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IMRT BOOST DOSE PLANNING ON DOMINANT INTRAPROSTATIC LESIONS: GOLD MARKER-BASED THREE-DIMENSIONAL FUSION OF CT WITH DYNAMIC CONTRAST-ENHANCED AND $^1$H-SPECTROSCOPIC MRI

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Departments of *Radiation Oncology, †Radiology, and ‡Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Purpose: To demonstrate the theoretical feasibility of integrating two functional prostate magnetic resonance imaging (MRI) techniques (dynamic contrast-enhanced MRI [DCE-MRI] and $^1$H-spectroscopic MRI [MRSI]) into inverse treatment planning for definition and potential irradiation of a dominant intraprostatic lesion (DIL) as a biologic target volume for high-dose intraprostatic boosting with intensity-modulated radiotherapy (IMRT).

Methods and Materials: In 5 patients, four gold markers were implanted. An endorectal balloon was inserted for both CT and MRI. A DIL volume was defined by DCE-MRI and MRSI using different prostate cancer-specific physiologic (DCE-MRI) and metabolic (MRSI) parameters. CT-MRI registration was performed automatically by matching three-dimensional gold marker surface models with the iterative closest point method.

DIL-IMRT plans, consisting of whole prostate irradiation to 70 Gy and a DIL boost to 90 Gy, and standard IMRT plans, in which the whole prostate was irradiated to 78 Gy were generated. The tumor control probability and rectal wall normal tissue complication probability were calculated and compared between the two IMRT approaches.

Results: Combined DCE-MRI and MRSI yielded a clearly defined single DIL volume (range, 1.1–6.5 cm$^3$) in all patients. In this small, selected patient population, no differences in tumor control probability were found. A decrease in the rectal wall normal tissue complication probability was observed in favor of the DIL-IMRT plan versus the plan with IMRT to 78 Gy.

Conclusion: Combined DCE-MRI and MRSI functional image-guided high-dose intraprostatic DIL-IMRT planned as a boost to 90 Gy is theoretically feasible. The preliminary results have indicated that DIL-IMRT may improve the therapeutic ratio by decreasing the normal tissue complication probability with an unchanged tumor control probability. A larger patient population, with more variations in the number, size, and localization of the DIL, and a feasible mechanism for treatment implementation has to be studied to extend these preliminary tumor control and toxicity estimates.

Prostate cancer, MRI, Dynamic contrast enhanced, Spectroscopic MRI, Dominant intraprostatic lesion, Intensity-modulated radiotherapy, Image fusion, Dose escalation.

INTRODUCTION

The use of defining a biologic target volume (BTV) and intensity-modulated radiotherapy (IMRT) for advanced “dose painting,” as proposed by Ling et al. (1) has been gradually introduced into clinical practice. This has been made possible by advanced imaging techniques. Prostate magnetic resonance imaging (MRI) techniques can be fused with planning computed tomography (CT), and this has been shown to enable improved target delineation (2, 3).

Functional MRI techniques have been developed. Dynamic contrast-enhanced MRI (DCE-MRI) can visualize prostate cancer neovascularity (4, 5). $^1$H-spectroscopic MRI (MRSI) has been shown to provide a high specificity for prostate cancer (6, 7). These techniques can lead to a more accurate staging and localization of prostate cancer (8–12) and are valid methods for early evaluation of the RT effect (13). The “classic” whole-prostate dose escalation has improved treatment outcomes (14–16). Nevertheless, intraprostatic failures do occur and can be detected by MRI (17). Cellini et al.

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performed an MRI-based analysis of intraprostatic failure and concluded that, in all their observed cases, local recurrence originated within the initial tumor volume. Strategies, mainly for brachytherapy and small-size (<50 cm³) prostates, have been tested to detect the so-called dominant intraprostatic lesion (DIL) by MRSI, and an extra boost dose has been given to this DIL to increase the therapeutic ratio (19–23). To acquire high-resolution anatomic MRI data, an endorectal coil is usually inserted, causing deformation of the prostate gland. Consequently, accurate image registration with the initial planning CT scan (without an endorectal coil) is often difficult. CT–MRI matching can be done by mutual information-based automatic registration (24) or manually by visual approximation (19, 22). To overcome the difficulties in registration, we developed a gold marker-based three-dimensional (3D) CT–MRI fusion protocol (25), in which an endorectal balloon (ERB) is used during CT and treatment that has the same dimensions as the MRI endorectal coil (26). ERBs have also been used in prostate RT for their rectal wall-sparing effect (27–29). These markers are clearly visible on both CT and T2*-weighted MRI. Reliable and accurate image fusion is feasible using the above-mentioned conditions (25, 33).

To date, the combination of two functional MRI techniques (DCE-MRI and MRSI), gold markers, and an ERB for biologic image-guided external beam RT has not been described. The purpose of this study was to demonstrate the feasibility of the fusion of these functional MRI techniques with CT, using gold markers as fiducials, and to integrate these images into inverse treatment planning to define a BTV for high-dose intraprostatic DIL boosting with IMRT. The next goal was to make an estimation of the potential gains, in terms of tumor control probability (TCP), and rectal toxicity, by analyzing the normal tissue complication probability (NTCP).

METHODS AND MATERIALS

This pilot study was performed during a 6-month period, to December 2004. Patients with biopsy-proven prostate cancer were selected for our study. At the start of this study, only patients with unilateral prostate cancer were selected. The patient exclusion criteria were previous hormonal therapy, positive lymphadenectomy, contraindications to MRI (e.g., cardiac pacemakers, intracranial clips), and contraindications to endorectal coil insertion (e.g., anorectal surgery, inflammatory bowel disease). Finally, 5 patients were enrolled in this study, after giving informed consent.

In each patient, four fine gold markers (1-mm diameter, 7-mm length) (Hospimed International B.V., Dalfsen, The Netherlands) were implanted in the prostate through transrectal ultrasound guidance by an experienced urologist (J.A.W.) (Fig. 1a). Two markers were inserted in the base, one in the apex, and one in the central part (next to the urethra) of the prostate gland. A standard 18-gauge prostate biopsy tool was used (Microvasive Topnotch, Boston Scientific, Natick, MA) (Fig. 1b) and prophylactic antibiotics were given (ciprofloxacin 500 mg twice daily for 3 days).

After ≥1 week, to resolve swelling of the gland after marker implantation, the patients underwent both CT and MRI on the same day, within 4 h. Patient positioning during CT and MRI was identical to that during treatment: supine on a flat couch that was covered with a thin disposable paper sheet. Only a pillow and foam knee support were used for relaxed positioning of the head and legs, respectively. Before the imaging sessions, patients used a laxative diet and a laxans (Microlax clysma 5 mL, Pharmacia BV, Woerden, The Netherlands) and were required to drink 500 mL of water to ensure a full bladder.

CT and MRI protocol

The planning CT scan was obtained at a 3-mm slice thickness with a multislice CT scanner (150 mA, 140 kV, feed 12.5 mm, rotation 0.5 s, AcQsim spiral CT, Philips Medical Systems, Bothell, WA). An ERB was inserted and inflated with 80 mL of air to mimic the MRI conditions and reduce the prostate deformation differences. The ERB used during CT imaging was a modified MRI endorectal balloon without the coil wiring and had the same dimensions and shape as the MRI endorectal coil (MedRad, Indianola, PA) (26, 29) (Fig. 2a).

Magnetic resonance imaging was performed using a 1.5-T MRI scanner (Magnetom Sonata, Siemens, Erlangen, Germany). Patients were imaged in the supine position. Integrated endorectal phased-array coils were used (MedRad). After a digital rectal examination, the endorectal coil was inserted and inflated with 80 mL of air. Peristalsis was suppressed by an
intramuscular injection of 1 mg glucagon (Glucagen, Novo Nordisk A/S, Bagsvaerd, Denmark) before the examination. Localizing images were acquired for anatomic orientation and to confirm coil positioning. The three-part scanning protocol is listed in order of acquisition in Table 1. First, for anatomic information, T₂-weighted fast spin echo images were acquired in three planes (Fig. 2b). A transverse T₂*-weighted gradient echo sequence (MEDIC) provided clear visualization of the gold markers (Fig. 2c). Second, MRSI was obtained using a 3D chemical shift imaging sequence. Third, DCE-MRI was performed using one intermediate-weighted and repeated T₁-weighted imaging during 2 min. A dose of 0.2 mmol/kg gadolinium-diethylenetriamine pentaacetic acid (Magnevist, Schering, Berlin, Germany) was injected using a power injector (Spectris, MedRad) with saline flush.

**Image registration**

Computed tomography and MRI sets were aligned by registering the MEDIC MRI volume to the CT volume, using an in-house-developed application as described by Huisman et al. (25). In brief, the markers, displayed on T₂*-weighted (MEDIC) MRI

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**Fig. 2.** (a) Endorectal balloon used during computed tomography (CT) and magnetic resonance imaging (MRI). (b) Sagittal MRI T₂-weighted image (fast spin echo) (left panel) and CT image (right panel) with endorectal balloon inserted. Prostate and outer rectal wall highlighted. (c) Transverse T₂*-weighted MR image (left panel) and CT image (right panel). Gold marker indicated (arrow).
and CT, were semiautomatically segmented and converted into 3D surface models (Fig. 3a,b). The 3D surface models from both data sets were then registered by minimizing the root-mean-square distance between the surfaces using the iterative closest point method (25). The registration was visually verified by observing the fused CT and MEDIC MRI images. The MRI marker surface model was depicted in green and the CT marker surface model was overlaid in red, with the CT window and level set to reveal only the

### Table 1. MRI protocol: Scanning parameters

<table>
<thead>
<tr>
<th>Sequence</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>α (°)</th>
<th>Slice thickness (cm)*</th>
<th>FOV (mm)</th>
<th>Matrix</th>
<th>In-plane voxel size</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSE</td>
<td>4100</td>
<td>119</td>
<td>180</td>
<td>4.0 (15)</td>
<td>280</td>
<td>512 × 256</td>
<td>0.35 × 0.35</td>
</tr>
<tr>
<td>MEDIC</td>
<td>700</td>
<td>18</td>
<td>30</td>
<td>3 (22)</td>
<td>285</td>
<td>512 × 448</td>
<td>0.56 × 0.56</td>
</tr>
<tr>
<td>3D-MRSI</td>
<td>640</td>
<td>120</td>
<td>PRESS</td>
<td>4.3 (12)</td>
<td>84</td>
<td>14 × 14</td>
<td>4.3 × 4.3 (interpolated)</td>
</tr>
<tr>
<td>TurboFLASH (pre)</td>
<td>800</td>
<td>1.61</td>
<td>8</td>
<td>4.0 (10)</td>
<td>280</td>
<td>192 × 256</td>
<td>1.09 × 1.09</td>
</tr>
<tr>
<td>TurboFLASH (post)</td>
<td>34</td>
<td>1.61</td>
<td>10</td>
<td>4.0 (10)</td>
<td>280</td>
<td>192 × 256</td>
<td>1.09 × 1.09</td>
</tr>
</tbody>
</table>

**Abbreviations:** FOV = field of view; FSE = fast spin echo; MEDIC = transverse T₂*-weighted gradient echo sequence; 3D-MRSI = three-dimensional ¹H-spectroscopic MRI; PRESS = point resolved spectroscopy; pre = before contrast; post = after contrast.

* Number of slices in parentheses.

Fig. 3. Marker registration by iterative closest point method. Markers semiautomatically segmented on (a) T₂*-weighted magnetic resonance image (MRI) and (b) computed tomography (CT) image. (c) MRI (green) and CT (red) marker surface models registered by minimizing root-mean-square distance of separate models.
DIL delineation

The radiologist (J.F.) performing the DIL delineation was unaware of the tumor characteristics (local staging by digital rectal examination, prostate-specific antigen determination, or Gleason score) during the evaluation of the images. Postprocessing entailed two stages. First, the acquired DCE-MRI and MRSI data were processed to extract the functional feature images. The DCE-MRI data set, to identify regions of neovascularity, was analyzed using multiple physiologic parameters, such as the K_\text{ep}, quantifying the permeability surface area, \( K_{\text{trans}} \), defined as the volume transfer constant, and ECV, for quantification of the extracellular volume (5, 9). Then, on the basis of these findings, the MRI data set was evaluated to make the final diagnosis of prostate cancer or normal prostatic tissue by analyzing the separate 1H-MRI spectra of the prostate gland voxels. A choline plus creatine/citrate ratio >0.9 was considered to be positive for prostate cancer (6, 7, 9, 10).

In the second postprocessing stage, these DCE-MRI and MRSI feature images and the T2-weighted prostate images were fused; the functional images were overlaid in transparent colors on T2-weighted MRI scans in three perpendicular planes. A 3D editor, built within the registration application, was used to delineate the boundary of the DIL (Fig. 4a). During the editing process of the DIL, the radiologist was able to switch between the DCE-MRI and MRSI feature images and the T2-weighted MR images with the cross-section of the resulting tumor model visible in all planes. The definitive tumor model was then saved as a binary DIL volume. The registration parameters that aligned the MEDIC MRI data and CT data were used to align the DIL volume with the CT data. The aligned DIL volume, together with the MEDIC MRI and T2-weighted MRI images were then transferred and imported into the RT planning system. An illustrated case example is described in the “Results.”

IMRT planning

The radiation oncologist (E.V.L.) and radiologist (J.F.) reviewed the MEDIC MR images, T2-weighted MR images, and aligned DIL volume. Together, they delineated the prostate gland in the MEDIC and T2-weighted MR images. The resulting contours were automatically transferred to the corresponding CT slices and defined as the prostate clinical target volume (CTV). The registered DIL volume in the image fusion window of the Pinnacle3 treatment planning system (Philips Medical Systems, Andover, MA) was reviewed and the DIL CTV defined (Fig. 4b). On each CT slice, the normal surrounding structures were outlined: bladder, urethra, femoral heads, and rectal wall. The rectal wall (Rwall) was defined as the difference between the inner and outer rectal wall contour (34). The Rwall was delineated from the ischial tuberosities up to the rectosigmoid flexure. For each patient, two IMRT plans were made to compare the TCP and predicted rectal toxicity, as estimated by the NTCP. First, the DIL-IMRT plan was identified, irradiating a planning target volume (PTV) with a prescription dose of 70 Gy (PTV_{70}) and PTV_{90}. The PTV_{70} was defined as the prostate gland plus a 7-mm isotropic margin with a prescription dose of 70 Gy. The PTV_{90} consisted of the DIL plus a 5-mm isotropic margin, with a prescription dose of 90 Gy. Next, a more standard IMRT plan (whole prostate irradiated to 78 Gy [IMRT-78]) was constructed, in which the PTV_{78} consisted of the prostate gland plus a 7-mm isotropic margin. For this plan, the prescription dose was 78 Gy (14). For both plans, the dose/fraction was 2 Gy for the prostate. In the DIL-IMRT plan, the dose/fraction for the DIL was 2.57 Gy.

For both plans, the step-and-shoot IMRT plan consisted of seven coplanar, nonopposing 10-MV photon beams. One beam was oriented posteroanteriorly and the other six beams were configured with equidistant gantry angles.

For both plans, equal dose–volume histogram and maximal dose objectives for the normal tissues were defined (Table 2). In addition, the maximal allowable dose outside the delineated structures was set to 38 Gy (weight factor [W] = 1). For the DIL-IMRT and IMRT-78 plans, the following target volume objectives were defined. The objectives regarding the CTV were a minimal allowable dose of 90% of the prescription dose (W = 10), maximal allowable dose of 110% of the prescription dose (W = 10). The PTV objectives were a minimal dose of 90% (W = 2), maximal dose of 110% (W = 5), and dose uniformity (W = 1). For the PTV, the dose–volume histogram objectives were also defined: >99% of the PTV should receive a minimal dose of 95% of the prescription dose (W = 10). For the DIL-IMRT plan, the maximal allowable dose within the DIL was set to 94 Gy (W = 1).

For comparison of the IMRT-78 and DIL-IMRT plans, the mean dose for the prostate and DIL was calculated. For the Rwall, the NTCP for serious (Grade 3 or worse rectal toxicity) was computed, applying the Lyman-Kutcher-Burman model with Emami parameters (n = 0.12, m = 0.15, and median toxicity dose = 80 Gy) (35–37). The resulting spatial dose distribution over the inner surface of the rectal wall, representing the rectal wall mucosa, was visualized by generating inner rectal wall dose–surface maps (38).

For the TCP calculations, the Poisson-based model of Webb and Nahum (39) was used, taking the interpatient variation in radiosensitivity over a representative cohort of patients into account. The model parameters used were taken from Nahum et al. (40): mean ± standard deviation radiosensitivity (\( \alpha_{\text{mean}} \) and \( \sigma_{\alpha} \), respectively) of 0.26 ± 0.06 Gy^{-1} and an \( \alpha/\beta \) ratio of 8.3 Gy were used. Furthermore, it was assumed that the initial clonogenic cell density for the DIL was 10^7 cells/cm^3 and for the rest of the prostate was 10^5 cells/cm^3. Proliferation effects were ignored in the calculations.

RESULTS

Imaging and postprocessing

The marker implantation posed no problems. This procedure took 5 min/patient in the urology outpatient clinic. The ERB was tolerated well, and no problems arose during the imaging procedures. The planning CT scan took 15 min total, and MRI at the radiology department took 1 h (10 min of patient preparation and 50 min of imaging), which was rather strenuous for this elderly patient population. In 1 patient, MRI was interrupted because of lower back pain, but eventually could be finished. Postprocessing was performed by an experienced radiologist within 40 min; the DCE-MRI evaluation took 10 min, MRSI evaluation took 20 min, DIL delineation took 5 min, and file preparation for transmission to the radiotherapy department took 5 min. The next day, the radiation oncologist and radiologist reviewed the images. The target volumes and normal tissues were delineated within 60 min. Inverse DIL-IMRT and IMRT-78 treatment planning was performed in 1.5–2 h.
Fig. 4. (a) Three-dimensional (3D) editor for delineation of dominant intraprostatic lesion (DIL) volume. DIL highlighted in red. (b) DIL volume (highlighted in red) transferred to treatment planning system and displayed on transverse T2-weighted magnetic resonance image (left panel) and computed tomography image (right panel). Central gold marker indicated in yellow.
was found in the right peripheral zone (Fig. 5d,e), and a choline plus creatine/citrate map was constructed to visualize the MRI-based tumor nodule (Fig. 5f). On the basis of the combined DCE-MRI and MRSI data, this prostate tumor was staged as T2a located in the right peripheral zone. The DIL volume was delineated within the 3D editor and transferred to the treatment planning system. The DIL volume was 2.2 cm³, and a 3D margin of 5 mm was drawn for the PTV\textsubscript{70}. The prostate gland measured 41 cm³ and a 3D margin of 7 mm was drawn for the PTV\textsubscript{70} (Fig. 6). DIL-IMRT planning resulted in a dose distribution as displayed in Fig. 7a. For this plan, a TCP of 89% and an Rwall NTCP of 5% were estimated. The IMRT-78 treatment plan (Fig. 7b) yielded a TCP of 87% and an Rwall NTCP of 6%.

A summary of the comparison of DIL-IMRT and IMRT-78 data for the investigated patients is given in Table 3. Overall, in this small selected group of patients, the TCPs, ranging from 83% to 89%, did not differ between the two IMRT plans. However, in 4 of 5 patients, the DIL-IMRT reduced the Rwall NTCP (range, 1–3%). For every individual patient, the therapeutic (TCP/NTCP) ratio was increased by the DIL-IMRT plan. An example of the different dose distribution patterns of the inner rectal wall surface for the two treatment plans is displayed in Fig. 7c,d. The combination of DIL-IMRT and a daily inserted ERB, which dilates the rectal wall, resulted in a different dose distribution over the inner rectal wall (Fig. 7c) compared with the IMRT-78 plan and ERB (Fig. 7d). In the case of DIL-IMRT, a smaller area was exposed to a dose >80 Gy, surrounded by a larger area with a dose of about 70 Gy, and the dorsal rectal wall was exposed to doses of <40 Gy.

**DISCUSSION**

In this study, we have shown the feasibility of using combined functional imaging techniques of the prostate gland to integrate them into inverse treatment planning and to define a BTV (1) for high-dose intraprostatic IMRT boosting. This MRI-based BTV was then superimposed onto a treatment planning CT scan with a CT-MRI gold marker-based fusion protocol. With two different IMRT

### Table 3. Patient characteristics and DIL-IMRT and IMRT-78 planning results

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>PSA (ng/mL)</th>
<th>Gleason score</th>
<th>Stage</th>
<th>Prostate volume (cm³)</th>
<th>DIL volume (cm³)</th>
<th>DIL localization</th>
<th>Mean dose (Gy)</th>
<th>Rwall NTCP (%)</th>
<th>TCP (%)</th>
<th>Mean dose to prostate (Gy)</th>
<th>Rwall NTCP (%)</th>
<th>TCP (%)</th>
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<tr>
<td>1</td>
<td>7.8</td>
<td>7</td>
<td>T1c</td>
<td>79</td>
<td>1.1</td>
<td>R-PZ</td>
<td>90.0</td>
<td>71.3</td>
<td>2</td>
<td>89</td>
<td>77.7</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>8.2</td>
<td>6</td>
<td>T2a</td>
<td>106</td>
<td>1.8</td>
<td>L-PZ</td>
<td>91.2</td>
<td>71.6</td>
<td>3</td>
<td>85</td>
<td>77.8</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>7.7</td>
<td>5</td>
<td>T2a</td>
<td>74</td>
<td>6.5</td>
<td>R-PZ</td>
<td>90.5</td>
<td>71.5</td>
<td>6</td>
<td>86</td>
<td>78.4</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>5.8</td>
<td>7</td>
<td>T2a</td>
<td>41</td>
<td>2.2</td>
<td>R-PZ</td>
<td>90.8</td>
<td>71.4</td>
<td>5</td>
<td>89</td>
<td>78.1</td>
<td>6</td>
</tr>
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<td>7.0</td>
<td>8</td>
<td>T2a</td>
<td>51</td>
<td>1.8</td>
<td>L-PZ</td>
<td>90.7</td>
<td>71.5</td>
<td>3</td>
<td>88</td>
<td>78.6</td>
<td>6</td>
</tr>
</tbody>
</table>

**Abbreviations:** DIL = dominant intraprostatic lesion; IMRT = intensity-modulated radiotherapy; PSA = prostat-specific antigen; Rwall = rectal wall; NTCP = normal tissue complication probability; TCP = tumor control probability; L-PZ = left peripheral zone; R-PZ = right peripheral zone.
Fig. 5. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and $^1$H-spectroscopic (MRSI) results for Patient 4. (a) Axial T2-weighted MR image with decreased signal intensity in right peripheral zone (arrows), without evidence of capsular invasion. (b,c) DCE-MRI results. (b) Start-of-enhancement parameter demonstrated earlier enhancement in part of low-signal-intensity lesion (arrows) compared with left peripheral zone. (c) Volume transfer constant ($K_{trans}$) was elevated in low-signal-intensity lesion (arrows) indicating tumor tissue. (d) MRSI detected elevated choline and low citrate peaks in seven voxels. Blue box indicates voxel from which spectrum (Fig. 5e) originated. (e) $^1$H-MRI spectrum from voxel in right peripheral zone. Increased choline (Cho) plus creatine (Cr)/citrate (Ci) ratio indicated prostate cancer. (f) Strongly interpolated (choline + creatine)/citrate map was used to visualize MRSI-based tumor nodule.
plans and the commonly used TCP and NTCP models, preliminary data were produced to investigate the potential gains of the DIL-IMRT concept.

Pickett et al. (21) were the first to report on the possible advantages of incorporating MRI, both anatomic and functional, into a static field prostate IMRT plan. In their case report, the feasibility of treating a single lobe to 90 Gy, by MRSI guidance, was demonstrated. Previous investigations have shown that using anatomic MRI for more accurate prostate delineation resulted in a 30% reduction of prostate volume and a reduction of the proportion of irradiated rectal wall (2, 3). This is demonstrated in Fig. 6, in which, as a result of MRI, a sharp delineation of the ventral part of the gland tissue on the CT could be made. Integration of anatomic prostate MRI with the described CT-MRI marker-based fusion method has been implemented into our daily clinical practice.

Because of the increasing availability and improvements in MRI, its role in prostate RT has developed rapidly in the past years. With high sensitivity and specificity, both DCE-MRI and MRSI can provide accurate tumor staging (4, 5, 8–12). MRSI has been shown to provide a high specificity for prostate cancer (7, 41). This technique has proved to be capable of accurately detecting prostate cancer in the peripheral zone (9, 10, 12). However, the availability of this imaging modality is still limited. Only a few institutions have the opportunity and the experience to use MRSI clinically. Experience with DCE-MRI in breast and bladder cancer has indicated that, because of neovascularization, malignant lesions demonstrate an earlier and faster enhancement compared with that of benign lesions (42, 43). This technique is widely available and is capable of detecting regions of prostate cancer in both the peripheral and the central prostate gland zone (4, 5, 9, 10). Thus, DCE-MRI can identify regions of neovascularity, suggestive of prostate cancer, and MRSI can detect malignant tumor nodules on voxel size with high specificity.

Functional prostate MRSI can also help to assess local tumor control in early-stage prostate cancer (13). MRI-
based analysis of 118 prostate cancer patients, irradiated to a dose of 65–70 Gy, revealed that all 12 observed intraprostatic recurrences originated within the initial tumor (18). This supports the concept of intraprostatic boosting, with a dose of 70–70 Gy, while maintaining the dose to the remainder of the prostate at an intermediate dose level (around 65–70 Gy). The concept of a BTV for prostate cancer means detection and localization of the dominant tumor nodules with greater tumor cell density, the so-called DIL, in contrast to non–DIL prostatic tissue in which the tumor cell density is lower and therefore a lower irradiation dose might be sufficient. On the basis of that hypothesis, we tested the DIL-IMRT 70–90 Gy treatment plan in a small selected patient population and compared it with a more standard whole-prostate IMRT-78 Gy plan. Our data suggested a comparable high TCP (range, 83–89%) for both IMRT plans. The DIL-IMRT plan produced, in 4 of 5 patients, a lower Rwall NTCP compared with the IMRT-78 plan; in all patients, the therapeutic (TCP/NTCP) ratio was increased.

Nutting et al. (20) performed an IMRT planning study in 6 patients in which the DIL volume and localization were derived from prostatectomy specimens that were projected into the planning CT scans. An IMRT plan (70 Gy to the whole prostate plus a 20-Gy boost to the DIL) was compared with a whole homogeneous irradiated prostate with IMRT to 70 Gy. With the DIL boost, the estimated TCP increased from
64.4% to 95.6%. Instead of 70 Gy, we choose 78 Gy, because of the positive M.D. Anderson Cancer Center randomized trial (14). Nutting et al. (20) observed a 1.8% increase in the rectal NTCP, to a mean value of 7.7% for the DIL boost plan. The rectal volume was delineated as the rectal wall plus content, so a direct comparison with our NTCP data would be difficult. With our DIL-IMRT plan, the estimated Rwall NTCP decreased for the individual patients by 1–3% to a mean NTCP of 4%. In our study, the CTV and PTV margins were smaller (7 and 5 mm, respectively) than in the study by Nutting et al. (20) in which the margins were 10 mm. This could also explain the differences in NTCP.

The TCP/NTCP ratio, as observed by Nutting et al. (20), was very dependent on the localization of the DIL: anteriorly in the prostate or posteriorly, close to the anterior rectal wall. In our pilot study, we detected the DILs in the posterior part of the peripheral zone of the prostate in all 5 patients. According to extensive pathologic examinations, this was also the localization in which the greatest portion (74%) of the cancer foci was located (44). Nevertheless, we must expand our patient population to obtain more variations in DIL localization and different DIL volumes to investigate further the impact on the TCP/NTCP ratio. Currently, we are enrolling more patients for this study. Also, the effect of this novel approach on other surrounding radiosensitive structures, such as the neurovascular bundle, penile bulb, and urethra need to be investigated. This will be the topic of future investigations.

In prostate brachytherapy, the MRI-guided DIL boosting concept has been tested for patients with a prostate gland volume of <50 cm³ (19, 22, 23). Only MRSD was used for DIL detection and localization. Zaider et al. (23) registered MRSI and ultrasound images for boosting of the intraprostatic tumor regions. In a single patient, three different DIL volumes (1.36–3.71 cm³) were defined: one from the actual MRSI information and two hypothetically constructed. Depending on the size of the DILs, the image-guided boost yielded TCP values ranging from 94.3% to 96.5%, without increasing the maximal urethral dose. In contrast, standard brachytherapy resulted in TCP values ranging from 64.9% to 76.1%. An endorectal probe, filled with 100 mL of air, was used for MRSI, causing gland deformation; therefore, difficulties arose with the registration procedure. They have developed an algorithm to overcome this problem and achieved absolute 3D-positional errors of 2.2 ± 1.2 mm (mean ± SD) (24). Dibiase et al. (19) and Poullet et al. (22) encountered similar problems with precise MRI-CT registration because of gland deformation by the endorectal coil. MRI-defined prostate boost volumes were manually entered into the planning system, and the gland distortion was only addressed visually. In our study, we used an ERB filled with 80 mL of air, identical to the MRI endorectal coil, for CT scanning. This resulted in almost equal deformation of the prostate gland in MRI and CT and accurate DIL projection onto the CT scan. The iterative closest point method, in which the gold marker surface models are automatically registered, was used (25). This yielded an MRI-CT fusion precision of 1.1 mm in a data set of 21 patients, using five operators.

Endorectal balloons are used in prostate RT for their rectal wall sparing effect and are well tolerated by most patients (27–29, 38). For 2 years, the ERB, as mentioned in this study, has been used in our department, and no severe ERB-related toxicity, apart from local anal irritation, has been reported. The ERB is applied and removed by the therapists and, per treatment fraction, an extra 3 min is added for the whole ERB procedure (26). The ERB is often referred to as a prostate immobilizer, but because of the presence of gas and stool surrounding the ERB, the daily-to-day interfraction prostate displacements can be great, 4.7 mm (SD) for the AP direction (26). Therefore, we now use the ERB in combination with a gold marker-based portal imaging verification and correction protocol (26, 30–32). As reported previously, to increase their acceptability, the development of user- and patient-friendly ERBs is warranted (38).

The presented DIL-IMRT plan, in combination with a daily inserted ERB, which dilates the rectal wall, gives a typical dose distribution over the inner rectal mucosa (Fig. 7c). A relatively small area is exposed to high doses (>80 Gy), surrounded by a larger area of intermediate doses, and a low dose over the dorsal rectal wall. Recent data have shown that this type of spatial dose distribution, and the amount of rectal wall surface irradiated to low doses, may further reduce the Rwall NTCP (34). Therefore, in treated DIL-IMRT patients, the actual Rwall late toxicity may be even lower than the estimations calculated in this study using the Lyman-Kutcher-Burman model with Emami parameters (35–37). Execution of the DIL-IMRT concept and thorough follow-up may also provide us with additional information to construct more accurate Rwall NTCP models.

Regarding the TCP calculations, debate is still ongoing in published reports regarding the linear quadratic (LQ) parameter values, especially whether the α/β ratio is low (i.e., in the range typical for late-responding tumors) (44–46). For the TCP calculations, we have applied parameters comparable to those applied by Nutting et al. (20); that is, an α/β value typical of early responding tissues (as applied by Nahum et al. [40]) and also assuming a heterogeneous distribution of radiation sensitivities (α) and a ratio of 100 in the clonogen densities between DIL (10⁷ cells/cm³) and the rest of the prostate (10⁵ cells/cm³). An extensive comparison of different TCP models is beyond the scope of this report. However, we have verified that choosing lower α/β TCP models does not alter the conclusions. If the parameters proposed by Wang et al. (45) (i.e., α/β = 3.1 Gy, α = 0.15 ± 0.04 Gy⁻¹, potential doubling time [T[50]] = 42 days, and number of clonogens is within the range of 10⁶–10⁷) or those proposed by Fowler et al. (46) (i.e., α/β = 1.5 Gy, α = 0.0391 ± 0.0098 Gy⁻¹) were used, the absolute TCP values would have changed, but the relative values for the DEL-IMRT and IMRT-78 plans were still comparable and did not differ.

The issue of multifocality of prostate cancer was not
addressed in this technical feasibility study. In a large pathology study, 83% of the prostatectomy specimens had more than one cancer focus (47). For this feasibility study, we selected patients with unilateral, palpable, ultrasonound-detected, and biopsy-proven tumors. This was done to avoid possible extra difficulties in interpreting and executing the implementation of the described CT-MRI fusion and DIL-IMRT planning. Pouliot et al. (22) have reported on multiple DIL volumes, and it was possible to deliver separate boost volumes to these tumor nodules with MRSI-guided brachytherapy, without compromising the surrounding normal tissues. In another study, a multiple boost implant in 1 patient with four tumor foci was impractical to perform (19). For all other patients, an MRSI-guided brachytherapy boost was given successfully, with toxicity comparable with conventional treatment. The goal of our study was to demonstrate the feasibility of incorporating two MRI techniques in a (single) external beam DIL-IMRT concept for a wide range of prostate gland volumes (41–106 cm³). The next step will be to include more patients and patients with more than one DIL and to investigate the possible advantages or disadvantages in terms of TCP and toxicity. Xia et al. (48) have already demonstrated the feasibility of planning two DILs ≤90 Gy with IMRT on a selected patient case, but their DIL volumes were derived from MRSI only and, because of the ERB-induced gland deformation in the MRSI study, the MRI-CT image fusion was a visual approximate process. The DIL-IMRT concept may not be applicable in the case of more than two or three DILs localized near the rectal wall or urethra, because of unacceptably high estimated toxicity scores. Currently, we are also enrolling patients with bilateral prostate tumors with multiple DILs and we are evaluating the presented intraprostatic IMRT boost under DCE-MRI and MRSI guidance.

**CONCLUSION**

In this study, we demonstrated the feasibility of integrating two functional prostate MRI techniques into inverse treatment planning for the definition of a DIL for DIL-IMRT. In all patients, the combination of DCE-MRI, identifying regions of neovascularity suggestive of prostate cancer, and MRSI, detecting tumor nodules with high specificity, yielded a clearly defined single DIL volume. This DIL volume could be accurately transferred to the RT planning system, by CT-MRI registration using matching 3D gold marker surface models and the same type of ERB for CT and MRI. Compared with the IMRT-78 plan, the DIL-IMRT plan estimated a similar TCP, but a decreased Rwall NTCP. This resulted in an increase in the therapeutic (TCP/NTCP) ratio, in favor of the DIL-IMRT plan. Also, the typical Rwall spatial dose distribution, as a result of the DIL boost, may indicate additional reduced actual rectal toxicity. Before bringing DIL-IMRT into clinical practice, a larger patient population, with more variation in the number and localization of the DILs, has to be studied and should include the preliminary TCPs and toxicity estimates.

**REFERENCES**


