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14. ABSTRACT A combination of MRI/MRSI is used to define the distribution of Dominant Intraprostatic Lesions (DIL) within the prostate. This information is used to perform dose escalation of the DIL without compromising the dose coverage of the prostate and the protection to the urethra, rectum, and bladder for prostate cancer patients treated with High Dose Rate (HDR) brachytherapy. The multi-image fusion process has been presented at national meetings during this period. The steps and criteria involved in the series of image fusions and in the planning and verification of the dose delivery process are presented. Information from one image data set to another in the series of MRS → MRI → CT ← CBCT can be accurately transferred and used for the planning and verification of the dose delivery during prostate HDR brachytherapy. Final CHR approval was obtained in 2008 and patient enrollment has begun. So far, 17 patients were screened and 10 patients were treated with HDR brachytherapy with a DIL boost level ranging from 0 to 30%, using the previously established class solution for the set of parameters used by the inverse planning in order to boost the dominant intra-prostatic lesion (DIL) defined by MRI/MRSI. The DIL dose was significantly increased without any violation of standard dosimetric index requirements. This year, an amendment was made to the protocol to facilitate recruitment.					
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PC030909 Addendum Report
May 25, 2010 – May 25, 2011

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INTRODUCTION

Research Project Description

Men with prostate cancer, in particular those with advanced local disease, benefit from dose escalation. The main objective of the DOD-PC-030909 is to exploit the ability of Magnetic Resonance Imaging combined with Magnetic Resonance Spectroscopy imaging (MRI/MRSI) to identify cancer regions within the prostate and to target those regions with a higher tumor burden with higher dose without compromising the dose coverage of the prostate and the protection to the urethra, rectum and bladder for prostate cancer patients treated with HDR brachytherapy.

BODY

The feasibility of a comprehensive approach that incorporates MRI/MRSI (anatomical and functional imaging) into the HDR brachytherapy treatment planning has been demonstrated. Using the inverse planning program IPSA, dose escalation of target regions with a higher tumor burden can be performed without increasing the dose to critical normal structures. This is the first trial using both MR imaging and functional imaging MRSI for HDR brachytherapy planning.

Three main tasks were identified to fulfill the aims of this project:

Task 1: To determine the need for alignment and to establish alignment methods for MRI/MRSI data to HDR brachytherapy treatment planning MRI and CT images.

Task 2: To elaborate class solutions (a set of optimization constraints) appropriate for DIL boosts of the order of 150% of the prescribed dose and protection for the penile bulb and the neuro-vascular bundle valid for 90% of the cases.

Task 3: To perform feasibility and short-term measures of improved effectiveness and decreased side effects of performing the proposed treatment planning protocol in a small cohort of patients.

The status of the different tasks is as follow:

Task 1:	Completed,
Task 2:	Completed
Task 3:	In progress

Information on Tasks 1 and 2, and 3a, was provided in previous annual reports. Patient enrollment will continue. The main activity this year was to revise the protocol with two changes to increase patient enrollment. The information provided in this annual report supports the following: Report on Multi-Image Fusion, Continue to perform DIL boost on enrolled patients, Report on the revision of the protocol with two changes to increase patient enrollment, and Change of the fractionation scheme by treating patient with HDR brachytherapy boost at 19Gy in 2 fractions.

Patient enrollment and performing DIL boost (current period).

The period of performance has been extended for one year, until May 25th, 2011. Patient enrollment has been initiated in 2008 and the first HDR delivery with DIL boost was performed on September 2008. Seventeen patients were screened, and ten patients were treated with HDR so far. Eight of these patients had level 5 DIL, allowing DIL boost of at least 120-130%. So far, these results are as expected and very encouraging. The procedure is now well integrated clinically and the brachytherapy team has been completely trained. We anticipate a smooth continuation of the protocol as patient enrollment proceeds. We believe the results of this research, once completed, will greatly impact the treatment of prostate cancer. The ability to provide a higher dose of radiation to regions of cancer within the prostate is expected to improve the disease free survival rate with no additional side effects.

During the current period, we have focused our activities on three aspects,

- 1- Report on the use of our Multi-Image fusion in a clinical setting
- 2- Perform DIL boost on enrolled patients.
- 3- Revise the protocol with two changes to increase patient enrollment.
- 4- Treating patient with HDR brachytherapy boost at 19Gy in 2 fractions of 9.5Gy each or 15Gy in 1 fraction
- 5- Reduce the accrual target number
- 6- Quarterly reports

1- Multi-Image Fusion (current period).

We have shown that information from one image data set to another in the series of MRS → MRI → CT ← CBCT can be accurately transferred and used for the planning and verification of the dose delivery during prostate HDR brachytherapy.

Studies have shown that greater control of localized prostatic tumors can be achieved with higher radiation doses. High Dose-Rate (HDR) brachytherapy can provide a focal dose escalation, and prior studies have shown that combined external beam radiation therapy (EBRT) and HDR yields favorable outcomes, particularly in patients with locally advanced disease. In our current HDR brachytherapy clinical protocol, a combination of magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging (MRSI) is used to define Dominant Intraprostatic Lesions (DIL). This information is used to perform dose escalation of the DIL without compromising the dose coverage of the prostate nor the protection to the urethra, rectum, and bladder. There are two difficulties, however, inherent in this approach. The first is the merging of information from the staging MRI/MRSI exam with anatomic CT exam required for treatment planning; the second is the capacity of the treatment modality/ treatment planning system to deliver radiation doses in a precise fashion. Three imaging modalities, Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopic Imaging (MRSI), and Computed Tomography (CT) - are used at different steps during the process.

However, since the endorectal probe used for MRI/MRSI acquisition can induce significant prostatic compression and deformation, a non-rigid transformation is required to register accurately the probe-in MRSI data with the probe-out CT images used for treatment planning. We have developed and clinically implemented a new method combining rigid translations (for centroid alignment), rotations (to model the X axis rotation), and an in-plane non-rigid control-point based morphing method that utilizes a local weighted-mean transformation. This method was designed to be computationally inexpensive and easily implemented on the MATLAB (The Mathworks, Natick, MA) platform using built-in functions.

For each patient enrolled in the study, a pre-therapy staging MRI/MRS exam using an endorectal probe (i.e. probe in, or PI) were acquired and registered so that the MRSI-defined DIL was delineated on the anatomic MRI volume. On the HDR treatment day, the planning CT and the MRSI were imported in the brachytherapy planning system and registered to each other. The prostate anatomy alone was used to guide the fusion. Target and organs at risk were delineated on the CT while the DIL was contoured on the MRSI using spectroscopic information. Catheters were then digitized, the plan was optimized using the inverse planning tool IPSA, with dose escalation to the DILs, while simultaneously treating the entire prostate without increasing the dose to surrounding normal tissues. The dose for the first fraction is then delivered.

The complete procedure was clinically integrated and has been used for the treatment of ten HDR patients with MRSI information. The data analysis is completed for six patients. For those six patients, the mean prostatic rotation induced by the coil was $20^{\circ} \pm 9^{\circ}$, and the mean gland volume was 27 ± 14 cc. Urethra, peripheral zone margins, prostate boundaries, and various hyper / hypointense features on the images served as effective landmarks for the MRI-PI - MRI-PO fusion.

This makes information about the prostate cancer location routinely available, and allowing the use of inverse planning IPSA to boost dominant intraprostatic lesions during HDR brachytherapy, while preserving the prostate coverage and keeping the dose delivered to the organs at risk to the same level compared to an inverse planned dose distribution without DIL boost. Information from one image data set could be accurately transferred to another in the series of MRS \rightarrow MRI \rightarrow CT. This workflow was routinely used for the dose planning, including a DIL boost. This work illustrates the clinical benefit of image registration tools.

2- Perform DIL boost on enrolled patients

Patient enrollment has been initiated in 2008 and the first HDR delivery with DIL boost was performed on September 2008. During that period, we have screened 17 patients and 10 were enrolled and completed their HDR Brachytherapy. Five patients have completed the study.

The table below presents the dosimetric characteristics of the ten patients enrolled in the protocol that received HDR brachytherapy. Irrelevant of the DIL boost level, a plan must fulfill the RTOG-0321 dose criteria for target dose coverage $V100^{\text{Prostate}} > 90\%$ and organ-at-risk dose sparing $V75^{\text{Bladder}} < 1$ cc, $V75^{\text{Rectum}} < 1$ cc, $V125^{\text{Urethra}} < 1$ cc. As it can be seen, all dosimetric indices fulfill the limits used for a regular treatment. One patient in the cohort of ten patients did not have a level 5 MRS-defined DIL. Therefore, no boost was attempted on the patient. Boost levels from 20% (120% of the prescribed dose) to 50% were easily achieved. One patient received a 50% boost. The DIL dose was significantly increased without any violation of standard dosimetric indices requirements.

DOSE DISTRIBUTION STATISTICAL ANALYSIS OF THE PATIENTS TREATED WITH HIGH DOSE RATE BRACHYTHERAPY

#	NAM	Firs	ID#	Prostate	Prostate	Prostate	Urethra	Urethra	Bladder	Rectum	DIL1	DIL2	DIL3	DIL	# DIL	Highest
				Volume (cc)	V100(%)	V150(%)	Vol(cc)	V120(cc)	V75(cc)	V75(cc)	Volume(cc)			Boost level		MRS Level
1	H.	M.	718	17.6	96.0	37.00	0.95	0.03	0.00	0.60	0.67			150	1	5
2	C.	K.	4351	23.3	97.3	29.50	0.88	0.15	0.00	0.90	1.47			130	1	5
3	H.	G.	9408	42.2	91.7	26.58	1.29	0.11	0.64	0.21	none			n/a	0	3
4	I.	R.	3238	35.8	95.8	35.70	1.10	0.20	0.10	0.50	0.80	1.40		130	2	5
5	O.	G.	9954	33.7	95.6	33.35	1.11	0.36	0.00	0.68	0.92	0.10		130	2	5
6	Y.	Z.	8583	34.8	92.5	32.02	0.96	0.24	0.50	1.00	6.33			125	1	5
7	G.	M.	4923	30.6	96.0	32.20	1.04	0.10	0.00	0.10	1.40	0.30	0.20	120	3	5
8	L.	D.	611	26.9	95.7	38.60	0.86	0.14	0.19	0.21	No MRS info			n/a	0	n/a
9	U.	S.	8214	75.3	93.4	32.03	1.59	0.03	0.45	0.80	0.75	0.33		130	2	5
10	G.	C.	5882	42.1	92.3	32.20	0.76	0.15	0.00	0.84	1.04	0.11		120	2	4

3- Revise the protocol with two changes to increase patient enrollment.

1. To include patient who started hormone therapy within 60 days or less:

We initially thought hormonal therapy would mask the lesion making it less likely to be detected by MRS, however, our MRS expert (Dr. Kurhanowiz) told us this was not the case. Since referring physicians often put the patient on hormonal therapy as soon after notifying of their diagnosis, if we can include these patients it would improve the impact and feasibility of this treatment approach.

2. Change the required PSA blood work from 30 days to 120 days prior to enrollment:

The reason for this change is to accommodate the new patients that will be enroll into the study with hormone therapy. Since some patients will be on hormone therapy before we identify them as potential candidates for this study, we need to be able to use the baseline PSA value which occurs before hormone therapy. That time frame can range within 120 days. Therefore the new change will allow the flexibility we need to recruit.

4- Treating patient with HDR brachytherapy boost at 19Gy in 2 fractions of 9.5Gy each or 15Gy in 1 fraction:

The reason for the change in the fraction is based on recently published result using single fraction HDR boost. In addition, our department has changed our standard HDR boost from 2 fractions to 1 fraction. We also adapted flexible timing of HDR (same as the published article) of doing the implant prior to EBRT.

5- Change the accrual target number from 56 to 25

The reason for the change of target number is that we over estimated with the number of HDR treatment that was given each year. We believe that the twenty-five patients entered on study can be tested for the null hypothesis of a 16% proportion of patients with unacceptable toxicity versus an alternative of 35% or greater ($H_0: p = 0.16$ have toxicity vs. $H_1: p = 0.35$). Previous experience resulted in approximately 15% acute grade 2 or higher toxicity. With this sample size of 25 patients the test will have a power of 82% with a directional level of significance of 0.10.

Please note these changes should result in equivalent radiotherapy results.

6- Quarterly reports

As per protocol, both P.I., the study coordinator, our statistician and brachytherapy physicist, perform quarterly meetings since patient enrollment has begun. During our meetings, we review data, evaluate toxicity and discuss related topics, including patient recruitment. The report entitled "Patient Enrollment Status" includes the patient identifier, the screening date, the enrollment date and the patient conclusion status.

Patient Enrollment Status

PHASE I STUDY OF TARGETING DOMINANT INTRAPROSTATIC LESION USING FUNCTIONAL MR SPECTROSCOPY AND HIGH DOSE RATE BRACHYTHERAPY

Department of Defense Collaborative Research Trials

Date: June 13, 2011

Principal Investigators: Drs. Jean Pouliot and Joe I-Chow Hsu

CHR Study Number: H11386-24294
Account and Fund: PC 03090
Grant Ending Period:

Study Coordinator: Tracy Diep
ZZ Account # 49178603
ZZ visit Number 14459290

# of Pts.	Patient Identifier (AB123)	Screening Date (date checklist was completed)	Date Consent Form was signed	Patient Conclusion Status		
				Ongoing	Dropout (enter date)	Completed (enter date)
1	M. H. 0718	7/03/08	6/30/08	No- Study completed		10/01/2009
2	C. K. 4351	6/23/08	6/20/08	No- Study completed		11/19/2009
3	G. H. 9408	7/18/08	8/13/08	No- Study completed		12/03/2009
4	R. I. 5238	1/19/09	1/15/09	No- Study completed		05/13/2010
5	G.O. 9954	1/30/09	1/30/09	No-Study completed		04/8/2010
6	F.F. 8197	2/12/09	2/12/09	No - MD recommend alternative treatment		
7	G.H 6128	2/16/09	2/12/09	No- ineligible/ started hormone		
8	D.A.6117	2/26/09	Pending consultation 3/11/09	No - ineligible/ CT +metastatic disease		
9	R. S. 3230	3/16/09	Pending for CT/Bone scan 3/12	Possible metastases		
10	Z. Y. 8583	4/21/09	4/21/09	Yes		09/16/2010
11	M.G. 4923	9/17/09	9/2/09	Yes		12/02/2010
12	D.L. 0611	10/5/09	10/01/09	Yes		02/10/2011
13	E. P. 0523	1/25/10	1/25/10	No-ineligible/ PSA too high	01/28/10	
14	S. U. 8214	1/29/10	1/21/10	Yes		06/16/2011
15	C. G. 5882	3/3/10	3/1/10	Yes		
16	E. G. 8239	11/24/10	11/24/10	No- ineligible/salvage	11/24/10	
17	R. D. 2630	1/21/2011	1/19/2011	No- Patient withdraw	5/16/11	

KEY RESEARCH ACCOMPLISHMENTS

□

- **An MRSI to MRI/CT alignment protocol**, developed to exploit the high specificity of combined MRI/MRSI for detecting and localizing prostate cancer within the prostate, allows the accurate transfer of this information to the planning images.
- **The accurate merging of MRSI to MRI/CT allows the use of inverse planning IPSA** to boost dominant intraprostatic lesions during HDR brachytherapy.
- **Boost levels of 120-150% of DIL can be easily achieved** on most patients while keeping the dose levels to organs at risk within the usual limits.

REPORTABLE OUTCOMES

Peer-reviewed Publications (Last year only)

- Reed G., Cunha J.A., Noworolski S.M., Kurhanewicz J., Vigneron D.B. , Hsu I.C., and Pouliot J., Interactive, **Multi-Modality Image Registrations for Combined MRI/MRSI-Planned HDR Prostate Brachytherapy**. Journal in Contemporary Brachytherapy, 2011 (3)1: 26-31.

Presentations at International Conferences

- **Key trends in treatment planning : combining physics and technology innovations**, European Best Practice Workshop, Valencia, Spain, June 13-15, 2010.

Presentations at National Meetings

- **Multi-Image Registrations and Their Role in Inverse Planned HDR Prostate Brachytherapy for Dose Escalation of Dominant Intraprostatic Lesion Defined By Combined MRI/MRSI**, Innovative Minds in Prostate Cancer Today (IMPACT) Conference, Orlando, Florida, on March 9-12, 2011.

CONCLUSION

An MRSI to MRI/CT alignment protocol was previously developed to exploit the high specificity of combined MRI/MRSI for detecting and localizing prostate cancer within the prostate, and to accurately transfer this information to the planning images. This information from one image data set can be accurately transferred to another in the series of MRS -> MRI -> CT. This workflow is now routinely used in clinic for the HDR brachytherapy dose planning, including a DIL boost. This makes information about the prostate cancer location routinely available, and allowing the use of inverse planning IPSA to boost dominant intraprostatic lesions during HDR brachytherapy, while preserving the prostate coverage and keeping the dose delivered to the organs at risk to the same level compared to an inverse planned dose distribution without DIL boost. This work illustrates the clinical benefit of accurate and consistent image registration tools, combined with inverse planning.

The screening and enrollment of patients in the study continues and the workflow procedure is now well integrated in clinic. Because the enrollment rate was slow, we have revised the protocol to facilitate recruitment for the coming year. Boost levels of 120-150% of DIL can be easily achieved on most patients while keeping the dose levels to organs at risk within the usual limits.

APPENDICES

Abstract

MULTI-IMAGE REGISTRATIONS AND THEIR ROLE IN INVERSE PLANNED HDR PROSTATE BRACHYTHERAPY FOR DOSE ESCALATION OF DOMINANT INTRAPROSTATIC LESION DEFINED BY COMBINED MRI/MRSI,

J. Pouliot et al, DOD-IMPACT meeting, Innovative Minds in Prostate Cancer Today (IMPACT) Conference, Orlando, Florida, on March 9-12, 2011.

Publication (last year only)

Reed G., Cunha J.A., Noworolski S.M., Kurhanewicz J., Vigneron D.B. , Hsu I.C., and Pouliot J., **Interactive, Multi-Modality Image Registrations for Combined MRI/MRSI-Planned HDR Prostate Brachytherapy.** Journal in Contemporary Brachytherapy, 2011 (3)1: 26-31.

ABSTRACT 1

DOD-IMPACT meeting, Innovative Minds in Prostate Cancer Today (IMPACT) Conference, Orlando, Florida, on March 9-12, 2011.

Multi-Image Registrations and Their Role in Inverse Planned High-Dose Rate Prostate Brachytherapy for Dose Escalation of Dominant Intraprostatic Lesion Defined By Combined Magnetic Resonance and Spectroscopic Imaging

Jean Pouliot¹, Adam Cunha¹, Galen Reed², Susan Noworolski^{2,3}, John Kurhanewicz^{2,3}, and I-Chow Hsu².

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- 2- Department of Radiology and Biomedical Imaging, University of California San Francisco
- 3- The Graduate Group in Bioengineering, University of California San Francisco and Berkeley

Objective: Men with prostate cancer, in particular those with advanced local disease, benefit from dose escalation. The main objective of the DOD-PC-030909 is to exploit the ability of Magnetic Resonance Imaging combined with Magnetic Resonance Spectroscopy imaging (MRI/MRSI) to identify cancer regions within the prostate and to target those regions with a higher tumor burden, also called Dominant Intraprostatic Lesion (DIL), with higher dose without compromising the dose coverage of the prostate and the protection to the urethra, rectum and bladder for prostate cancer patients treated with High-Dose Rate (HDR) brachytherapy. To reach this objective, we developed specific image alignment methods for MRI/MRSI data to HDR brachytherapy treatment planning images, and elaborated class solutions (a set of optimization dose objectives) to govern the dose optimization process.

Methods & Materials: For each patient, three imaging modalities - Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopic Imaging (MRSI), and Computed Tomography (CT) - are used at different steps during the process. A series of rigid and nonrigid transformations previously developed by our group are applied to the data to correct for endorectal coil-induced deformations and for alignment with the planning CT. Target and organs at risk are delineated on the CT while the DIL is defined on the fused images and used as optimization structures for boost. An inverse planning optimization algorithm (IPSA) is then used to determine a dose distribution that can boost the dose to the MRS-defined DIL while providing protection to the urethra, penile bulb, rectum, and bladder. The complete procedure is clinically integrated and has been used for the treatment of ten HDR patients with MRSI information.

Results: The morphing algorithm successfully modeled the probe-induced prostatic distortion. The mean prostatic rotation induced by the coil is $20^{\circ} \pm 9^{\circ}$, and the mean gland volume is 27 ± 14 cc. Urethra, peripheral zone margins, prostate boundaries, and various hyper / hypointense features on the images serve as effective landmarks for the MRI-Probe-IN - MRI-Probe-OUT fusion. Using the class solution, a certain level of DIL-boost is feasible for all patients under dosimetric requirements depending on rectal and bladder doses. The DIL dose is significantly increased. All dosimetric indices for target and organs at risk fulfill the limits used for a regular treatment. Boost levels from 20% (120% of the prescribed dose) to 50% were easily achieved. One patient received a 50% boost.

Conclusion: The feasibility of a comprehensive approach that incorporates MRI/MRSI (anatomical and functional imaging) into the HDR brachytherapy treatment planning has been demonstrated. This insures the accurate merging of MRSI to CT, and allows the use of inverse planning IPSA to boost dominant intraprostatic lesions during HDR brachytherapy. Dose escalation of target regions with a higher tumor burden can be performed without increasing the dose to critical normal structures.

Publication

Reed G., Cunha J.A., Noworolski S.M., Kurhanewicz J., Vigneron D.B. , Hsu I.C., and Pouliot J., **Interactive, Multi-Modality Image Registrations for Combined MRI/MRSI-Planned HDR Prostate Brachytherapy**. Journal in Contemporary Brachytherapy, 2011 (3)1: 26-31.

Interactive, multi-modality image registrations for combined MRI/MRSI-planned HDR prostate brachytherapy

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Abstract

Purpose: This study presents the steps and criteria involved in the series of image registrations used clinically during the planning and dose delivery of focal high dose-rate (HDR) brachytherapy of the prostate.

Material and methods: Three imaging modalities – Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopic Imaging (MRSI), and Computed Tomography (CT) – were used at different steps during the process. MRSI is used for identification of dominant intraprostatic lesions (DIL). A series of rigid and nonrigid transformations were applied to the data to correct for endorectal-coil-induced deformations and for alignment with the planning CT. Mutual information was calculated as a morphing metric. An inverse planning optimization algorithm was applied to boost dose to the DIL while providing protection to the urethra, penile bulb, rectum, and bladder. Six prostate cancer patients were treated using this protocol.

Results: The morphing algorithm successfully modeled the probe-induced prostatic distortion. Mutual information calculated between the morphed images and images acquired without the endorectal probe showed a significant ($p = 0.0071$) increase to that calculated between the unmorphed images and images acquired without the endorectal probe. Both mutual information and visual inspection serve as effective diagnostics of image morphing. The entire procedure adds less than thirty minutes to the treatment planning.

Conclusion: This work demonstrates the utility of image transformations and registrations to HDR brachytherapy of prostate cancer.

J Contemp Brachyther 2011; 3, 1: 26-31

DOI:

Key words: MRSI, HDR, prostate, image registration.

Purpose

Studies have shown that greater control of localized prostatic tumors is directly correlated with radiation doses delivered [1-3]. However, excessive dose to the normal tissues causes side effects [4-6]. High dose rate (HDR) brachytherapy can provide a focal dose escalation, and prior studies have shown that combined external beam radiation therapy (EBRT) and HDR brachytherapy yields favorable outcomes, particularly in patients with locally advanced disease [7-9]. We have recently initiated an HDR brachytherapy clinical protocol in which a combination of magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging (MRSI) is used to define dominant intraprostatic lesions (DIL). This information is used to perform dose escalation of the DIL without compromising the dose coverage of the prostate nor the protection to the urethra, rectum, and bladder. There are two difficulties, however, inherent in this approach. The first is the merging of information from the staging MRI/MRSI exam

with the anatomic computed tomography (CT) exam required for treatment planning; the second is the capacity of the treatment modality/treatment planning system to deliver radiation doses in a precise fashion.

The combined MRI/MRSI exam has been shown to be an effective method of detecting and localizing intraprostatic lesions [10-13]. The high sensitivity and specificity yielded by this exam has demonstrated great utility in focal treatment via ^{125}I brachytherapy implants [14] and combined HDR brachytherapy + EBRT [15,16].

However, since the endorectal probe used for MRI/MRSI acquisition can induce significant prostatic compression and deformation, a non-rigid transformation is required to accurately register the probe-in MRSI data with the probe-out CT images used for treatment planning. To model this deformation, prior studies have implemented finite-element based biomechanical simulations [17,18], elastic spline deformation [19], thin plate spline deformation [19-23], symmetric forces algorithms [24], Newton-

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Ralphson algorithms [25], and in-plane linear scaling assuming constant volume [14]. Kim *et al.* [26] showed that the deformation induced by the inflatable endorectal coil is negligible in the z (superior/inferior) dimension since the induced distortions are less than the axial MRI slice thickness of 3 mm. The same study also showed that the coil induces a non-negligible rotation about the x (right/left) axis. These findings suggest that an x axis rotation followed by an axial in-plane non-rigid deformation sufficiently models the prostatic deformation induced by the endorectal coil.

In this study, we developed and implemented a new method combining rigid translations (for centroid alignment), rotations (to model the x axis rotation), and an in-plane non-rigid control-point based morphing method that utilizes a local weighted-mean transformation [27]. Additionally, we present the steps and criteria involved in the series of image registrations used clinically during the planning of the dose delivery process.

Material and methods

For each patient enrolled in the study, a pre-therapy staging MRI/MRSI exam using an endorectal probe (i.e. probe in, or PI) was acquired. The MRI and MRSI images were registered so that the MRSI-defined DIL could be delineated on the anatomic MRI volume. An axial MRI series with the endorectal probe not inserted (i.e. probe out, or MRI-PO) was also acquired. Pairs of points at corresponding anatomic features on the MRI-PI and MRI-PO series were chosen and used to determine the PI-PO transformation. This transformation algorithm was used to correlate spectroscopic data (MRSI-PI) to the MRI-PO data. Mutual information was calculated to measure warping accuracy. On the HDR brachytherapy treatment day, the planning CT and the MRSI-PO were imported into the brachytherapy planning system and registered to each other. The prostate anatomy alone was used to guide the fusion. The target and organs at risk were delineated using the CT, while the DIL was contoured using spectroscopic information from the MRSI-PO. Catheters were then digitized, and the plan was optimized using the Inverse Planning by Simulated Annealing (IPSA) algorithm [16]. The optimization was instructed to provide a clinically effective dose to the entire prostate while concurrently delivering a dose escalation to the DILs. This was done without increasing the dose to surrounding non-cancerous tissues. Once the plan was approved, the dose for the first fraction was delivered.

Subjects

Six patients were scanned and subsequently treated with this protocol. Their age ranged from 44 to 80 years old (mean 61). All patients had biopsy-proven Gleason 3 + 3 disease, and five of the six subjects showed Gleason 3 + 4 pattern in histological analysis. The mean PSA measurement for all subjects was 8.8 ng/mL (ranging from 4.3 ng/mL to 19.5 ng/mL). Written informed consent was obtained for all subjects following a protocol approved by the UCSF Committee of Human Research.

Identification of DIL with MRS and MRI

MR imaging was acquired with a GE 3T SIGNA scanner (GE Medical Systems, Waukesha, WI) using body-coil excitation. The GE 8-channel pelvic phased array and Medrad endorectal coil (Medrad, Pittsburgh, PA) were used for signal reception. Axial T₁-weighted images were acquired with TR/TE = 600/12. Fast spin echo T₂-weighted images were acquired (TR/TE = 6000/102, 14 cm FOV, 256 × 256 matrix) in the axial, sagittal, and coronal planes. Images and spectroscopic data were first acquired with the endorectal probe inserted. The probe was then removed, and an additional sagittal locator and an axial FSE T₂ image data set were then acquired using the pelvic phased array for signal reception.

Spectroscopic data was acquired using a specialized prostate 3D MRSI sequence [28,29] with a 12 × 8 × 8 acquisition grid, 5.4 mm isotropic resolution yielding 0.157 cm³ voxels. Water and lipid suppression was achieved using dual-band spectral spatial pulses [30]. Very-selective spatial saturation (VSS) pulses were used to suppress periprostatic lipids [31]. In each voxel 1024 points were acquired over a 1000 Hz frequency domain. The k-space data was zero-filled in the superior/inferior and anterior/posterior dimensions to a final array size of 12 × 16 × 16. The spectral data was then apodized with a 3 Hz Gaussian filter, Fourier transformed, baseline corrected, frequency aligned, and peaks numerically-integrated. Numerical integration of each of the prostate metabolite peaks (choline, creatine, and citrate) and the suppressed water peak was performed using the known frequency positions of each of these peaks [32].

Spectroscopic voxels were classified using the standardized scoring system proposed by Jung *et al.* [33] where 1 = definitely normal, 2 = probably normal, 3 = equivocal, 4 = probably abnormal, and 5 = definitely abnormal. After the generation of these scores by a trained reader, grayscale images of these scores were created at the MRSI resolution, so that the suspicious voxels could be delineated by color on the high-resolution T₂ volume (Fig. 1). All peripheral zone voxels were tagged; central zone voxels were only tagged when suspicious for malignancy.

Warping the MRSI grid

Rotation

Sagittal images acquired with and without the endorectal probe were analyzed to determine the probe-induced rotation of the prostate about the x axis. The prostatic alignment of each series is determined by the margin of the peripheral zone and central zone as shown in Fig. 2. The image volumes are rotated by the net rotation angle $\theta_{\text{probein}} - \theta_{\text{probeout}}$ using tri-linear interpolation.

Translation

Prostatic margins were then hand-drawn on both the axial probe-out volume and the rotated axial probe-in volume. Masks were drawn on the ten to twelve corresponding slices in each volume. The centroids of the masks were calculated, and the rotated axial probe-in volumes were translated so their centroids line up with the centroid of

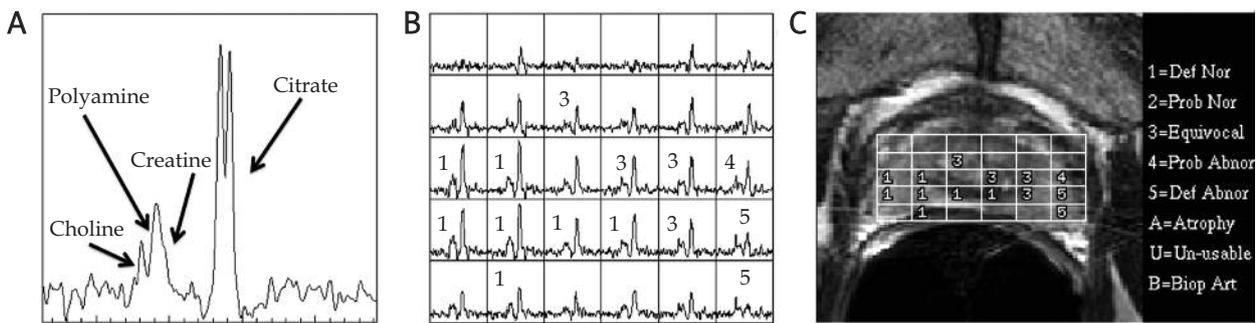


Fig. 1. A shows a typical healthy prostate NMR spectrum, with high citrate and polyamine sigal and low choline. B shows the spectral data of a patient enrolled in the study; elevated choline and reduced citrate in the left peripheral zone are indicative of malignancy. C shows the suspicious regions (scores of 3, 4, and 5) delineated on the T₂ image. All peripheral zone voxels were tagged; central zone voxels were only tagged when suspicious for malignancy. Only intraprostatic voxels are shown

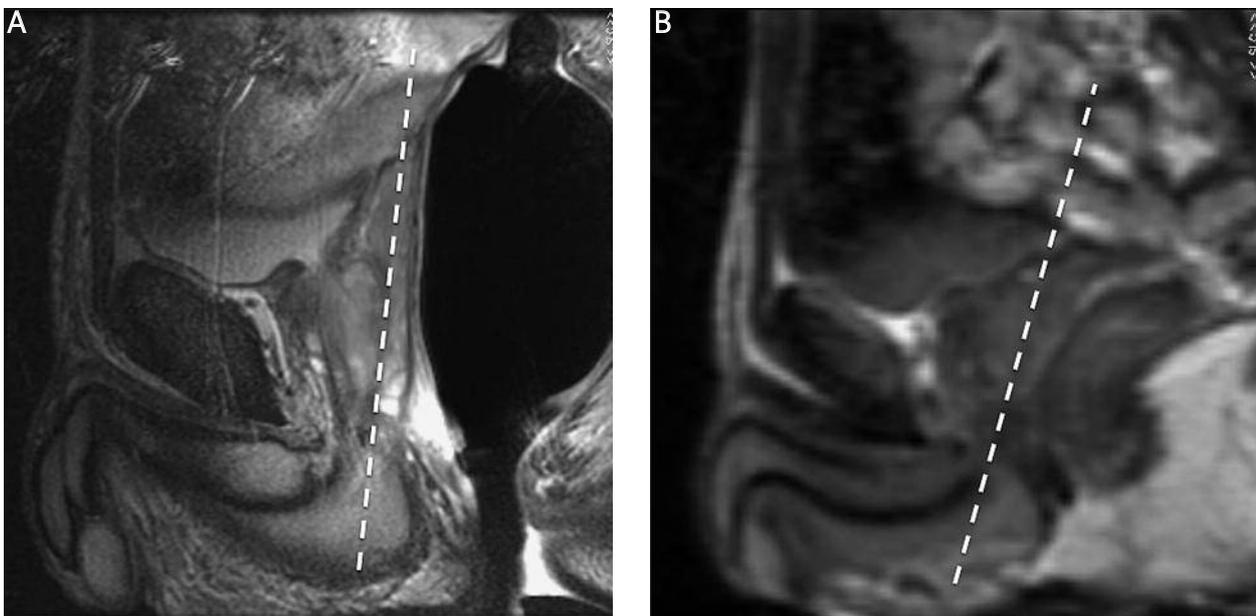


Fig. 2. Mid-sagittal probe-in (A) and probe-out (B) images showing the prostatic rotation induced by the endorectal coil. The angles were measured between the y axis and the peripheral zone/central zone margin denoted by the dotted line

the probe-out volume. Defining R_{CI} and R_{CO} as the centers and C_I and C_O as the prostate centroids of the probe-in and probe-out volumes respectively, the translation

$$\Delta R = R_{CI} - R_{CO} + C_O - C_I \tag{1}$$

aligns the prostate in both volumes provided they are acquired using the same landmark.

Non-rigid deformation

After the rotation and translations were applied, a non-rigid deformation was used to model the prostatic deformation induced by the endorectal coil. To model this deformation, the probe-in and probe-out T₂ imaging series were compared slice-wise. In each slice, control point pairs were assigned to matching anatomical landmarks within the prostate (Fig. 3). The control point locations were assigned using the MATLAB control point selection tool. These

point pairs were then used to define a local weighted-mean [27] PI-PO transformation. This non-rigid transformation placed higher weighting on image regions with a higher control point density. Therefore, the operator could apply more control points onto the regions where higher accuracy was required with the registration. Examples are regions of higher prostatic compression (the posterior aspect) and regions of suspected malignancy. The transformation was applied to the MRI-PI volume (to calculate morphing accuracy) and to the MRSI-PI data. Finally, the MRSI-PI data (after rotation, translation, and deformation) were delineated on the probe-out T₂ volume (Fig. 4).

Evaluation

Mutual information (MI) was calculated between the MRI-PO images and both the warped and non-warped MRI-PI images after rotations and translations were applied. This value was calculated similar to previous

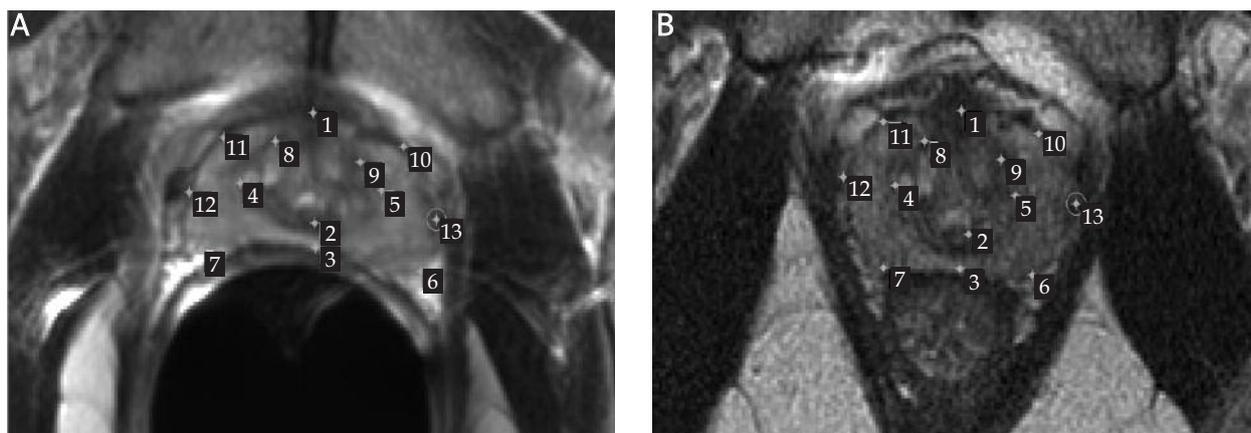


Fig. 3. Probe-in (A) and probe-out (B) axial slices showing control point placement. The probe-in volume is rotated by the prostatic angle so the slices are assumed to be coplanar. Despite the lower signal-to-noise ratio on the probe-out image, numerous landmarks are still identifiable on both images

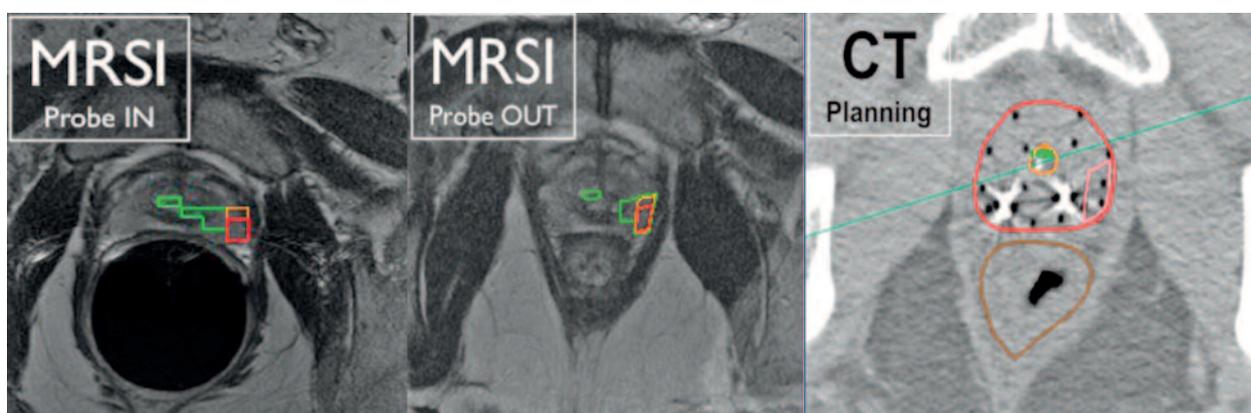


Fig. 4. The left image shows the original acquisition image with the suspicious regions delineated. The center image shows the axial probe-out volume with the rotate, translated, and warped spectral delineations. MRSI scores of 4 and 5 are delineated on the planning CT (right)

works [34] using the histogram method. MI was calculated only in the smallest-fitting rectangular boundary around the hand-drawn mask for each slice so that the erroneous morphing in the extra-prostatic regions (where no control points are placed) did not excessively sway the metric.

Target delineation for dose planning optimization

MRSI – planning CT registration

On the HDR brachytherapy treatment day, a CT scan with 3 mm slice thickness was acquired immediately after the patient recovered from the implant procedure. The imaging volume included the whole of the prostate and was limited superiorly to include the bladder and inferiorly to visualize all the catheters down to the perineum. The planning CT and the MRSI-PO were imported in the brachytherapy planning system (OncentraBrachy™, Nucletron, Veenendaal, the Netherlands), and a rigid body registration was obtained. The prostate anatomy alone was used to guide the fusion, since the prostatic position can vary with respect to extra-prostatic landmarks. Typically, 3 pair-points were defined: two by the urethra in the base and

apex areas, and a third one more lateral to the prostate in the median plane. Target and organs at risk were delineated on the CT while the DILs were contoured on the MRSI-PO using spectroscopic information. Catheters were then digitized, the plan was optimized using IPSA, and the dose for the first fraction was delivered.

Definition of volumes of interest

Clinical target volumes (prostate) and organs at risk (urethra, bladder, rectum and bulb) were contoured on each CT slice (Fig. 5A). The DILs – defined by MRSI voxel scores of 4 or 5 – were manually contoured on the CT, but the transparency level was adjusted to make the MRS information visible on the CT (Fig. 4 right). After the catheters were digitized on the CT, all information requested for the optimization of the dose distribution was available (Fig. 5B).

Dose optimization with inverse planning IPSA

The inverse planning optimization algorithm was then used to increase the dose delivered to the dominant intra-

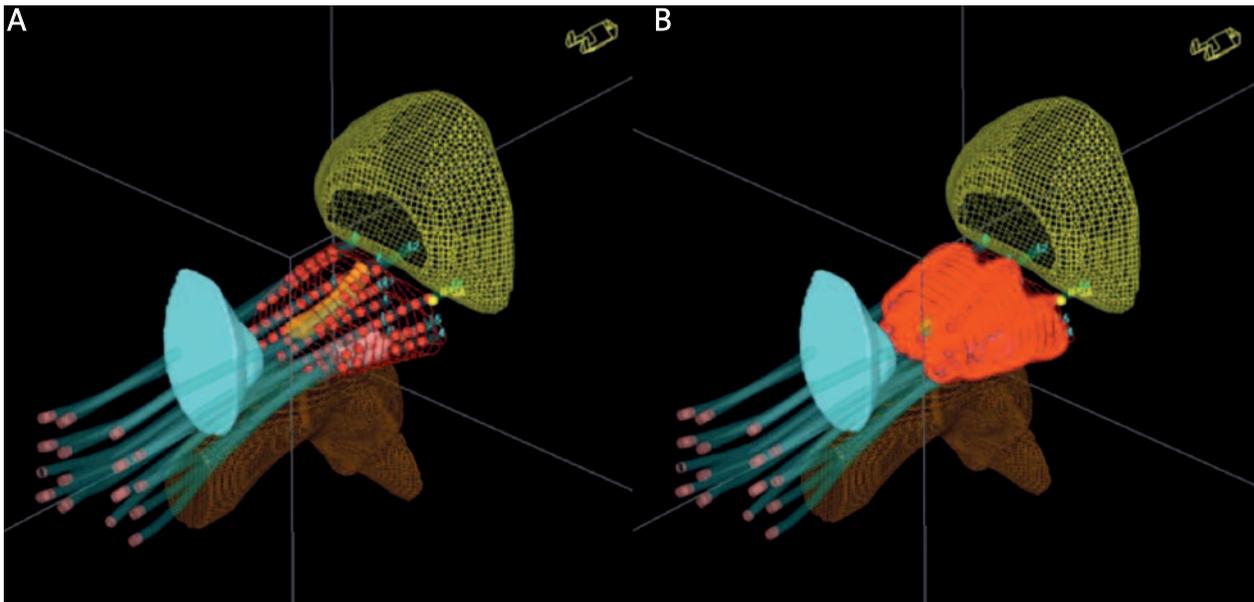


Fig. 5. Digitized catheters and delineated target organs: rectum (brown), urinary bladder (yellow mesh), and urethra (solid yellow). The MRSI-defined DIL is shown in pink on the left, and the right figure shows an isodose contour

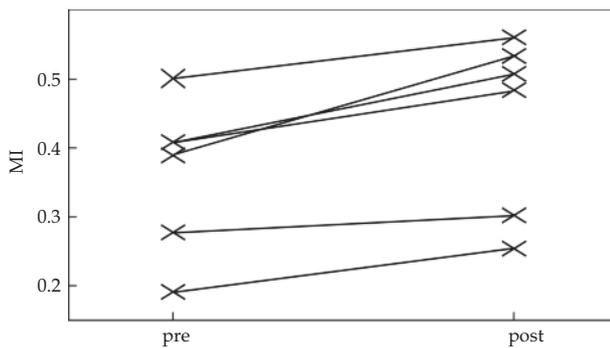


Fig. 6. Mutual information before and after applying the described transformations to the MRI volumes for each of the six patients in the trial. Each data point represents the mean values of all slices in the prostate

prostatic lesions defined by MRI/MRSI while providing the usual dose coverage of the prostate and the protection to the urethra, rectum, bulb and bladder.

A class solution – a set of weights provided to the optimization to guide it to satisfy the dose requirements of each region of interest – was previously developed [15] for dose escalation of a DIL defined by combined MRI/MRSI in inverse planned HDR prostate brachytherapy. Using this class solution, a certain level of DIL-boost was feasible for the majority of patients under the RTOG-0321 dosimetric requirements depending on rectal and bladder doses. The class solution in inverse planned HDR prostate brachytherapy for dose escalation of a DIL defined by combined MRI/MRSI was an excellent starting point to explore a customized set of dose constraints to obtain a satisfactory treatment plan for each patient in the ongoing protocol.

Results and Discussion

The complete procedure was clinically integrated and has been used for the treatment of six HDR brachytherapy patients with MRSI information. Out of the 6 patients scanned, the mean prostatic rotation induced by the coil was 20 ± 9 , and the mean gland volume was $27 + 14 \text{ cm}^3$. Urethra, peripheral zone margins, prostate boundaries, and various hyper/hypointense features on the images served as effective landmarks for the MRI-PI-MRI-PO fusion (Fig. 3). At least 12 point pairs – selected primarily from regions with high deformation, such as the posterior aspect of the peripheral zone, and regions of spectroscopic abnormality – are required as inputs to the MATLAB image transformation function. Visual inspection as well as the computed MI (Fig. 6) served as effective diagnostics of the morphing. MI showed $25\% \pm 13\%$ increase for the six patients. A paired *t*-test showed this improvement to be significant ($p = 0.0071$). On the day of the first fraction, performing the MRSI-CT fusion was followed by the delineation of the DIL adding less than fifteen minutes to the entire planning process. The 3 pair-points registration procedure is considered valid when the sum of squared distances between each pair-point is less than 2 mm. A careful visual inspection of the fusion in the prostate area was also performed.

Conclusions

An MRSI to MRI/CT alignment protocol was developed to exploit the high specificity of combined MRI/MRSI for detecting and localizing prostate cancer within the prostate, and to accurately transfer this information to the planning images. This makes information about the prostate cancer location routinely available, and allowing the use of inverse

planning IPSA to boost dominant intraprostatic lesions during HDR brachytherapy, while preserving the prostate coverage and keeping the dose delivered to the organs at risk at the same level compared to an inverse planned dose distribution without DIL boost. Information from one image data set could be accurately transferred to another in the series of MRS → MRI → CT. This workflow was routinely used for the dose planning, including DIL boost. This work illustrates the clinical benefit of image registration tools.

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