physicist as part of the project. It is worth noting that the individual interobserver variability in choosing the plan of the day could influence the margins selected. Although this has not been accounted for in the present study, a supplementary study is underway to estimate interobserver and intraobserver variabilities in choosing the plan of the day. In the RMH study [11], interobserver variability was estimated among 12 radiographers of varying experience, two clinicians, and one physicist. There was a 76% concurrence rate among them in choosing the plan of the day.

Conclusion

Curative radiotherapy to the bladder requires a careful assessment of interfraction setup errors and intrafraction deformation to generate optimal PTV margins. These margins may be anisotropic as the deformation of this organ is seldom uniform in all directions. Image guidance techniques are dependant on local protocols and infrastructure availability and, therefore, tailoring of unique solutions may be required. As demonstrated in this clinical study, IGRT based adaptive RT, involving the daily choice of one of several PTVs is a feasible and effective alternative to generic large PTV margins and allows greater sparing of surrounding normal tissues and dose escalation in bladder cancer.

Conflicts of interest statement

Actual or potential conflicts of interest do not exist.

References

[1] Shipley WU, Kaufman DS, Zehr E, et al. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. Urology 2002;60:62–7 [discussion 67–68].

[2] Rodel C, Grabenbauer GG, Kuhn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. J Clin Oncol 2002;20:3061–71.

[3] Majewski W, Maciejewski B, Majewski S, Suwinski R, Miszczyk L, Tarnawski R. Clinical radiobiology of stage T2–T3 bladder cancer. Int J Radiat Oncol Biol Phys 2004;60:60–70.

[4] Pos FJ, Hart G, Schneider C, Sminia P. Radical radiotherapy for invasive bladder cancer: what dose and fractionation schedule to choose? Int J Radiat Oncol Biol Phys 2006;64:1168–73.

[5] Pos F, Remeijer P. Adaptive management of bladder cancer radiotherapy. Semin Radiat Oncol 2010;20:116–20.

[6] Wright P, Redpath AT, Hoyer M, Grau C, Muren LP. The normal tissue sparing potential of adaptive strategies in radiotherapy of bladder cancer. Acta Oncol 2008;47:1382–9.

[7] Mangar SA, Scurr E, Huddart RA, et al. Assessing intra-fractional bladder motion using cine-MRI as initial methodology for Predictive Organ Localization (POLO) in radiotherapy for bladder cancer. Radiother Oncol 2007;85:207–14.

[8] 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 2006;66:892–7.

[9] Yee D, Parliament M, Rathee S, Ghosh S, Ko L, Murray B. Cone beam CT imaging analysis of interfractional variations in bladder volume and position during radiotherapy for bladder cancer. Int J Radiat Oncol Biol Phys 2010;76:1045–53.

[10] Fokdal L, Honore H, Hoyer M, Meldgaard P, Fode K, von der Maase H. Impact of changes in bladder and rectal filling volume on organ motion and dose distribution of the bladder in radiotherapy for urinary bladder cancer. Int J Radiat Oncol Biol Phys 2004;59:436–44.

[11] 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 2010.

[12] Lotz HT, Pos FJ, Hulshof MC, et al. Tumor motion and deformation during external radiotherapy of bladder cancer. Int J Radiat Oncol Biol Phys 2006;64:1551–8.

[13] Meijer GJ, Rasch C, Remeijer P, Lebesque JV. Three-dimensional analysis of delineation errors, setup errors, and organ motion during radiotherapy of bladder cancer. Int J Radiat Oncol Biol Phys 2003;55:1277–87.

[14] Muren LP, Smaaland R, Dahl O. Organ motion, set-up variation and treatment margins in radical radiotherapy of urinary bladder cancer. Radiother Oncol 2003;69:291–304.

[15] Redpath AT, Muren LP. CT-guided intensity-modulated radiotherapy for bladder cancer: isocentre shifts, margins and their impact on target dose. Radiother Oncol 2006;81:276–83.

[16] 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 2010.