

Current and Emerging Standards in Radiation Therapy for Prostate Cancer

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Abstract

Improved radiation technology has allowed physicians to precisely target and deliver radiation to the prostate. More precise techniques attempt to minimize dose to tissue surrounding the prostate and organs at risk such as the rectum, bowel, and bladder, as well as reduce costs and improve patient convenience. Radiotherapy for prostate cancer care continues to evolve with increasing evidence regarding more rapid fractionation schema. This review describes current and emerging standards in treatment, such as moderate hypofractionation, stereotactic body radiation therapy, proton beam radiotherapy, high-dose rate brachytherapy, and prostate-rectum hydrogel spacing.

Several topics are covered: 1) Moderate hypofractionation aims to decrease treatment length by several weeks, thereby saving healthcare costs, and has been demonstrated as being noninferior to standard fractionation in randomized controlled trials. 2) Although stereotactic body radiation therapy delivers radiotherapy at an accelerated rate with the use of more intensive prostate tracking and patient immobilization, studies report excellent outcomes. Moreover, this

technique is less expensive than standard intensity-modulated radiation therapy. 3) As proton beam radiotherapy continues to be rapidly adopted, further evidence is required to determine the relative efficacy and long-term benefit in prostate cancer compared with photon beam radiotherapy. 4) High-dose rate brachytherapy may be a safe and effective dose escalation technique, as either monotherapy or boost, and has many advantages such as optimized dosimetry and highly conformal dose distributions, though long-term prospective data are lacking. Lastly, 5) Prostate-rectum hydrogel spacing separates the prostate anteriorly from the rectum, remains a gel in Denonvilliers' space and then dissolves into liquid that is reabsorbed by the body.

Evidence is being generated to support more conformal dose escalation and hypofractionation with improved dosimetry compared with standard therapy. As research continues, these techniques remain promising and represent current and emerging standards in radiotherapy.

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Introduction

Prostate cancer radiotherapy continues to evolve. In the past several years, significant evidence has accumulated regarding the rapid delivery of external beam radiotherapy using larger doses of radiation per treatment. This radiation technique, known as moderate hypofractionation, has largely centered on the acceleration of treatment delivery over 4 to 6 weeks rather than the standard 8 to 9 weeks. Multiple large randomized trials support the efficacy and safety of moderate hypofractionation in comparison with standard radiation therapy. A more rapid form of treatment, known as stereotactic body radiotherapy (SBRT), has also accumulated evidence, though randomized studies are lacking.

In addition to moderate hypofractionation and SBRT, other emerging treatments for prostate cancer include proton beam radiotherapy, high-dose rate brachytherapy, and the use of a hydrogel spacer.

Moderate Hypofractionation

Standard radiation therapy for prostate cancer with external beam radiation typically involves 38 to 45 treatment fractions of 1.8 Gy to 2.0 Gy per treatment, for 8 to 9 weeks. Moderate hypofractionation aims to decrease the treatment length by several weeks, and to deliver 2.4 Gy to 4.0 Gy per fraction over 4 to 6 weeks.

Multiple randomized trials have recently reported^{1,3} (Table) the noninferiority of moderate hypofractionation compared with standard fractionation for the treatment of localized low- and intermediate-risk prostate cancer. These studies used 2.5 Gy to 3 Gy per fraction. Toxicity seemed to be equivalent, although the temporal patterns of toxicity were different. Temporal differences were expected given that moderate hypofractionation delivers radiotherapy faster. Bowel and bladder toxicity peaked earlier and also subsided earlier for moderate hypofractionation compared with standard fractionation.³ Similarly, Radiation

TABLE. Large Randomized Trials Comparing Moderate Hypofractionation and Standard Fractionation.

Trial, N	Conventional Dose	Hypofractionated Dose(s)	Median Follow-Up	Cancer Control Conclusions	Toxicity Comparison
PROFIT, ⁴ N = 1206	78 Gy	60 Gy, given in 3 Gy fractions daily	6 years	Moderate hypofractionation noninferior to standard	Overall, no significant differences
RTOG 0415, ¹ N = 1115	73.8 Gy	70 Gy, given in 2.5 Gy fractions daily	5.8 years	Moderate hypofractionation noninferior to standard	More grade 2 genitourinary and gastrointestinal late toxicity for moderate hypofractionation
CHHiP, ⁵ N = 3216	74 Gy	60 Gy, given in 3 Gy fractions daily and 57 Gy, given in 3 Gy fractions daily	5.2 years	Moderate hypofractionation given in 3 Gy in 20 fractions is noninferior to standard (3 Gy in 19 fractions is inferior)	Overall, no significant differences in toxicity
HYPRO, ⁴ N = 820	78 Gy	64.6 Gy, given in 3.4 Gy fractions, 3 fractions a week	5 years	Moderate hypofractionation not superior to standard	Late grade 3 or worse toxicity was significantly higher for moderate hypofractionation (P = .021)

Therapy Oncology Group (RTOG) 0415 examined hypofractionated 70 Gy in 28 fractions of 2.5 Gy versus conventional 73.4 Gy in 41 fractions of 1.8 Gy in patients treated for favorable-risk prostate cancer and reported equivalent biochemical control, albeit with higher late grade 2 gastrointestinal and genitourinary toxicity.¹

Notably, 1 study indicated nonsuperiority in terms of cancer control⁴ and worse toxicity⁵ for hypofractionated 64.6 Gy in 19 fractions of 3.4 Gy given 3 fractions per week. Therefore, if moderate hypofractionation is to be used, evidence supports 2.5 Gy × 28 fractions (RTOG 0415) or 3 Gy × 20 fractions (PROFIT and CHHiP). It is recommended that 3.4 Gy × 19 fractions should not be used.

Moderate hypofractionation has the potential to reduce the cost of prostate radiotherapy by reducing the number of treatments required. For example, in the United Kingdom (UK), moderate hypofractionation has the potential to reduce the number of fractions by 200,000 per year.³ Already, 19% of patients in the UK are undergoing moderate hypofractionation as it has become the standard of care. In the United States, for the typical radiation oncology practice that treats 75 prostate cancer patients per year, moderate hypofractionation could reduce technical revenue annually by up to \$678,070⁶ at a reduction of \$9040 per prostate cancer patient.

Stereotactic Body Radiation Therapy

SBRT involves more rigorous immobilization of the patient and tracking of the prostate. With improved technology, a smaller target margin around the prostate is required. Each SBRT treatment involves 6 Gy to 10 Gy and treatments are typically completed in 1 to 2 weeks. However, this extreme acceleration of radiotherapy has caused some radiation oncologists to recommend caution, given the unknown impact on normal tissue.⁷ Economically, SBRT is less expensive than standard intensity-modulated radiation therapy, with 1 estimate indicating a 35% reduction in cost,⁸

and it is more convenient as it often involves just 5 treatments.

Multiple studies have investigated SBRT for prostate cancer. These studies generally report excellent biochemical control of cancer, low rates of major toxicity,^{9,11} and excellent patient-reported outcomes.^{12,13} However, most studies investigating outcomes have follow-up of 5 years or less¹¹ and are noncomparative. The only known comparative study assembled a multi-institutional cohort and compared patient-reported outcomes for SBRT and for moderate hypofractionation.¹⁴ This study found that patients who underwent moderate hypofractionation were more likely to have minimally detectable declines in quality of life compared with those who underwent SBRT.

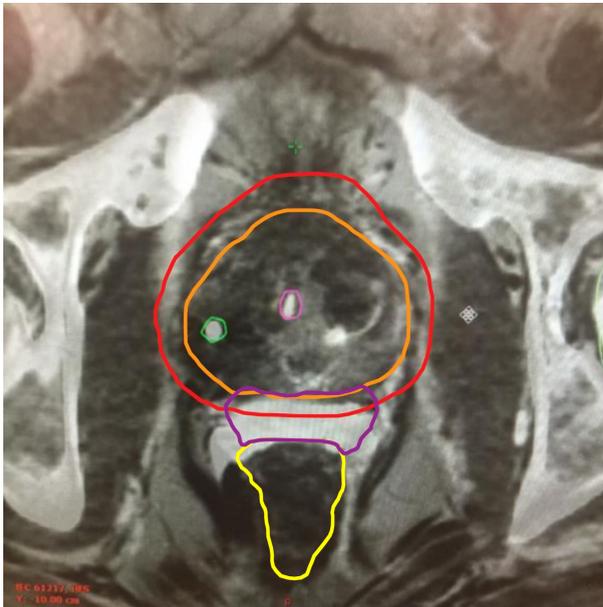
Given the relative equipoise between moderate hypofractionation and SBRT, a randomized trial is currently being designed by NRG Oncology comparing these 2 techniques.

Proton Beam Radiotherapy

Proton beam radiotherapy is being adopted rapidly. The United States has 25 proton centers as of May 2017, 12 are currently under construction or under development, and more are likely to be built in coming years. Proton radiation has grown exponentially over the past 2 decades, because of lowered capital costs (with the advent of superconducting synchrocyclotron technology), more physicians and physicists who have trained at proton centers, and patient perception of better outcomes.¹⁵ As practitioners become more familiar with the pros and cons of proton beam radiation, and as competition between regional hospitals and providers of radiation oncology increases, proton growth will likely continue to be exponential.¹⁵

For prostate cancer, the relative benefit of proton beam radiotherapy over modern image-guided radiotherapy is likely modest. The dosimetric advantages of proton beam radiotherapy largely involve the reduction of low and moderate doses of radiation to the rectum and bladder.¹⁶ Comparative studies that have involved Medicare claims¹⁷ or retrospective case-matched

FIGURE 1. Merged Axial T2 MRI and CT Simulation Image of a Patient With SpaceOAR Hydrogel and Calypso Beacons.



The image shows SpaceOAR hydrogel spacing the prostate anteriorly and rectum posteriorly. The merged MRI T2 sequence and CT simulation show the prostate (orange), planning treatment volume (red), hydrogel spacer volume (purple), and rectum contour (yellow). Green and magenta outline fiducial markers.

studies¹⁸ have not shown significant long-term benefit of the use of proton beam radiotherapy in the prevention of toxicity. Recent single-institutional data are promising,¹⁹ and a randomized study is ongoing (PARTIQoL; NCT01617161).

High-Dose Rate Brachytherapy

High dose rate (HDR) brachytherapy delivers radiotherapy through transperineal temporary catheters, delivering a dose greater than 12 Gy/hour using a technique known as remote

afterloading. HDR brachytherapy typically requires a brief hospitalization, and it delivers 1 to 5 fractions of treatment. The major advantage of HDR brachytherapy is the ability to design radiation treatment after placement of the catheters. Thus, any irregularity or deviation in catheter placement can be adjusted for using different radiation source dwell times and positions allowing for optimal conformal dose escalation.

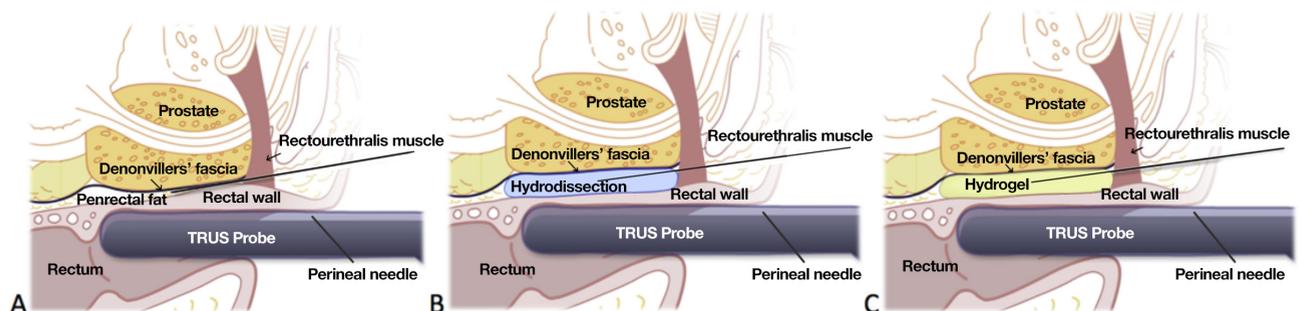
HDR brachytherapy was initially used as a “boost” treatment after regional external beam radiotherapy.²⁰ As transrectal ultrasound image guidance improved, HDR as monotherapy for localized disease was introduced with reproducible anatomy-based 3D dosimetry. HDR monotherapy has been associated with low rates of major toxicity and equivalent biochemical disease-free survival compared with permanent seed implant (otherwise known as low-dose rate brachytherapy),^{21,22} indicating its utility as a safe and effective treatment modality. However, given the significant potential toxicities associated with large doses of radiotherapy, continued longitudinal studies are necessary.

Prostate-Rectum Hydrogel Spacing

A recent innovation in the treatment of prostate cancer with radiotherapy involves the use of a hydrogel spacer (brand name SpaceOAR) to separate the prostate anteriorly from the rectum. The hydrogel is placed via a transperineal needle under ultrasound guidance, and it spaces the prostate anteriorly away from the rectum (Figures 1 and 2). The hydrogel remains in a gel form in the rectoprostatic space (Denonvilliers’ space) for about 12 to 13 weeks, and then it dissolves into liquid form and is resorbed by the body.

Supporting the use of hydrogel are multiple prospective studies showing greater dose escalation and hypofractionation with improved radiation dosimetry²³ as well as a 3- to 4-fold reduction in minimally important declines in bowel and urinary quality of life compared with standard therapy.^{24,25} A decision analysis model using real-world costs and 2016 costs of SpaceOAR conducted by Hutchinson et al found that although the

FIGURE 2. Insertion of Hydrogel Spacer.



(A) With transrectal ultrasound (TRUS) guidance, an 18-gauge injection needle is inserted perineally and carefully directed towards potential space between the Denonvilliers’ fascia and the anterior rectal wall. (B) The needle is advanced into the Denonvilliers’ space, hydrodissected using up to 25 ml injectable saline. (C) If hydrodissection is safely accomplished, the rectal spacer is placed in the space created.

rectal spacer resulted in an increase in cost of \$518 over 10 years with conventional radiotherapy, significant reduction in rectal toxicity is observed. It is possible that the increase in cost is balanced by reduced toxicity and improved quality of life. Moreover, for high-dose SBRT the effect was amplified with immediate savings of \$2332 due to higher rates of rectal toxicity with high-dose SBRT.²⁶ Thus, as increased emphasis is placed on reducing healthcare costs associated with delivery of radiotherapy or complications, SpaceOAR remains a viable option to achieve this goal. Despite the evidence supporting the cost-effectiveness of SpaceOAR implantation, obtaining reimbursement for placement of the SpaceOAR may be impacting rapid adoption of this potentially beneficial technology.

Conclusion

Several changes in standards are emerging in prostate radiotherapy. The field is moving towards more rapid fractionation schema in order to reduce the cost of radiotherapy as well as improve patient convenience. Strong evidence supports the equivalence of moderate hypofractionation and standard radiotherapy, and the evidence supporting the equivalence of SBRT and moderate hypofractionation are the subject of ongoing study. Proton beam and HDR brachytherapy are 2 additional areas emerging as options for prostate radiation, and evidence continues to be generated. Hydrogel rectal spacing is a useful tool that has been proven to improve prostate radiation dosimetry and patient outcomes.

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