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Evaluating the need for adaptive therapy when delivering conformal bladder radiotherapy

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Abstract

Background and Purpose

To audit positioning errors during bladder Image Guided Radiotherapy (IGRT) and quantify survival outcomes

Materials and Methods

Retrospective review of 141 patients treated between March 2007 and July 2010 with 3D conformal radiotherapy (CRT). An offline imaging protocol using kV cone beam CT (CBCT) was used. Positioning errors, clinical interventions and re-planning rates were quantified. Cancer outcomes and survival were collected by review of patient notes and a registry search.

Results

43% of patients required no intervention. Isocentre corrections were used for systematic bony set-up error (SUE) in 13% and to improve bladder coverage in 28%. Clinical interventions to improve bladder coverage were required in 16% and repeat CT planning in a further 16%. Overall, 44% of patients demonstrated some form of organ deformation that would have resulted in inadequate dose to the bladder or significant overdose to an organ at risk if not corrected for. Post treatment check cystoscopy was undertaken in 107 patients (76%) with 72 noted to have a complete response. Overall survival was 47.8% at 3 years.

Conclusions

Organ deformation during radiotherapy for bladder cancer is a significant problem for over 40% of patients. Strategies to compensate are essential to ensure optimal plan delivery.

Keywords: Adaptive radiotherapy, bladder cancer, external beam radiotherapy, image guided radiotherapy, organ motion

Introduction

Bladder cancer is the 7th most common cancer in the Western world [1]. Despite no consistent evidence for the superiority of radical cystectomy over radiotherapy [2] cystectomy is often the treatment of choice in younger, fitter patients [3]. Primary radiotherapy is generally offered to older patients or those with significant comorbidity.

Radiotherapy alone offers initial complete response rates of the order of 75 % but in the longer term sustained local control is only achieved in 30 - 50 % [4,5].

The bladder is subject to significant organ motion over the course of radiation delivery and geographical miss may contribute to reduced local control and subsequent survival. A standard margin of the order of 15 - 20 mm is added around the bladder to account for organ motion and set-up error. These standard margins may be inadequate with the percentage of patients observed with a partial geometric miss at least once during a treatment course ranging from 19 to 65% [6-8].

Image guided radiotherapy (IGRT) is likely to be of significant benefit in bladder treatments both to reduce the risk of geographical miss and minimise treatment related bowel toxicity. Volumetric bladder imaging using cone beam CT provides images of ample quality for use in IGRT [9,10]. The National Radiotherapy Implementation Group (NRIG) published guidelines for IGRT implementation and use in 2012 [11]. This work considers the impact of the routine introduction of an offline kV CBCT based IGRT protocol in bladder radiotherapy patients, in terms of rate of re-planning, isocentre correction and clinical intervention. Furthermore, cancer outcomes are presented in terms of cystoscopic response rates and both overall and bladder cancer specific survival.

Materials and Methods

A retrospective review of IGRT prospectively recorded data of 141 non-metastatic bladder cancer patients consecutively treated from March 2007 to July 2010 was undertaken. All patients were treated with 3DCRT and volumetric IGRT with curative intent.

Treatment planning and delivery

All patients were treated in the head-first supine position with a knee rest but no other formal immobilisation. Patients were instructed to empty the bladder immediately prior to CT scanning and no drinking protocol was used. For patients with node-negative disease, the CTV was defined as the whole bladder including any extra-capsular spread. Isotropic margins of 1.5 - 2.0 cm were then added to generate the PTV. For patients with node-positive disease, the whole pelvis was treated with a phase 2 boost to the bladder with a 1.5 cm margin. A standard conformal 3 or 4 field technique was used.

In patients undergoing bladder-only treatment, a dose of 52.5 - 55.0 Gy was prescribed to 100%, with the PTV encompassed by the 95% isodose Treatment was delivered in 20 daily fractions over 28 days (treatment was delivered Monday – Friday only). In those undergoing additional whole pelvis treatments, 40-46 Gy was delivered to the whole pelvis followed by a phase 2 treatment to the bladder, delivering a total dose of 60-66 Gy in 2 Gy per fraction.

Treatment verification with IGRT

IGRT was performed using a kV CBCT system (XVI, Version 4.2 (2007-2010), Elekta AB, Stockholm, Sweden) equipped on a linear accelerator (Elekta Synergy™ (2007 - 2010), Elekta AB, Stockholm, Sweden). CBCTs were acquired on the day before the first treatment delivery day, to verify positioning and readiness prior to treatment, and on the first two treatment days. All images were reviewed online and corrective action implemented immediately for gross errors (>1 cm) and reviewed offline to identify and correct for systematic errors. Image matching was performed through an initial automatic bony alignment of the CBCT to the reference CT scan, followed by a manual alignment of the CTV (bladder). These first three images were analysed in an offline setting and any systematic errors in bladder position > 3 mm or more than 5 degrees corrected for by an adjustment of isocentre position for subsequent fractions. The patient was then imaged

weekly. Additional kV CBCT was required for patients displaying daily random error and also after the application of any isocentre correction. Megavoltage (MV) portal imaging was not performed. Imaging review and interventions were radiographer led, with the involvement of medical physics and/or the prescribing clinician where appropriate. Image analysis was undertaken independently by 2 radiographers from a pool of staff who had all undergone training and competency assessment in bladder IGRT using CBCT.

IGRT interventions

A number of interventions were undertaken. Isocentre shifts were used to correct for systematic bony SUE and/or small systematic changes in bladder position, shape or volume relative to surrounding bony anatomy. Repeat CT scanning was used when systematic changes in bladder volume or shape were found to result in the 15-20 mm bladder to PTV margin providing either inadequate bladder coverage, or excessive dose to organs at risk. Other clinical interventions identified as a result of CBCT were recorded, such as catheterisation or regular laxatives used, with the aim to reduce the effect of organ volume changes and/or improve CTV coverage.

Population bone setup errors

Automatic bone matching software was used to generate displacements and rotations in Right-Left, Superior-Inferior and Anterior-Posterior directions for each CBCT. The systematic and random components of bone error were calculated using the method described in BIR publication, 'Geometric Uncertainties in Radiotherapy Treatment Planning' [12]. The systematic positioning error (Σ) is defined as the standard deviation (SD) of the distribution of the average individual positioning errors in the group. The random error (σ) is defined as the SD of the day-to-day positions averaged over the study group.

Population bladder organ motion

Manual soft tissue matching was implemented by matching CTV (bladder) on the CBCT to the planning CT therefore the shifts were used a surrogate of bladder motion at time of treatment compared to simulation. Population bladder organ motion data were generated in the Right-Left,

Superior-Inferior and Anterior-Posterior directions. The bladder was not re-contoured on any images.

Statistics

Positioning errors are analysed using simple descriptive statistics. Kaplan-Meier curves were produced for overall and bladder cancer specific survival using SPSS version 21 (IBM Corporation, New York, USA).

Results

Patient characteristics and clinical outcomes

The patient group was heterogeneous (Table 1). It was an elderly cohort with a mean age at treatment of 77 years and range of 51-92 years. At least 80% had a WHO performance status (PS) of 2 or above. The majority of cancers were transitional cell (TCC). The majority of patients had organ-confined disease and underwent radiation to the bladder only. Only 3 patients who were pelvic node positive on staging CT had additional whole pelvis treatment.

The median follow-up was 62.9 months. At the time of analysis there were 103 deaths, including 69 deaths from bladder cancer. Median overall survival was 30.3 months with one, two and three year overall survival of 82.1%, 57.6% and 47.8% respectively (Figure 1a). Median bladder cancer specific survival was 53.1 months, with one, two and three year bladder cancer specific survival of 85.5%, 64.4% and 55.9% respectively (Figure 1b).

At 3-6 months 107 (76%) patients underwent check cystoscopy to assess treatment response. 72 (67% of patients undergoing check cystoscopy) had a complete response to radiation. Post-treatment CT scanning was not routinely undertaken as most of these patients would not be considered suitable for palliative chemotherapy should nodal or metastatic disease be demonstrated. Of those patients not undergoing check cystoscopy, the majority had progressive disease with 17 (12%) dying from bladder cancer in the immediate post-treatment period. 6 patients (4%) died from unrelated causes, predominantly cardiovascular disease, demonstrating

the competing causes of death in this population with high rates of smoking history and its associated co-morbidities.

IGRT Interventions

60 (43%) patients required no intervention to correct positioning errors during treatment. 18 (13%) of 141 patients did not require any action beyond isocentre correction of bony set-up errors. The remaining 63 (44%) demonstrated systematic soft tissue deformation requiring an isocentre shift, clinical intervention or repeat simulation CT and re-planning (Table 2). For 40 (28%) patients, an isocentre shift was used successfully to account for soft tissue changes, whereas 23 (16%) patients required the use of a catheter, α-blockers or laxatives to reduce the effect of soft tissue deformations, and a further 23 (16%) patients required repeat simulation CT and re-planning. Multiple interventions were needed for 17 (12%) patients, with 5 (4%) patients needing 3 or more interventions during their treatment course, and 6 (4%) patients receiving the same type of intervention twice. For 6 out of 23 patients managed initially with a clinical intervention, the chosen approach was unsuccessful and repeat simulation CT and re-planning was needed.

For the 63 patients demonstrating soft tissue deformations, 12 patients would have received a much greater dose to small bowel had it not been for the use of IGRT, whereas the remaining 51 patients would have received inadequate dose to the target volume due to partial geometric miss. Changes in bladder or rectal volume, shape or position were the source of soft tissue deformations with 10% of patients demonstrating a smaller rectal volume, 4% with an increased rectal volume, 9% with a reduced bladder volume, and 38% with an increased bladder volume. These soft tissue deformations were observed at the start of treatment in the vast majority of patients. 88% of problems were identified at the first CBCT, and confirmed as consistent over subsequent days. Only 12% of problems were identified during weekly review after the first week of treatment.

Population Bone Set-up errors

Population systematic and random bone setup errors measured by automatic matching from CBCT were all in the range 1-3 mm and < 1.5° (Table 3) demonstrating consistent patient positioning in line with published recommendations [13,14].

Population bladder organ motion errors

Organ motion was observed to be greatest in the Superior-Inferior direction in which 61% of patients exhibited organ motion of > 5 mm for at least one fraction imaged (Table 4). In each direction Right-Left, Superior-Inferior and Anterior-Posterior directions, 3 % of patients demonstrated organ motion of > 15 mm for at least one fraction. The Right-Left direction demonstrated the least organ motion in terms of proportion of patients exhibiting organ motion of < 5 mm for all imaged fractions (51%) and severity of observed organ motion for those patients with motion > 5 mm.

Discussion

This work is the largest retrospective review of the impact of introducing kV CBCT IGRT in a cohort of patients undergoing radical radiotherapy for bladder cancer. Prior to the introduction of volumetric IGRT, only 13% of this group would have had correction of bone setup error with the use of MV portal imaging. The offline CBCT IGRT protocol required intervention in 57% of patients to limit geographical miss of the target or excessive irradiation of organs at risk. This increased need for intervention needs to be accounted for when allocating treatment schedules and resources. Most errors were identified at the first 3 imaged fractions although beyond these first 3 images, daily imaging was not acquired and a weekly regime was adopted. Random errors were also identified, with 12% of patients requiring multiple interventions. Soft tissue changes can be unpredictable in bladder cancer patients and patients who display random error in setup may require daily volumetric CBCT imaging throughout their course of treatment. The compromises of increasing imaging to daily CBCT, from the local protocol of weekly after 3 CBCTs, include patient radiation dose and scheduling issues, both in terms of staffing and appointment lengths on the machine.

Without IGRT, the use of population margins of 1.5 - 2 cm from CTV to PTV can be either inadequate or excessive for individual patients. Recognising that population data for CTV - PTV margins do not always provide the best treatment for a given individual, adaptive radiotherapy (ART) may be a good option for bladder radiotherapy [9]. ART uses either multiple CTs or CBCTs acquired over initial treatments, to assess random and systematic error for that individual and then produce an adapted plan with a PTV designed to encompass the target volume on all scans. Our work suggests that ART may benefit the 28% of patients who demonstrated soft tissue changes that could be encompassed with an isocentre shift. However, the isocentre shift was effective without the additional work needed for ART. 28% of patients in this review do demonstrate gross changes in target volume on the first verification image. For these patients, there may be concerns with continuing with the original plan. A 'plan of the day' adaptive approach may be more effective. Patients can be planned with treatments to encompass small, medium and large bladder volumes. After CBCT acquisition, the most appropriate plan from the library can be chosen for that day. This would also be effective for the 4% patients who demonstrate large changes resulting in repeat CT planning at some point after the first week of treatment.

The term 'adaptive' has been used in its broadest sense in this work i.e. any intervention during treatment delivery that improves accuracy of treatment delivery. More technical adaptive strategies, including 'plan of the day' approaches, have been adopted in other, smaller bladder cancer patients series, and have been shown to be feasible and to result in a smaller volume of normal tissue irradiation as well as improvements in target coverage [8,9,15,16]. Intuitively such strategies should result in improved local control and overall survival. This is the subject of clinical trials. In the HYBRID trial palliative patients are randomised between standard radiotherapy using the same plan for each fraction, or an adaptive strategy where the best of three possible plans (small, medium and large bladder volumes) are selected on each treatment day [17]. In the radical setting the RAIDER trial will investigate adaptive strategies by randomising patients between standard radiotherapy using one plan, an adaptive approach which selects one of three (small, medium and large) plans for each treatment and an adaptive approach which also delivers escalated doses to the whole bladder and tumour [18].

Similar to prostate radiotherapy patients, this work demonstrates that rectal filling impacts on bladder positioning [10,9]. Intervention such as the use of daily enemas may result in more consistent positioning in these patients [20]. Changes in our practice include the introduction of a crude assessment of rectal volume and intervention if a maximum rectal diameter at CT planning of $\geq$5 cm adjacent to the bladder is noted.

A small proportion of our patients underwent neo-adjuvant chemotherapy. Subsequently BC2001, a large phase 3 RCT, has demonstrated an improvement in two-year disease free survival from 54% to 67% with the addition of concurrent chemotherapy to radical radiotherapy [21] and this is now our standard practice in suitable patients. Volumetric IGRT was not available when the BC2001 trial recruited and increased toxicity was noted during treatment in the group undergoing concurrent chemotherapy. It would be likely that the routine use of volumetric IGRT would reduce treatment toxicity when concurrent chemotherapy is delivered.

This work is limited in that it doesn't quantify the impact IGRT has on treatment related toxicity and local control. We would expect IGRT to reduce radiation related bowel toxicity and improve local bladder cancer control. We currently lack randomised trial evidence to quantify the impact of IGRT and adaptive treatments in bladder cancer. The overarching principle of radiotherapy is to treat the target consistently with minimal dose to adjacent OAR. Volumetric IGRT achieves this but is more labour intensive and the optimal imaging strategy is yet to be defined.

Conclusions

Organ deformation during radiotherapy for bladder cancer can be significant and places the patient at risk of geographical miss or excessive normal tissue irradiation. Strategies to monitor and compensate for deformation, including volumetric imaging, shifts, adaptive radiotherapy techniques and an openness to re-planning if necessary, are essential to ensure optimal plan delivery. Modern phase III radiotherapy trials will investigate the ultimate impact of such adaptive approaches on bladder cancer toxicity and survival outcomes.

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Conflict of interest

None declared

Table 1: Patient demographics and clinical outcomes

Demographics		No of patients (%)
Age (years)	**Mean**	77
	Range	51-92
Sex	**Male**	103 (73)
	Female	38 (27)
WHO PS*	**PS 0-1**	74 (52)
	PS 2	39 (28)
	PS 3	10 (7)
	Not recorded	18 (13)
Smoking	**Current/ex smoker**	90 (64)
	Never smoked	27 (19)
	Not recorded	24 (17)
Histology	**Transitional cell cancer**	130 (92)
	Small cell cancer	3 (2)
	Other	8 (6)
Neo-adjuvant chemotherapy		
	Yes	19 (13)
	No	122 (87)
Check cystoscopy at 3-6 months		
	Yes	107 (76)
	No	34 (24)
Outcomes at 1st check cystoscopy		
	Complete response	72 (68)
	Residual disease	35 (32)
Reasons for no check cystoscopy		
	Death from bladder cancer	17 (12)
	Death from unrelated causes	6 (4)
	Treatment related death	0
	Patient refused	6 (4)
	Unknown	5 (3.5)

Table 2: Interventions prompted by IGRT

Type of intervention prompted by IGRT	Number of intervention episodes (% of patients)	
	Identified day 1-3	Identified after day 5
No intervention	60 (43)	
Isocentre shift to correct for bone error	13 (9)	5 (4)
Isocentre shift to correct for systematic change in bladder position caused by:		
Smaller bladder	4 (3)	0
Larger bladder	23 (16)	0
Smaller rectum	10 (7)	0
Larger rectum	3 (2)	0
Clinical intervention		
Catheterisation	15 (11)	0
Use of α blockers	5 (4)	0
Laxatives and other medication	3 (2)	0
Repeat planning to correct for systematic soft tissue deformations originating from:		
Smaller bladder	6 (4)	2 (1)
Larger bladder	9 (6)	2 (1)
Smaller rectum	1 (<1)	3 (2)
Larger rectum	0	0
TOTAL	164 (Total patients = 141)	

Please note: some patients required multiple interventions.

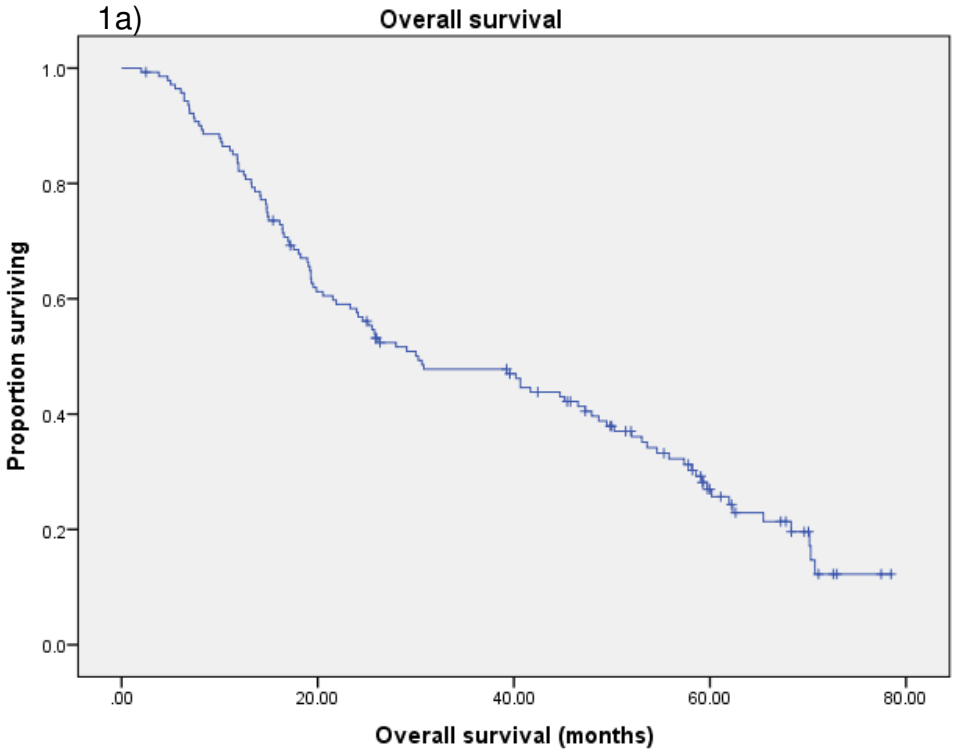
Table 3: Systematic and random bone translation (and rotation) set-up errors calculated using the BIR technique [11] based on all CBCTs acquired using an automatic bone match data.

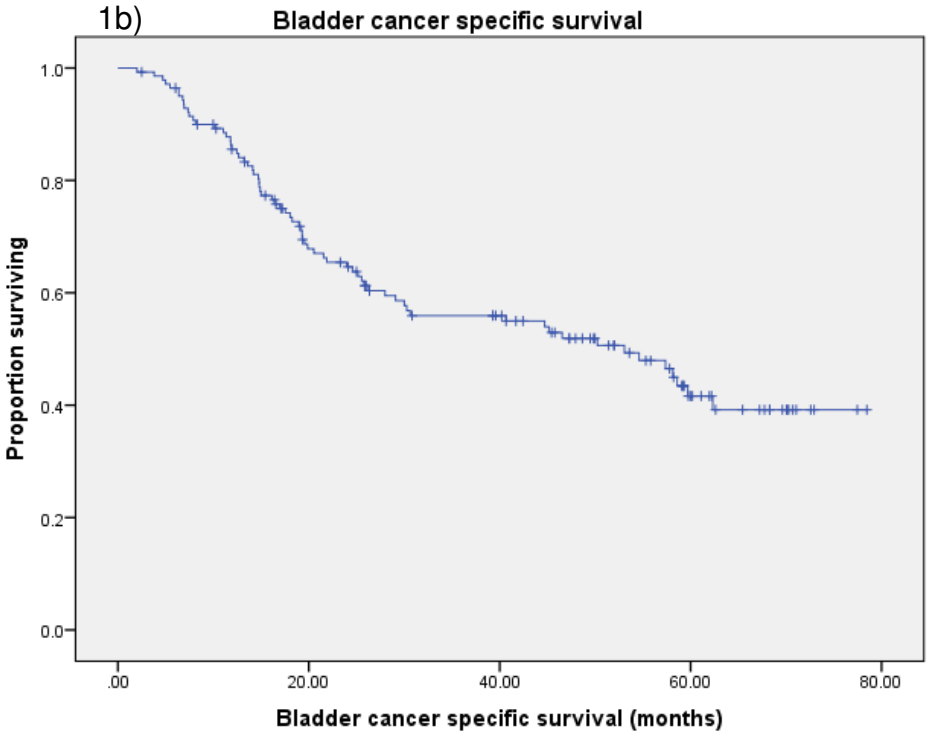
Direction of error	Systematic set-up error in mm (rotations)	Random set-up error in mm (rotations)
Left-Right	2.5 (1.4°)	2.3 (1.2°)
Superior-Inferior	2.7 (1.0°)	1.9 (0.7°)
Anterior-Posterior	2.3 (0.7°)	1.6 (0.6°)

Table 4: Analysis of bladder soft tissue matching of CBCT images compared to planning CT (Population bladder motion)

Organ Motion compared to Planning CT Scan	Percentage of Patients		
	L/R	S/I	A/P
< 5 mm for all fractions	51	39	49
> 5 mm for any fraction	49	61	51
5 - 10 mm for at least 1 fraction	48	58	51
Percentage with motion 5 - 10 mm for 1 fraction	26	24	20
2 fractions	11	18	15
3 fractions	4	7	6
4 fractions	4	7	4
5 fractions	3	2	5
6 fractions			1
10 - 15 mm for at least 1 fraction	9	11	14
Percentage with motion 10 - 15 mm for 1 fraction	7	6	12
2 fractions	1	3	1
3 fractions	1	1	
4 fractions	1	1	
5 fractions			1
6 fractions			
> 15 mm for at least 1 fraction	3	3	3
Percentage with motion > 15 mm for 1 fraction	3	3	2
2 fractions			1
3 fractions			
4 fractions			
5 fractions			
6 fractions			

Figure 1(a) Overall and (b) bladder cancer specific survival for cohort of 141 patients treated with bladder IGRT 2007-2010.





References

[1] Cancer Research UK. *Bladder Cancer Statistics* 2015. [cited 2015 15th June]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer#heading-Zero
[2] Chahal R, Sundaram SK, Iddenden R, Forman DF, Weston PM, Harrison SC. A study of the morbidity, mortality and long-term survival following radical cystectomy and radical radiotherapy in the treatment of invasive bladder cancer in Yorkshire. *Eur Urol* 2003;43:246-257.
[3] (NICE) NIfCE. *Bladder cancer: diagnosis and management* 2015. [cited 2015 15th June]. Available from: http://www.nice.org.uk/guidance/ng2/evidence/full-guideline-3744109
[4] Tester W, Caplan R, Heaney J, et al. Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: results of Radiation Therapy Oncology Group phase II trial 8802. *J Clin Oncol* 1996;14:119-126.
[5] Kaufman DS, Shipley WU, Feldman AS. Bladder cancer. *Lancet* 2009;374:239-249.
[6] Sur RK, Clinkard J, Jones WG, et al. Changes in target volume during radiotherapy treatment of invasive bladder carcinoma. *Clin Oncol (R Coll Radiol)* 1993;5:30-33.
[7] Lalondrelle S, Huddart R. Improving radiotherapy for bladder cancer: an opportunity to integrate new technologies. *Clin Oncol (R Coll Radiol)* 2009;21:380-384.
[8] 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* 2011;79:705-712.
[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* 2006;66:892-897.
[10] Button MR, Staffurth JN. Clinical application of image-guided radiotherapy in bladder and prostate cancer. *Clin Oncol (R Coll Radiol)* 2010;22:698-706.
[11] NRIG Report. Image Guided Radiotherapy (IGRT): Guidance for implementation and use.NHS England August 2012.
[12] Greener AG. Practical determination of systematic and random set-up errors using portal imaging. In: McKenzie A, editor. Geometric Uncertainties in Radiotherapy Treatment Planning. The British Institute of Radiology, 2003. pp. 44-6.
[13] Hurkmans CW, Remeijer P, Lebesque JV and Mijnheer BJ. Set-up verification using portal imaging; review of current clinical practice. Radiother Oncol 2001; 58: 105-20.
[14] On target:ensuring geometric accuracy in radiotherapy. RCR/IPEM/SOR joint publication 2008.
[15]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* 2011;81:765-771.
[16] Murthy V, Master Z, Adurkar P, et al. 'Plan of the day' adaptive radiotherapy for bladder cancer using helical tomotherapy. *Radiother Oncol* 2011;99:55-60.
[17] McDonald F, Lalondrelle S, Taylor H, et al. Clinical implementation of adaptive hypofractionated bladder radiotherapy for improvement in normal tissue irradiation. *Clin Oncol (R Coll Radiol)* 2013;25:549-556.
[18] The Institute of Cancer Research. *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* 2015. [cited 2015 15th June]. Available from:

http://www.icr.ac.uk/our-research/our-research-centres/clinical-trials-and-statistics-unit/clinical-trials/raider
[19] 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;59:436-444.
[20] Hutton D, Blair D, Baker A, Callender J. Evaluating the role of a micro-enema to reduce rectal volume variation and gas during radiotherapy for bladder cancer. Radiotherapy and Oncology, Volume 115, Supplement 1, April 2015, S200-201.
[21] James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle invasive bladder cancer. N Engl J Med 2012; 366: 1477-88.