Computer-assisted Targeted Therapy (CATT) for Prostate Radiotherapy Planning by Fusion of CT and MRI

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ABSTRACT

In this paper, we present a comprehensive, quantitative imaging framework for improved treatment of prostate cancer via computer-assisted targeted therapy (CATT) to facilitate radiotherapy dose escalation to regions with a high likelihood of disease presence. The framework involves identification of high likelihood prostate cancer regions using computer-aided detection (CAD) classifier on diagnostic MRI, followed by mapping of these regions from MRI onto planning computerized tomography (CT) via image registration. Treatment of prostate cancer by targeted radiotherapy requires CT to formulate a dose plan. While accurate delineation of the prostate and cancer can provide reduced exposure of benign tissue to radiation, as well as a higher dose to the cancer, CT is ineffective in localizing intraprostatic lesions and poor for highlighting the prostate boundary. MR imagery on the other hand allows for greatly improved visualization of the prostate. Further, several studies have demonstrated the utility of CAD for identifying the location of tumors on \textit{in vivo} multi-functional prostate MRI. Consequently, our objective is to improve the accuracy of radiotherapy dose plans via multimodal fusion of MR and CT. To achieve this objective, the CATT framework presented in this paper comprises the following components: (1) an unsupervised pixel-wise classifier to identify suspicious regions within the prostate on diagnostic MRI, (2) elastic image registration to align corresponding diagnostic MRI, planning MRI, and CT of the prostate, (3) mapping of the suspect regions from diagnostic MRI onto CT, and (4) calculation of a modified radiotherapy plan with escalated dose for cancer. Qualitative comparison of the dose plans (with and without CAD) over a total of 79 2D slices obtained from 10 MR-CT patient studies, suggest that our CATT framework could help in improved targeted treatment of prostate cancer.

Keywords: targeted therapy, magnetic resonance imaging, computerized tomography, image registration, prostate, cancer, therapy planning, CAD, texture, non-linear dimensionality reduction, clustering, IMRT

1. INTRODUCTION

Treatment of prostate cancer (CaP) by targeted radiotherapy requires the use of computerized tomography (CT) to formulate a dose plan. Successful conformal planning can reduce rectal and bladder toxicity by more accurately targeting the prostate, in turn allowing dose escalation to the planning target volume (PTV) and more effective treatment. Localization of the dominant intraprostatic lesion (DIL) can be used to create dose plans with even less exposure to benign tissue. More importantly, a more focused dose plan can afford significant dose escalation to the tumor, potentially providing greatly reduced rates of recurrence. However, CT does not provide good tumor localization.\textsuperscript{1} Further, CT has been shown to overestimate the prostate volume and provide inaccurate discrimination between base and apex and surrounding structures.\textsuperscript{2} As such, there is a need for improved image information in planning of guided therapy.

Magnetic resonance imaging (MRI) of the prostate has been shown to provide improved resolution of intraprostatic structures and the prostate boundary compared to CT\textsuperscript{3} and ultrasound.\textsuperscript{4,5} We have previously demonstrated the utility of a computer-aided detection (CAD) system for prostate cancer on high resolution \textit{ex vivo} MRI,\textsuperscript{6} as well as on \textit{in vivo} multiprotocol MRI.\textsuperscript{7-9} Pickett demonstrated the combined use of MRI and magnetic resonance spectroscopy (MRS) for tumor detection to provide escalated dose to the DIL,\textsuperscript{10} although
In order to utilize MRI for dose planning, it is necessary to align, or register, MRI with CT so that MRI-derived diagnoses may be mapped onto CT. Therefore, registration of MRI with CT of the prostate has been investigated by a few groups. One approach [3] has involved using bones or implanted gold fiducials as landmarks for alignment. Such intraprostatic marker-based registration techniques have been limited by time requirements and uncertainty associated with both the implantation and identification of marker centers on images. While surface-based registration using the iterative closest point (ICP) algorithm have been shown in [11] to be superior to fiducial-based methods, manual segmentation of the prostate on both CT and MRI is required for this type of approach. In addition to manual registration of the prostate on both CT and MRI using rigid body transformations, these registration methods are subject to interobserver variability.

Significant non-linear deformations may occur between the acquisition of planning CT and diagnostic MRI, due to the use of an endorectal coil (needed for diagnostic MR imaging) and variability in the size of the bladder, both of which push against the prostate. As such, a robust elastic registration framework is necessary for accurate and efficient delineation of prostate and tumor boundary on planning CT images using high resolution diagnostic MR. Direct registration of diagnostic MRI with planning CT images, such as those shown in Figures 1(a) and (b), is complicated on account of both resolution and modality differences. Resolution differences are associated with differences in field of view (FOV), where diagnostic MRI has a small FOV centered on the prostate, and the planning CT has a wider FOV as well as reduced resolution to resolve soft tissue details. However, a second image set (planning MRI) can be acquired in the same scanning session with a similar FOV and patient positioning to that of the CT.

In this paper, we present a complete quantitative framework for Computer-Assisted Targeted Therapy (CATT). The CATT planning method presented here is comprised of three main components, (1) an unsupervised texture-driven classifier for identifying suspected locations on diagnostic MRI, (2) an elastic registration method for alignment of diagnostic MRI, planning MRI and CT images of the prostate, and (3) mapping of tumor location onto CT, and generation of a dose plan that is targeted at the tumor location. The CAD system utilizes multiple textural features to enhance characterization of tissue and facilitates the discrimination of benign and malignant regions of the prostate. Figure 1(c) shows the planning MRI that corresponds to the diagnostic MRI (Figure 1(a)) and planning CT (Figure 1(b)). Using planning MRI, we present a novel two-step elastic registration procedure to overcome the modality differences between CT and MRI and bring diagnostic MRI into alignment with planning CT. In the first step, the registration of diagnostic and planning MRI is driven by exploiting the similarity of two MRI datasets to overcome FOV differences. Following coregistration of both
The rest of the paper is organized as follows. In Section 2 we describe the components of the CATT framework, including the unsupervised CAD classifier for localization of cancer, the elastic registration procedure for alignment of diagnostic MRI to CT (via the planning MRI), and the mapping of cancer onto CT for improved dose planning. In Section 3 we present the results of the CATT framework for improved dose planning on 79 sets of CT and multiprotocol MR images from 10 prostate studies, and generate radiotherapy dose plans based on target volumes defined using both the prostate boundary and the suspected cancer region. Concluding remarks and future directions are presented in Section 4.

2. METHODS

2.1 Data Description and Preprocessing

For 10 patients with prostate cancer, scheduled to undergo radiotherapy treatment, two MRI and one CT image sets were acquired. These image data sets are described in Table 1, where the large FOV differences between diagnostic MRI (row 1) and planning MRI and CT (rows 2,3) should be noted. The CT image set is a planning, or simulation study that is used to determine attenuation characteristics necessary to formulate a radiotherapy dose plan capable of delivering sufficient levels of radiation to the targeted volumes. As such, a large FOV is necessary to encompass the entire body.

<table>
<thead>
<tr>
<th>Set Number</th>
<th>Slice Notation</th>
<th>Modality</th>
<th>Description/Purpose</th>
<th>Dimensions (mm³)</th>
<th>Voxel Size (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$I^d$</td>
<td>T2-w MRI</td>
<td>Diagnostic</td>
<td>$120 \times 120 \times 107$</td>
<td>$0.5 \times 0.5 \times 4$</td>
</tr>
<tr>
<td>2</td>
<td>$I^p$</td>
<td>T2-w MRI</td>
<td>Treatment Planning</td>
<td>$340 \times 340 \times 256$</td>
<td>$1.3 \times 1.3 \times 8$</td>
</tr>
<tr>
<td>3</td>
<td>$I^{CT}$</td>
<td>CT</td>
<td>Planning/Simulation</td>
<td>$500 \times 500 \times 320$</td>
<td>$1 \times 1 \times 2$</td>
</tr>
</tbody>
</table>

In the remainder of this paper, we denote a 2D slice of a volume as $I = (C, f)$, where $C$ is a finite 2D rectangular grid of pixels and $f(c)$ is the image intensity at each pixel $c \in C$. Slices of diagnostic MRI, planning MRI, and planning CT are thus defined as $I^d$, $I^p$ and $I^{CT}$, respectively. Note that these images are defined on independent coordinate grids $C^d$, $C^p$ and $C^{CT}$, and it is the goal of any registration technique to determine spatial transformations that map locations in $C^d$ and $C^p$ to corresponding locations in $C^{CT}$.

Several preprocessing steps were performed. Correction of MRI bias field inhomogeneity was first performed using the automatic low-pass filter based technique presented by Cohen in [13]. Delineation of the prostate boundary on the diagnostic MRI volume was then manually performed (Figure 3(a)) to allow for application of...
Figure 3. (a) Original diagnostic MRI image with prostate boundary manually delineated (green). (b),(c) The median and Haralick correlation features of the 60 total textural features extracted from (a). Note the enhanced visibility of the hypointense lesion in (b) that is not visible in (a). (d) RGB visualization of 3 dimensional embedded feature space obtained by application of the non-linear dimensionality reduction scheme to the full texture space of the prostate voxels. (f) Map of the cancer region obtained by replicated $k$-means clustering in the embedded feature space in (e).

The location of cancer on diagnostic MRI is identified using a computer-aided detection (CAD) system comprising the following components, (1) extraction of multiple descriptive textural features at every spatial location (voxel) within the prostate, (2) non-linear dimensionality reduction on the texture feature space via graph embedding\textsuperscript{14} to project the textural signatures associated with each voxel into a reduced-dimensional sub-space, and (3) replicated $k$-means clustering\textsuperscript{8} to reliably partition voxels of the prostate into distinct tissue classes, including cancer. These components are briefly described below.

### 2.2.1 Texture feature extraction

We have previously shown the utility of texture features in distinguishing cancerous from non-cancerous regions in the prostate.\textsuperscript{15} We extract 60 unique features from three classes of 3D texture attributes. These include, (1) first order statistical attributes calculated on graylevel distributions, (2) gradient operators, and (3) second order statistical quantities calculated on distributions of spatial co-occurrence of graylevels.\textsuperscript{16}

**First order statistical features** Each of mean, standard deviation, median and range, are calculated over a neighborhood $N_{c,\kappa}$ of size $\kappa \in \{5, 7\}$ centered on each voxel.
Gradient features Gradient features comprising the responses from 9 distinct Sobel operators, oriented along each of the 3 coordinate axes and 6 diagonals, and from the spatial derivatives in each direction plus the gradient magnitude are calculated.

Second order statistical features Haralick or second order statistical features characterize spatial co-occurrence, where any pixel \( d \in \mathcal{N}_{c,k} \) is defined as a \( k \) neighbor of \( c \). A \( M \times M \) co-occurrence matrix \( P_{c,k} \) associated with \( \mathcal{N}_{c,k} \) is then computed, where \( M \) is the chosen number of gray level bins. The value at any location \([u, v]\), where \( u, v \in \{1, \ldots, M\} \), in the matrix \( P_{c,k}[u, v] \) represents the frequency with which two distinct pixels with associated image intensities \( f(c) = u, f(d) = v \) are adjacent. From \( P_{c,k} \), the 13 Haralick features comprising energy, entropy, inertia, correlation, inverse difference moment, two information correlation measures, sum average, sum variance, sum entropy, different average, difference variance and difference entropy were extracted at every pixel \( c \in C \), for \( k \in \{5, 7\} \), and \( M \in \{64, 128\} \).

Each pixel \( c \in C \) is now associated with a high dimensional texture feature vector \( \mathbf{F}(c) \) rather than a scalar intensity \( f(c) \). Details of the calculation of these textural features described in [15]. Figures 3 (b),(c) show the median and haralick correlation feature images corresponding to the intensity image in Figure 3 (a). Note that the hypointense lesion in the medial section of the gland is more easily discernible on the texture maps (Figures 3 (b),(c)) compared to Figure 3 (a).

2.2.2 Non-linear dimensionality reduction

Object-class discriminability can be improved by projecting the data into a reduced-dimensional embedding space, thus allowing for greater separation of the data classes. To reduce the high dimensional texture space \( \mathbf{F}(c) \) to a lower dimensional representation \( \mathbf{S}(c) \) for \( c \in G^d \), graph embedding is employed via the normalized cuts algorithm.\(^{14}\) The aim of graph embedding\(^{14, 17}\) is to find a vector \( \mathbf{S}(c) \), \( \forall c \in G^d \) such that the relative adjacency of any two pixels \( c_i, c_j \in G^d, i, j \in \{1, \ldots, |G^d|\} \) in high dimensional space is preserved in the low dimensional space. To compute \( \mathbf{S}(c) \), \( \forall c \in G^d \), an affinity matrix \( \mathcal{W} \in \mathbb{R}^{N \times N} \), where \( N = |G^d| \) is defined as,

\[
W(i, j) = e^{-||\mathbf{F}(c_i) - \mathbf{F}(c_j)||_2},
\]

for each \( c_i, c_j \in G^d \). The embedding space \( \mathbf{S}(c) \), for each \( c \in G^d \), for \( m \ll 60 \) dimensions, is defined by the eigenvectors \( \mathcal{X} \) corresponding to the \( m \) smallest eigenvalues of \( (D - \mathcal{W})\mathcal{X} = \lambda D\mathcal{X} \), where \( D \) is a diagonal matrix with elements \( D(i, i) = \sum_j W(i, j) \). Thus, \( \mathbf{S}(c_i) \) is obtained by extracting the first \( m \) components of the \( i \)th row of \( \mathcal{X} \). Since linear projections are not utilized to compute these projections (such as done by PCA),\(^{18}\) graph embedding is capable of discovering inherent non-linearity in the data. The reduced dimensional space can be visualized for \( m = 3 \) by representing every location \( c \in G^d \) on \( \mathcal{T}^d \) by its embedding coordinates \( \mathbf{S}(c) \) and scaling these values to display as an RGB image, as shown overlaid on a diagnostic MRI slice in Figure 3(d). Note how dissimilar regions can be more easily discerned in Figure 3(d), where similar colors represent the same class, as compared to Figure 3(a).

2.2.3 Replicated k-means clustering

Unsupervised replicated clustering is used to partition each pixel \( c \in G^d \) into one of \( k \) classes based on the embedding representation \( \mathbf{S}(c) \) obtained from corresponding textural descriptions. The \( k \)-means algorithm provides an efficient and unsupervised method for clustering observations. However, when random initialization of cluster centroids is used, \( k \)-means is not deterministic. Replicated clustering has been shown to provide more stable clusters\(^8\) by selecting from \( T \) independent runs of \( k \)-means, the clustering with the smallest average intra-class variance. Defining \( V^q_t \subset G^d \) as the set of pixels belonging to cluster \( q \in \{1, \ldots, k\} \) from \( k \)-means replication \( t \in \{1, \ldots, T\} \), the cluster centroid is defined by \( \mathbf{S}_q = \frac{1}{|V^q_t|} \sum_{c \in V^q_t} \mathbf{S}(c) \). The optimal clusters \( V^q_t \subset G^d \), \( \tau \in \{1, \ldots, T\} \) are found by

\[
\tau = \arg\min_t \left[ \frac{1}{k} \sum_{q} \frac{1}{|V^q_t|} \left\| \mathbf{S}(c) - \mathbf{S}_q \right\|_2 \right].
\]

Therefore, replicated \( k \)-means is utilized here to classify \( \mathbf{S}(c), \forall c \in G^d \) as one of \( k \) classes. We select \( k = 6 \) to allow clustering of many dissimilar tissue classes, including benign epithelium, stroma and hyperplasia, cancer,
atrophy, and structures such as blood vessels and the urethra. Figure 3(c) shows a tumor region identified as one of the clusters generated using the replicated k-means technique. Note that since the technique is unsupervised, the cluster corresponding to cancer must be manually selected based on appearance and spatial configuration of the cluster within the prostate. In our experiments this was done by an expert radiologist. The set of pixels belonging to the cluster representing cancer is denoted \( \Omega^d \subset G^d \subset C^d \).

### 2.3 Elastic Registration of Diagnostic MRI, Planning MRI, and CT

The goal of registration is to determine the spatial transformations \( T^{dc}(c) \) and \( T^{pc}(e) \) in order to map coordinates \( c \in C^d \) and \( e \in C^p \) onto the corresponding locations in \( C^{CT} \). This allows for the transformation of both \( \mathcal{I}^d \) and \( \mathcal{I}^p \) into alignment with \( C^{CT} \). A two stage registration approach is used to first determine \( T^{dp}(c) \), the transformation from each location \( c \in C^d \) to a corresponding \( e \in C^p \), followed by \( T^{pC}(e) \), the transformation from each location \( e \in C^p \) into \( C^{CT} \). The registration of \( \mathcal{I}^d \) to \( C^{CT} \) involves the steps below.

1. **Multimodal Registration:** Automated affine registration of \( \mathcal{I}^d \) to \( \mathcal{I}^p \) via maximization of NMI\(^{10} \) is performed to determine the mapping \( T^{dp} : C^d \rightarrow C^p \) by

   \[
   T^{dp} = \arg\max_{T} \left[ \text{NMI}(\mathcal{I}^p, T(\mathcal{I}^d)) \right],
   \]

   where \( T(\mathcal{I}^d) = (C^p, f^d) \) so that every \( c \in C^d \) is mapped to new spatial location \( e \in C^p \) (i.e. \( T(c) \Rightarrow e \) and \( c \Leftrightarrow T^{-1}(e) \)). The NMI between \( \mathcal{I}^p \) and \( T(\mathcal{I}^d) \) is defined as,

   \[
   \text{NMI}(\mathcal{I}^p, T(\mathcal{I}^d)) = \frac{H(\mathcal{I}^p) + H(T(\mathcal{I}^d))}{H(\mathcal{I}^p, T(\mathcal{I}^d))},
   \]

   in terms of the marginal and joint entropies,

   \[
   H(\mathcal{I}^p) = - \sum_{c \in C^p} p^p(f^p(e)) \log p^p(f^p(e)),
   \]

   \[
   H(T(\mathcal{I}^d)) = - \sum_{e \in C^p} p^d(f^d(T^{-1}(e))) \log p^d(f^d(T^{-1}(e))), \text{ and}
   \]

   \[
   H(\mathcal{I}^p, T(\mathcal{I}^d)) = - \sum_{e \in C^p} p^{pd}(f^p(e), f^d(T^{-1}(e))) \log p^{pd}(f^p(e), f^d(T^{-1}(e))),
   \]

   where \( p^p(\cdot) \) and \( p^d(\cdot) \) are the grayscale probability density estimates, and \( p^{pd}(\cdot, \cdot) \) is the joint density estimate. Note that the similarity measure is calculated over the pixels in \( C^p \), the coordinate grid of planning MRI. Despite the small FOV of \( \mathcal{I}^d \) and the large FOV of \( \mathcal{I}^p \) (Figures 1(a),(c)), an affine transformation is sufficient since the two MRI protocols are acquired in the same scanning session with minimal patient movement between acquisitions. Since both T2-weighted MRI protocols are also similar in terms of intensity characteristics, NMI is effective in establishing optimal spatial alignment.

2. **Multimodal Registration:** Elastic registration of \( \mathcal{I}^p \) to \( C^{CT} \) using control point-driven thin plate splines (TPS)\(^{20} \) to define mapping \( T^{pc} : C^p \rightarrow C^{CT} \) is performed. An intuitive point-and-click graphical interface was developed and employed for identifying pairs of corresponding spatial locations between \( \mathcal{I}^p \) and \( C^{CT} \). Having nearly the same FOV and similar spatial resolution, landmarks on \( \mathcal{I}^p \), including the femoral head, pelvic bone and prostate capsule, are identifiable on the corresponding \( C^{CT} \). For example, in Figures 1(b),(c) corresponding \( C^{CT} \) and \( \mathcal{I}^p \) images are shown, where the wide FOV of planning MRI encompasses peripheral anatomical features such as the hip bones and spine, which are not visible on \( \mathcal{I}^d \) (see Figure 1(a)). Note that while \( T^{dp}(c) \) determined in Stage 1 is implemented as an affine transformation, \( T^{pC}(e) \) is a non-parametric deformation field, elastically mapping each coordinate in \( C^p \) to \( C^{CT} \).

3. **Combination of Transformations:** The direct mapping \( T^{dc}(c) : C^d \rightarrow C^{CT} \) of coordinates of \( \mathcal{I}^d \) to \( C^{CT} \) is obtained by the successive application of \( T^{dp} \) and \( T^{pC} \),

   \[
   T^{dc}(c) = T^{pC}(T^{dp}(c)).
   \]

   Thus, using \( T^{dc}(c) \), each coordinate in \( C^d \) is mapped into \( C^{CT} \).
In summary, the procedure described above is used to obtain the following spatial transformations: (1) $T^{dp}$ mapping from $C^d$ to $C^p$, (2) $T^{pC}$ mapping from $C^p$ to $C^{CT}$, and (3) $T^{dC}$ mapping from $C^d$ to $C^{CT}$. Using $T^{dC}$ and $T^{pC}$, the diagnostic and planning MRI that are in alignment with CT are obtained as $\tilde{I}^d = T^{dC}(I^d) = (C^{CT}, f^d)$ and $\tilde{I}^p = T^{pC}(I^p) = (C^{CT}, f^p)$, respectively. For example, Figure 1(d) shows $\tilde{I}^d$ obtained by aligning with the corresponding $I^{CT}$. Note the non-linear nature of $T^{dC}$ is clearly visible in Figure 1(d).

2.4 Mapping of Tumor Location from Diagnostic MRI onto CT

After registration, the CAD result, represented by a set of spatial locations labeled as $\Omega^d$ on $I^d$, is mapped via the transformation $T^{dC}$ to set $\Omega^{CT}$ on $I^{CT}$. For example, the label $\Omega^d$ shown in red on $I^d$ (Figure 3(e)) is mapped onto CT slice $I^{CT}$ (Figure 3(f)) via $T^{dC}$.

2.5 Dose Plan Generation

Two target volumes are defined and used to generate a single IMRT dose plan using the Varian® Eclipse software. These are the planning target volume (PTV), which is based on the radiologist’s outline of the prostate on CT plus margins, and a cancer PTV (cPTV), based on $\Omega^{CT}$ plus margins. The IMRT plan utilizes 7 beam angles and a dynamic multileaf collimator (MLC) to shape the beam and deliver no less than 7920 cGy to the PTV and no less than 8640 cGy to the cPTV. Figure 4(a) shows a 3D view of the 7 beam angles and the shapes of the MLC at various points over the course of the treatment. An axial view of the beams are shown in Figure 4(b).
Figure 5. (a) Diagnostic MRI is affinely registered to (b) planning MRI. (c) The registered diagnostic MRI is shown in (d) overlaid onto (b). (e)-(h) Checkerboard patterns of four additional pairs of aligned diagnostic and planning MRI demonstrate accuracy of registration, as evidenced the continuity of prostate capsule and internal structures across checks.

4(b) with the resulting dose map thresholded at 7920 cGy overlaid onto the CT slice. The increased dose to the cPTV is demonstrated in Figure 4(c) where the dose map thresholded at 8640 cGy covers the cPTV, which is indicated by the inner boundary. Note that while dose escalation to the cancer is achieved, the rest of the PTV receives no less radiation, hence ensuring that the entire prostate receives a full dose.

3. RESULTS AND DISCUSSION

3.1 Unsupervised CAD Classifier to Identify Tumor Labels on Diagnostic MRI

The unsupervised CAD classifier (Section 2.2) was applied to identify pixels belonging to the cancer class \(G^d\) for each of 10 diagnostic MRI studies. Figures 3(a)-(c) show a 2D section of diagnostic MRI of the prostate and two representative textural feature images. The features show in Figures 3(b),(c) are the median calculated for each pixel \(c\) with neighborhoods \(N_{c,\kappa}\) of size \(\kappa = 5\) and the Haralick correlation for \(N_{c,\kappa}\) of size \(\kappa = 7\). Shown in Figure 3(d) is a color representation of the 3 dimensional feature space \(S(c)\) obtained by application of the graph embedding scheme to \(F(c)\) for each \(c \in G^d\). The corresponding cancer label \(\Omega^d\) was obtained for each of the 10 prostate volumes by applying the replicated \(k\)-means clustering technique to all \(S(c), c \in G^d\). The identified cancer cluster \(\Omega^d\), manually identified by a radiologist, is shown in Figure 3(e). No quantitative evaluation of CAD accuracy is possible was not available for these patients; in previous work\(^{21}\) we identified ground truth for prostate cancer on MRI by registering the imaging with corresponding whole mount \textit{ex vivo} histological sections.

3.2 Multiprotocol and Multimodal Image Registration

Registration was performed as described in Section 2.3 for the 79 data sets of \(I^d, I^p,\) and \(I^{CT}\) from the 10 patients. Figures 5(a) and (b) show a corresponding pair of diagnostic and planning MRI slices (\(I^d\) and \(I^p\)). Figure 5(c) shows \(\tilde{I}^d, I^d\) after automated affine registration to \(I^p\), while the fusion of \(\tilde{I}^d\) and \(I^p\) is shown as a blended overlay in Figure 5(d). In Figures 5(e)-(h), the registration of four different \(I^d\) and \(I^p\) slices is demonstrated as checkerboard patterns of \(I^p\) and \(\tilde{I}^d\). The continuity of the internal structures in the prostate and surrounding tissues between the registered images can be appreciated in Figure 5(e)-(h). Clearly, by sequentially
acquiring the diagnostic and planning MRI volumes in the same imaging session, an affine transformation using the NMI similarity measure appears to be sufficient to bring $I^d$ and $I^p$ into alignment.

Figures 6(a)-(d) demonstrate the elastic registration results of 4 sets of corresponding $I^d$, $I^p$ and $I^{CT}$ images as overlays of $I^{CT}$ and the registered images $\tilde{I}^d$ and $\tilde{I}^p$. The alignment of internal structures is evident in the vicinity of the prostate, between the hip joints (within the FOV of the diagnostic MRI). The non-linearity of the image transformations required to align MRI with CT (Figures 6(a)-(d)) is clearly demonstrated by the grids shown in Figures 6(e)-(h).

3.3 Tumor Mapping onto CT

The transformations $T^{dc}$ determined between each $I^d$ and $I^{CT}$ slice are applied to the corresponding cancer label $\Omega^d$ of each $I^d$ to obtain new spatial locations $\Omega^{CT}$ on each $I^{CT}$. Figures 7(a), (b) show two different CT slices with $\Omega^{CT}$ as a white mask and the resulting cPTV boundary as a red line.

3.4 Dose Planning

From the CT volumes with PTV and cPTV delineated (shown as red lines in Figures 7(a),(b)), dose plans were generated for each of the 10 patient studies. Figures 7(c) and (d) show the radiation dosage maps for the slices in Figures 7(a) and (b). To illustrate the dose to the PTV, the radiation intensity is thresholded at 7920 cGY in Figures 7(c) and (d), while to illustrate the dose escalation to the cPTV, the radiation intensity is thresholded at 8640 cGY in Figures 7(e) and (f).

4. CONCLUDING REMARKS

With high resolution diagnostic MRI, it is now possible to visually identify presence and extent of prostate cancer. Additionally, computer-aided classifiers for detecting disease extent on MRI have been developed. The tumor location identified on the MRI by CAD classifiers was mapped onto CT via a two step registration methodology, allowing formulation of a more precise dose plan. The implications of a dose plan targeted only at the tumor include (1) reduced exposure to the bladder, rectum, and other benign tissues, and (2) dose escalation to the tumor. Thus, the approach described here could translate to a real reduction in side effects and an increase in the efficacy of radiotherapy treatments.

It is important to note that there is no straightforward way of evaluating the accuracy of tumor localization...
Figure 7. (a), (b) Two different CT studies shown with cancer labels $\Omega^{CT}$ (white) mapped from MRI by registration and the resulting cPTV (red line). Resulting dose intensity maps for the slices in (a), (b) are shown thresholded at the minimum dose for PTV (7920 cGY, outer orange line) in (c), (d) and thresholded at the minimum dose for cancer (8640 cGy, inner red line) in (e), (f). These demonstrate dose escalation to the cancer PTV while maintaining dose to the prostate PTV. Note that the original dose plan has not been shown.
on CT. Validation of the computer-assisted dose pans would involve a long-term, clinical trial whereby CAD-assisted therapy is compared against conventional therapy targeted at the entire prostate without the benefit of CAD. The work presented here will pave the way for such a clinical trial.

For future work, we are currently implementing a fully automated registration paradigm using free form deformations, such as previously described in our work on MR-histology registration. Another avenue of future work will focus on automated prostate segmentation using a previously developed feature-driven active contour technique. Finally, we plan to investigate the use of a supervised classifier to drive the CAD system, which will remove the interactive component of the current clustering scheme and potentially provide more accurate cancer labels.

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REFERENCES


