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PARAMETERS FAVORABLE TO INTRAPROSTATIC RADIATION DOSE ESCALATION IN MEN WITH LOCALIZED PROSTATE CANCER

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Abstract

Purpose—To identify, within the framework of a current Phase I trial, whether factors related to intraprostatic cancer lesions (IPLs) or individual patients predict the feasibility of high-dose intraprostatic irradiation.

Methods and Materials—Endorectal coil MRI scans of the prostate from 42 men were evaluated for dominant IPLs. The IPLs, prostate, and critical normal tissues were contoured. Intensity-modulated radiotherapy plans were generated with the goal of delivering 75.6 Gy in 1.8-Gy fractions to the prostate, with IPLs receiving a simultaneous integrated boost of 3.6 Gy per fraction to a total dose of 151.2 Gy, 200% of the prescribed dose and the highest dose cohort in our trial. Rectal and bladder dose constraints were consistent with those outlined in current Radiation Therapy Oncology Group protocols.

Results—Dominant IPLs were identified in 24 patients (57.1%). Simultaneous integrated boosts (SIB) to 200% of the prescribed dose were achieved in 12 of the 24 patients without violating dose constraints. Both the distance between the IPL and rectum and the hip-to-hip patient width on planning CT scans were associated with the feasibility to plan an SIB ($p = 0.002$ and $p = 0.0137$, respectively).

Conclusions—On the basis of this small cohort, the distance between an intraprostatic lesion and the rectum most strongly predicted the ability to plan high-dose radiation to a dominant intraprostatic lesion. High-dose SIB planning seems possible for select intraprostatic lesions.

Keywords

IMRT; Prostate cancer; Dose escalation; Radiotherapy; Treatment planning

INTRODUCTION

With prostate-specific antigen screening leading to more men being diagnosed with localized prostate cancer earlier in life (1), optimizing long-term local control becomes increasingly important. Patients with local tumor recurrence are at risk for subsequent metastatic disease, suggesting that improved local control may improve long-term survival (2–4). One method of attempting to increase local control is through escalating doses of radiation to the prostate gland during externalbeam radiotherapy (EBRT). High-dose radiation delivered via three-dimensional conformal radiotherapy (3D-CRT) has been found to improve biochemical control consistently for intermediate-risk prostate cancer patients (3, 5, 6) in addition to those with low-risk (6, 7) and high-risk disease (5). In addition to improved biochemical control, some reports have found a survival benefit to dose escalation (8).

Despite these positive results, the cost of dose escalation is increased rectal and bladder toxicity (5, 6). Rectal toxicity has been found to be significantly decreased when patients are treated with intensity-modulated radiotherapy (IMRT), when compared with 3D-CRT (9). Ten-year follow-up data reveals that high-dose (81 Gy) IMRT has resulted in less rectal toxicity than 3D-CRT at lower doses (70.2 and 75.6 Gy), though bladder toxicity was found to be significantly higher in the high-dose group (10). In addition, ultra-high doses up to 86.4 Gy with IMRT have been well tolerated and represent the dose used for a majority of patients at Memorial Sloan-Kettering Cancer Center (11).

Although results of these retrospective and prospective studies are promising, minimizing Grade 2 and 3 bladder and rectal toxicity while utilizing high-dose radiation remains an important goal. One method of dose escalation that has been attempted at our center and few others has been to dose escalate MRI-identified intraprostatic cancer lesions while maintaining a standard dose of radiation to surrounding prostate tissue (12, 13). The rationale for this technique is based on two findings. The first is that local failure can occur in up to one third of patients receiving a total dose of 79.2 Gy (6). The second is that local recurrence is likely to originate at the primary site of disease (14). Early results are encouraging, with patients who were treated up to 94.5 Gy experiencing acceptable levels of early toxicity (12). The parameters that confer a positive response to this method of dose escalation remain largely unknown. We sought to define parameters based on lesion size and location and the body habitus of patients, to predict which individuals may receive optimal coverage and the least rectal and bladder toxicity from dose escalation. We did this through a dosimetric analysis of patients previously treated at our clinic. Within the framework of a current dose-escalation Phase I trial at our institution and by using patient images and clinical data, we assessed which patients would be most amenable to high-dose intraprostatic irradiation

METHODS AND MATERIALS

Phase I trial

The objective of the clinical protocol on which this dosimetric analysis is based, is to determine the maximum tolerated dose of EBRT to MRI-defined and biopsy-proven dominant intraprostatic cancer lesions. It consists of six dose-escalated cohorts, shown in Table 1. The results obtained from the first patients enrolled in the study, who received a dose of 94.5 Gy, have been previously reported (12). In this currently reported study, treatment plans were designed and tested for feasibility but not administered.

Image selection

Charts of patients treated for prostate cancer at our clinic from January 1, 2000 to September 1, 2008 were reviewed to identify the patients with Stage T1 or T2 disease who had undergone endorectal coil (ERC) MRI of the prostate with dynamic contrast enhancing (DCE), apparent diffusion coefficient (ADC), and magnetic resonance spectroscopy (MRS) imaging. Computed tomography treatment-planning images were retrieved on the Eclipse planning system (Varian Medical Systems, Palo Alto, CA) for the patients who had undergone MRI. T1, T2, MRS, ADC, and DCE images of the prostate were reviewed with a radiologist experienced in prostate MRI (P.C.) to identify dominant intraprostatic lesions (IPLs), as shown in Fig. 1. For the 4 patients who were evaluated for our clinical protocol, the lesions were biopsy proven. For the remaining patients, we considered lesions identified on T2 and ADC images as having a low likelihood of being tumor. Those identified on T2, ADC, and DCE or MRS had a moderate likelihood, and those identified on T2, ADC, DCE, and MRS were considered high likelihood. We included moderate- and high-likelihood IPLs in our analysis.

Treatment planning

Treatment-planning MR (without endorectal coil) prostate images were fused to treatment-planning CT images in 14 cases. The remaining 10 patients did not have planning MRI. The distortion and compression of the prostate gland caused by endorectal coil balloon on the MR images did not permit proper fusion, so MR images and planning CT images were compared side by side during contouring of IPLs. The IPLs were identified according to landmarks on CT and MRI, which is exactly how CT–MRI fusion is done. When done appropriately, the manual method, although more pains-taking and labor intensive, should provide results as accurate as those done by automated computerized fusion. This manual method of CT–MRI matching has been used by other studies involving IPL boosts (15–17). Intraprostatic lesions, the prostate gland, the bladder, and the rectum were contoured as shown in Fig. 2. The gross tumor volume was defined as the IPL. The planning treatment volume (PTV1) was defined as the nodule plus a margin of 3 mm. The 3-mm margin was chosen on the basis of previous investigations using cine-MRI (18), ultrasound (19), and fiducial seed matching (20, 21) that suggest most intrafraction displacement is within 3 mm. The PTV2 was defined as the prostate gland with a margin of 9 mm except the posterior prostate, which was given a 5-mm margin. Plans were to be generated to give the IPLs a simultaneous integrated boost (SIB) to the highest dose level in our current National Cancer Institute Phase I protocol (#05-C-0191D), which was 151.2 Gy in 42 daily fractions (Table 1). In addition, the PTV2 received the prescribed dose of 75.6 Gy in 42 daily fractions. Nine-field plans were generated using the Eclipse planning system. This beam arrangement was selected after comparisons of various beam arrangements revealed optimal tumor coverage and organ sparing using nine equally weighted 6-MV photon beams (12). Beam gantry angles used with this technique were 20°, 60°, 100°, 140°, 180°, 220°, 260°, 300°, and 340°, with the couch at 180° and collimator rotation at 180°.

Normal tissue dose limits

Normal tissue dose goals were consistent with those determined by the Radiation Therapy Oncology Group (RTOG) protocol 04-15, which were in turn based on a review of patient dosimetry of RTOG 94-06. Bladder and rectal dose constraints are found in Table 2. In addition, no portion of the rectum was to receive >120 Gy, and no portion of the bladder was to receive >100 Gy. Dose heterogeneity could not be prevented because of the high dose prescribed to the IPL. However, we limited the minimum dose to 85% of the prescribed dose while ensuring that the prescription dose was delivered to 95% of the PTV. Last, no prescribed isodose lines were permitted to cross into any osseous structures.

Plan evaluation

Treatment plans were evaluated to assess the sufficiency of target coverage and ability to limit normal tissue doses to those outlined above. The maximum dose for normal tissues, as well as the IPLs and prostate gland, were determined by evaluation of a dose–volume histogram. Target coverage was considered adequate if 95% of the PTV1 received the target dose (151.2 Gy) and 95% of the PTV2 received the prescription dose (75.6 Gy). In addition, doses to the bladder and rectum were evaluated. If IPLs could not be dose escalated, while keeping the doses to normal tissues within the outlined constraints, we preceded to de-escalate to a lower cohort, as indicated in Table 1. This process was repeated until either a plan fulfilled the dose constraints or the lowest cohort dose was unsuccessfully attempted.

Statistical analysis

To evaluate the parameters that favored escalation to the highest cohort dose, a number of parameters were measured. The IPL, rectal, and bladder volumes, the distance between IPL and rectum and IPL and bladder, and the volume of the IPL relative to the prostate gland were all measured. Distances were defined as the closest distance between regions of interest. This was standardized for all distance measurements. In addition, the anterior–posterior (AP) length and hip-to-hip width were measured for each patient on planning CT scans. Last, body mass indices (BMI) were calculated according to height and weight information obtained from patient charts. Body mass index was calculated as weight in kilograms divided by height in meters squared. Statistical analyses were conducted using the R statistical package (22). Receiver operating characteristic curves were used to identify the optimal thresholds to predict the accuracy of measures in each group separately and significance analysis of each measure estimated by two-tailed Fischer's exact test. Feasibility of dose escalation based on nodule locations was calculated using χ^2 analysis (GraphPad Prism 5; GraphPad Software, San Diego, CA). A *p* value of <0.05 was considered significant.

RESULTS

Forty-two patients with both prostate MRI and treatment planning CT images were identified. Dominant IPLs were identified in 24 patients (57.1%). Of these 24 patients, 21 had one dominant lesion and 3 had two dominant lesions. A total of 27 lesions were identified. The most common location of IPLs in the axial plane was in the posteriolateral prostate gland ($n = 11$). In the cranial–caudal direction, most lesions were located in the mid-gland ($n = 15$). There was no difference in the feasibility of dose escalation according to the location of IPLs (Tables 3 and 4). Simultaneous integrated boost to 151.2 Gy was achieved in 12 of the 24 patients (50.0%) without violating dose constraints, as shown in Fig. 3. For 9 of the remaining 12 patients, SIB was possible to a lower dose cohort (Fig. 4). For all cases, resultant doses to the bladder and rectum greater than 85 Gy and 90 Gy, respectively, was limited to <1% of the respective volumes.

IPL characteristics

The average volumes of IPL, prostate gland, rectum, and bladder were 1.57 cm³, 46.65 cm³, 79.0 cm³, and 156.3 cm³, respectively. There was a trend of inability to deliver an SIB while respecting dose constraints for patients with rectal volume larger than 62.4 cm³ ($p = 0.0995$). There was not a significant association between bladder or lesion volume and feasibility of SIB (Table 5).

Intraprostatic lesions were located an average distance of 0.57 cm from the rectum and 2.0 cm from the bladder, with a standard deviation of 0.45 cm and 1.13 cm, respectively. Lesions located less than 0.42 cm from the rectum were significantly associated with

infeasibility of SIB ($p = 0.0002$). A significant relationship was not seen for bladder distance (Table 5). With most IPLs located in the posterior prostate gland, the dose–volume criteria for the rectum most often limited dose escalation to IPLs.

Patient characteristics

Patients had an average hip-to-hip width of 35.9 cm and an AP length of 22.1 cm. Height and weight information was attained for 19 patients. The average BMI was 30.0 kg/m². Patients with a larger hip-to-hip width (>37.22 cm) were more likely to achieve dose escalation to the highest cohort ($p = 0.0137$). There was no significant relationship between AP length and BMI with SIB feasibility (Table 5).

DISCUSSION

Although dose escalation has been found to increase biochemical control in prostate cancer, the risk of toxicity to normal structures has generated interest in delivering higher radiation doses to prostatic tumors without injuring surrounding structures. Intensity-modulated radiotherapy delivery of a SIB to MRI-identified intraprostatic cancer lesions has been a relatively recent strategy used in only a few trials in the past decade. This is possible because of the superior imaging of prostate lesions with MRI when compared with CT and ultrasound (23, 24) and the ability of IMRT to deliver high doses of radiation with low rates of late toxicity (10). Our present analysis finds that the lesions that are most amenable to high-dose SIB are those that are a distance greater than 0.42 cm from the rectum, and are in patients with hip-to-hip widths greater than 37.22 cm ($p = 0.0002$ and $p = 0.0137$, respectively).

Feasibility studies conducted at the University of California, San Francisco reported on the ability of IMRT to deliver 90-Gy SIBs to IPLs while treating the rest of the prostate with 73.8 Gy and 75.6 Gy (25, 26). Prostate mapping has also been explored using prostatectomy specimens instead of MRI to predict IPL localization (27). Using nine-field IMRT techniques, Nutting *et al.* (27) conceived a model of SIB of 90 Gy to dominant IPLs. The authors reported increased rectal dose when boosting posterior vs. lateral IPLs and concluded that SIB would be most appropriate for lesions in the lateral prostate, provided that there was a distance of several millimeters between the rectal wall and the IPL. In the present study, we quantify the distance for which a significant increase in rectal toxicity occurs as 0.42 cm.

De Meerleer *et al.* (15) reported on 15 patients who received an 80-Gy SIB to biopsy-proven IPLs. The mean distance between the IPL and the rectal wall was 3 mm and ranged from 0 to 12 mm, which varies from our mean of 5.7 mm and range of 0.9–22.8 mm. The median volume of IPLs in their cohort was 4 cm³, whereas ours was less than half of that volume. The longer distance measured between the IPL and rectum in our study is likely a function of the smaller IPL volume measurements, which in turn may be due to the MRI we used in identifying IPLs. De Meerleer *et al.* localized IPLs with T2 imaging, whereas in the present study T2 images were combined with DCE, ADC, and MRS for better tumor localization. The addition of MRS and DCE to T2 imaging has been found to improve the accuracy of prostate lesion localization (28). Though lacking the sensitivity of DCE-MRI in the detection of prostatic lesions, MRS is highly specific (29). It is possible that we were better able to differentiate between tumor and benign tissue or hemorrhage, giving us a more conservative estimate of tumor volume. It is important to note that De Meerleer *et al.* did not place a margin around the IPL. Our plans did include a 3-mm lesion margin. The average volume of the IPL with a 3-mm margin was 5.36 cm³, and this was more comparable to the gross tumor volume treated by De Meerleer *et al.* Conversely, our IPL volumes are similar to those of van Lin *et al.* (30), who used both MRI-DCE and MRS imaging in localization of

IPLs. The IPL volumes ranged from 1.1 to 6.5 cm³, which was similar to our range of 0.1–5.8 cm³. The localization of most lesions in the posterior prostate gland is consistent with both previous histologic (31, 32) and MRI (30) findings, as is the finding that most lesions are in the mid-gland (33).

Only a few trials have attempted to deliver a SIB to IPLs through the use of IMRT. In their study of 5 patients, van Lin *et al.* (30) treated IPLs in 5 patients to 90 Gy, with the PTV receiving 70 Gy. Our center previously reported success in 3 patients with the administration of 94.5 Gy to prostatic lesions and 75.6 Gy to the prostate (12). The largest experience was a Belgium trial in which patients were treated to a mean SIB dose of 81–82 Gy, with the prostate PTV receiving 78 Gy. From 230 patients who underwent ERC-MRI for evaluation of an IPL, an IPL was found in 118, or roughly 51%. This is similar to our finding that an IPL could be identified in just over half of the MRIs evaluated (13).

The finding of an association between hip width and feasibility of IPL dose escalation may be based on the fact that an increased hip-to-hip width implies greater prostate depth. However, BMI and AP length are similarly indicative of increased prostate depth but were not found to correlate with the feasibility of dose escalation. The reason for this discrepancy is unclear. Interestingly, the average BMI of the patients in this study was 30.0 kg/m². Whether our results would change if the study population had a broader range of body types and BMIs may be worth further investigation.

Our study has a number of limitations. Our results were dependent on the normal tissue constraints chosen. We used RTOG normal tissue constraints, which were more liberal than those used in the Belgium trial (13). We were comfortable with the RTOG criteria because the constraints are based on dosimetric analysis of previous large trials. The constraints are also similar to those used in large institutions with experience in high-dose radiation to the prostate (11, 34). In addition, De Meerleer *et al.* (15) used similar normal tissue constraints and reported 6 cases of Grade 2 toxicity and 1 case of Grade 3 toxicity during treatment in the 38 patients who were treated. No Grade 2 or Grade 3 toxicity was reported at 1 and 3 months' follow-up (15). However, there is no experience in the literature with similar high-dose EBRT to the prostate gland and resultant dose to normal tissue. We found that by limiting the maximum dose to 120 Gy to the rectum and 100 Gy to the bladder, we were able to maintain a number of dose constraints established by other authors. One of these, based on a review of brachytherapy data (35), is that less than 8 cm³ of rectum received a dose 100 Gy in all cases. Additionally, for all but 1 case, we were able to limit the volume of rectum receiving 78 Gy to less than 5%, a dose which has been found to limit the risk of late rectal toxicity for patients receiving prostate EBRT (36). Additionally, our bladder constraints ensured that less than 7 cm³ of the bladder volume received 82 Gy, a dose reported to limit the development of chronic urinary toxicity when delivered to less than 7 cm³ of the bladder wall (37).

Another limitation is that we did not include a urethral constraint, which is not typically done in planning EBRT to the prostate. The few trials that have used SIB to an IPL did not use urethral dose constraints and reported acceptable rates of acute genitourinary toxicity (12, 13, 15, 30). However, the dose at which we planned SIBs was much higher in this study. Such high doses could put patients at risk for increased urinary symptoms or urethral strictures. In the future, when planning extremely-high-dose radiation to IPLs, it may be necessary to use urethral constraints to prevent urethral toxicity, as is done in prostate brachytherapy.

Additionally, none of our patients had more than two IPLs. Therefore, we could not conclude how many IPLs one may safely boost. The answer is likely multifactorial. In the

present study, it was feasible to boost at least two IPLs to a very high dose in all 3 patients with two IPLs. Lesions received doses of 151.2 Gy, 136.1 Gy, and 113.4 Gy to two lesions. The ability to boost two lesions has been reported in Xia *et al.*'s feasibility study (26) and has been performed clinically (12). Last, we report results based on only one commonly used delivery method, IMRT nine-field delivery. It is unknown whether the results would vary with other delivery methods. This may be worth exploring in future investigations.

CONCLUSION

By using one commonly used method of treatment delivery, we were able to evaluate how feasibility of high-dose irradiation to MRI-identified IPLs varied, from patient to patient, according to varying body habitus and lesion sizes and locations. Our study is novel in that it is the first to address the patient-related and tumor-related factors that confer a possibility of high-dose irradiation to intraprostatic cancer lesions. Although this study gives an indication of which patients may be most amenable to high-dose intraprostatic SIB, there are still many unanswered questions regarding SIB to IPLs. Early toxicity has been found to be acceptable for doses up to 94.5 Gy in a few patients, but there are currently no data on the use of IMRT to deliver SIBs to higher doses. Even with acceptable toxicity profiles, improved local control with high-dose SIB has yet to be reported. Further trials are underway to elucidate these questions. These preliminary data may help direct patient selection for future trials.

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Fig. 1.
Endorectal coil MR image of the prostate gland. Arrow indicates the lesion suspicious for carcinoma.

Fig. 2.
Planning CT with contours of prostate, intraprostatic lesion, and rectum.

Fig. 3.
(a) Example of successful treatment plan. (b) Isodose line key.

Fig. 4.
Categorization of patients into dose cohorts according to feasibility of dose escalation.

Table 1

Cohort prescription doses

Cohort	Relative [*] dose (%)	Absolute dose (Gy)
I	125	94.5
II	138	104.3
III	150	113.4
IV	165	124.7
V	180	136.1
VI	200	151.2

* Relative to 75.6 Gy prescribed to prostate.

Table 2

RTOG bladder and rectum dose constraints

Organ	No more than 15% volume receives dose that exceeds	No more than 25% volume receives dose that exceeds	No more than 35% volume receives dose that exceeds	No more than 50% volume receives dose that exceeds
Bladder	80 Gy	75 Gy	70 Gy	65 Gy
Rectum	75 Gy	70 Gy	65 Gy	60 Gy

Abbreviation: RTOG = Radiation Therapy Oncology Group.

Table 3

Axial localization of lesions

Location	High dose possible	High dose not possible	Total	<i>p</i> , *
Posterolateral	8	3	11	
Posteromedial	2	1	3	
Hemilobed	1	5	6	
Anteriolateral	0	1	1	
Lateral	1	2	3	
Medial	2	0	2	
Bilobular	0	1	1	
Total	14	13	27	0.143

* *p* value by χ^2 test for association between variables.

Table 4

Cranial–caudal localization of lesions

Location	High dose possible	High dose not possible	Total	<i>p</i> *
Base	1	2	3	
Apex	6	2	8	
Mid-gland	10	5	15	
Base to apex	0	1	1	
Total	17	11	27	0.332

* *p* value by χ^2 test for association between variables.

Table 5

Parameters associated with feasibility of high-dose (151.2 Gy) irradiation

Parameter	High dose feasible	High dose not feasible	<i>p</i> [*]
Lesion volume (cm ³)			0.6843
<1.2	7	5	
1.2	5	7	
Rectum volume (cm ³)			0.0995
<62.4	8	3	
62.4	4	9	
Bladder volume (cm ³)			0.4470
<141.5	6	8	
141.5	6	4	
Lesion distance from rectum (cm)			0.0002 [†]
<0.42	0	10	
0.42	13	4	
Lesion distance from bladder (cm)			0.4815
<0.56	0	2	
0.56	13	12	
Body mass index (kg/m ²)			1.0000
<30	6	7	
30	4	3	
Anterior–posterior length (cm)			0.1101
<20.78	2	6	
20.78	10	6	
Hip-to-hip width (cm)			0.0137 [†]
<37.22	6	12	
37.22	6	0	

^{*} *p* value by Fischer's exact test for association between variables.

[†] *p* < 0.05.