Clinical Oncology xxx (2010) 1–9

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.elsevier.com/locate/clon

Overview

Clinical Application of Image-guided Radiotherapy in Bladder and Prostate Cancer

M.R. Button *, J.N. Staffurth †

* Oncology Department, Velindre Cancer Centre, Cardiff, UK
† Research Department, Cardiff University, Velindre Cancer Centre, Cardiff, UK

Received 25 January 2010; accepted 30 June 2010

Abstract

Advances in radiotherapy planning reduced the volumes of irradiated normal tissue and allowed safe dose escalation in prostate cancer. Image-guided radiotherapy solutions to prostate and bladder cancer offer further improvements. The initial process is understanding the causes and extent of internal organ motion, followed by development of equipment and protocols to minimise geographical miss. Further refinements may allow margin reduction and further dose escalation. This paper reviews these issues for bladder and prostate cancer.

Key words: Bladder cancer; IGRT; image-guided radiotherapy; internal organ motion; prostate cancer

Statement of Search Strategies Used and Sources of Information

Both authors independently searched MEDLINE using technique-specific terms up to 11 January 2010. Further papers were extracted from the references of papers identified from this MEDLINE search strategy.

Introduction

There has long been an awareness of the need to add margins around the clinically demonstrable tumour to account for diagnostic uncertainties, microscopic spread, subclinical disease and uncertainties inherent in the radiotherapy delivery process. This overview focuses on the clinical perspectives of recent technological advances that attempt to compensate for the internal organ motion that occurs during radiotherapy for bladder and prostate cancer. Advances in planning, such as three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), have reduced the volume of normal tissues irradiated by increasing treatment conformality, which has led to reduced rates and severity of radiation toxicities [1]. Further advances are achievable through improved target volume delineation and increased accuracy of treatment delivery. The latter may allow a safe reduction in clinical target volume (CTV) to planning target volume (PTV) margins, reducing toxicity further. Radiotherapy for both bladder and prostate cancer requires consideration of significant degrees of internal organ motion. Standard practice has been to use population-based data; however, there is much ongoing research into the use of individually defined margins, with further research looking into adapting initial volumes/margins as information accrues during each patient's treatment. This paper reviews issues associated with internal organ motion for bladder and prostate cancer.

Bladder Cancer

Introduction

Bladder cancer is a comparatively uncommon tumour, affecting 8470 patients in England during 2005. There is a relatively poor prognosis, with 3883 dying in the same period in England, reflecting the aggressive tumour biology, often advanced stage at presentation, elderly age and/or

Author for correspondence: J. Staffurth, Research Department, Cardiff University, Velindre Hospital, Whitchurch, Cardiff CF14 2TL, UK. Tel: +29-2031-6964; Fax: +29-205209625. (J. Staffurth).
E-mail address: john.staffurth@velindre-tr.wales.nhs.uk (M.R. Button).

0936-6555/$36.00
doi:10.1016/j.clon.2010.06.020

multiple co-morbidities. For patients with muscle-invasive disease, radical radiotherapy offers equivalent long-term outcomes to cystectomy [2,3] and allows functional organ preservation in about 75% of long-term survivors [4]. Patients may relapse at the site of the primary tumour, at other sites within the genito-urinary tract, in pelvic lymph nodes or with distant metastases. Some patients thought to have localised disease at the time of radical therapy will already have subclinical metastatic disease.

Standard practice within the UK has been to irradiate the whole bladder plus margin in a single phase. The whole bladder is usually defined as the CTV as disease may be multifocal, although there is no proven role for radiotherapy for non-invasive disease [5]. A recent randomised trial showed that partial bladder irradiation (gross tumour volume [GTV] plus margin) could allow moderate dose escalation, with only 7% of patients relapsing within the bladder [6]. Defining the GTV in this setting is challenging, as it may not be well visualised on cross-sectional imaging, especially after trans-urethral resection. There is an uncertain role of pelvic nodal irradiation, although the surgical literature suggests an improved outcome with extended pelvic lymphadenectomy [7].

Neoadjuvant chemotherapy with a cisplatinum-containing regimen has been shown to improve 5 year survival rates by about 5%. It is hoped that concurrent chemoradiation may improve outcomes further. Despite complete response rates in the order of 70%, long-term survival rates remain between 50 and 60% [8,9]. We are presently unable to routinely select treatment modality on an individual basis, although some centres use the response to neoadjuvant chemotherapy or chemoradiation, which is integral to the SPARE study [10]. There are hopes that molecular biology analyses may be useful in this respect in the future.

Computer tomography/positron emission tomography with (11)C-choline, which is not excreted in the urine, shows encouraging preliminary results for the identification of residual muscle-invasive disease after trans-urethral resection and pelvic nodal metastases of 10–15 mm [11,12].

The critical normal structures during whole bladder radiotherapy are the bowel, rectum and, to a lesser extent, the bladder itself [3,10,13,14]. The bowel often lies in direct apposition to the bladder, especially at the dome, so the magnitude of margins applied to the CTV directly affects the volume of bowel within the high-dose region. Henningsohn *et al.* [14] reviewed quality of life in 71 patients irradiated between 1977 and 1995; the results were compared with a population control sample of 310 patients. Irradiated patients had an increased relative risk of 'much' or 'moderate' distress from bowel toxicity of 3.4 and from urinary function of 1.9.

It has been known for many years that bladder volume changes during radiotherapy can cause large variations in the shape and position of the bladder, leading to geographical miss [15]. Furthermore, changes in rectal filling may lead to positional, but not conformational, changes [16–18]. The magnitude of the effect of rectal filling is significantly less than that of bladder filling. Conventionally, relatively large population-based isotropic margins of 15–20 mm are applied to the CTV to avoid geographical miss, but this may be a suboptimal approach for many patients: excessive normal tissue is irradiated in those with smaller variations in position, but geographical miss may still occur in those with larger variations.

Improving Outcomes for Bladder Radiotherapy

Radiotherapy Delivery — the Problem of Motion

The core issue is variation in bladder volume and shape, although changes in bowel and rectal volume can also have clinical relevance. Henry *et al.* [19], in a study with repeat cone-beam computed tomographic imaging (CBCT) during a course of radiotherapy, showed that there are both systematic (Σ) and random (σ) variations in bladder volume, with some patients exhibiting systematic reductions in bladder volume. Changes in bladder volume result in three-dimensional changes in the bladder shape that show inter-individual variations for a given bladder volume change. Studies consistently show larger movements in the anterior and superior direction (up to 30 mm) and smaller movements laterally, inferiorly and posteriorly (requiring margins of about 10 mm) [20–22]. This strongly argues for the use of anisotropic margins for internal organ motion. There are also inter-individual variations in bladder filling rates, which may lead to unpredictable intra-fractional motion. However, there seems to be relatively constant intra-individual bladder filling rates during a course of radiotherapy [23,24].

Investigators from the Netherlands Cancer Institute have tried to quantify the effect of such intra-fractional bladder filling over a 10 min period using both magnetic resonance imaging (MRI) and CBCT. Betgen *et al.* [24] studied bladder cancer patients and reported a mean increase in bladder volume of only 0.5 cm^3/min with changes mainly in the cranial-ventral part of the bladder. There was a large variation in inflow rate between the individual patients (1.2–9.6 cm^3/min). Lotz *et al.* [25] studied healthy volunteers and reported a linear increase in bladder volume with a large inter-individual variation in the inflow rate (2.1–15 cm^3/min), but a small intra-individual variation over time. There was little short-term variation in bladder volume or position.

Invasive bladder cancer seems to affect the relative motion of the bladder wall compared with normal bladder. In a cine-MRI study evaluating intra-fraction motion, McBain *et al.* [26] found that wall displacement was greater, less symmetrical and less predictable in tumour-bearing bladders than in normal bladders — maximum displacement in a 14 min period was over 15 mm on eight of 19 occasions. Tumour position may also be crucial — the above study also reported that bladder expansion is often greatest away from tumour-bearing areas, suggesting that these areas may be less elastic, although no statistical relationship could be concluded [26].

Please cite this article in press as: Button MR, Staffurth JN, Clinical Application of Image-guided Radiotherapy in Bladder and Prostate Cancer, Clinical Oncology (2010), doi:10.1016/j.clon.2010.06.020

Imaging Options During Radiotherapy

Two-dimensional ultrasound imaging of the bladder is simple, rapid, non-invasive and does not result in additional radiation exposure to the patient. It is useful in assessing bladder volume, but this is only a surrogate for position. It can also result in pressure deformation and is somewhat operator dependent. Its use may lie in assessing both inter- and intra-fraction volume changes, thereby differentiating between patients with and without large (random or systematic) volume changes: the latter may benefit from reduced margins [27]; treatment individualisation through the use of more advanced image-guided radiotherapy (IGRT) techniques can be reserved for those with significant variations.

Several imaging modalities can be used to obtain high-quality soft tissue imaging of the bladder during the planning or treatment phase. As well as the conventional modalities (ultrasound, computer tomography and MRI), on-treatment CBCT is usually able to give sufficient resolution to visualise the bladder and rectum [19,24,28]. Fiducial markers can be visualised using electronic portal imaging for IGRT [29] or to aid GTV delineation when considering partial bladder radiotherapy or focal boost. Mangar *et al.* [30] implanted five to six gold seeds into the mucosa or perivesical fat around the tumour bed and into the contralateral wall, 1 week before planning computer tomography in eight patients. A similar technique has also been used to aid target volume delineation [31]. Cystoscopically inserted lipiodol has also been used in a small study to aid tumour delineation and for IGRT [32]. Daily pre-treatment imaging is thus technically feasible, but the optimum frequency and timing of imaging is yet to be established.

Adaptive Radiotherapy Solutions

Inter- and intra-fraction volume changes lead to shape changes rather than a three-dimensional vector displacement of a stable volume. Therefore, any solution must go beyond simply repositioning the isocentre. Immediate re-planning after online imaging would require image acquisition, image transfer, outlining, planning, plan approval, plan checking and plan transfer, posing significant organisational challenges for any radiotherapy department. Furthermore, the time taken would lead to further volume and shape changes. Burridge *et al.* [20] proposed a 'PTV of the day', a technique requiring multiple approved PTVs and plans, corresponding to variable superior CTV to PTV margins (in their report 5, 10 or 15 mm), with a 15 mm CTV to PTV margin in other directions. They proposed CBCT imaging to select the most appropriate plan, ensuring at least 2 mm coverage of the bladder, but other imaging modalities could be used. The main benefit was sparing of small bowel from the high-dose region, but additionally 25% of patients may have benefited from re-planning due to a systematic error. Education of staff to ensure correct plan selection would be required.

A slightly different approach is adaptive predictive organ localisation (A-POLO). The daily target volume and plan is selected individually using a model based on the patient's three-dimensional bladder filling pattern, which is applied to a daily pre-treatment CBCT. The added benefit of A-POLO over Burridge *et al.'s* approach is incorporation of the volume changes from bladder filling during the online processing of the CBCT image [33,34]. As we know that individual bladder filling rates are consistent over time, information from serial imaging, such as cine-MRI during the planning phase, can be used. A similar concept was raised by Muren *et al.* [22] with their use of a larger urine volume during planning (70 ml) than during treatment, incorporating some of the asymmetrical three-dimensional shape changes due to enlarging bladder volume into the planning process. An alternative approach would be to limit changes in bladder volume by restricting fluid intake, but this was unsuccessful in an initial study [35].

An alternative approach is the individualised margin proposed by Pos *et al.* [36], although this report discusses a bladder tumour boost as opposed to whole bladder irradiation. They treated 21 patients using a plan with a 20 mm isotropic margin around the tumour for the first 2 weeks. During the first week, five CBCT images were acquired and used to define an individualised composite GTV by defining the maximal volume on each slice. This was expanded with an isotropic 10 mm margin to create an adaptive PTV, which was treated in a second phase during weeks three and four, with CBCT used to confirm delivery accuracy. They reported 95% GTV coverage and an average 40% reduction in PTV volume. A similar approach has been tried by Foroudi *et al.* [37] for whole bladder radiotherapy with an adaptive CTV outlined as the average volume per slice and expanded isotropically by 15 mm. The varying bladder volumes from the first week's CBCT were also used to create 'plans of the day'. Both techniques could be used to improve subsequent CTV coverage. Rectal irradiation may also be reduced as tighter margins can be safely employed.

Conclusion for Bladder Cancer

This is an important time for bladder cancer radiotherapy, with the prospect of better patient selection based on molecular biology, functional imaging and response to neoadjuvant chemotherapy. Further improvements in outcome should be realised with anisotropic margins and one of several potential IGRT solutions, which should improve delivery accuracy, allow reduced margins and safe dose escalation. The solutions that would probably realise clinical benefits seem to be better patient preparation, off-line adaptive planning and using a 'plan of the day'. Prospective clinical evaluation is needed to show that these complex treatment protocols are deliverable and lead to improved organ preservation or reduced late toxicity.

Prostate Cancer

Introduction

Prostate cancer is now the most common tumour affecting men, with over 35 000 men affected in the UK in 2006 [38]. Five and 10 year survival rates are better than for

Please cite this article in press as: Button MR, Staffurth JN, Clinical Application of Image-guided Radiotherapy in Bladder and Prostate Cancer, Clinical Oncology (2010), doi:10.1016/j.clon.2010.06.020

bladder cancer and many cured men will live for years with the side-effects of their treatment, so optimising the therapeutic ratio is paramount. As there are several radical treatment options that are thought to offer equivalent long-term tumour outcomes, treatment decisions are often based on the respective urinary, gastrointestinal and sexual side-effect profiles. Rectal avoidance, with 3D-CRT, has been shown to reduce the incidence of late rectal toxicity [39]. This has led to a series of dose escalation trials, which have shown an improved long-term tumour control at the expense of increased rectal toxicity [40–44]. Further technological advances that reduce rectal irradiation may allow further safe dose escalation.

Standard practice in the UK is to irradiate the whole prostate (± the seminal vesicles) in either a single phase or two phases. The entire prostate is generally outlined as the GTV (although it truly represents the CTV) as tumours are often multifocal but are difficult to accurately localise. Identification of dominant nodules (with magnetic resonance spectroscopy) or areas of relative radioresistance (with functional MRI identifying hypoxic regions) may allow partial volume irradiation or focal boosting [45–48]. Pelvic nodal radiotherapy remains controversial as it lacks a robust evidence base [49], but functional imaging with (11)C-choline positron emission tomography or MRI with ultra-small iron oxide particles offers hope for the future [50,51].

Improving Outcomes for Prostate Radiotherapy

Radiotherapy delivery — the problem of motion

The considerable internal organ motion of the prostate is primarily due to changes in rectal volume. This has now been shown to impact on tumour control. Two studies in the pre-IGRT era showed that the reduction in biochemical control associated with a large rectal volume at computer tomography planning (over 25 and 20%, respectively, in certain risk groups) was greater than the benefit seen within the dose escalation studies [52,53]. A large rectal cross-sectional area has also been associated with a reduced freedom from biochemical failure, despite the use of implanted fiducial markers and daily image guidance [54]. This surprising result was felt to be related to the relatively tight margins (5 mm in the anterior–posterior direction) and the steeper dose gradients of the conformal arc technique used.

Rectal volume changes and the resultant prostate movements can be sudden, unpredictable and profound, with a wide inter- and intra-patient extent of motion [55–57]. Movements generally lead to a three-dimensional vector shift rather than a change in shape, which can be corrected by repositioning rather than re-planning [58]. The greatest movement is in the anterior–posterior and superior–inferior directions, with larger movement and greater deformation in the seminal vesicles than the prostate [59]. Different systems that allow direct or indirect imaging of the prostate have been developed (discussed below); they reduce the systematic and random error from inter-fractional motion compared with localisation based on bone anatomy and may allow a reduction in margins. Margins required without IGRT have been calculated to be 5.3–9.2, 7.0–14.6 and 8.7–11.0 mm in the left–right, superior–inferior and anterior–posterior dimensions, respectively [60–63]. Offline and online IGRT can be used to reduce these margins, but regardless of the system used, the degree of inter- and intra-patient variation suggests that an individualised, daily online approach is desirable. Residual errors include those from delineation errors, intra-fractional motion, observer error and delivery errors [64,65].

Several authors have studied the intra-fractional component of these residual errors by studying positional accuracy at the end of treatment [66], but the recent introduction of real-time radiographic tracking of fiducial markers and electronic transponders has provided more detail on the extent and impact of intra-fractional errors. Kotte *et al.* [67] studied the intra-fractional motion of 427 patients for 11 426 fractions by taking portal images of the first segment of all five beams and studying the position of the implanted fiducial markers. In 66% of fractions, a motion >2 mm was observed and in 28% a motion >3 mm. Motion was primarily in the superior–inferior and anterior–posterior directions, with population-level systematic errors of 0.5 and 0.6 mm, respectively. As both had random errors of 0.9 mm, a margin of 2 mm should be applied [68]. Several studies from the same group used data from tracked electronic transponder motion during treatment for up to 10 min [55,57,69,70]. They have shown that movements ≥ 3 mm occur for more than 13.6% of treatment time in 41% of treatment sessions and that movement ≥ 5 mm occurs for more than 3.3% of treatment time and in 15% of treatment sessions. The average vector shift from the isocentre was 1.5 ± 0.9 mm. A 2 mm margin minimised the dosimetric consequence of intra-fractional motion.

One solution to reduce motion is improved patient preparation with patient education, dietary advice, laxatives or enemas. These should be started before the planning scan and continued throughout treatment [71–76]. An individualised approach includes re-scanning patients if they have a large rectal diameter at the planning scan stage [77].

Imaging options before radiotherapy

Conventional portal imaging devices cannot visualise the prostate. Several systems that allow direct or indirect imaging of the prostate have been developed, all of which have entered routine clinical practice:

Rectal balloon catheters are inserted into the rectum and filled with ~40 ml air to act as an internal immobilisation device [78]. They have been used with 3D-CRT, IMRT and proton therapy and seem to be well tolerated, although they have never entered routine practice in the UK [79]. Balloons have two main benefits — reducing the extent of prostate motion and increasing the distance from the prostate to the posterior rectal wall [80].

Fiducial markers (e.g. 1 mm diameter gold seeds) can be implanted trans-rectally and imaged using kV or MV

Please cite this article in press as: Button MR, Staffurth JN, Clinical Application of Image-guided Radiotherapy in Bladder and Prostate Cancer, Clinical Oncology (2010), doi:10.1016/j.clon.2010.06.020

electronic portal imaging devices and CBCT [81,82]. Seed implantation requires an invasive procedure with risk of morbidity equivalent to the diagnostic biopsy and seed migration may occur, albeit rarely [83]. Seeds may cause significant image artefact during target volume delineation. New devices are being developed to reduce these issues [84–86]. Fiducial markers allow daily imaging and daily shifts of the isocentre, but require an additional radiation dose. Their use does not remove all geometrical uncertainties — there is evidence of some prostate deformation during radiotherapy [87] and a potentially significant difference in the extent of prostate and seminal vesicle motion [88]. Most of the residual error is due to post-correction intra-fractional organ motion, discussed above, and outlining errors.

BeamCath® is an immobilisation device based on a urethral catheter with radio-opaque fiducial markers in the urethral section to enable visualisation with electronic portal imaging devices [89]. Issues include the need for repeated catheterisation and the sensitivity of the cranio-caudal position of the catheter to the precise volume of air within the catheter balloon [90].

Three-dimensional ultrasound can be used to visualise the prostate and its borders with the rectum and bladder. Several commercial systems are available, e.g. B-Mode Acquisition and Targeting System (BAT, NOMOS Corp, Cranberry Township, PA, USA) and SonArray (Varian Medical Solutions, Palo Alto, CA, USA), which allow visualisation of the outlines of these structures from the planning scan and calculation of the required three-dimensional vector shifts. Criticisms of the systems include inter-observer variations, length of procedure, and that the ultrasound procedure causes temporary prostatic displacement, such that some investigators have suggested that overall, residual errors are not significantly less than weekly or daily pelvic imaging based on bony anatomy [91–94].

Computer tomographic imaging can be used to image the prostate and/or implanted fiducial markers. There are various systems available: kV CBCT [95], kV computer tomography on-rails [96], MV CBCT [97] and helical MV computer tomography within the Tomotherapy Hi-ART system (Tomotherapy Inc., Madison, WI, USA) [98]. Each system allows the acquisition of images of high quality with excellent spatial resolution at the cost of time and ~5–15 cGy per image, which should not be ignored [97,99,100]. Acquired images can be used for the accurate identification of implanted markers and if image quality is sufficient, for direct soft tissue matching as the entire prostate and seminal vesicles can be visualised. Image datasets collected during the initial fractions can also be used to adapt the initial treatment based on individualised margins or delivered dose — 'dose-guided radiotherapy' [101–106].

Imaging options during radiotherapy

Electronic transponders, e.g. Calypso 4D Localisation System (Calypso Medical Technologies Inc., Seattle, WA, USA) can be implanted into the prostate to allow accurate, pre-treatment localisation without additional irradiation of the patient. They give a comparable isocentre position to fiducial markers (within 2 mm) and can be used to assess real-time, intra-fractional motion data [55,57,69,70].

Robotic gantry systems offer the potential for tracking during radiation delivery. One system, Cyberknife (Accuray Incorporated, Sunnyvale, CA, USA), has a linear accelerator mounted on a robotic arm and uses a stereoscopic X-ray system and integrated software to track implanted fiducial markers during IMRT [107]. If intra-fraction motion exceeds the robotic tracking limits, treatment is halted while the patient is repositioned. Patients are generally treated in radically hypofractionated schedules of 35–37.5 Gy at 7–7.5 Gy per fraction [108–110].

In-room kV X-ray systems not only allow the identification of fiducial markers pre-radiotherapy. One commercial system, ExacTrac X-Ray 6D (BrainLab, Germany) incorporates both infrared optical positioning and radiographic kV X-ray imaging from two oblique X-ray imagers. Image fusion based on the kV images is transferred to positional adjustment, which is confirmed with the infrared system [111,112]. They also offer the potential for tracking and gating during radiotherapy, but this clinical application in prostate cancer is presently very limited.

Clinical concepts with image-guided radiotherapy

Advanced radiotherapy delivery systems, such as IMRT (including helical tomotherapy and intensity-modulated arc therapy), robotics and proton therapy, offer increased levels of conformality compared with 3D-CRT, but require more accurate delineation and delivery [113]. The temptation is to immediately use online IGRT solutions to reduce margins and then to explore further dose escalation. However, a period of familiarisation with IGRT to ensure accurate delivery should come first. Data from patients tracked with implanted transponders suggest that population-based margins of 2 mm are sufficient to exclude significant dosimetric consequences from intra-fractional error. This margin will be insufficient for some patients and becomes more important with hypofractionation as the contribution of each fraction is relatively higher [114].

Prostate movements during treatment increase with time, yet IGRT requires image acquisition, analysis and repositioning, all of which increase the time taken to deliver a treatment. Hypofractionation and IMRT also increase treatment time. Inter-beam realignment is possible and may allow further margin reduction at the cost of yet more time [115]. This might be worthwhile for extreme hypofractionation, which is now being explored in prospective clinical studies with advanced IGRT utilising fiducial markers and Cyberknife, but the dosimetric consequences of such intensive imaging protocols must be considered [110,116]. Attention to patient preparation to minimise changes in rectal volume may reduce the benefit from such intensive IGRT solutions and may be the most effective solution to introduce.

IGRT offers the potential of improved accuracy of treatment delivery, which may improve tumour control and

Please cite this article in press as: Button MR, Staffurth JN, Clinical Application of Image-guided Radiotherapy in Bladder and Prostate Cancer, Clinical Oncology (2010), doi:10.1016/j.clon.2010.06.020

allow reduced margins. Reduced margins would be expected to reduce toxicity and may allow a further series of dose escalation studies. One step in this process is the recently approved IGRT substudy within the CHHiP trial expansion (ISRCTN 97182923) [117]. In this substudy, patients will be eligible for randomisation between the standard CHHiP protocol, daily online IGRT with standard margins and daily online IGRT with reduced margins (Professor Dearnaley, personal communication). This trial may be particularly important for the UK, where advanced radiotherapy has been difficult to introduce, despite the National Radiotherapy Action Group report [118,119], yet much progress is expected from the introduction of the National Radiotherapy Implementation Group, the e-learning Advanced Radiotherapy project and the formation of the National Cancer Research Institute's clinical and translational research radiotherapy group [120,121].

Conclusion for Prostate Cancer

Prostate cancer continues in the forefront of research into advanced radiotherapy delivery systems. There is a great deal of data on the extent, time course and direction of prostate motion, which has been the predominant clinical issue and several functional IGRT solutions exist. The improved accuracy from these has increased the significance of delineation errors. Clinical trials to quantify the level of benefit with IGRT and to explore the potential benefit of further dose escalation are underway.

Conclusion

Bladder cancer and prostate cancer are two malignancies where significant target motion occurs, necessitating the use of margins to account for this. The causes and solutions are different: for bladder cancer, changes in the shape of the target volume require changes to the volume treated; for prostate cancer, a three-dimensional vector displacement requires accurate alignment of the isocentre. Historically these margins have been population derived yet this is now known to be suboptimal — individualised margins are desirable and are possible, optimising the accuracy of radiotherapy delivery for each patient. The optimal method for this is yet to be defined.

Radiation oncology is a technologically driven speciality throughout a patient's journey, with parallel advances at each stage (diagnosis, staging, planning, radiotherapy delivery and follow-up investigations) affecting other areas of the process and potentially improving outcome. Isolating, assessing and costing the clinical impact of IGRT is challenging, especially when the time course of clinical end points (late toxicities and long-term tumour control) is considered against the current pace of technological advances.

Acknowledgements

We would like to thank Dr Nachi Palaniappan for identifying two recent references on bladder IGRT.

References

[1] Staffurth JN. A review of clinical evidence for IMRT. *Clin Oncol* 2010;22:8.
[2] Kotwal S, Choudhury A, Johnston C, Paul AB, Whelan P, Kiltie AE. 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* 2008;70(2):456–463.
[3] 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(3):246–257.
[4] Shipley WU, Kaufman DS, Tester WJ, Pilepich MV, Sandler HM. Overview of bladder cancer trials in the Radiation Therapy Oncology Group. *Cancer* 2003;97(Suppl. 8):2115–2119.
[5] Harland SJ, Kynaston H, Grigor K, *et al*. A randomized trial of radical radiotherapy for the management of pT1G3 NXM0 transitional cell carcinoma of the bladder. *J Urol* 2007;178:807–813.
[6] Cowan RA, McBain CA, Ryder WD, *et al*. Radiotherapy for muscle-invasive carcinoma of the bladder: results of a randomized trial comparing conventional whole bladder with dose-escalated partial bladder radiotherapy. *Int J Radiat Oncol Biol Phys* 2004;59(1):197–207.
[7] Sanderson KM, Stein JP, Skinner DG. The evolving role of pelvic lymphadenectomy in the treatment of bladder cancer. *Urol Oncol* 2004;22(3):205–211. discussion 212–213.
[8] Efstathiou JA, Zietman AL, Kaufman DS, Heney NM, Coen JJ, Shipley WU. Bladder-sparing approaches to invasive disease. *World J Urol* 2006;24(5):517–529.
[9] Choueiri TK, Raghavan D. Chemotherapy for muscle-invasive bladder cancer treated with definitive radiotherapy: persisting uncertainties. *Nat Clin Pract Oncol* 2008;5(8):444–454.
[10] Zietman AL, Sacco D, Skowronski U, *et al*. Organ conservation in invasive bladder cancer by transurethral resection, chemotherapy and radiation: results of a urodynamic and quality of life study on long-term survivors. *J Urol* 2003;170 (5):1772–1776.
[11] De Jong IJ, Pruim J, Elsinga PH, Jongen MM, Mensink HJ, Vaalburg W. Visualisation of bladder cancer using (11)C-choline PET: first clinical experience. *Eur J Nucl Med Mol Imaging* 2002;29(10):1283–1288.
[12] Picchio M, Treiber U, Beer AJ, *et al*. Value of 11C-choline PET and contrast-enhanced CT for staging of bladder cancer: correlation with histopathologic findings. *J Nucl Med* 2006;47 (6):938–944.
[13] 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 (14):3061–3071.
[14] Henningsohn L, Wijkstrom H, Dickman PW, Bergmark K, Steineck G. Distressful symptoms after radical radiotherapy for urinary bladder cancer. *Radiother Oncol* 2002;62(2):215–225.
[15] Harris SJ, Buchanan RB. An audit and evaluation of bladder movements during radical radiotherapy. *Clin Oncol* 1998;10 (4):262–264.
[16] Pos FJ, Hulshof M, Lebesque J, *et al*. Adaptive radiotherapy for invasive bladder cancer: a feasibility study. *Int J Radiat Oncol Biol Phys* 2006;64(3):862–868.
[17] Lotz HT, Remeijer P, van Herk M, *et al*. A model to predict bladder shapes from changes in bladder and rectal filling. *Med Phys* 2004;31(6):1415–1423.

Please cite this article in press as: Button MR, Staffurth JN, Clinical Application of Image-guided Radiotherapy in Bladder and Prostate Cancer, Clinical Oncology (2010), doi:10.1016/j.clon.2010.06.020

[18] Fokdal L, Hoyer M, von der Maase H. Radical radiotherapy for urinary bladder cancer: treatment outcomes. *Expert Rev Anticancer Ther* 2005;6(2):269–279.
[19] Henry AM, Stratford J, McCarthy C, *et al*. X-ray volume imaging in bladder radiotherapy verification. *Int J Radiat Oncol Biol Phys* 2006;64(4):1174–1178.
[20] 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(3):892–897.
[21] 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(5):1277–1287.
[22] 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(3):291–304.
[23] McBain CA, Green MM, Stratford J. Ultrasound imaging to assess inter- and intra-fraction motion during bladder radiotherapy and its potential as a verification tool. *Clin Oncol* 2009;21:385–393.
[24] Betgen A, Van Herk M, Lotz H, Pos F, Remeijer P, Sonke J. Changes in patient setup and bladder volume during irradiation of bladder cancer patients. *Radiother Oncol* 2005;76(S2): S104.
[25] Lotz HT, Pos F, Hulshof M, *et al*. Tumor motion and deformation during external radiotherapy of bladder cancer. *Int J Radiat Oncol Biol Phys* 2006;64(5):1551–1558.
[26] McBain CA, Khoo V, Buckley DL. Assessment of bladder motion for clinical radiotherapy practice using cine-magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 2009;75: 664–671.
[27] Mangar SA, Miller NR, Khoo V, *et al*. Evaluating inter-fractional changes in volume and position during bladder radiotherapy and the effect of volume limitation as a method of reducing the internal margin of the planning target volume. *Clin Oncol* 2008;20:698–704.
[28] Foroudi F, Haworth A, Pangehel A, *et al*. Inter-observer variability of clinical target volume delineation for bladder cancer using CT and cone beam CT. *J Med Imaging Radiat Oncol* 2009;53(2):100–106.
[29] Lalondrelle S, Thompson A, Khoo V. Fiducial markers in external beam radiotherapy for bladder cancer. *Radiother Oncol* 2007;85(2):324.
[30] Mangar S, Thompson A, Miles E, Huddart R, Horwich A, Khoo V. A feasibility study of using gold seeds as fiducial markers for bladder localization during radical radiotherapy. *Br J Radiol* 2007;20:279–283.
[31] Hulshof M, van Andelb G, Bela A, Gangela P, van de Kamera JB. Intravesical markers for delineation of target volume during external focal irradiation of bladder carcinomas. *Radiother Oncol* 2007;84:49–51.
[32] Pos F, Bex A, Dees-Ribbers HM, Betgen A, van Herk M, Remeijer P. Lipiodol injection for target volume delineation and image guidance during radiotherapy for bladder cancer. *Radiother Oncol* 2009;93(2):364–367.
[33] Lalondrelle S, Hansen V, Aitken A, Khoo V. Adaptive-predictive organ localisation (A-POLO): evaluation of a novel adaptive planning methodology. *Radiother Oncol* 2008;88 (Suppl. 2):S32.
[34] Lalondrelle S, Huddart R. Improving radiotherapy for bladder cancer: an opportunity to integrate new technologies. *Clin Oncol* 2009;21(5):380–384.
[35] Muren LP, Redpath AT, Lord H, McLaren DB. Image-guided radiotherapy of bladder cancer: bladder volume variation and its relation to margins. *Radiother Oncol* 2007;84(3):307–313.
[36] Pos FJ, van Tienhoven G, Hulshof MC, Koedooder K, Gonzalez Gonzalez D. Concomitant boost radiotherapy for muscle invasive bladder cancer. *Radiother Oncol* 2003;68 (1):75–80.
[37] Foroudi F, Wong J, Haworth A, *et al*. Offline adaptive radiotherapy for bladder cancer using cone beam computed tomography. *J Med Imaging Radiat Oncol* 2009;53(2): 226–233.
[38] http://info.cancerresearchuk.org/; 2009.
[39] Dearnaley DP, Khoo VS, Norman AR, *et al*. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet* 1999;353(9149):267–272.
[40] Zietman AL, DeSilvio ML, Slater JD, *et al*. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005;294(10):1233–1239.
[41] Dearnaley DP, Hall E, Lawrence D, *et al*. Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: PSA control and side effects. *Br J Cancer* 2005; (92):488–492.
[42] Kuban DA, Tucker SL, Dong L, *et al*. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70(1):67–74.
[43] Peeters ST, Heemsbergen WD, Koper PC, *et al*. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006;24(13): 1990–1996.
[44] Dearnaley DP, Sydes MR, Graham JD, *et al*. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007;8(6):475–487.
[45] Nutting CM, Corbishley CM, Sanchez-Nieto B, Cosgrove VP, Webb S, Dearnaley DP. Potential improvements in the therapeutic ratio of prostate cancer irradiation: dose escalation of pathologically identified tumour nodules using intensity modulated radiotherapy. *Br J Radiol* 2002;75(890): 151–161.
[46] Testa C, Schiavina R, Lodi R, *et al*. Prostate cancer: sextant localization with MR imaging, MR spectroscopy, and 11C-choline PET/CT. *Radiology* 2007;244:797–806.
[47] Piert M, Park H, Khan A, *et al*. Detection of aggressive primary prostate cancer with 11C-choline PET/CT using multimodality fusion techniques. *J Nucl Med* 2009;50(10): 1585–1593.
[48] Farsad M, Schiavina R, Castellucci P, *et al*. Detection and localization of prostate cancer: correlation of 11C-choline PET/CT with histopathologic step-section analysis. *J Nucl Med* 2005;46(10):1642–1649.
[49] Roach 3rd M, DeSilvio M, Lawton C, *et al*. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol* 2003;21(10):1904–1911.
[50] Harisinghani MG, Barentsz J, Hahn PF, *et al*. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *N Engl J Med* 2003;348(25):2491–2499.
[51] de Jong I, Jan Pruim J, Elsinga P, Vaalburg W, Mensink H. Preoperative staging of pelvic lymph nodes in prostate cancer by 11C-choline PET. *J Nucl Med* 2003;44(3):331–335.
[52] de Crevoisier R, Tucker SL, Dong L, *et al*. Increased risk of biochemical and local failure in patients with distended rectum on the planning CT for prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;62(4):965–973.

Please cite this article in press as: Button MR, Staffurth JN, Clinical Application of Image-guided Radiotherapy in Bladder and Prostate Cancer, Clinical Oncology (2010), doi:10.1016/j.clon.2010.06.020

[53] Heemsbergen WD, Hoogeman MS, Witte MG, Peeters ST, Incrocci L, Lebesque JV. Increased risk of biochemical and clinical failure for prostate patients with a large rectum at radiotherapy planning: results from the Dutch trial of 68 Gy versus 78 Gy. *Int J Radiat Oncol Biol Phys* 2007;67(5):1418–1424.

[54] Engels B, Soete G, Verellen D, Storme G. Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distended rectum on the planning computed tomogram despite image guidance by implanted markers. *Int J Radiat Oncol Biol Phys* 2009;74(2):383–391.

[55] Willoughby T, Kupelian P, Pouliot J, *et al*. Target localization and real-time tracking using the Calypso 4D localization system in patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2006;65(2):528–534.

[56] Padhani AR, Khoo VS, Suckling J, Husband JE, Leach MO, Dearnaley DP. Evaluating the effect of rectal distension and rectal movement on prostate gland position using cine MRI. *Int J Radiat Oncol Biol Phys* 1999;44(3):525–533.

[57] Kupelian P, Willoughby T, Mahadevan A, *et al*. Multi-institutional clinical experience with the Calypso system in localization and continuous, real-time monitoring of the prostate gland during external radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;67(4):1088–1098.

[58] Lerma F, Liu B, Wang Z, *et al*. Role of image-guided patient repositioning and online planning in localized prostate cancer IMRT. *Radiat Oncol* 2009;93(1):18–24.

[59] Frank S, Dong L, Kudchadker R, *et al*. Quantification of prostate and seminal vesicle interfraction variation during IMRT. *Int J Radiat Oncol Biol Phys* 2008;71(3):813–820.

[60] Chen J, Lee RJ, Handrahan D, Sause W. Intensity-modulated radiotherapy using implanted fiducial markers with daily portal imaging: assessment of prostate organ motion. *Int J Radiat Oncol Biol Phys* 2007;68(3):912–919.

[61] Trichter F, Ennis RD. Prostate localization using transabdominal ultrasound imaging. *Int J Radiat Oncol Biol Phys* 2003;56:1225–1233.

[62] Chandra A, Dong L, Huang E, *et al*. Experience of ultrasound based daily prostate localization. *Int J Radiat Oncol Biol Phys* 2003;56:436–447.

[63] Antolak JA, Rosen II , Childress CH, Zagars GK, Pollack A. Prostate target volume variations during a course of radiotherapy. *Int J Radiat Oncol Biol Phys* 1998;42(3):661–672.

[64] Craig T, Satkusagingham J, Chan K, *et al*. Advanced image guidance allows margin reduction in radiation therapy of prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;72(Suppl. 1):S551.

[65] McNair H, Hansen V, Parker C, *et al*. A comparison of the use of bony anatomy and internal markers for offline verification and an evaluation of the potential benefit of online and offline verification protocols for prostate radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;71(1):41–50.

[66] Drabik DM, MacKenzie M, Fallone GB. Quantifying appropriate PTV setup margins: analysis of patient setup fidelity and intrafraction motion using post-treatment megavoltage computed tomography scans. *Int J Radiat Oncol Biol Phys* 2007;68(4):1222–1228.

[67] Kotte A, Hofman P, Lagendijk JJ, van Vulpen M, van der Heide UA. Intrafraction motion of the prostate during external beam radiation therapy: analysis of 427 patients with implanted fiducial markers. *Int J Radiat Oncol Biol Phys* 2007;69(2):419–425.

[68] van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;47(4):1121–1135.

[69] Langen K, Willoughby T, Meeks S, *et al*. Observations on real-time prostate gland motion using electromagnetic tracking. *Int J Radiat Oncol Biol Phys* 2008;71(4):1084–1090.

[70] Li H, Chetty I, Enke C, *et al*. Dosimetric consequences of intrafraction prostate motion. *Int J Radiat Oncol Biol Phys* 2008;71:801–812.

[71] O'Doherty U, McNair H, Norman A, *et al*. Variability of bladder filling in patients receiving radical radiotherapy to the prostate. *Radiother Oncol* 2006;79(3):335–340.

[72] Smitsmans M, Pos F, de Bois J, *et al*. The influence of a dietary protocol on cone beam CT-guided radiotherapy for prostate cancer patients. *Int J Radiat Oncol Biol Phys* 2008;71(4):1279–1286.

[73] Nichol AM, Warde PR, Lockwood GA, *et al*. A cinematic magnetic resonance imaging study of milk of magnesia laxative and an antiflatulent diet to reduce intrafraction prostate motion. *Int J Radiat Oncol Biol Phys* (in press).

[74] Stasi M, Munoz F, Fiorino C, *et al*. Emptying the rectum before treatment delivery limits the variations of rectal dose-volume parameters during 3DCRT of prostate cancer. *Radiat Oncol* 2006;80(3):363–370.

[75] Ogino I, Uemura H, Inoue T, Kubota Y, Nomura N. Reduction of prostate motion by removal of gas in rectum during radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;72(2):456–466.

[76] Fiorino C, Di Muzio N, Broggi S, *et al*. Evidence of limited motion of the prostate by carefully emptying the rectum as assessed by daily MVCT image guidance with helical tomotherapy. *Int J Radiat Oncol Biol Phys* 2008;71(2):611–617.

[77] Stillie AL, Krony T, Foxy C, *et al*. Rectal filling at planning does not predict stability of the prostate gland during a course of radical radiotherapy if patients with large rectal filling are re-imaged. *Clin Oncol* 2009;21:760–767.

[78] Teh BS, Lu HH, Sobremonte S, *et al*. The potential use of intensity modulated radiotherapy (IMRT) in women with pectus excavatum desiring breast-conserving therapy. *Breast J* 2001;7(4):233–239.

[79] Ronson BB, Yonemoto LT, Rossi CJ, Slater JM, Slater JD. Patient tolerance of rectal balloons in conformal radiation treatment of prostate cancer. *Int J Radiat Oncol Biol Phys* 2006;64(5):1367–1370.

[80] Gerstner N, Wachter S, Dorner D, Goldner G, Colotto A, Pötter R. Significance of a rectal balloon as internal immobilization device in conformal radiotherapy of prostatic carcinoma. *Strahlenther Onkol* 1999;175(5):232–238.

[81] Crook J, Raymond Y, Salhani D, Yang Y. Prostate motion during standard radiotherapy as assessed by fiducial markers. *Radiat Oncol* 1995;37(1):35–42.

[82] Wu J, Haycocks T, Alasti H, Ottewell G. Positioning errors and prostate motion during conformal radiotherapy using on-line isocentre set-up verification and implanted prostate markers. *Radiat Oncol* 2001;61(2):127–133.

[83] Poggi M, Gant D, Sewchand W, Warlick W. Marker seed migration in prostate localization. *Int J Radiat Oncol Biol Phys* 2003;56(5):1248–1251.

[84] Carl J, Nielsen J, Holmberg M, Højkjaer Larsen E, Fabrin K, Fisker RV. A new fiducial marker for image-guided radiotherapy of prostate cancer: clinical experience. *Acta Oncol* 2008;47(7):1358–1366.

[85] Pouliot J, Aubin M, Langen K, *et al*. (Non)-migration of radiopaque markers used for on-line localization of the prostate with an electronic portal imaging device. *Int J Radiat Oncol Biol Phys* 2003;56(3):862–866.

Please cite this article in press as: Button MR, Staffurth JN, Clinical Application of Image-guided Radiotherapy in Bladder and Prostate Cancer, Clinical Oncology (2010), doi:10.1016/j.clon.2010.06.020

[86] Adamson J, Wu Q. Inferences about prostate intrafraction motion from pre- and posttreatment volumetric imaging. *Int J Radiat Oncol Biol Phys* 2009;75(1):260–267.
[87] Nichol A, Brock K, Lockwood G, *et al*. A magnetic resonance imaging study of prostate deformation relative to implanted gold fiducial markers. *Int J Radiat Oncol Biol Phys* 2007;67: 48–56.
[88] Miralbell R, Ozsoy O, Pugliesi A, *et al*. Dosimetric implications of changes in patient repositioning and organ motion in conformal radiotherapy for prostate cancer. *Radiat Oncol* 2003;66(2):197–202.
[89] Bergstrom P, Lofroth PO, Widmark A. High-precision conformal radiotherapy (HPCRT) of prostate cancer—a new technique for exact positioning of the prostate at the time of treatment. *Int J Radiat Oncol Biol Phys* 1998;42(2):305–311.
[90] Poulsen PR, Fokdal L, Petersen J, Høyer M. Accuracy of image-guided radiotherapy of prostate cancer based on the BeamCath urethral catheter technique. *Radiother Oncol* 2007;83(1):25–30.
[91] Scarbrough TJ, Golden NM, Ting JY, *et al*. Comparison of ultrasound and implanted seed marker prostate localization methods: implications for image-guided radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;65(2):378–387.
[92] Artignan X, Smitmans M, Lebesque J. Online ultrasound image guidance for radiotherapy of prostate cancer: impact of image acquisition on prostate displacement. *Int J Radiat Oncol Biol Phys* 2004;59(2):595–601.
[93] Langen K, Pouliot J, Anezinos C, *et al*. Evaluation of ultrasound-based prostate localization for image-guided radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;57(3):635–644.
[94] McNair H, Mangar S, Coffey J, *et al*. A comparison of CT- and ultrasound-based imaging to localize the prostate for external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;65 (3):678–687.
[95] Smitsmans M, de Bois J, Sonke J, *et al*. Automatic prostate localization on cone-beam CT scans for high precision image-guided radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;63(4):975–984.
[96] Wong J, Grimm L, Uematsu M, *et al*. Image-guided radiotherapy for prostate cancer by CT-linear accelerator combination: prostate movements and dosimetric considerations. *Int J Radiat Oncol Biol Phys* 2005;61(2):561–569.
[97] Pouliot J, Bani-Hashemi A, Chen J, *et al*. Low-dose megavoltage cone-beam CT for radiation therapy. *Int J Radiat Oncol Biol Phys* 2005;61(2):552–560.
[98] Keiler L, Dobbins D, Kulasekere R, Einstein D. Tomotherapy for prostate adenocarcinoma: a report on acute toxicity. *Radiother Oncol* 2007;84(2):171–176.
[99] Ding G, Coffey C. Radiation dose from kilovoltage cone beam computed tomography in an image-guided radiotherapy procedure. *Int J Radiat Oncol Biol Phys* 2009;73(2):610–617.
[100] Letourneaue D, Wong J, Oldham M, *et al*. Cone-beam CT guided radiation therapy: technical implementation. *Radiat Oncol* 2005;75:279–286.
[101] Martinez AA, Yan D, Lockman D, *et al*. Improvement in dose escalation using the process of adaptive radiotherapy combined with three-dimensional conformal or intensity-modulated beams for prostate cancer. *Int J Radiat Oncol Biol Phys* 2001;50(5):1226–1234.
[102] Cheung J, Aubry J, Yom S, Gottschalk A, Celi J, Pouliot J. Dose recalculation and the dose-guided radiation therapy (DGRT) process using megavoltage cone-beam CT. *Int J Radiat Oncol Biol Phys* 2009;74(2):583–592.
[103] Sorcini B, Tilikidis A. Clinical application of image-guided radiotherapy, IGRT (on the Varian OBI platform). *Cancer Radiother* 2006;10(5):252–257.
[104] Owen R, Kron T, Foroudi F, *et al*. Comparison of CT on rails with electronic portal imaging for positioning of prostate cancer patients with implanted fiducial markers. *Int J Radiat Oncol Biol Phys* 2009;74(3):906–912.
[105] Varadhan R, Hui S, Way S, Nisi K. Assessing prostate, bladder and rectal doses during image guided radiation therapy—need for plan adaptation? *J Appl Clin Med Phys* 2009;10(3):2883.
[106] Sterzing F, Kalz J, Sroka-Perez G, *et al*. Megavoltage CT in helical tomotherapy — clinical advantages and limitations of special physical characteristics. *Technol Cancer Res Treat* 2009;8(5):343–352.
[107] Hossain S, Xia P, Chuang C, *et al*. Simulated real time image guided intrafraction tracking-delivery for hypofractionated prostate IMRT. *Med Phys* 2008;35(9):4041–4048.
[108] Townsend N, Huth B, Ding W, *et al*. Acute toxicity after CyberKnife-delivered hypofractionated radiotherapy for treatment of prostate cancer. *Am J Clin Oncol 2010* (in press), doi:10.1097/COC.0b013e3181c4c7c4.
[109] Friedland J, Freeman D, Masterson-McGary M, Spellberg D. Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. *Technol Cancer Res Treat* 2009;8(5):387–392.
[110] King C, Brooks J, Gill H, Pawlicki T, Cotrutz C, Presti J. Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. *Int J Radiat Oncol Biol Phys* 2009;75(2):632.
[111] Jin J, Yin F, Tenn S, Medin P, Solberg T. Use of the BrainLAB ExacTrac X-ray 6D system in image-guided radiotherapy. *Med Dosim* 2008;33(2):124–134.
[112] Soete G, Van de Steene J, Verellen D, Vinh V. Initial clinical experience with infrared-reflecting skin markers in the positioning of patients treated by conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;52 (3):694–698.
[113] Yoon M, Kim D, Shin DH. Inter- and intrafractional movement induced dose reduction of prostate target volume in proton beam treatment. *Int J Radiat Oncol Biol Phys* 2008;71:1091–1102.
[114] Song W, Schaly B, Bauman G, Battista J, Van Dyk J. Impact on the outcomes of hypofractionated prostate cancer treatments: a radiobiologic analysis. *Int J Radiat Oncol Biol Phys* 2006;64(1):289–300.
[115] Litzenberg D, Balter J, Hadley S, *et al*. Influence of intrafraction motion on margins for prostate radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;65(2):548–553.
[116] Tang CI, Loblaw DA, Cheung P, *et al*. Phase I/II study of a five fraction hypofractionated accelerated radiotherapy treatment for low-risk localised prostate cancer: early results of pHART3. *Clin Oncol* 2008;20:729–737.
[117] Khoo VS, Dearnaley DP. Question of dose, fractionation and technique: ingredients for testing hypofractionation in prostate cancer—the CHHiP trial. *Clin Oncol* 2008;20(1): 12–14.
[118] Hoskin PJ. Hypofractionation in prostate cancer: how far can we go? *Clin Oncol* 2008;20:727.
[119] National Radiotherapy Advisory Group. *Radiotherapy: developing a world class service for England. Report to Ministers from the National Radiotherapy Advisory Group*, http://www.cancer.nhs.uk/nrag.htm; 2007. Available at.
[120] Maughan TS. A new opportunity for radiotherapy research in the UK. *Clin Oncol* 2009;21(3):157–158.
[121] http://www.dh.gov.uk/en/Healthcare/Cancer/Treatment/index.htm; 2009.

Please cite this article in press as: Button MR, Staffurth JN, Clinical Application of Image-guided Radiotherapy in Bladder and Prostate Cancer, Clinical Oncology (2010), doi:10.1016/j.clon.2010.06.020