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TITLE: Targeting MRS-Defined Dominant Intraprostatic Lesions with Inverse-Planned High Dose Rate Brachytherapy

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14. ABSTRACT During the last 16 month period from 26 JAN 2007 to 25 MAY 2008, we have obtained the UCSF CHR re-confirmation. We have commissioned a new imaging fusion and planning system to facilitate the registration of MRI/MRS images with planning CT images. We have also published our results on the class solution for the boost of DIL defined by MRI/MRSI, as well as for the sparing of organs at risk including bladder, rectum, urethra and penile bulb. Patient's enrollment has been initiated.					
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PC030909 Final Report **(addendum)**
January 2007 – May 2008

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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.

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 will be 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. (Months 1-24).

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 (Months 1-12).

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 (Months 18-36).

The Information provided in this third annual (final) report supports the following:

Task 1:	Months 1-24	Completed , (except for alignment of the non-endorectal MR images to the treatment planning CT, pending patient enrollment)
Task 2:	Months 1-12	Completed
Task 3:	Months 18-36	Initiated

C.H.R. Approval Process Time Table

The PC-030909 grant officially opened on February 2004. A lot of effort and time were devoted by the P.I. and Co-P.I. at applying and obtaining approval from the various committees at UCSF. During the first year, we sequentially applied and successfully received approvals from the UCSF Genito-Urinary Committee (GU, March 2004), the UCSF Protocol Review Committee (PRC, July 7th, 2004), and the UCSF Committee on Human Research (CHR, approval number H11386-24294-01, December 17th, 2004). Immediately after receiving the CHR approval, the complete package was submitted to the DOD CHR for final approval. This approval was received on December 2006. UCSF CHR Committee re-confirmation was obtained and patients enrollment has been initiated in June 2008.

Research activities (Present and Future)

In the last three years, a number of research activities related to the Tasks described in the Statement of Work of the proposal have been performed. In particular, Task 1 has been accomplished during year 1 and published on the journal "Medical Physics", and Task 2 has been accomplished during year 2 and submitted for publication. Specific details were provided in the first two annual reports. A Postdoctoral Fellow (Yongbok Kim, Ph.D.) continued to perform the work until March 2006. We have requested a no-cost extension and the research will proceed with patients enrollments as described in the research protocol.

BODY SECTION

MRI/MRSI is used to differentiate between normal and malignant prostate and define cancer-validated Dominant Intra-prostatic Lesions (DIL). A retrospective study was first conducted using data from 15 HDR patients with MRI/MRSI defined DIL. For each patient, MRSI data was first fused on the axial T2-weighted MR images. Using the prostate anatomy, the combined MRI/MRSI images were then registered on HDR planning axial CT or MR images. Targets, organs at risk and DIL were segmented. Dose constraints parameters were adjusted to define a class solution for a DIL-boost plan under the dosimetric requirements of the RTOG-0321 protocol. To determine a maximum attainable level of DIL-boost for each patient, our inverse planning dose optimization algorithm (called IPSA) was used to generate dose distributions for five different levels of DIL-boost, at least 110%, 120%, 130%, 140% and 150% of the prescribed dose. Dose volume histograms of the target and each organ at risk were compared with optimized plans without DIL boost.

On the cohort of 15 patients, dose escalations of the MRI/MRSI defined DIL were achieved in the range of 120% to 150% of the prescription with only an average of 1% increase of the V50 bladder dose, and 1 to 3% rectum depending on the boost level. Dose to the whole prostate, with the exception of the DIL, did not change. All dose limits complied with RTOG dosimetric requirements. This is accomplished by using inverse treatment planning software that can focus normally occurring high dose regions within the target volume to coincide with the DIL. Combined CHR approvals from our institution and from DOD has been obtained and patients enrollment has been initiated in June 2008.

In the previous annual reports, we have described the research accomplishments related to the three following topics:

- Endorectal coil probes for prostate MRI: Assessments of tissue distortions and image alignments
- Registration of MR prostate images with biomechanical modeling and nonlinear parameter estimation
- Class solution for Inverse Planning for Dose Escalation of Dominant Intraprostatic Lesions

In the last 16 months, we have

- Published the work on the establishment of Class Solutions and established the correct registration procedure between the MRSI and planning MRI/CT images
- Tested a new imaging fusion tool and planning system that will greatly facilitate the transfer and the accurate delineation of the DIL location from the MRS/MRI study onto the planning CT.

KEY RESEARCH ACCOMPLISHMENTS

Class solution for Inverse Planning

- The class solution was published for the DIL-boost as well as the sparing organs at risk, including bladder, rectum, urethra and penile bulb.

MRS/MRI - planning MRI/CT Registration protocol for Planning purpose

- A double registration procedure was established to bring on a same image the initial MR image, the MR spectroscopy information and the planning image dataset.

REPORTABLE OUTCOMES

Peer-reviewed Publications

1) Inverse Planning For HDR Prostate Brachytherapy Use to Boost Dominant Intra-Prostatic Lesion Defined by Magnetic-Resonance Spectroscopy Imaging.

Pouliot, J., Kim, Y., Lessard E., Hsu, I-C. Vigneron D. and Kurhanewicz, J. Int. J. Radiation Oncology Biol. Phys. 59 (4) 1196-1207; 2004.

The results of this paper constituted the proof of principle presented to DOD to obtain the grant

2) Endorectal and rigid coils for prostate MRI: Impact on prostate distortion and rigid image registration.

Kim Y., Noworolski S.M., Pouliot J., Hsu I.C. and Kurhanewicz J., Med. Phys. 32(12); 3569-3578, 2005.

Publication is provided

3) Kim Y., Hsu I.C., Lessard E., Kurhanewicz J., Noworolski S.M. and Pouliot J., Class solution in inverse planned HDR prostate brachytherapy for dose escalation of DIL defined by combined MRI/MRSI, Int. J. Radiation Onc. Biol. Phys. 2006

We have responded to the initial reviewers comments. The paper is undergoing the second round of review. Publication is provided

4) Registration of MR prostate images with biomechanical modeling and nonlinear parameter estimation

Alterovitz R., Goldberg K., Pouliot J., Hsu I.C., Kim Y., Noworolski S.M., and Kurhanewicz J., Med. Phys. 33(2), 446-454; 2006.

This work is directly related to present work (Task 1) but not supported by DOD -PC030909.

Presentations at International Conferences

Advances in Optimization Strategies, Physics Symposium, Int. Society for Therapeutic Radiology and Oncology, Joint GEC-ESTRO-ISORT Meeting, Montpellier, May 9-12, 2007.

Dose escalation using functional imaging, 12th International Conference Optimal Use of Advanced Radiotherapy in Multimodality Oncology, Rome, Italy, 20th to 23rd June 2007.

Inverse planning in Brachytherapy: HDR and LDR, VI Last Generation Radiotherapy Course, São Paulo, Brazil, Oct. 19, 2006.

Principles and Clinical Applications of IPSA; Nucletron International Physics Seminar, Vaals, Netherlands, Sept 13-16, 2006.

IPSA, optimization in Brachytherapy, Basis and Principles, 4^{ième} séminaire francophone de curiethérapie, Arcachon, France, June 15th, 2006.

Clinical experience with IPSA for prostate cancer treatment in HDR Brachytherapy, 4^{ième} séminaire francophone de curiethérapie, Arcachon, France, June 15, 2006.

Advanced Technologies: Functional Imaging, IMRT and IGRT, NZIMRT – AIR Annual meeting, Auckland, New Zealand, August 27th, 2005.

Inverse planning for dose optimization in Brachytherapy, Institut Gustave-Roussy, Paris, France, June 28, 2004.

Presentations at National Meetings

Dose Escalation of Dominant Intra-Prostatic Lesion Defined by Magnetic-Resonance Spectroscopy Imaging Using Inverse Planning for HDR Prostate Brachytherapy, DOD-PCRP- Meeting, Innovative Minds in Prostate Cancer Today (IMPACT), Atlanta Georgia, Sept. 5-8, 2007.

New advances in Brachytherapy Physics, 27th Annual Meeting of American Brachytherapy Society, Philadelphia, May 12, 2006.

Advanced 3D Planning in Brachytherapy, AAPM-ABS summer school, Seattle July 18-23, 2005.

Analysis of prostate deformation due to different MRI/MRS endorectal coils for image fusion and brachytherapy treatment planning. Med. Phys.31 (6); 1728-1728, 2004 (Abstract).

Dose Constraints in Inverse Planning HDR Prostate Brachytherapy for The Dose Escalation of DIL Defined by MR Spectroscopy Imaging. *Annual Meeting of the American Brachytherapy Society*, San Francisco 2005.

DETAILS OF REPORTABLE OUTCOMES

The details of the previous reportable outcomes were provided in the two previous annual reports as well as in the publications provided in Appendices. References cited in the publications (published or in press) support our experimental objectives, choices made in experimental design, and interpretation of results.

Class solutions

A class solution was developed for dose escalation of a DIL defined by combined MRI/MRSI in inverse planned HDR prostate brachytherapy. Using the class solution, a certain level of DIL-boost is feasible for some patients under RTOG-0321 dosimetric requirements depending on rectal and bladder doses. While the target dose was slightly increased, the DIL dose was noticeable enhanced (on average, 82% of the DIL volume could receive 150% of the prescribed dose) without any violation of the dosimetric requirements. With further adjustment of the class solution, the DIL could be boosted by 150 – 150 for 13 out of 15 patients while satisfying dosimetric requirements. Hence, the established class solution for a DIL-boost is a good starting point to explore a customized HDR prostate brachytherapy plan for a specific patient.

Registration procedure between the MRSI and planning MRI/CT images

A new imaging fusion tool and planning system was commissioned and tested. The availability of this system will greatly facilitate the transfer and the accurate delineation of the DIL location from the MRS/MRI study onto the planning CT. The MRI/MRS registration procedure resulting on an MR image with defined validated cancer areas (Figure in the center) was established and reported in year 2. This allows to import the image in the planning software. The planning image showing the current anatomy and the catheters can then be registered with the combined MRI/MRS image, providing all the anatomical information in the same reference system (Figure, right).

LIST OF ACRONYMS

CHR: Committee on Human Research
CT: Computed Tomography
DIL: Dominant Intraprostatic Lesion
S/I: Superior-Inferior
R/L: Right-Left
A/P: Antero-Posterior
DOD: Department of Defense
ERC: Endo-Rectal Coil
GU: Genito-Urinary Committee
HDR: High Dose-Rate
IPSA: Planning with Simulated Annealing
MRI: Magnetic Resonance Imaging
MRSI: Resonance Spectroscopy Imaging
PRC: Review Committee
ROI: Region of Interest
RTOG: Radiation Therapy Oncology Group
UCSF: University of California California, San Francisco
DIL: Dominant Intra-prostatic Lesion
CG: Central Gland
PZ: Peripheral Zone
TRUS: Trans-rectal Ultra-Sound
OAR: Organs at Risk

APPENDICE

Publications

- 1- Pouliot, J., Kim, Y., Lessard E., Hsu, I-C. Vigneron D. and Kurhanewicz, J. **Inverse Planning For HDR Prostate Brachytherapy Use to Boost Dominant Intra-Prostatic Lesion Defined by Magnetic-Resonance Spectroscopy Imaging.** Int. J. Radiation Oncology Biol. Phys. 59 (4) 1196-1207; 2004. (The results of this paper constituted the proof of principle presented to DOD to obtain the grant).
- 2- Kim Y., Noworolski S.M., Pouliot J., Hsu I.C. and Kurhanewicz J., **Expandable and rigid endorectal coils for prostate MRI: Impact on prostate distortion and rigid image registration,** Med. Phys. 32(12); 3569-3578, 2005.
- 3- Kim Y., Hsu I.C., Lessard E., Kurhanewicz J., Noworolski S.M. and Pouliot J., **Class solution in inverse planned HDR prostate brachytherapy for dose escalation of DIL defined by combined MRI/MRSI,** Radiotherapy and Oncology, 88(1):148-55; 2008. (The complete paper is included below).
4. Alterovitz R., Goldberg K., Pouliot J., Hsu I.C., Kim Y., Noworolski S.M., and Kurhanewicz J., **Registration of MR prostate images with biomechanical modeling and nonlinear parameter estimation,** Med. Phys. 33(2), 446-454; 2006. (related to present work but not supported by DOD -PC030909).
- 5- Kim Y., Hsu I.C., and Pouliot J., **Measurement of craniocaudal catheter displacement between fractions in computed tomography-based high dose rate brachytherapy of prostate cancer,** Journal of Applied Clinical Medical Physics, Vol. 8, No. 4, Fall 2007. (related to present work but not supported by DOD -PC030909).

ABSTRACT

**DOSE ESCALATION OF DOMINANT INTRA-PROSTATIC LESION
DEFINED BY MAGNETIC-RESONANCE SPECTROSCOPY IMAGING
USING INVERSE PLANNING FOR HDR PROSTATE BRACHYTHERAPY**

Jean Pouliot; I-Chow Hsu; Etienne Lessard; Yongbok Kim; (Comprehensive Cancer Center, University of California, San Francisco, San Francisco, California) Susan Moyher Noworolski; John Kurhanewicz (Center for Molecular and Functional Imaging, Department of Radiology, University of California, San Francisco, San Francisco, California)

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.

MRI/MRSI is used to differentiate between normal and malignant prostate and define cancer-validated Dominant Intra-prostatic Lesions (DIL). A retrospective study was first conducted using data from 15 HDR patients with MRI/MRSI defined DIL. For each patient, MRSI data was first fused on the axial T2-weighted MR images. Using the prostate anatomy, the combined MRI/MRSI images were then registered on HDR planning axial CT or MR images. Targets, organs at risk and DIL were segmented. Dose constraints parameters were adjusted to define a class solution for a DIL-boost plan under the dosimetric requirements of the RTOG-0321 protocol. To determine a maximum attainable level of DIL-boost for each patient, our inverse planning dose optimization algorithm (called IPSA) was used to generate dose distributions for five different levels of DIL-boost, at least 110%, 120%, 130%, 140% and 150% of the prescribed dose. Dose volume histograms of the target and each organ at risk were compared with optimized plans without DIL boost.

On the cohort of 15 patients, dose escalations of the MRI/MRSI defined DIL were achieved in the range of 120% to 150% of the prescription with only an average of 1% increase of the V50 bladder dose, and 1 to 3% rectum depending on the boost level. Dose to the whole prostate, with the exception of the DIL, did not change. All dose limits complied with RTOG dosimetric requirements. This is accomplished by using inverse treatment planning software that can focus normally occurring high dose regions within the target volume to coincide with the DIL. Combined CHR approval from our institution and from DOD is expected early 2007 and patients enrollment will be initiated soon.

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 will be the first trial using both MR imaging and functional imaging MRSI for HDR brachytherapy planning.

IMPACT: This new approach will allow dose escalation to be targeted to areas of high cancer cell density. We believe these refinements of HDR brachytherapy planning will lead to new therapeutic approaches that may improve clinical results.

Class solution in inverse planned HDR prostate brachytherapy for dose escalation of DIL defined by combined MRI/MRSI

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Abstract

Purpose: To establish an inverse planning set of parameters (class solution) to boost dominant intra-prostatic lesion (DIL) defined by MRI/MRSI.

Methods: For 15 patients, DIL were contoured on CT or MR images and a class solution was developed to boost the DIL under the dosimetric requirements of the RTOG-0321 protocol. To determine the maximum attainable level of boost for each patient, 5 different levels were considered, at least 110%, 120%, 130%, 140% and 150% of the prescribed dose. The maximum attainable level was compared to the plan without boost using cumulative dose volume histogram (DVH).

Results: DIL dose escalation was feasible for 11/15 patients under the requirements. The planning target volume (PTV) dose was slightly increased, while the DIL dose was significantly increased without any violation of requirements. With slight adjustments of the dose constraint parameters, the dose escalation was feasible for 13/15 patients under requirements.

Conclusion: Using a class solution, a dose escalation of the MRI/MRSI defined DIL up to 150% while complying with RTOG dosimetric requirements is feasible. This HDR brachytherapy approach to dose escalation allows a significant dose increase to the tumor while maintaining an acceptable risk of complications.

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Keywords: Class solution; Dominant intra-prostatic lesion; MR Spectroscopy imaging; Dose escalation; Inverse planned HDR brachytherapy

High dose rate (HDR) brachytherapy can safely and accurately deliver radiation dose to prostate cancer with a single Ir-192 source. The HDR brachytherapy employs catheters inserted directly into the prostate, guided by transrectal ultrasound (TRUS), and adjusts source dwell times along the catheters with a remotely controlled afterloader. Advancements recently made in imaging technology have improved the accuracy and effectiveness of HDR prostate brachytherapy planning. The anatomical information obtained from computed tomography (CT) and magnetic resonance imaging (MRI) images can be displayed along with the dose distribution within the target and the organs at risk (OAR) and significantly improves the control of the dose distribution [3,16,19]. The functional imaging information, MR spectroscopic imaging (MRSI) combined with MRI and translated into the planning CT or MRI, was introduced into HDR prostate brachytherapy in order to better identify dominant intra-prostatic malignant lesions (DILs) within the prostate and to escalate the dose on the DIL [22]. Several clinical follow-up studies demonstrated that improved biochemical control, a higher survival rate and a lower risk of complications are achieved by the dose escalation of prostate cancer

with HDR brachytherapy [2,4,17,18,25,26]. In addition, the development of anatomy-based inverse planning dose optimization for HDR brachytherapy can produce a highly conformal dose profile within one minute, with more than 90% of the prostate volume covered with the prescribed dose and a clinically acceptable sparing of OAR [1,3,5,13–15,28]. Furthermore, the concept of class solution commonly used in intensity modulated radiation therapy (IMRT) [8,20,21,24,27] is now available in brachytherapy. The class solution of an inverse planning routine can reduce the variation of treatment plan quality across different users and can dramatically decrease the treatment planning time. In this study we developed a class solution for boosting MRI/MRS defined DILs in inverse planned HDR brachytherapy of prostate cancer.

Methods and materials

Patient cohorts

We used data from 15 HDR patients with MRI/MRSI defined DILs (patients A to O). The mean ± standard deviation

value of their prostate volume was 43.7 ± 16.3 cc with a range from 28.1 to 86.0 cc. In general, 16 catheters (range from 15 to 18) were inserted using TRUS guided freehand technique to cover the entire prostate instead of conventional pre-fabricated templates. Our current protocol calls for a single interstitial implant and two subsequent HDR fractions with each providing 9.5 Gy. The detail of the freehand TRUS guided HDR brachytherapy treatment procedure for prostate cancer used at our institution was described in other studies [9,10,23].

Definition of the DIL

We overlaid the MRSI data on the axial T2-weighted MR images through post-processing. The resolution of the MRS is 0.3 cc. Each MRSI voxel is scored using a standardized 5-point scale (1 – definitely benign, 2 – likely benign, 3 – equivocal, 4 – likely abnormal and 5 – definitely abnormal), based on the change of metabolite markers (choline, citrate, creatine and polyamines): elevation of the choline peak and reduction of the citrate, creatine and polyamine peaks in an abnormal MRSI voxel [7]. Based on the combined MRI/MRSI information, DILs were manually contoured on HDR planning axial CT or MR images by a physician. A lesion was defined as a DIL (Fig. 1(b)) wherever it contained at least 3 contiguous MRSI validated cancer voxels scored with a 4 or a 5 on combined MRI/MRSI images (Fig. 1(a)).

Dosimetric requirements for a class solution

We developed a class solution that would comply with the dosimetric requirements used in the current RTOG-0321 protocol [6]. The RTOG protocol requires more than 90% of the planning target volume (PTV) to be covered by the prescription dose (9.5 Gy). The PTV was the same as clinical target volume (CTV) and defined by the physician on CT scans. It included the prostate only for T1c-T2b and the prostate and extra-capsular extension for T3a-T3b. In addition, each volume of the bladder and the rectum receiving 75% of the prescription dose (7.12 Gy) must be less than 1 cc and the volume of the urethra receiving 125% of the prescription dose (11.87 Gy) must be less than 1 cc. When the bladder and rectum were contoured, the outer most border of the mucosa was included. For the urethra, the outer surface of the Foley catheter was contoured. Throughout the paper, PTV V100[%] is defined as the percent volume [%] of the PTV receiving at least 100% of the prescribed dose while rectum V75[cc] is defined as the absolute volume [cc] of the rectum receiving at least 75% of the prescribed dose.

Anatomy-based inverse planning

Our in-house inverse planning routine based in simulated annealing (IPSA) was implemented on a commercial HDR treatment planning system (Plato V14.2, Nucletron, The Netherlands) for evaluation and was clinically/routinely used for HDR brachytherapy at our institution. First, the PTV and OAR are delineated and catheters are digitized on axial CT or MR images. Approximately two thousand dose points are generated on the surface and inside of all the organs (PTVs and OAR). For the surface and inside of all organs, a set of dose constraints is defined as an acceptable

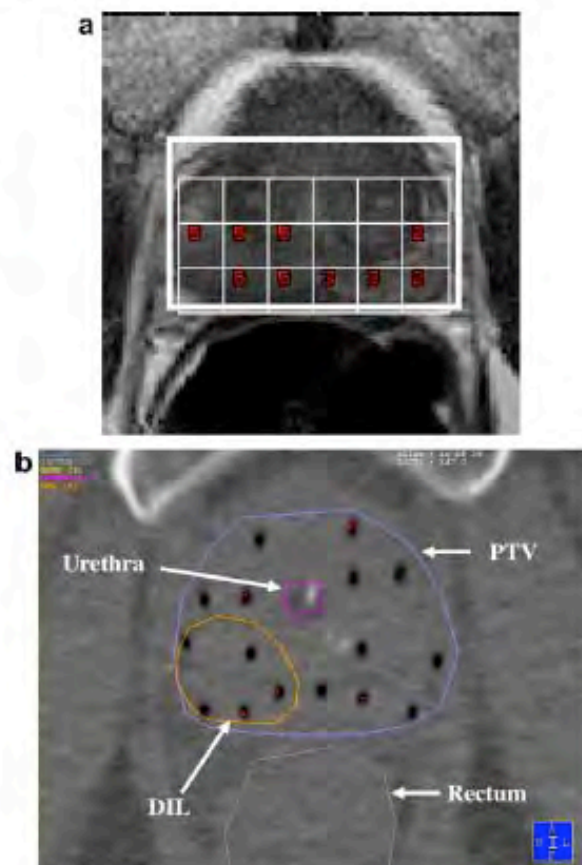


Fig. 1. (a) Axial MR image and MRSI voxel grids with their spectral scores at the midgland of prostate I. (b) HDR brachytherapy planning axial CT image at the midgland of prostate I shows the contours of PTV, urethra, rectum. A DIL was manually drawn based in (a). As seen as black dots on planning CT image, 16 catheters were implanted to cover the entire target volume.

dose range (minimum and maximum doses) and weighting factors for penalty values imposed to the minimum and maximum doses. Dwell times were set to zero for all dwell positions outside target and these positions were excluded from the optimization process afterward. Hence, the active dwell positions were only within the PTV. Under user-defined dose constraints, IPSA searches the optimal solution (a dwell time combination) through the simulated annealing algorithm to minimize the possibility that any dose point resides outside the acceptable dose range [14]. This process takes less than one minute. Owing to the anatomy-based inverse planning, IPSA can deal with any additional targets and OAR, i.e., seminal vesicles (additional target), DIL boost (target within a target), neurovascular bundle or bulb of penis (OAR outside of the target), and so forth.

Class solution for a plan without boost

Prior to developing a class solution for the DIL-boost plan, a class solution for a plan without a boost was determined. In general, the acceptable dose range is al-

ways the same both on the surface and inside of all organs (targets and OAR). The clinically acceptable dose range is from 100% to 150% of the prescribed dose for the PTV and from 100% to 120% for the urethra, which has to be spared from a high dose (hot spot). In our institution, 120% of the prescription dose was used for maximum dose of urethra to ascertain its protection instead of 125%. To other OAR located outside of the PTV such as the bladder and the rectum, ideally no dose should be delivered. Hence, naught is assigned to the minimum dose while a clinically appropriate value such as 50% or 75% of the prescribed dose with its pertinent weighting factor is assigned to the maximum dose. The most important clinical objective is the maximum relative weight. The maximum relative weight is given the arbitrary value of 100. All other clinical objectives are given an equal or smaller weight corresponding to their relative importance. For weighting factors to the dose limit, both on the surface and inside of the OAR the same value was applied because any dose should be avoided both on the surface and inside of the OAR simultaneously. However, they were different between on the surface and inside of the PTV. On the surface of the PTV, the weighting factor on the minimum dose should be high enough (the maximum relative weight of 100) to ensure a clinically acceptable PTV coverage by the prescribed dose and the weighting factor on the maximum dose should also be high enough (the maximum relative weight of 100) to avoid containing the maximum dose within the PTV for protecting the surrounding normal tissues. Based on our clinical experience, the value of 100 was high enough to penalize the cost function during dwell time optimization when the PTV dose was less than the prescribed dose. Inside the PTV, the weighting factor for the minimum dose was also high enough (the maximum relative weight of 100) that the inside of PTV is fully covered by the prescribed dose. The weighting factor for the maximum dose was reduced to 30 to achieve better conformal dose distribution. This was a dose constraint on the V150 of the PTV and it balanced the compromise between dose homogeneity and dose coverage. Over the years, our clinical experience demonstrated that a weighting factor of 30 reduced adequately the size of the hot spots while keeping excellent dose coverage. For the urethra, the same weighting factors as the inside of the PTV are used based on previous clinical experience. Regarding weighting factors to the dose limits of the bladder and the rectum, they are well established but sometimes vary depending upon an individual patient. In order to yield a clinically better plan for a patient, a better tradeoff should be made between higher PTV coverage by the prescribed dose and enhanced protection of the bladder and the rectum. Therefore, if the maximum dose limit of the bladder and the rectum is decreased and/or their weighting factor is increased unduly, the bladder and the rectum are overprotected while the PTV coverage is undesirably reduced. On the other hand, if their maximum dose is increased and/or their weighting factor is reduced excessively, the PTV coverage with the prescribed dose can be improved but the rectum and bladder receive an intolerable dose and consequently higher complications are predicted after

treatment. Therefore, in this study, by adjusting the maximum dose and the weighting factor of the bladder and the rectum a class solution was determined for a plan without boost under the dosimetric requirement.

Class solution for a DIL

A class solution for a DIL was developed based on two perspectives. Primarily the dosimetric requirements should be satisfied. Second, we used 150% of the prescribed dose as the maximum dose escalation goal for the DIL. The maximum dose escalation level (150%) to DIL is the same as the maximum dose desired for the PTV in dwell time optimization even though the dose next to the active dwell positions is higher than 150%.

Prior to examining various levels of a DIL-boost for each patient, the same dose range as the PTV was applied to the DIL to construct a DIL-boost plan equivalent to a plan without a boost. As with the PTV and OAR, the same dose range was used both on the surface and the inside of the DIL. On the surface of the DIL the same weighting factors as the inside of the PTV were employed because the DIL surface has the same clinical importance as the inside of the PTV. In addition, the weighting factor for the minimum dose inside the DIL was the same value as inside the PTV since the DIL should be covered by at least the minimum dose. Finally, for an appropriate weighting factor to the maximum dose limit inside the DIL, seven different values of the weighting factor (from 0 to 30 with 5 points increment) were attempted in the DIL-boost plan equivalent to a plan without boost under dosimetric requirement.

Maximum attainable level of DIL-boost using the class solution

The class solution for the DIL-boost plan was developed by adding a dose constraint of the DIL to the previously obtained class solution for a plan without a boost. By increasing the minimum dose with a 10% increment in the class solution for the DIL-boost plan equivalent to a plan without boost, 5 different levels of DIL-boost plans were investigated for each patient: 110–150, 120–150, 130–150, 140–150, and 150–150 (acceptable dose range: minimum–maximum dose in percent relative to the prescribed dose). The highest DIL-boost plan without any violation of requirement was considered as the maximum attainable DIL-boost plan for each patient. For patients reaching certain level of DIL-boost without violation of the requirement, the maximum attainable DIL-boost plan was compared with a plan without boost by analyzing a cumulative dose volume histogram (DVH) of the PTV and the DIL. Specific dosimetric indices of the PTV (V100[%] and V150[%]) and the DIL (V120[%], V150[%] and V200[%]) were compared between the two plans. In addition, some dosimetric parameters for OAR between the two plans were compared such as bladder V75[cc], rectum V75[cc] and urethra V125[cc]. Furthermore, under the dosimetric requirements, the class solution was manually adjusted to achieve the 150–150 DIL-boost for patients whose previous level of DIL-boost was lower than 150–150.

Results

DIL

The mean $\pm$ the standard deviation value of the DIL volume in percent relative to the prostate volume was $13.9 \pm 7.3\%$ with a range from 2.5% to 31.3% (6.3 ± 4.3 cc with range from 1.2 cc to 15.3 cc for the absolute DIL volume) for the 15 patients. All patients have one DIL except for patient J who has two DILs. In this study the DIL was always located at the peripheral zone of prostate and its specific location was different depending on each patient: right side, left side or midline in the peripheral zone of the prostate when seen in an axial planning CT or MR image. For example, a DIL was delineated at the right side in the peripheral zone of the prostate in an axial CT image (Fig. 1(b)) acquired for HDR prostate brachytherapy planning. This location was determined from the corresponding MRI/MRSI image (Fig. 1(a)) which demonstrates a validated cancer lesion that comprises five contiguous voxels with a score of 5 (definitively abnormal).

Class solution for a plan without a boost

Table 1(a) is a class solution developed for a plan without a boost under the dosimetric requirements. All plans employing the class solution, Table 1, satisfied all dosimetric requirements with a mean PTV coverage ($V_{100}[\%]$) of 92.4% (range from 90 to 94.7%), except for 3 patients (B, J, L). For those patients, the weighting factor to the maximum dose for the bladder and the rectum was tuned to meet the requirements. Table 2 shows the change of dosimetric indices corresponding to the change of their weighting factors. For patient B, the bladder and rectum were overprotected with undesirably low PTV coverage (84.5%). The reduction of their weighting factor increased PTV coverage up to 90.3% while keeping their $V_{75}[\text{cc}]$ less than 1 cc. For patient J, bladder $V_{75}[\text{cc}]$ was more than 1 cc. By increasing its weighting factor, bladder $V_{75}[\text{cc}]$ was reduced

to less than 1 cc at the expense of slightly decreased PTV coverage (from 91.3% to 90.5%). For patient L, by decreasing rectum weighting factor, the low PTV coverage (88.8%) was improved to 90% while rectum $V_{75}[\text{cc}]$ was kept less than 1 cc.

Class solution for a DIL

One out of 7 weighting factors to the maximum dose was chosen and a class solution of DIL for the same level of DIL-boost as the PTV was constructed under the dosimetric requirement. As the weighting factor applied to the maximum dose is increased, the value of DIL $V_{150}[\%]$ is reduced due to the heavily imposed penalty value to the maximum dose as shown in Fig. 2. In the case of no penalty value (zero weighting factor) applied, a much higher dose can be delivered to the DIL: $V_{150}[\%]$ value is improved in Fig. 2, but the DIL volume receiving more than 150% of the prescribed dose is also undesirably increased. If the rectum and/or bladder are very closely located to the DIL, the dosimetric requirement would be violated: in this study, patients B, E and J violated the bladder dose limit and patients B, F and O violated the rectum dose limit under requirement. Six different DIL-boost plans using its 6 different non-zero weighting factors (ranging from 5 to 30 with 5 points increment) applied to the maximum dose showed almost the same protection of the OAR (the same value of OAR dosimetric indices) for all patients (Fig. 2). The 6 DIL-boost plans violated the rectum dose limit for patients F and O and the bladder dose limit for patient J, respectively, under the requirement. Without any advantage in the protection of the OAR, the higher weighting factors deteriorated the DIL $V_{150}[\%]$ value (Fig. 2). Therefore, the value of 5 was chosen as the best weighting factor to the maximum dose inside the DIL. Finally, the class solution of the DIL was achieved on the surface and inside of the DIL and is summarized in Table 1(b) for the DIL-boost study.

Table 1(a)
Class solution for a plan without boost under RTOG 0321 dosimetric requirement

Volume	Weighting factor to D_{Min} for its penalty	$D_{\text{Min}} [\%]$	$D_{\text{Max}} [\%]$	Weighting factor to D_{Max} for its penalty
PTV (target)				
ON	100	100	150	100
IN	100	100	150	30
Urethra (organ at risk)				
ON	100	100	120	30
IN	100	100	120	30
Bladder (organ at risk)				
ON	0	0	50	30
IN	0	0	50	30
Rectum (organ at risk)				
ON	0	0	50	30
IN	0	0	50	30

ON, on the surface of the contour; IN, inside the volume.

$D_{\text{Min}} [\%]$ and $D_{\text{Max}} [\%]$, minimum and maximum doses in percent with respect to the prescribed dose, respectively.

0, any number is acceptable for the minimum dose since the weighting factor is null.

Table 1(b)
Class solution for a DIL under RTOG 0321 dosimetric requirements

Volume	Weighting factor to D_{Min} for its penalty	D_{Min} [%] ^a	D_{Max} [%]	Weighting factor to D_{Max} for its penalty
DIL (target)				
ON	100	Vary	150	30
IN	100	Vary	150	5

^a D_{Min} [%] varies depending upon the level of DIL-boost (110, 120, 130, 140 or 150).

Table 2

Manual adjustment of weighting factor to the maximum dose of bladder and rectum and its impact on dosimetric indices for 3 patients in whom a class solution for a plan without DIL boost was not available

Patient	Manual adjustment	Weighting factor		Dosimetric index			
		Bladder	Rectum	PTV [%]	Bladder V75[cc]	Rectum V75[cc]	Urethra V125[cc]
B	Before	30	30	84.54	0.65	0.07	0.04
	After	25	20	90.26	0.96	0.74	0.03
J	Before	30	30	91.29	1.27	0.39	0.14
	After	40	30	90.46	0.99	0.43	0.15
L	Before	30	30	88.81	0.40	0.05	0.02
	After	30	25	90.01	0.34	0.13	0.02

Maximum attainable DIL-boost plan using the class solution

The class solution obtained by combining a class solution for without-boost plan (Table 1(a)) with a class solution of the DIL (Table 1(b)) was exploited to acquire the maximum attainable level of the DIL-boost for each patient. Under the dosimetric requirements, a DIL-boost was not attainable for

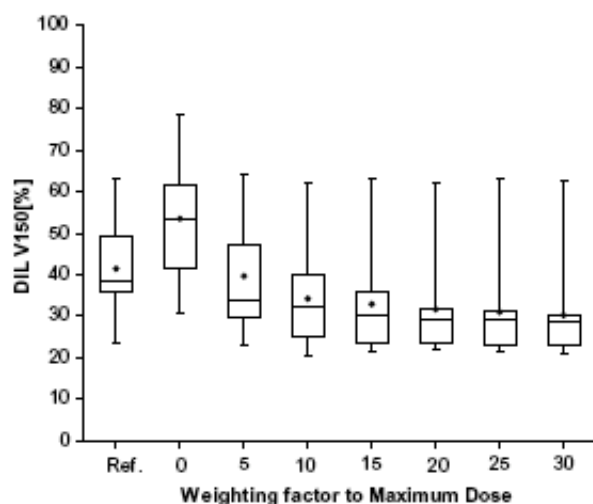


Fig. 2. Percent volume of the DIL receiving at least 150% of the prescribed dose (V150[%]) for 7 DIL-boost plans. Each boost plan has a different weighting factor for its penalty value imposed to the maximum dose (150% of the prescribed dose) of the DIL in comparison with a plan without boost (Ref.) under the RTOG-0321 dosimetric requirements. Parallel bars represent the maximum, 75, 50, 25 percentiles and minimum values. The black dot represents the mean value.

four (B, F, J, O) out of the 15 patients, whereas a certain level of DIL-boost was feasible for the remaining 11 patients (Fig. 3). By averaging all PTV and DIL DVHs of those patients, a group average DVH [11] was generated for the PTV (Fig. 4) and the DIL (Fig. 5) between the maximum attainable DIL-boost plan and the plan without boost. The group average PTV DVHs between the two plans were almost the same (<1% difference) up to 100% of the prescribed dose and they slightly differed in the rest of the dose range (5–6% difference between 120% and 160% of the prescribed dose in Fig. 4). In particular, the PTV coverage by the prescribed dose (Table 3) was increased just by 0.9%, on average, because the prostate was already satisfactorily covered by the prescribed dose (92.8%) prior to the DIL-boost. The difference was statistically insignificant with p -value of 0.0537

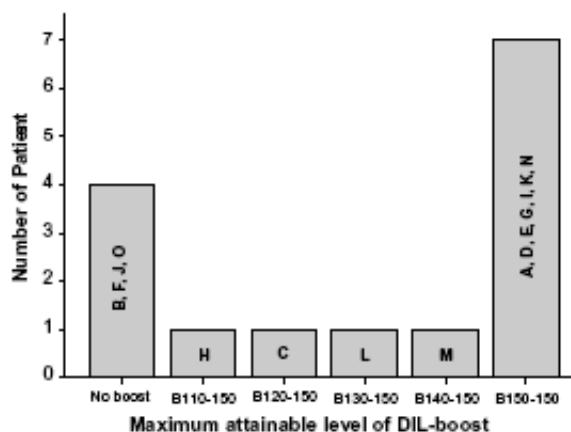


Fig. 3. Under the RTOG 0321 dosimetric requirements, the maximum attainable level of a DIL-boost for 15 patients (A–O).

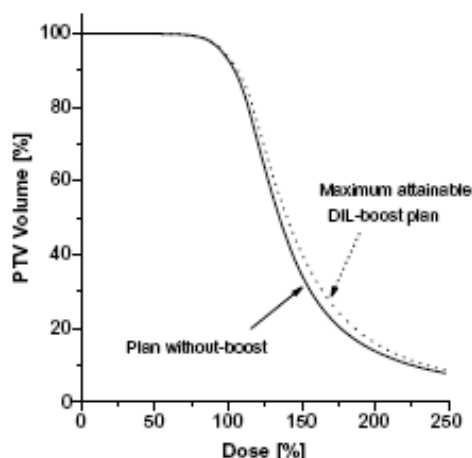


Fig. 4. Group average PTV DVH for 11 patients who allowed a certain level of DIL-boost.

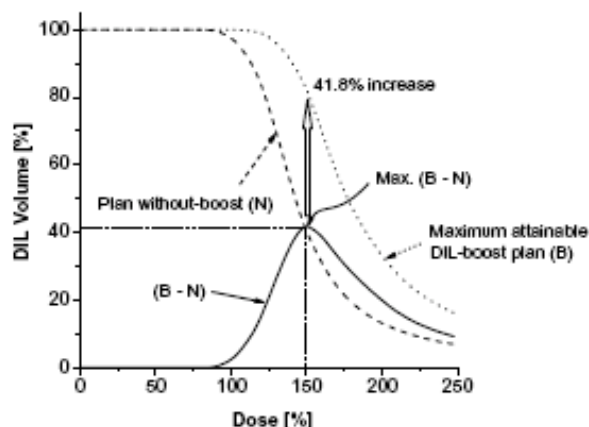


Fig. 5. For 11 patients who allowed a certain level of DIL-boost, the group average DIL DVH compares the maximum attainable DIL-boost plan (B) with the plan without boost (N). The solid line graph shows the increased DIL volume due to DIL boost. The maximum increase (41.8%) was observed at 150% of the prescribed dose.

using non-parametric test, Wilcoxon matched-pairs signed-rank test. The PTV coverage deficiency occurred close to the rectum/bladder because of their dose limit, depending upon the proximity between the PTV and the rectum/bladder. The PTV V150[%] was increased by 5.9%, on average, from 34.5% to 40.4% with p -value of 0.002 in Table 3. On the contrary, the group average DIL DVH of the maximum attainable DIL-boost plan was noticeably shifted into a higher dose range (from the dashed line (N) to the dotted line (B) in Fig. 5) due to the DIL-boost with a maximum increase of 41.8% at 150% of the prescribed dose (Max. (B-N) of the solid line (B-N) in Fig. 5). Dosimetric indices were significantly improved (p -value < 0.05) for all 11 patients in Table 3. On average, V120[%] was increased from 83.6% to 99% with p -value of 0.001, V150[%] was increased from 40.6% to 82.4% with p -value of 0.001, and V200[%] was increased from 13.2% to 33.2% with p -value of 0.002. A 150–150

DIL-boost was not attainable in 8 patients; in 4 of these (B, F, J and O), no boost was attainable (Fig. 3). Out of these 8 patients, the bladder dose limit was violated in patients J and L, while the rectal dose limit under requirement was violated in the remaining 6 patients. The OAR dosimetric parameters were compared between the maximum attainable DIL-boost plan and the plan without boost in Table 3. The relative location of bladder to the PTV was different between patients so that the bladder V75[cc] was patient-specific. The bladder V75[cc] was increased from 0.46 to 0.53 cc, on average. The urethra was highly protected in both of plans using IPSA planning and the maximum V125[cc] value was 0.22 cc in a DIL boost plan of patient A. The urethra V125[cc] was slightly increased from 0.03 to 0.09 cc, on average. In contrast, the rectum dose was extremely elevated due to the dose escalation of the DIL because the DIL was located in the peripheral zone of prostate next to the border of the rectum. Hence, the rectum V75[cc] was significantly increased from 0.23 to 0.63 cc, on average, by 0.4 cc (p -value of 0.001 using Wilcoxon matched-pairs signed-rank test).

By small manual adjustment of the class solution, the 150–150 DIL-boost was obtainable without any violation of requirements for 6 out of 8 patients (except for patients B and J) who did not reach the boost level of 150–150 using the class solution.

Discussion

The class solution in inverse planned HDR prostate brachytherapy for dose escalation of a DIL defined by combined MRI/MRSI is an excellent starting point to explore a customized set of dose constraints to obtain a satisfactory treatment plan for each patient. In this study, a minimum of 150% of the prescribed dose to the DIL (150–150 DIL-boost) was feasible for 13 out of 15 HDR brachytherapy plans after small manual tuning of the class solution, complying with the RTOG-0321 dosimetric requirement. The class solution in this study may be applicable to other protocols (for example, GEC/ESTRO-EAU recommendations) [12], depending upon its dosimetric requirement.

There was an uncertainty in the DIL delineation by transferring MRI/MRSI information to planning CT/MR either manually or with image fusion. In our clinic, the DIL is identified based on the pretreatment MRI/MRSI. Since most patients had hormonal therapy and pelvic radiotherapy by the time of HDR brachytherapy, the volume of DIL was probably significantly reduced compared to the pretreatment. Hence, our DIL is probably an overestimation of the area at risk. One way of eliminating this error is to acquire an MRI/MRSI at the time of implant. We did not have a practical way of doing so at the time of this study. Because the overall high dose to the prostate and OAR is not increased in this study, we feel this is a reasonable approach.

Despite manual adjustment of the class solution, two patients in this study failed to achieve the 150–150 DIL-boost due to a deficient number of catheters implanted to cover the whole prostate. In HDR brachytherapy, properly locating catheters into the PTV is essential in obtaining the desired

Table 3
Comparison of dosimetric parameters between the maximum attainable DIL-boost plan and the plan without boost for 11 patients which allowed a certain level of DIL-boost

Dosimetric parameter	Plan without boost	Maximum attainable DIL-boost plan	p-Value
PTV			
V100[%]	92.8 ± 1.5 (90.0–94.7)	93.7 ± 1.1 (91.9–94.9)	0.0537
V150[%]	34.5 ± 2.8 (30.1–40.3)	40.4 ± 3.9 (31.8–45.5)	0.002
DIL			
V120[%]	83.6 ± 13.6 (53.4–99.6)	99.0 ± 2.5 (91.4–100.0)	0.001
V150[%]	40.6 ± 12.0 (23.4–63.4)	82.4 ± 21.2 (39.2–99.2)	0.001
V200[%]	13.2 ± 4.2 (7.1–22.7)	33.2 ± 16.2 (11.1–59.4)	0.002
Bladder			
V75[cc]	0.46 ± 0.35 (0.01–0.99)	0.53 ± 0.36 (0.02–0.98)	0.0273
Rectum			
V75[cc]	0.23 ± 0.17 (0.01–0.55)	0.63 ± 0.24 (0.16–0.99)	0.001
Urethra			
V125[cc]	0.03 ± 0.04 (0.0–0.11)	0.09 ± 0.08 (0.0–0.22)	0.0139

Vx[%], percent volume (%) of organ of interest receiving at least x% of the prescribed dose.

Vx[cc], absolute volume (cc) of organ of interest receiving at least x% of the prescribed dose.

The data for each dosimetric parameter represent means ± standard deviation value (minimum–maximum value). p-Value was calculated using Wilcoxon matched-pairs signed-rank test.

dose distribution with a certain optimization technique such as IPSA. No dose would be delivered to a specific lesion without a catheter. In addition, the proximity of the PTV to the rectum and/or bladder could prohibit the 150–150 DIL-boost. The volume of prostate B is 86 cc (the largest prostate in this study) and the number of catheters employed implanted was only 17, whereas in general 18 or more catheters are implanted for a large prostate. To make matters worse, one of the 17 catheters was implanted outside of the PTV. Also, the rectum is located very close to the prostate. Therefore, the 150–150 DIL-boost under dosimetric requirement could not be attained for the patient B. For the patient J, the size of prostate (51.3 cc) is just larger than average and 18 catheters were well implanted to cover the entire prostate. However, both rectum and bladder were located extremely close to the PTV such that the rectal and bladder dose limits of dosimetric requirements were violated in 150–150 DIL-boost plan even though the class solution was manually adjusted.

Under the dosimetric requirements, for most patients the DIL-boost increased the DIL dose compared to the plan without boost in Fig. 5. However, DIL V200[%] was decreased from 14.3% to 14.0% for patient H. For the patient, since the maximum attainable level of DIL-boost was 110% of the prescribed dose as shown in Fig. 3, the most sensitive dose range of DIL due to DIL-boost was 110% or so. Hence, V120[%] was considerably improved from 53.4% to 91.4%. The V150[%] was also increased from 29.6% to 39.2%. However, such an insufficient DIL-boost in conjunction with the dosimetric requirements on OAR (bladder and rectum dose limits), sometimes, may cause the decreased V200[%] during redistribution of the hot spots in the prostate. For the patient H, as a result of the redistribution of the hot spots in the prostate, PTV V150[%] value was slightly decreased in the 110% DIL-boost plan (31.8%) compared to the plan without boost (32.1%). The movement of hot spots

into the DIL lesion was also verified in the planning axial CT images showing isodose lines.

In this study the 150% of the prescribed dose was used for both the minimum and the maximum dose limits of the DIL, which means to boost DIL with at least 150% of the prescribed dose as well as to prevent excessive high dose (more than 150% of the prescribed dose) within the DIL simultaneously. This purpose was moderately feasible by relaxing the weighting factor applied to the maximum dose of the inside of the DIL with the value of 5 instead of 30 applied on the surface of the DIL. As seen as a solid line in Fig. 5, the increase of DIL volume due to the DIL-boost has a maximum value at the vicinity of 150% of the prescribed dose: on average, a 41.8% increase in absolute volume from 40.6% to 82.4% at the 150% of the prescribed dose under the requirements. This can be interpreted that the most sensitive dose of DIL to dose escalation using the class solution obtained in this study was 150% of the prescribed dose.

Conclusion

A class solution was developed for dose escalation of a DIL defined by combined MRI/MRSI in inverse planned HDR prostate brachytherapy. Using the class solution, a certain level of DIL-boost is feasible for some patients (11/15) under the RTOG-0321 dosimetric requirements depending on rectal and bladder doses. While the PTV dose was slightly increased, the DIL dose was noticeably enhanced (on average, 82% of the DIL volume could receive 150% of the prescribed dose) without any violation of the dosimetric requirements. With further adjustment of the class solution, the DIL could be boosted by 150–150 for 13/15 patients while satisfying the dosimetric requirements. Hence, the established class

solution for a DIL-boost is a good starting point to explore a customized HDR prostate brachytherapy plan for a specific patient.

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