**Title:** Identifying the Dominant Prostate Cancer Focal Lesion using Image Analysis and Planning of a Simultaneous Integrated SABR Boost

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Abstract

Background: Prostate cancer is now the only solid organ cancer in which therapy is commonly applied to the whole gland. One of the main challenges in adopting focal boost or true focal therapy is in the accurate mapping of cancer foci defined on magnetic resonance (MR) images onto the computerised tomography (CT) images used for radiotherapy planning.

Materials and Methods: Prostate cancer patients (n=14) previously treated at the Edinburgh Cancer Centre (ECC) were selected for this study. All patients underwent MR scanning for the purpose of diagnosis and staging. Patients received 3 months of androgen deprivation hormone therapy followed by a radiotherapy planning CT scan. The dominant focal prostate lesions were identified on MR scans by a radiologist and a novel image analysis approach was used to map the location of the dominant focal lesion from MR to CT. An offline planning study was undertaken on suitable patients (n=7) to investigate boosting the radiation dose to the tumour using a stereotactic ablative body radiotherapy (SABR) technique.

Results: The non-rigid registration algorithm showed clinically acceptable estimates of the location of the dominant focal disease on all CT image data of patients suitable for a boost treatment. Standard rigid registration was found to produce unacceptable estimates of the dominant focal lesion on CT. A SABR boost dose of 47.5 Gy was delivered to the dominant focal lesion of all patients whilst meeting all dose volume histogram (DVH) constraints. Normal tissue complication probability (NTCP) for the rectum decreased from 1.28% to 0.73% with this method.

Conclusions: These preliminary results demonstrate the potential of this image analysis method for reliably mapping dominant focal disease within the prostate from MR images onto planning CT images. Significant dose escalation using a simultaneous integrated SABR boost was achieved in all patients.
Introduction

Prostate cancer, which accounts for 25% of new male cancers, is now the only solid organ cancer in which therapy is applied to the whole gland [1]. Traditionally whole gland ablative treatment with radiotherapy or surgery has been utilized due to the perception that disease is multifocal within the prostate. There has however been significant progress in detecting localized low-risk prostate cancer through prostate-specific antigen (PSA) screening and in identifying its location within the prostate gland using trans-rectal biopsies, template mapping biopsies and multi-parametric magnetic resonance (MR) imaging. Identification of early disease with small dominant focal volumes opens up the possibility of truly focal treatment of the cancer within the prostate using techniques such as radiotherapy, thus preserving genitourinary and rectal function in low- to moderate-risk prostate cancer patients [2]. Alternatively a boost may be applied to the tumour whilst a tumoricidal lower dose is delivered to the rest of the prostate gland providing that dose constraints to the surrounding normal tissues are met. This form of treatment may be applicable to patients with low-risk unifocal disease and patients with high-risk multi-focal disease.

Histological validation studies have confirmed that a dominant unifocal lesion greater than 0.5 cc may be present in up to 70% of men newly diagnosed with localized prostate cancer [3-5]. Treating the dominant focus or boosting the dose to this area while reducing the dose to as much healthy tissue as possible has significant potential for improving treatment [1]. The availability of multi-parametric MR imaging, which incorporates a number of MR sequences such as: T2- and diffusion-weighted; dynamic contrast enhanced (DCE); and spectroscopy has opened up the possibility of reliably identifying cancer foci within the prostate gland [6] (Figure 1). However, although MR is commonly used for diagnosis, staging and performing MR-guided prostate core biopsies, it is not used routinely in radiotherapy planning to identify focal areas for localized radiotherapy in prostate cancer. With the capabilities of
modern linear accelerators, which now include high-definition multi-leaf collimators (MLC), increased dose rates, six-degree of freedom couches and cone-beam computed tomography (CBCT) as standard, there are no technical barriers to delivering radiotherapy to small focal lesions within the prostate gland [7].

Mapping the dominant cancer foci defined on diagnostically acquired MR images, where there is no haemorrhage or distortion as a result of biopsy and gold marker implantation, onto CT is essential for radiotherapy planning. However, this is technically challenging. The focus of this paper, and our research, is in developing novel image analysis techniques to help identify the dominant tumour focus on MR and then to automatically and accurately replicate these volumes on the planning CT scan in all dimensions to allow truly focal boost or focal only therapy. Here, the image analysis methodology was tested in a planning study that shows the potential tumour dose escalation that could be achieved using a stereotactic ablative body radiotherapy technique (SABR) combined with a simultaneous integrated boost (SIB) (SABR-SIB), when the dominant focal lesion was accurately mapped from MR to the radiotherapy planning CT images.

In this pilot study a novel image analysis/registration algorithm was developed to map dominant focal cancerous lesions identified on diagnostic pre-biopsy T2-weighted MR images, where they are visible, onto radiotherapy planning CT images, where they are not visible. Using a SABR-SIB planning approach dose escalation was applied to the CT images where the dominant focal lesion was obtained from the MR images. The primary objectives were two-fold: 1) to determine if the proposed registration algorithm provides superior and reliable automatic mapping of focal prostatic tumour volume identified on T2-weighted MR images to radiotherapy planning CT images and 2) to determine if this registration method would permit reliable localized dose-escalation.
**Material and Methods**

**Clinical Data Acquisition and Planning**

Archival data from 14 prostate cancer patients previously treated at the Edinburgh Cancer Centre (ECC) with whole gland radiotherapy were selected for the study. The planning CT images, diagnostic T2-weighted MR images, radiotherapy treatment plan, and clinical structure set were available for each case. Pixel resolution in the transaxial plane was in the range 0.84 to 1.19 mm for CT and 0.39 to 0.70 mm for MR. All patients had gold fiducial markers implanted for treatment verification prior to the acquisition of the planning CT and received androgen deprivation therapy in the time between the acquisition of the MR and CT images. Each patient was treated using a volumetric arc therapy (VMAT) technique where the prescription dose was chosen from one of the two arms of the Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHIP) trial protocol [8]. Specifically, 57 Gy was prescribed in 19 fractions (fx) to the whole prostate including the seminal vesicles, or 74 Gy was prescribed in 37 fx with 74 Gy prescribed to the whole prostate and 60 Gy prescribed to an expanded volume including the seminal vesicles.

**The Registration Framework**

Image registration, or image fusion, is the process of aligning images acquired at different time-points or from different modalities in order to establish the correspondence between complementary image features so that direct comparisons can be made [9]. Rigid transformation methods usually involve translating and rotating one image to find the optimal correspondence in the other. An example of a rigid registration used in clinical practice is shown in Figure 1 where a radiotherapy planning CT image and diagnostic T2-weighted MR image have been co-registered. From the position of the bladder, prostate and rectum contours originally defined on...
the planning CT and mapped to the MR it is clear that rigid registration results in significant errors in cross-modality mapping.

Non-rigid, or deformable, registration is more appropriate for matching soft tissue structures that have undergone elastic deformation between image acquisitions [10-14]. However, non-rigid registration is not used as extensively as it could be due to the lack of confidence in the mapping between the reference and floating image. This is because there is no guarantee that a feature, or detail, on the reference image will be present on the target image and therefore an approximation has to be made based on the optimal correspondence between the two images. The constraints used to define the allowable range of movement of any single feature, or pixel, also play an important role in defining the final outcome. For example, as shown in Figure 2 (left), when using a rigid registration approach to map the position of a dominant focal lesion firstly identified on a diagnostic MR onto a radiotherapy planning CT, it is possible that the lesion will be placed outside of the prostate volume on the CT. By calculating the non-rigid deformation pattern that the prostate undergoes between MR and CT acquisition it is possible to obtain a more logical position for the focal lesion inside the prostate, as demonstrated in Figure 2 (right). This is because each point on the MR prostate volume has a unique position on the CT prostate volume and therefore voxels inside the MR volume will remain inside the CT volume.

Regardless of the approach used for image registration the underlying registration mechanism remains unchanged. Typically, given a fixed reference image and a floating image, image registration is the process of finding the transformation \( T \) that maximises a measure of similarity, or the match between common features, on two images. However, it is often difficult to identify suitable features acquired on different imaging modalities because of differences in resolution, scale and position. The algorithm developed here overcomes these issues and has the ability to perform rigid
only registration in situations where there is limited distortion, or rigid combined with non-rigid registration when there is significant distortion.

The rigid registration method presented here contains four key stages: pre-processing; feature extraction with the scale invariant feature transform (SIFT); calculation of the mutual information (MI); and optimization [15, 16]. De-noising, resampling of the original data set and the down-sampling of the resulting images were included in the pre-processing stage. To ensure a one-to-one mapping between the pixels on the MR and CT images bilinear interpolation was used to resample the images to have the same resolution and geometry. Common features on the reference and floating images were identified using the SIFT method described in the following section.

The SIFT method was first used to find robust scale invariant feature points in the MR and corresponding CT images of each patient [15]. Using a difference of Gaussian filtering function the SIFT method detects key points in the MR and CT images that are invariant to changes in scale. The most stable key points, or features, across all scales are used to map information between the MR and CT images. To reduce the error between corresponding feature points due to the difference in MR and CT image resolution, the feature points were expanded into three-dimensional (3D) cubes. Each cube, which was made up of 3×3×3 pixels, removed the sensitivity of the approach to the pixels surrounding each SIFT feature point. The MI of each feature point and neighbouring volume on the reference and target image was calculated to assess the degree of shared information between them. The matching of points is performed over a 7-dimensional parameter space involving translations \((T_x, T_y, T_z)\), rotations \((R_x, R_y, R_z)\) and a scale factor \(\mu\). From this
the optimum rigid transform between the reference and target image is found by maximising the MI of corresponding cubes.

Non-rigid registration was applied after rigid registration to form a general framework for dealing with image distortion between MR and CT images of the prostate. A commonly used interpolation technique for deformable registration is the cubic B-spline interpolation method [17]. This method was used to control the smooth transformation of the target image, in this case the rigidly obtained MR image, by making appropriate adjustments to the coefficients of the B-spline parameters (basis functions). Here the transformation was driven by optimisation of the previously calculated SIFT features and neighbouring volumes.

The registration framework developed here and used to establish the mapping between dominant cancerous foci on MR and CT comprises two stages. (1) Rigid registration using 3D SIFT-based features identified on the reference and target image and an MI-based similarity function for identifying the best match between 3D SIFT features on the reference and target images. (2) Part 1 is followed by the application of a cubic B-spline approach to non-rigidly establish a mapping between the reference and target image. This stage also contains a constraint to ensure that the dominant focal lesion remains inside the prostate volume after the non-rigid transformation and avoids the issue highlighted in Figure 2.

**Integrated Focal Boost Planning**

Using the Varian Eclipse™ treatment planning system (Varian Medical Systems, Inc. Palo Alto, CA, USA) SABR-SIB plans were produced for the 7 patients who were originally treated with 57 Gy in 19 fx to a single volume. Patients in the 74 Gy in 37 fx cohort had more advanced disease with much larger focal lesion volumes and were therefore not suitable candidates for SABR-SIB. Dual arc VMAT deliveries using 10
MV flattening filter free (10FFF) beams were planned for all cases and a plan comparison was made with the original whole prostate plans used to treat each patient.

The prostate clinical target volume (CTV) was identified on the planning CT images as the prostate plus seminal vesicles. For the SABR-SIB plans, a prostate CTV-planning target volume (PTV) margin of 5 mm in all directions except for 3 mm posteriorly was used to define the PTV(prostate). This margin was smaller than the 10 mm in all directions except for 5 mm posteriorly used in the original treatment plans. The dominant focal lesion CTV was identified on the planning CT using the image registration process presented. A uniform margin of 3 mm was applied to the CTV to form the PTV(focal) and the PTV(focal) was subtracted from the PTV(prostate). The rectum, bladder and femoral heads were manually outlined according to ECC protocols.

A radiation dose of 36.25 Gy in 5 fx was planned to the whole prostate according to the guidelines set out in the PACE trial [18] with an SIB dose to the focal lesion of 47.5 Gy. The OAR constraints from the PACE trial were also applied (Table 1) [19]. The planning aim was to cover 95% of the PTV(focal) with 95% of the boost dose and 100% of the boost dose to at least 95% of the CTV(focal). To meet these criteria plans were normalised so that 36.25 Gy covered 95% of the PTV(prostate).

The original whole prostate plans selected for this study satisfied the CHHIP trial constraints. The SABR-SIB plans were compared with the original whole prostate plans by calculation of the biological parameters Tumour Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) [20]. TCP was calculated for the PTV(prostate), and PTV(focal) and NTCP was calculated for the rectum and bladder. The models and parameters used are summarised in Table 2. The NTCP for rectum
and bladder was compared between SABR-SIB and whole prostate plans using a Wilcoxon ranked-signs test (significance threshold p < 0.05).

Results

Non-rigid Registration

An example of a typical focal lesion within the prostate on a T2-weighted MR slice mapped to the corresponding CT slice by the registration framework is shown in Figure 2. The result of a standard rigid registration results in the dominant focal lesion being placed outside of the prostate volume on CT (blue). The result of using the framework described to non-rigidly register the dominant focal lesion (yellow) using the same deformation pattern that the prostate has undergone between MR and CT acquisition places the dominant focal lesion inside the prostate. Evaluation of the contours produced by the framework was performed by an experienced radiation oncologist and the clinical acceptability of the contour recorded, as shown in Table 3. The best performing method, rigid or non-rigid, was also assessed and recorded as shown in Table 3.

In 11 of the 14 cases investigated the non-rigid method gave clinically acceptable results and an overall improvement over the standard rigid method. The ratio of focal lesion volume to the prostate volume was statistically significantly smaller in the 57 Gy prescription group than the 74 Gy group (using a two sample t-test, with significance threshold of p<0.05). The cases where the non-rigid result was unacceptable were all patients in the 74 Gy prescription group. With lesions that occupied a greater proportion of the prostate patients in this group would not be suitable for treatment using a focal technique.
Planning

The results of the SABR-SIB planning study are shown in Table 4. All SABR-SIB plans met every mandatory constraint defined in Table 1 and clinically acceptable PTV coverage was achieved for both the prostate and focal regions. The maximum point dose ranged from 108% to 118% of the boost dose and was located within the PTV(focal) in all cases. The comparison of NTCP and TCP between SABR-SIB plans and the original whole prostate plans is shown in Table 5. The NTCP for bladder was negligible in both cases. The NTCP for the rectum showed a statistically significant decrease with the SABR-SIB planning approach. The TCP for the whole prostate was significantly greater in the SABR-SIB plans.

Discussion

External beam radiotherapy is an important curative treatment modality for men with prostate cancer. There are very few men who are potentially unsuitable for treatment and therefore it will continue to play a major role. The ability to accurately target the prostate while sparing the surrounding normal tissues has resulted in a significant increase in the radiation doses that can be tolerated [21, 22]. Radiotherapy techniques such as High Dose Rate (HDR) and Low Dose Rate (LDR) brachytherapy deliver very high radiation doses to the prostate with excellent long-term tumour cure rates [23]. However not all men are suitable for these techniques and there is a clear need to deliver equivalently high radiotherapy doses using external beam to treat these men.

Stereotactic ablative radiotherapy (SABR) is a hypofractionated regime where a high biological dose of radiation is delivered in 3 to 8 fx over a 2 to 3 week time period. Significant improvements in local control have been reported for SABR compared to more conventional radiotherapy (55-66Gy in 20-33 fx) delivered over 4 to 6 weeks using conventional delivery mechanisms [24, 25]. The problem however is that the
accurate localisation of the tumour within the prostate is very difficult because the
planning CT lacks soft tissue contrast. Modern multi-parametric MR, using
techniques such as diffusion weighting and dynamic contrast enhancement provide
excellent soft tissue contrast, especially when it is performed pre-biopsy where image
interpretation is not affected by haemorrhage. Furthermore, the ability of MR to
accurately identify dominant focal prostate lesions in 3D is particularly valuable for
radiotherapy planning. However, there is currently no single method capable of
mapping pre-biopsy MR image information onto radiotherapy planning CT images in
a reliable and accurate way. Currently clinicians use MR images to aid prostate
contouring on the planning CT by visual cross-referencing of the MRI to the planning
CT. This technique requires significant clinical interpretation, which in turn leads to
inter- and intra-operator variability in the accuracy of the prostate and tumour
outlining. Larger margins are ultimately added to the CTV to account for this
variability thus larger volumes of normal tissue are irradiated. The registration
approach presented in this paper summarises our progress in developing an image
analysis-based solution for this problem. From the preliminary results presented this
approach, with further development and validation involving a much larger data set,
offers a solution to the problem of accurately mapping dominant focal lesion contours
from diagnostic MR onto planning CT. This will potentially enable accurate focal
targeting of the localised cancerous volume as identified prior to androgen
depression therapy, which can result in a shrinkage of the prostate and may be best
characterised by a non-rigid transform as used in the registration framework.
Although the method was demonstrated here using T2-weighted MR images, it could
be extended to work on multiparametric images, or functional imaging, including
PET.

The novel registration technique used in this study has allowed SABR-SIB plans of a
clinically acceptable quality to be produced. The success of the non-rigid registration
method for patients in the 57 Gy group led to SABR-SIB plans being prepared for this group. These patients had low to intermediate risk disease, while patients in the 74 Gy group had more advanced disease and subsequently a larger lesion volume on the MR images. Although these cases were used in developing and assessing the performance of the registration framework they do not represent cases that are likely to be considered for integrated boost therapy. For this reason SABR-SIB plans were produced for the 57 Gy group only. The PACE trial constraints for the bladder, rectum and femoral heads were met in all cases despite the inclusion of a focal boost at 47.5 Gy in 5 fx (biologically equivalent dose (BED) 348 Gy, assuming an α/β of 1.5 Gy) [26]. This represents a significant dose escalation compared with the whole prostate dose of 36.25 Gy (BED 211 Gy) as specified in the trial [30].

Although the planning study used only a small sample of 7 patients, a range of focal lesion positions were encountered including some located posteriorly and close to the rectum. The fact that the constraints were met in all cases is encouraging, however, focal lesion position and size is likely to impact on the ability to meet OAR constraints and must be investigated for a larger group of patients. The main purpose of this study was to establish a methodology for reliably mapping the dominant tumour focus on MR onto the radiotherapy planning CT. As demonstrated by the results of the SABR-SIB plans, having confidence in the position of the dominant focal lesion makes it possible to deliver steep dose gradients to these foci and a reduced dose to the remainder of the prostate.

The ability to identify the true position of the dominant focal lesion with improved confidence on radiotherapy planning CT will allow higher doses to be delivered to the tumour, thus improving the care of patients with prostate cancer. The importance of image registration for this cannot be over-emphasised. This paper presents our progress on the development of a new registration framework and demonstrates that
it is possible to treat the dominant cancer focus using a SABR boost with clinically acceptable PTV coverage and without compromising normal tissue constraints.

**Acknowledgements**

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References


Figure 1
Figure 2
### Table 1

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<th>Structure</th>
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<td>Rectum</td>
<td>D1cc &lt; 36 Gy</td>
</tr>
<tr>
<td></td>
<td>D20% &lt; 29 Gy</td>
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<tr>
<td></td>
<td>D50% &lt; 18.1 Gy</td>
</tr>
<tr>
<td>Bladder</td>
<td>D5cc &lt; 37 Gy (optimal)</td>
</tr>
<tr>
<td></td>
<td>D10cc &lt; 37 Gy</td>
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<td></td>
<td>D40% &lt; 18.1 Gy</td>
</tr>
<tr>
<td>Femoral heads</td>
<td>D5% &lt; 14.5 Gy</td>
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Table 2

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<th>Effect</th>
<th>$\alpha/\beta$ ratio (Gy)</th>
<th>D50 (Gy)</th>
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<td>81.8</td>
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<td>Prostate volume (cc)</td>
<td>Volume ratio (lesion/prostate)</td>
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<td>Best performing registration method</td>
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<td>1</td>
<td>3.23</td>
<td>116.06</td>
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<td>8</td>
<td>1.89</td>
<td>110.71</td>
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<td>11</td>
<td>1.65</td>
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<td>18</td>
<td>2.99</td>
<td>78.17</td>
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Table 4

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<td>47.2</td>
<td>46.6 - 48.1</td>
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<td>Max (Gy)</td>
<td>52.8</td>
<td>51.6 - 56.2</td>
</tr>
<tr>
<td>CTV (focal)</td>
<td>V100% (%)</td>
<td>96.4</td>
<td>94.3 - 100.0</td>
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<tr>
<td>PTV (prostate)</td>
<td>D95% (Gy)</td>
<td>36.25</td>
<td>36.2 - 36.2</td>
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<tr>
<td></td>
<td>Max (Gy)</td>
<td>49.7</td>
<td>49.1 - 51.5</td>
</tr>
<tr>
<td>Rectum</td>
<td>D1cc (Gy)</td>
<td>35.5</td>
<td>34.9 - 35.9</td>
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<tr>
<td></td>
<td>D20% (Gy)</td>
<td>23.8</td>
<td>19.2 - 26.4</td>
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<tr>
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<td>D50% (Gy)</td>
<td>15.4</td>
<td>7.3 - 16.5</td>
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<tr>
<td>Bladder</td>
<td>D5cc (Gy)</td>
<td>37.0</td>
<td>36.7 - 37.7</td>
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<tr>
<td></td>
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<td>36.0</td>
<td>30.1 - 36.9</td>
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<tr>
<td></td>
<td>D40% (Gy)</td>
<td>16.1</td>
<td>5.5 - 17.5</td>
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<tr>
<td>Femoral Heads</td>
<td>D5% (Gy)</td>
<td>13.3</td>
<td>6.0 - 14.4</td>
</tr>
<tr>
<td>NTCP (%)</td>
<td>SIB</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>-----------</td>
<td>-----</td>
<td>--------</td>
<td>-------</td>
</tr>
<tr>
<td>Rectum</td>
<td>0.73</td>
<td>0.43 - 1.18</td>
<td>1.28</td>
</tr>
<tr>
<td>Bladder</td>
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<td>0.00 - 0.02</td>
<td>0.01</td>
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<tr>
<td>TCP (%)</td>
<td>PTV(focal)</td>
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<td>99.9 - 100</td>
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<tr>
<td>PTV(prostate)</td>
<td>95.41</td>
<td>93.9 - 96.4</td>
<td>66.21</td>
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Figure Legends

Figure 1. Left: Radiotherapy planning CT acquired on a Philips Brilliance Big Bore CT scanner fitted with a flat couch. Right: T2-weighted MR image set acquired on a Siemens Symphony 1.5T scanner without a flat couch, which has been co-registered to the planning CT volume so that the image sets have the same resolution and geometry. The bladder, prostate and rectum contours were originally defined on the planning CT and then mapped to the MR using the rigid registration transform. It is clear from the position of these structures on the MR images that rigid registration results in significant errors in cross-modality mapping.

Figure 2. Left: Section of a T2-weighted MR image showing the prostate (red) and focal lesion (blue). Right: Section of the planning CT image with prostate (red) and rigidly registered focal contour (blue), which lies outside of the prostate volume. The result of non-rigidly registering the focal lesion (yellow) using the same deformation pattern that the prostate has undergone between MR and CT acquisition places the focal lesion inside the prostate.
Table Legends

Table 1: The OAR planning constraints used for the SABR-SIB plans, which were taken from the PACE radiotherapy trial [13].

Table 2: The biological models and parameters used in calculation of the TCP and NTCP between SABR-SIB plans and the original whole prostate plans [22-24].

Table 3: The dominant focal lesion and prostate volume for all patients and the results of assessment of the mapped contours using the non-rigid method. The p value represents the difference between the the ratio of the focal prostatic volume to the whole prostate volume between the two prescription groups.

Table 4: The results obtained from SABR-SIB plans produced to treat the dominant focal lesion.

Table 5: Results of a comparison of NTCP and TCP between SABR-SIB plans and the original whole prostate plans.