CLINICAL INVESTIGATION

VESSEL-SPARING PROSTATE RADIOTHERAPY: DOSE LIMITATION TO CRITICAL ERECTILE VASCULAR STRUCTURES (INTERNAL PUDENDAL ARTERY AND CORPUS CAVERNOSUM) DEFINED BY MRI

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Purpose: Most evidence suggests that impotence after prostate radiation therapy has a vascular etiology. The corpus cavernosum (CC) and the internal pudendal artery (IPA) are the critical vascular structures related to erectile function. This study suggests that it is feasible to markedly decrease radiation dose to the CC and the IPA and directly determine the impact of dose limitation on potency.

Methods and Materials: Twenty-five patients (10 external beam, 15 brachytherapy) underwent MRI/CT-based treatment planning for prostate cancer. In addition, 10 patients entered on the vessel-sparing protocol underwent a time-of-flight MRI angiography sequence to define the IPA. The distance from the MRI-defined prostate apex to the penile bulb (PB), CC, and IPA was measured and compared to the distance from the CT-defined apex. Doses (D5 and D50) to the PB, CC, and IPA were determined for an 80 Gy external beam course. In 5 patients, CT plans were generated and compared to MRI-based plans.

Results: The combination of coronal, sagittal, and axial MRI data sets allowed superior definition of the prostate apex and its relationship to critical vascular structures. The apex to PB distance averaged 1.45 cm (0.36 standard deviation) with a range of 0.7 cm to 2.1 cm. Peak dose (D5) to the proximal CC in the MRI-planned 80 Gy course was 26 (9) Gy (0.36 of CT-planned dose), and peak dose to the IPA was 39 (13) Gy (0.61 of CT-planned dose). Conclusion: The distance between the prostate apex and critical vascular structures is highly variable. Current empiric rules for CT contouring (apex 1.5 cm above PB) overestimate or underestimate the distance between the prostate apex and critical vascular structures. When defined by MRI T2 and MRI angiogram with CT registration, limitation of dose to critical erectile structures is possible, with a more significant gain than has been previously reported using dose limitation by commonly applied intensity modulated radiation therapy studies based on CT imaging. These techniques make “vessel-sparing” prostate radiotherapy feasible. © 2005 Elsevier Inc.

Prostate radiotherapy, Potency preservation, MRI treatment planning.

INTRODUCTION

Impotence after radiation therapy for prostate cancer remains a major problem. Studies of sexual function after radiation therapy can be divided into three types: incidence studies (rate of impotence posttherapy) (1–34), correlative studies (correlation of impotence with dose to critical erectile structures) (35–42), and mechanism studies (measurement of nerve and vascular integrity after radiation therapy) (43–45). Incidence studies suggest a wide range in erectile dysfunction after radiation therapy, from 20% to 90% depending on radiation technique, the instrument used to measure erectile dysfunction, and the length of follow-up. Direct and indirect evidence from these studies supports a vascular mechanism for impotence postradiotherapy. Vascular etiologies remain the most common cause of impotence in the nonradiation literature as well (46, 47).

To decrease the incidence of impotence due to radiation therapy, it would be logical to decrease dose to the key structures involved in erection. The critical vascular erectile structures are the corpus cavernosum (CC) and the internal pudendal artery (IPA). These structures are definable by MRI and MRI angiography, respectively. They are separable from the prostate, especially for the MRI-defined prostate structure. This study reports a technique employing MRI T2, MRI angio, and CT registration, which allow dose limitation to these critical vascular structures.

Previous attempts to limit dose to critical vascular structures have employed two strategies. First, empiric rules regarding key anatomic relationships (prostate apex to pelvic

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nile bulb [PB] distance or prostate apex to urethrogram apex distance) have been employed to limit prostate volume overestimation on CT. Overestimation of the apex decreases the distance between the prostate and CC/IPA. There is a twofold hazard to application of such rules. Average distances between anatomic structures may underestimate the distance in an individual patient with profound separation of these structures, leading to increased radiation exposure to CC/IPA. A greater hazard is for patients with a separation less than the empiric rule suggests, leading to a marginal miss of the target. In this study, we encountered a wide variation in separation, which suggests that such rules are hazardous to apply.

The second strategy to limit dose is intensity-modulated radiation therapy (IMRT). Although IMRT provides a tremendous advantage at a target and normal tissue interface such as prostate and CC/IPA, the available study (48) employed CT-based planning and empiric contouring rules. Although there is clear superiority of IMRT over the three-dimensional (3D) planning demonstrated in the study, in practice the sparing depends as much on imaging as treatment planning. In the present study, the dose limitation to the CC matched or exceeded the dose limitation accomplished by IMRT.

Improvement in erectile function after radiotherapy ultimately depends on a more complete understanding by radiation oncologists of the erectile apparatus and nonradiation impotence literature. Although the most common causes for impotence in the nonradiation literature are narrowing of the IPA and the iliac system, no dose correlation studies of impotence and dose to the IPA after radiation therapy have been completed, in contrast to studies of other vessels (49–63). This is because of the lack of visualization of this vessel on CT and the necessity for angiography to fully define its course. Although the CC, the actual erectile structure, is visualized on CT and MRI, dose or correlative studies are lacking, with the exception of the recent series by Mulhall et al. (40) and Merrick et al. (42). It is important to note that the CC and IPA are inferior and lateral to the prostate and PB. Dose limitation to these structures could be accomplished more easily than dose limitation to the PB.

Although there is strong evidence for a vascular etiology for impotence, the exact mechanism of impotence posttherapy remains unknown and may be due to a complex interaction of vascular and neural factors. Practically, however, dose limitation to the neurovascular bundle is not a realistic strategy, given its proximity to the peripheral zone. This study suggests that it is feasible to markedly decrease dose to critical vascular structures and directly determine the impact of dose limitation on potency. In the present study, we employed coronal, sagittal, and axial MRI T2 pelvic sequences to define the prostate and CC. In addition, an MRI angiogram sequence (noncontrast) was performed to define the IPA. These MRI data sets were registered to the CT data set used for treatment planning. Registration of these multiple data sets can be efficiently accomplished through mutual information technology, an automated registration program (64). Once the structures are defined, erectile vessel–sparing radiotherapy is possible. A study is in progress to determine its efficacy.

METHODS AND MATERIALS

**Radiographic studies**

Twenty-five patients diagnosed with prostate cancer (10 external beam, 15 brachytherapy) were entered on two institutional review board–approved treatment protocols incorporating MRI T2 sequencing. MRI T2 sequences (axial, coronal, and sagittal) were obtained with a pelvic coil using 3-mm slice thickness and no gap. The 10 patients entered on the vessel-sparing protocol underwent treatment planning CT with 3-mm slice thickness. In addition, a noncontrast MRI angiogram was obtained to define the IPA. The proximal CC was clearly defined on axial and coronal T2 MRI. Critical to this study was accurate and efficient registration of various data sets. Mutual information software was employed for all registrations.

**Mutual information**

After specification of initial starting points in like structures, the mutual information program proceeded automatically until there was maximization of mutual information. All information contained in the data sets, or regions of interest cropped from the data sets using intensity information only (as opposed to anatomic surfaces or contours), was used for the registration. The sagittal and coronal MRI data sets were registered to the axial MRI data set using full scan information. In general, the registration of MRI data sets was extremely accurate as a result of like data sets and like patient positions. The quality of the registration was assessed by visual inspection of bony anatomy and prostate contour agreement at midgland.

After registration of the MRI T2 sequences, the MRI T2 axial data set was registered by mutual information with the CT data set using a cropped region of interest. Registration quality was assessed by the same parameters used for MRI registration quality. Because prostate motion may change the position of the prostate relative to bony anatomy, and the principal concern of the study is comparison of prostate contours, cropping of the axial MRI data set to the prostate and periurethral soft tissues for use in the MRI/CT registration was necessary in patients with a disparity between relative positions of the bony pelvis and prostate. This allows extremely accurate prostate registration at the expense of possible misalignment of the bony pelvis. The axial MRI/CT registration matrix was used to register the mutually registered MRI data sets to the CT data set. The CT-derived surfaces could then be displayed on all MRI sequences, and the distance from the CT apex to the MRI-defined apices could be measured to allow the comparison of CT- vs. MRI-defined apex levels.

Finally, the MRI angiogram sequence was also registered by mutual information to the axial MRI T2 and subsequently moved to the CT alignment using the transformation generated in the axial MRI–CT registration process. Accuracy of the registration was assessed by visual comparison to the IPA on MRI, as well as by bony anatomy agreement.

**Prostate contour comparison**

The prostate was contoured on all MRI scans. The contours were entered on individual data sets (axial, sagittal, and coronal) before registration. Uncertainty (prostate vs. nonprostate) on each
data set was resolved in favor of the prostate to avoid underestimation. Regions of uncertainty varied by data set. The axial data set had minimal uncertainty at the midgland and greater uncertainty at the apex and base. The sagittal scan was advantageous in defining the base and seminal vesicle interface, with uncertainty in the lateral midgland and apex, although in half the patients the apex was clearly defined on sagittal. The coronal scan was advantageous at the apex, because of the clear demarcation of the prostate and genitourinary (GU) diaphragm, with uncertainty in defining the base and seminal vesicle interface.

After registration of the 3 MRI data sets, it was possible to compare the definitions of the prostate volume. The contours from each data set could be overlaid on all data sets. In this study, great attention was given to the prostate apex, because it is the structure closest to the erectile structures. The relative location of the apex as defined by axial, sagittal, and coronal MRI was compared by measuring the apex level from contours projected on the coronal data set. This avoided the inaccuracy of comparing apex levels on axial data sets, where differences would be a function of slice thickness (3-, 6-, or 9-mm difference) rather than the continuous measurement possible on coronal projections.

Internal pudendal artery

For IPA definition, a time-of-flight echo sequence was employed. In this sequence, an excitation pulse followed by a rephasing pulse was applied to each slice. Stationary nuclei receive both pulses and produce a signal, whereas flowing nuclei may exit the slice before the rephasing pulse is applied. An axial data set was generated that defined the iliac vessels. The study required 6 to 8 minutes to complete, on average.

Review of the MRI angiogram revealed considerable variation in the IPA. In 6 of 10 patients, the course of the vessel was clearly defined to its termination in the CC. In 4 of 10 patients, the angio-defined vessel terminated 1 to 2 cm before the CC. (This incomplete definition may be a function of erection physiology. Erections result from arterial dilation of the IPA with rapid filling of the CC. The normal state of the vessel is vasoconstriction, and variation in degree of vasoconstriction may account for lack of filling of the distal IPA, along with variation in vessel diameter and occlusive disease.) In the group with poor definition of the distal IPA, the distal segment was defined by coronal MRI. The IPA is visible within the pudendal canal and was contiguous with the angio-defined proximal IPA.

Apex to penile bulb distance (genitourinary diaphragm thickness)

The distance from the prostate apex to the PB was measured with coronal MRI in 25 patients. Effectively this measured also the variation in GU diaphragm thickness. In addition, the distance from the prostate apex to the CC and IPA was measured on coronal MRI in the 10 patients entered on the vessel-sparing protocol. The distance from the CT-defined apex and the CC and IPA was measured to allow comparison of the separation of prostate and critical erectile tissues by CT relative to MRI.

Dosimetry

A composite prostate volume was generated using the axial, sagittal, and coronal MRI data sets. Treatment plans used a 1.0-cm and 0.5-cm expansion. This expanded volume was covered with the 95% isodose line. Forward planning with limited segments (fewer than 6 segments total per patient, e.g., 3 fields with 2 segments per field) was employed to attempt to limit dose to the CC and IPA. Dose–volume histograms (DVHs) were generated, and the D50 (dose to 50% of the volume) and D5 (dose to 5% of the volume) were determined. The D50 and D5 were expressed as the percentage of prescription dose delivered (e.g., 23% = 0.23 times the prescription dose). Dose in Gy from a full treatment course (80 Gy: 50 Gy to a 1.0-cm expansion and 30 Gy to a 0.5-cm expansion) was determined for 10 patients. For comparison to standard CT-based treatment, a plan was generated in 5 patients based on the CT-defined prostate (expanded 1.0 cm and 0.5 cm) and covered with the 95% isodose line (IDL). The ratio of the dose from the MRI plan vs. the CT plan was calculated to define the advantage of MRI-based planning.

For comparison to the available literature, D50 and D5 doses for the PB and CC were calculated and expressed as dose in Gy resulting from an 81 Gy course to a 1.0-cm prostate expansion. In addition, the PB D70 (dose to 70% volume relative to prescription dose) was calculated for an 80 Gy course.

RESULTS

Improved prostate volume definition by coronal MRI

On axial and sagittal MRI T2 scans, there is ambiguity in defining the inferior extent of the prostate apex. In contrast, the apex was sharply demarcated from the GU diaphragm on coronal MRI (Fig. 1a) and consistently above the apex level defined on axial and sagittal MRI. The apex level on axial MRI was, on average, 0.51 cm (0.18 standard deviation [SD]) inferior to the apex by coronal MRI. The apex level on sagittal MRI was on average 0.36 cm (0.15 SD) inferior to the apex by coronal MRI. The apex defined on CT (5 patients) was on average 1.2 cm (0.20 SD) inferior to the apex on coronal MRI.

The impact of this difference in apex level is demonstrated in Fig. 1b. The CT volume is projected on the coronal MRI. If the prostate is expanded 1.0 cm and covered, it is clear that minimal sparing of the critical vascular structures is possible.

Variation in distance from prostate apex to penile bulb (GU diaphragm thickness)

The average distance from the prostate apex to the PB was measured using coronal MRI. The measurement was taken at the level of the urethra coursing through the GU diaphragm. The distance reflects the thickness of the GU diaphragm. The average distance was 1.45 cm (0.36 SD), with a range from 0.7 cm to 2.1 cm. We observed an inverse relationship between penile bulb length on coronal view and distance to the prostate apex. In general, an extremely large penile bulb predicted a decreased distance to the prostate apex. Because of study size limitation, this relationship could not be definitively established, and this observation requires further investigation.

Definition of corpus cavernosum, internal pudendal artery, and penile bulb

The CC and PB can be clearly seen on T2 MRI. The MRI was superior to CT in clearly defining the crura/proximal CC and PB, although these structures can be visualized on CT.
A noncontrast time-of-flight scan provided clear definition of the IPA in most patients (See Fig. 2). The IPA follows a course posterior and lateral to the prostate with a variable angle turn at the inferior prostate, then courses inferior to the prostate before entering the GU diaphragm. The most distal IPA was defined in 4 of 10 patients with the coronal MRI, because of limited visualization on the MRI angio. The vessel is visible within the pudendal canal, contiguous with the angio-defined vessel. With multiple registrations, it became possible to define the entire course of the IPA by axial T2 MRI in the majority of patients. In subsequent patients, definition of the vessel before MRI angio registration correlated with the angio-defined vessel. It may ultimately prove possible to define the vessel by axial T2 MRI alone (data not shown).

The distance between the erectile tissues and prostate apex depends on the method of prostate apex definition. When the apex is defined by coronal MRI, the distance between the apex and critical vascular structures is greater than the distance for the CT-defined apex. The average distance from the MRI-defined coronal apex to the crura/proximal CC was 2.8 cm (0.36 SD); the average distance from the CT-defined apex to the crura/proximal CC was 1.5 cm (0.43 SD). The average distance from the MRI-defined coronal apex to the IPA was 2.2 cm (0.25 SD); the average distance from the CT-defined apex to the IPA was 0.92 cm (0.22 SD). The distance between the prostate and IPA may in part be a function of prostate size. Although the sample size prevents a definite conclusion about this relationship, in this limited series, the smallest separation was noted in patients with enlarged prostates.

The relationship of the IPA, proximal CC, and prostate is depicted in Fig. 3 by lateral and anterior beam’s-eye–view for 2 patients. In Patient A, the separation of prostate and erectile tissues is less than for patient B, reflected on coronal MRI and ortho beam’s-eye–view (1.0-cm prostate expansion). The resultant DVHs for CC and IPA for a 1.0-cm expansion are presented for comparison.

**MRI-based dosimetry**

Patients underwent 3D treatment planning using MRI-defined volumes with nonaxial, multiple-segment fields to explore the possibility of sparing the erectile tissues. Plans were generated for a 1.0-cm and 0.5-cm prostate expansion with 95% isodose line (IDL) covering the expansion. The D50 and D5 for the CC and IPA for the 10 patients in the vessel-sparing protocol are presented in Table 1. Penile bulb D50 and D5 (peak dose or highest dose region on DVH) results are included for comparison with available literature.

The peak dose (represented by D5) to the CC was 39(16)% of the prescription dose for a 1.0-cm prostate expansion (range, 23–60) and 23.0(8)% of prescription dose for a 0.5-cm expansion (range, 13–31). The peak dose to the IPA was 55(17)% of prescription dose for a 1.0-cm prostate expansion (range, 12–69) and 38(17)% of prescription dose for a 0.5-cm expansion (range, 6.5–67). The peak dose to the PB was 62(18)% of the prescription dose for a 1.0-cm expansion.
prostate expansion (range, 33–84) and 40.0(24)% of prescription dose for a 0.5-cm expansion (range, 13–80).

The actual peak dose in Gy was calculated for an 80 Gy treatment course (50 Gy to a 1.0-cm expansion and 30 Gy to a 0.5-cm expansion). The resultant dose to the CC and IPA is presented in Table 1. The same calculation was performed based on CT volumes and compared to MRI. Dose was limited to the proximal CC (0.36 MRI relative to CT dose) more than the IPA (0.61 MRI to CT dose), because of the marked variation in the course of the IPA. The high-dose region of the IPA varied. In most patients, the distal IPA received the greatest dose. In others, the high-dose region of the IPA was the segment coursing inferior and posterior to the prostate. In a third group, the high-dose region was the proximal IPA, because of its proximity to the lateral superior prostate.

Representative dose–volume histograms are presented in Fig. 4. The difference between CT- and MRI-based plans (Fig. 4a), and the difference between initial (1.0-cm expansion) and reduced-field (0.5-cm expansion) plans (Fig. 4b), are presented. The reduced-field dose to erectile tissues is typically two-thirds the initial plan dose, demonstrating that minimal changes in planning volume have relatively profound impact on dose to erectile tissues.

For comparison with available literature (48), D5s to the CC and PB for an 81 Gy course with a 1.0-cm target expansion are presented in Table 2. Results are compared to reported values for conventional IMRT (SS6X) and tomotherapy (Tomo6X) using CT-defined structures. D10 was 9.7(4.7) Gy for an 80 Gy course, compared to the reported potency preservation dose of 40 Gy (36, 37).

DISCUSSION

Early diagnosis through prostate-specific antigen screening and improvements in radiation therapy techniques has resulted in very high cure rates for the majority of patients diagnosed with prostate cancer. As cure rates have risen, the focus of attention has turned to quality of life after treatment. One major quality-of-life concern is preservation of sexual function (1–42). In the past few years, increasing evidence points to a vascular mechanism for radiation-induced impotence (32–42). The critical vascular structures, the CC and IPA, are often more than 1.5 to 2.0 cm from the prostate. Vessel-sparing prostate radiotherapy is becoming more feasible as imaging studies improve the definition of critical erectile tissues.

Limiting dose to erectile tissues has depended on two strategies: improved prostate apex definition and improved treatment planning and delivery. Strategies to improve apex definition include MRI imaging (consistently proven superior to CT) (64–69), apex fiducial markers (70), and rules relating the prostate apex position to well-defined structures (71, 72). For example, the reported average distance from the urethrogram apex to the prostate apex is 1.0 cm (71, 72), and the reported average distance from the PB to the prostate apex is 1.5 cm (72). The pitfall of applying such a rule is apparent in the current study. Although our observed average distance from prostate apex to PB was 1.45 cm, the range was 0.7 cm to 2.1 cm. If the prostate apex had been defined by the 1.5-cm rule, the prostate would have been underestimated in one-half of our patients, leading to marginal miss. The prostate would also have been overestimated in one-half of our patients, limiting the degree of erectile tissue sparing possible in a group with the greatest potential for sparing. Our data suggest that empiric rules based on average distances must be abandoned in view of the profound anatomic variation. Furthermore, the coronal view is on average superior to the axial and sagittal views in providing an unambiguous definition of the apex/GU diaphragm interface.

The superiority of the coronal apex view must be re-
Fig. 3. Variation in separation between prostate and erectile tissues. Coronal magnetic resonance imaging (MRI), orthogonal beam’s-eye–views (1.0-cm prostate expansion), and dose volume histogram (DVH) for (green) corpus cavernosum (CC), (red) internal pudendal artery (IPA), and (white) penile bulb (PB). (a–d) Patient A: (a) coronal MRI; (b, c) orthogonal views with 1.0-cm target expansion; and (d) DVH. (e–h) Patient B: (e) coronal MRI; (f, g) orthogonal views with 1.0-cm target expansion, and (h) DVH.
viewed in the context of earlier work comparing MRI and CT prostate contours. In general, MRI contours are more reproducible, with less intraobserver and interobserver variation in studies comparing axial CT to axial MRI (66–69). We previously noted a difference in prostate contours between T2 and other MRI sequences (73). The addition of a sagittal view improved the apex definition relative to the axial MRI in one series (74), but coronal views were not included in the study. We concurred that there was an advantage to the sagittal view compared to the axial MRI, but an additional advantage of coronal MRI over both axial and sagittal was noted. The advantage of a specific MRI sequence, or MRI view, is due to clarity of margin definition. On sagittal view, the pelvic musculature and genitourinary diaphragm supporting the prostate, as well as the prostate surface itself, is sloping inferior in the plane of the sagittal view. Thus the critical muscle and prostate interface is obscured, because of averaging of a rapidly changing interface. The coronal view is at a right angle to the sloping pelvic muscles and genitourinary diaphragm, and the interface is less ambiguous on average. The authors do not intend to set out another set of rules comparable to the penile bulb or apex rule, such as “the coronal view is always superior to the axial and sagittal.” We currently register axial, coronal, and sagittal in all patients and attempt to use the best information from each view.

The concept of best information is the critical limiting factor in further improvement of target definition beyond optimizing the MRI sequence and MRI view. If contouring on each view is limited to clearly defined margins, this constitutes the best information from that view, and the greatest advantage is derived. If one contours and includes best information with best guess (contours of ambiguous margins), the advantage is decreased. In general, the coronal view clarifies the apex, and the sagittal view clarifies the base, but the full advantage of multiple views is realized.

Table 1. Summary of prescription dose to CC, IPA, and PB:

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<th>(1.0 cm)%PD</th>
<th>(0.5 cm)%PD</th>
<th>(1.0 cm)%PD</th>
<th>(0.5 cm)%PD</th>
<th>(1.0/0.5 cm) (80 Gy)</th>
<th>MRI:CT</th>
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<tbody>
<tr>
<td>CC</td>
<td>15.0 (6)</td>
<td>10.0 (4)</td>
<td>39.0 (16)</td>
<td>23.0 (8)</td>
<td>0.5926 (9)Gy</td>
<td>0.36</td>
</tr>
<tr>
<td>IPA</td>
<td>35.0 (14)</td>
<td>23.0 (11)</td>
<td>55.0 (17)</td>
<td>38.0 (17)</td>
<td>0.6939 (13)Gy</td>
<td>0.61</td>
</tr>
<tr>
<td>PB</td>
<td>19.0 (12)</td>
<td>14.0 (7)</td>
<td>62.0 (18)</td>
<td>40.0 (24)</td>
<td>0.6443 (16)Gy</td>
<td>0.66</td>
</tr>
</tbody>
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Abbreviations: CC = corpus cavernosum; IPA = internal pudendal artery; PB = penile bulb; PD = prescription dose.
when the best information from each view is defined and employed in target definition. This concept explains the profound discrepancy of CT vs. MRI apex definition noted in the study. The 1.2-cm difference between CT and coronal MRI might have been decreased if CT contouring was better, but CT contouring at the apex is determined by a combination of best guess and fear of underestimation of the target. With experience of multiple MRI and CT registrations, CT contouring may improve, lessening the discrepancy between CT and MRI contours (see below). The CT contours in the current study were influenced by registration experience and may be underestimated in the current study relative to the findings of other investigators, despite the large difference noted between MRI and CT apex levels.

A related argument against MRI-based planning is that prostate overestimation by CT contouring has positive value and provides a level of security that the actual prostate is well covered. In this view, overestimation provides additional biologic margin and compensation for setup error. MRI planning could therefore be considered a risky approach. The common contouring error implied in the study is overestimation of the inferior extent of the prostate, decreasing the possibility of dose limitation to erectile vascular structures. However, if the apex of the prostate is defined by the 1.5-cm rule, prostate volume is underestimated relative to that defined by MRI. Thus, MRI planning may either decrease or increase the prostate volume relative to CT. The study solves the problem posed by overestimation based on CT contouring alone and the greater danger of underestimation based on the 1.5-cm penile bulb rule. For some patients, the dose to erectile tissues would actually increase compared to dose delivered if the 1.5-cm rule were employed. The study therefore provides the security of improved target definition. Full exploitation of this target definition requires daily targeting by fiducial markers.

Although the coronal view clarifies the apex position, correlations of axial and coronal MRI have improved our interpretation of the axial view. At the apex, the light peripheral zone and the light GU diaphragm blend to obscure this margin on axial view. However, the levator ani muscle is well defined, and the change from a concave shape (supporting the prostate) to convex hourglass shape correlates with the apex as defined by coronal view (Fig. 5).

Table 2. Comparison of current study to Sethi et al. (48) IMRT study: Dose to 5% target volume in an 81 Gy course to a 1.0-cm target expansion for MRI-based plans (current), SS6X IMRT, and Tomo6X IMRT

<table>
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<th></th>
<th>CC</th>
<th>PB</th>
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<tr>
<td>Current</td>
<td>32.4 (12.9)</td>
<td>50.2 (14.8)</td>
</tr>
<tr>
<td>SS6X (48)</td>
<td>49 (5.3)</td>
<td>48 (8.9)</td>
</tr>
<tr>
<td>Tomo6X (48)</td>
<td>41 (4.6)</td>
<td>40.0 (4.5)</td>
</tr>
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</table>

Abbreviations: CC = corpus cavernosum; IMRT = intensity-modulated radiation therapy; PB = penile bulb.

Although this change in shape of the levator ani is not universal, it is present in the majority of patients. Recognition of the hourglass shape on axial MRI may allow accurate apex definition without the coronal view (study in progress) and coronal registration. Furthermore, with higher-resolution CT, this same hourglass shape defining the upper GU diaphragm is identifiable in approximately half of pelvic CT scans, and recognition improves CT contouring as well. Because apex definition is as critical a strategy to vessel sparing as vessel definition, improving apex definition alone will result in vessel sparing in those with a natural separation between prostate and IPA.

The second strategy to spare erectile tissues uses IMRT. The prostate and erectile tissue interface fulfills the criteria for the application of IMRT (75), and one study has exhaustively compared various IMRT strategies (48). In that study, IMRT was found to reduce the exposure from standard 3D plans by up to 50%. The weaknesses of the study were the use of CT-based imaging and application of an empiric rule (1.0 cm above the urethrogram apex) to define the apex. Application of the rule may have overestimated the prostate extent in some and underestimated it in others. The authors present the D50 and D5 doses for the CC and PB, along with a D5 to the most proximal segment of the CC and PB. The values are presented as Gy delivered in an 81 Gy course. We have calculated the same parameters for the current study, and the comparison is presented in Table 2.

The resultant dose to the CC is lower in the current series relative to the IMRT series, even for the superior Tomo6X IMRT strategy. This is due to the profound separation of prostate and CC in a subset of our patients. The wide range of values in the current series is reflected in the larger standard deviation for all structures. The lower standard deviation in the IMRT series was likely due to a relatively fixed spacing between the target and erectile tissues, because of application of the 1.0-cm rule. Application of the 1.0-cm rule may have underestimated the prostate target in some patients (In our series, 2 patients had a prostate to PB distance of less than 1.0 cm), resulting in a lower average exposure to the PB at the expense of target coverage.

These data argue that imaging is as or more important than application of IMRT in sparing erectile tissues without loss of target coverage. Based on the study by Sethi et al. (48), however, there is strong evidence that results in the current series could be improved by the use of IMRT (study in progress) and that both imaging and IMRT will be necessary to optimally spare erectile tissues. In a separate study, impotence was correlated with dose to the PB (36, 37). For those that received 40 Gy or less to 70% of the PB, there was a greater likelihood of potency preservation than for those that received 70 Gy to 70% of the PB. In the current study, the dose to 70% of the PB was 9.7 (4.7) Gy for an 80 Gy course, far below the potency preservation threshold value.

The unique aspect of the study without reference in the current literature is the definition of the IPA. Including the IPA in planning considerations was considered necessary in
view of its importance in the literature from noncancer patients (43, 44). Narrowing of this vessel is the most common cause of impotence in the general population, and it is conceivable that radiation may contribute to this process. The literature on the late effects of radiation on larger arteries is retrospective, and interpretation is complicated by comorbidity, which may contribute to atherosclerosis (49–63). Despite the limitations of these studies, there are well-defined pathologic changes and clinically significant vascular sequelae postradiation. Implied in this literature is a well-established late effect on capillaries and arterioles, which is manifest earlier than the effect on larger arteries. In this context, it is notable that the IPA is a long and narrow vessel with a variable angle turn, which may be particularly vulnerable to the late effects of radiation. There are no studies to correlate dose to the IPA and impotence, so defining its relative importance will require long follow-up of the current study.

Although MRI angiogram proved useful in defining the vessel, it adds time and complexity to treatment planning. After review of multiple correlations, it became clear that the IPA can be defined on a combination of MRI T2 axial

Fig. 5. Change in levator ani at the prostate apex. (a) Concave shape (supporting the prostate). (b) Convex shape (hourglass) below the prostate.
and coronal scans. In fact, in a fraction of patients, the terminal IPA was not defined by the MRI angiogram but was defined on the coronal T2 MRI scan. There was considerable variation in artery diameter on angiogram; however, that proved to be a useful complement to vessel location as defined on axial T2 MRI. Conceivably, patients with fully patent vessels by angiogram may be far less likely to develop impotence than those with limited patency. We did not include impotent patients or patients with profound erectile dysfunction in the current study. Therefore, no correlation between erectile dysfunction and MRI angiogram patency was possible. However, in the nonradiotherapy literature, correlation of IPA occlusion and erectile dysfunction is well established. We were also unable to correlate degree of potency with the partial occlusion noted in the study patients, because of sample size, but this comparison will be possible with expansion of the study. Follow-up angiograms may allow correlation of dose and atherosclerotic narrowing, because most patients had one segment of the IPA with greater dose. A subset of patients had near exclusion of the terminal IPA and CC but high dose to the proximal IPA. Such patients may develop impotence later, because of proximal IPA narrowing rather than CC and distal IPA effects. Thus, a noninvasive serial IPA angiogram may provide a useful model for the study of the late radiation effects on small arteries.

We conclude that formal definition of the IPA course by T2 axial MRI or MRI angiogram is critical to test the hypothesis that vascular damage is the critical determinant of postradiation impotence. The argument has been made that if the apex is properly defined, and the prostate is expanded to the minimum degree appropriate to address organ motion and tumor biology, maximum potency sparing will be realized. Although it is true that proper apex definition will result in vessel sparing in those with a natural separation of prostate and IPA, there are three reasons this argument is incorrect in reference to a patient population or research setting. First, the IPA and CC are best separated from the prostate at anterior or anterior oblique angles of approach, an uncommon angle when rectum and bladder are the critical treatment planning concern. Second, the IPA relationship to the prostate is variable and complex. It follows the lateral curvature of the prostate in some patients, and though separate by enough distance to allow sparing, such sparing is possible only with an MRI imaging and IMRT approach. Finally, definition of the IPA/CC complex will allow direct correlation of dose and erectile dysfunction and begin to clarify the mechanism of postradiation impotence.

In summary, improved understanding of erectile function, improved visualization of prostate and erectile structures, and efficient registration of MRI data sets by mutual information allow dose limitation to the critical erectile tissues without compromising target coverage. Our results matched or exceeded results from available IMRT studies. It is possible that the erectile “vessel-sparing radiotherapy” may have as favorable an impact on sexual potency after radiation as “nerve-sparing” prostatectomy. These studies will allow correlation of dose to critical erectile structures and impotence and improve our understanding of radiation-induced impotence. Although coronal MRI for apex definition and MRI angiography for IPA definition are optimal for research purposes, with training it is possible to clearly define the apex and course of the IPA on axial MRI alone. This makes a modified vessel-sparing approach feasible for wide application and will allow large national prospective studies to test the vascular hypothesis.

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