

# IMRT for prostate cancer: improving the therapeutic ratio

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Numerous clinical studies have demonstrated a correlation between radiation dose and biochemical response to three-dimensional conformal radiation therapy of localized prostate cancer. Patients at all levels of risk who receive higher doses of irradiation experience longer disease-free survival. However, higher radiation doses also significantly increase the risk of damage to normal tissues, particularly the bladder, rectum, and erectile tissues of the penis. By improving the conformance of the radiation fields, intensity-modulated radiation therapy (IMRT) represents a major technical advance in radiation delivery, allowing radiation oncologists to increase the dose to the target field while minimizing the dose—and, therefore, toxicity—to normal tissues. This review outlines the rationale and indications for IMRT in the treatment of prostate cancer and discusses some of the pivotal studies supporting its increasing role in the management of patients with localized disease.

**R**adiation therapy has been utilized in the curative treatment of prostate cancer since the introduction of cobalt 60 high-energy irradiation in the 1950s. Radiation treatment has continued to evolve since that time, with the development of high-energy accelerators, advances in treatment planning and dosimetry, and accuracy of delivery. These technological advances allow for dose escalation and potential improvements in tumor control while limiting toxicity to normal tissues.

Intensity-modulated radiation therapy (IMRT) is currently the most conformal method available to deliver external-beam radiation therapy (EBRT). The technique required the development of multi-leaf collimation. Treatment to the prostate is often delivered through five to seven fields but with multiple segments of treatment being delivered from each field. The collimator leaves change position between each segment, allowing “painting” of the radiation dose to the tumor with increased precision and with a rapid falloff of the dose to the surrounding tissues. The rationale for use of IMRT in prostate cancer and two case studies are presented in this review.

## Dose escalation in prostate cancer

Prior to the development of CT-based treatment planning, prostate cancer patients undergoing EBRT were generally treated with a four-field beam arrangement. Large safety margins were necessary to ensure coverage of the prostate gland. Because of the volume of normal bowel and bladder

included in the treatment field, doses were limited to 66–70 Gy. The development of CT simulation and modern treatment-planning systems enabled the contouring of the target volume as well as normal or “avoidance” structures, ushering in the era of three-dimensional (3D) conformal radiation therapy.

Numerous studies of 3D conformal therapy of prostate cancer have demonstrated a correlation between dose and response for biochemical disease-free survival, as measured by changes in the prostate-specific antigen (PSA) level. For example, in a phase III dose-escalation trial conducted at The University of Texas M. D. Anderson Cancer Center, the rate of freedom from (biochemical) failure was 64% among patients with localized prostate cancer who were randomized to receive treatment with a total of 70 Gy, compared with 70% among those who received 78 Gy.<sup>1</sup> The difference was even more pronounced when the comparison was limited to patients with an initial PSA level of > 10 ng/mL. Patients in this subpopulation who were treated to 70 Gy had a 6-year freedom-from-failure rate of 43% versus 62% among those receiving 78 Gy. In

Manuscript received August 30, 2006; accepted September 28, 2006.

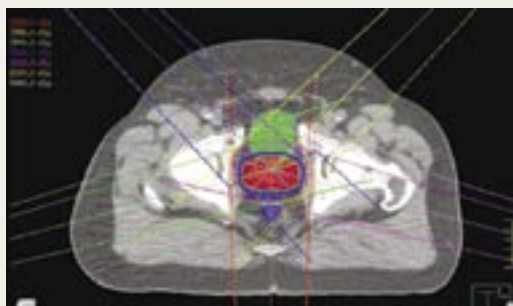
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Commun Oncol 2006;3:659–661 © 2006 Elsevier Inc. All rights reserved.

## CASE REPORT 1

This patient is a 63-year-old man who was evaluated because of a PSA level of 4.8 ng/mL. Prostate biopsies demonstrated a Gleason 3 + 3 = 6 adenocarcinoma involving one of six core biopsies from the left side of the gland. The patient denied bowel symptoms and erectile dysfunction but did complain of urinary frequency and urgency. A metastatic workup, including a bone scan and magnetic resonance imaging of the abdomen and pelvis, revealed no metastatic disease. On physical examination, the prostate was mildly enlarged with no nodularity.

The patient was staged as T1c and thus was a candidate for any definitive treatment option. The patient chose IMRT and was treated to 78 Gy in 39 treatments of 2



**FIGURE 1** IMRT plan for early-stage prostate cancer. The 98% isodose line is shown in bold. The prostate gland and treatment margin are shown in red, the bladder in green, and the rectum in blue.

Gy each. Treatment was delivered in five fields (Figure 1). Dose constraints restricted 50% of the rectal and bladder volume to less than 53 Gy and 40 Gy of irradiation, respectively. During treatment, the patient experienced urinary frequency and nocturia, which was treated with dutasteride. One month following treatment, his PSA value was 1.2 ng/mL, and his urinary symptoms were improving.

a separate study, Lyons et al<sup>2</sup> reported a retrospective series of 738 patients with localized prostate cancer receiving < 72 Gy versus ≥ 72 Gy of EBRT. The 5-year biochemical relapse-free survival rate was significantly higher (85%) among patients who received the higher doses than among those treated with lower doses of irradiation (54%), and this difference was maintained across all subsets of patients.<sup>2</sup>

### Toxicity to normal tissues

The limiting factor in dose escalation is toxicity to normal tissues, particularly the bladder, rectum, and erectile tissues. Consideration of late toxicity is extremely important in patients with localized prostate cancer, as most patients ultimately succumb to other causes of death many years following treatment. In the M. D. Anderson Cancer Center study, the difference in late rectal toxicity was significant between the 70-Gy and 78-Gy groups, with 12% of patients

in the 70-Gy arm experiencing late grade 2 or higher toxicity versus 26% in the 78-Gy arm ( $P = 0.001$ ).<sup>1</sup> The rate of grade 2 or higher urinary toxicity was 10% across all patients. Another large study of similar patients, which compared 68 Gy with 78 Gy of 3D conformal therapy, revealed an increase in late rectal bleeding requiring laser therapy or transfusion in the high-dose group and an increase in late nocturia as well.<sup>3</sup>

Development of impotence is another significant side effect of prostate radiotherapy. Roach et al<sup>4</sup> reported in 2004 the results from a phase I/II dose-escalation study of 3D conformal therapy for localized prostate cancer. The 5-year actuarial incidence of impotence among patients who were potent prior to the start of therapy was almost 50% after receiving ≥ 52.5 Gy to the bulb of the penis, compared with 25% among those who received < 52.5 Gy to the penile bulb ( $P = 0.048$ ).

## Rationale for the use of IMRT in prostate cancer

By improving the conformance of the radiation fields, IMRT represents a major technical advance in radiation delivery that allows us to increase the dose to the target volume while minimizing the dose to normal tissues. In theory, further conforming the dose to the prostate gland would lead to decreased toxicity but might also increase the risk of missing the target geographically.

Recent studies have demonstrated that full coverage of the target can be achieved with excellent outcome via IMRT. In a dose-escalation study performed at Memorial Sloan-Kettering Cancer Center, patients with clinical stage T1c to T3 disease received 64.8–86.4 Gy in 1.8-Gy fractions to the prostate only. Patients treated with up to 75.6 Gy and some patients treated with 81 Gy received 3D conformal therapy; the remaining patients treated with 81 Gy or 86.4 Gy received IMRT. In favorable- and intermediate-risk patients, a dose of 75.6 Gy or higher was associated with an improved biochemical outcome compared with that associated with lower doses. The 5-year PSA relapse-free survival rate for favorable-risk patients who received doses of 64.8–70.2 Gy was 77% versus 90% for those receiving 75.6–86.4 Gy ( $P = 0.05$ ), which compares favorably with the results of 3D conformal therapy.<sup>5</sup>

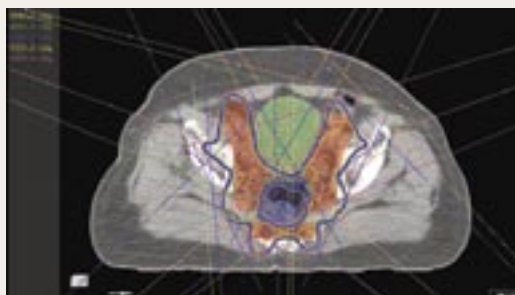
In this same trial, 3D conformal doses of 75.6 Gy or higher were associated with a 14% 5-year actuarial rate of late grade 2 rectal toxicity, compared with a 5% rate at lower dose levels. In patients receiving 81 Gy via IMRT, the 3-year actuarial incidence of late grade 2 toxicity was 2%, compared with 14% at the same dose of 3D conformal therapy. Again, no difference was seen in urinary toxicity.

The lack of improvement in urinary toxicity is not surprising, however, because at this time, most radiation

## CASE REPORT 2

This patient is a 73-year-old man who presented with frequency, urgency, dribbling, and nocturia, with a PSA value of 4.7 ng/mL. Physical examination demonstrated an enlarged prostate with induration on the right side of the gland without nodularity. Prostate biopsies revealed Gleason 4 + 5 = 9 adenocarcinoma in 4 of 10 cores taken from both sides of the gland. Again, a metastatic workup was negative. He was staged as T2c and, due to the high risk of his disease, neoadjuvant plus adjuvant hormonal therapy in combination with EBRT was recommended.

After 3 months of leuprolide therapy, the patient's PSA value fell



**FIGURE 2** Pelvic lymph node IMRT plan for high-risk prostate cancer. The 98% isodose line is shown in bold. The presacral and pelvic lymph-node regions are shown in red, the bladder in green, and the rectum in blue.

to 0.2 ng/mL. He was then treated with 45 Gy of IMRT in 1.8-Gy fractions to the prostate gland and pelvic lymph nodes (Figure 2) and subsequently with a reduced field to the prostate and seminal vesicles, for a total dose of 79.2 Gy. His only acute side effect was burning on urination. He will continue hormonal therapy for 2 years.

oncologists do not place constraints on the urethral or bladder-neck doses, due to the proximity to the target volume. Currently, no studies that evaluate erectile dysfunction in the setting of IMRT treatment are available, although investigators have shown a reduction in penile-bulb dose with this technique.<sup>6</sup>

## Indications for IMRT in prostate cancer

Patients with localized disease have several excellent definitive treatment options, including radical prostatectomy, <sup>125</sup>I brachytherapy, and EBRT with 3D conformal therapy or IMRT. The volume of tissue irradiated may vary based on the stage, Gleason grade, and PSA value. For patients with low-risk features (T1 or T2 disease with PSA values < 10 ng/mL and a Gleason score of 6 or less), the radiation volume may be limited to the prostate only with a 1-cm margin because the probability of tumor extension beyond that area is low. For patients in an intermedi-

ate-risk group, the seminal vesicles are often included in the treatment volume. For patients with high-risk disease, the treatment of choice is EBRT, and the inclusion of pelvic lymph nodes in these patients remains controversial. Short-term (6 months) or long-term (2–3 years) androgen ablation is recommended in conjunction with EBRT in intermediate-risk (PSA value  $\geq$  10 ng/mL or Gleason score  $\geq$  7) or high-risk (locally advanced disease) patients due to an improvement in overall survival with the addition of hormonal therapy in these patients.<sup>7,8</sup>

## Summary

The standard of care for treatment of clinically localized prostate cancer with EBRT now requires a dose of at least 70 Gy to the prostate, and preferably higher. Doses upward of 78–80 Gy are difficult to achieve when using 3D conformal therapy, due to the unacceptable risk of side effects. IMRT allows the radiation oncologist to treat to a higher dose, which is proven

to improve biochemical relapse-free survival while minimizing the risk of late effects to normal tissues. Such an improvement in the therapeutic ratio may significantly increase the quality of life of patients with localized prostate cancer, whether they have low-risk or high-risk disease.

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**Conflicts of interest:** None disclosed.