



Dorothy Fox. *Village Music*. Acrylic on paper, 30" × 36".

*The benefits of more conformal radiation therapy for prostate cancer still need confirmation in randomized trials.*

## Emerging Technologies in Prostate Cancer Radiation Therapy: Improving the Therapeutic Window

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**Background:** Radiation therapy is a standard of care in the treatment of prostate cancer. Relatively recent advances in technologies in the delivery of radiation therapy are altering our current approach to treatment of prostate cancer.

**Methods:** This review discusses the results of retrospective, prospective, and randomized clinical trials that have evaluated clinical outcomes in prostate cancer treated with newer radiation therapy technologies.

**Results:** Randomized trials have demonstrated that higher doses of radiation therapy improve clinical outcomes but with increased toxicity to normal tissue. The introduction of more conformal radiation therapy techniques such as intensity-modulated radiation therapy, proton therapy, stereotactic body radiotherapy, and brachytherapy have allowed for further dose escalation with simultaneous reduction in toxicity. However, use of more conformal treatments requires a better understanding of prostate motion and the ability to track prostate movements in real time.

**Conclusions:** Technological advancements have improved radiation dose delivery to the prostate and have reduced normal tissue toxicity. Randomized trials are warranted to ultimately evaluate clinical benefit and outcomes.

### Introduction

Over the past 20 years, multiple randomized trials have demonstrated that the delivery of higher doses of radiation in the treatment of localized prostate cancer results in improved tumor control.<sup>1-6</sup> Standard radiation doses have been shown to be inferior to doses  $\geq 76$  Gy in terms of biochemical-free survival (bFS) and local control. However, conventional techniques used

for dose escalation have resulted in higher toxicities to pelvic organs, especially rectal and bladder morbidity.<sup>7-9</sup>

In the 1980s, improvements in radiation therapy planning software, as well as the introduction of computed tomography (CT)-based planning, led to the development of three-dimensional conformal radiation therapy (3D CRT). The use of 3D CRT in prostate cancer permitted further dose escalation strategies with improved sparing of normal tissue. For the first time, radiation oncologists were able to compare different treatment plans by evaluating the doses received to 3D volumes of tissue, a relationship portrayed in a dose-volume histogram. However, even with these improvements, available technology still limited the optimal escalation of prostate dose in the setting of adjacent normal bladder and rectal tissue.

By the mid-1990s, further developments of treatment planning software, coupled with the integration

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of multileaf collimators (ie, mechanized radiation beam shaping devices), allowed for the introduction of a more conformal treatment modality — intensity-modulated radiation therapy (IMRT). With this technique, the radiation beam is divided into individual beamlets so that differences in position of tumor vs normal tissue can be exploited with varying doses. Planning is facilitated by assigning maximal doses to the targets at risk and assigning minimized doses to normal tissue volumes. IMRT, which has arguably become the standard of care for external beam prostate radiation therapy, has permitted not only further prostate dose escalation beyond 81 Gy<sup>10-12</sup> but also a better understanding of the relationship between doses to specific volumes of organs at risk and their reduced morbidity.<sup>10,13,14</sup>

With the introduction of more conformal radiation therapy techniques, it became apparent that daily prostate movement could result in inaccuracies with treatment delivery, thus producing geographical target misses. Prostate motion necessitated investigations into different imaging modalities for daily prostate localization now known as image-guided radiation therapy (IGRT). Most recently, all of these technologies have culminated in the recent experimentation with short courses of very conformal radiation therapy employing extremely high radiation doses per individual treatment known as stereotactic body radiation therapy (SBRT). Additionally, the development of proton acceleration for clinical use, now increasingly available to the general population, has provided an alternative to standard x-ray treatments. Furthermore, improved imaging technologies have advanced the conformal application of internally applied prostate radiation used in brachytherapy.

This review summarizes the body of literature supporting the use of dose escalation in the treatment of prostate cancer and in the use of conformal treatments such as IMRT to reduce associated toxicities. Furthermore, we review current data supporting the use of imaging technologies currently employed to account for prostate motion. Lastly, we discuss alternative forms of radiation therapy, including brachytherapy, proton therapy, and the recent emergence of prostate cancer SBRT.

## The Effect of Dose Escalation on Clinical Outcomes

Several studies performed by the Radiation Therapy Oncology Group (RTOG) in the 1970s and 1980s established radiation doses in the range of 70 Gy as a standard.<sup>15</sup> At least three trials were performed using a simple four-field technique to examine the use of higher doses of radiation.<sup>7,9</sup> However, these studies found unacceptably high toxicities to the rectum and bladder. Chism et al<sup>7</sup> demonstrated late grade 2 genitourinary (GU) and gastrointestinal (GI) toxicities at 3 years to be 12% and 38%, respectively, with doses of 79 to 84 Gy.

Additionally, patterns of care analyses suggest that severe complication rates double when conventional techniques are used to treat at doses > 70 Gy.<sup>16</sup>

In the 1980s, the advent of more sophisticated radiation therapy treatment planning software permitted the introduction of 3D CRT. For prostate cancer, this technique generally employs a six- or seven-beam configuration in which each of the beams is shaped to conform to the shape of the prostate in what is known as “the beam’s eye view.” The goal of delivering higher dose to tumor while minimizing the dose to normal tissue was the driving force behind the development of 3D CRT. Seminal work performed by Pollack et al<sup>5</sup> at the M.D. Anderson Cancer Center culminated in one of the first randomized trials to utilize 3D CRT for the purposes of prostate radiation dose escalation. Their study evaluated 301 patients treated with 70 Gy vs those treated with 78 Gy using a 3D CRT boost. Kuban et al<sup>17</sup> recently reported 10-year outcomes from this study, demonstrating biochemical and clinical freedom from failure rates of 73% vs 50% favoring the 78-Gy arm. Several other randomized trials employing 3D CRT to escalate doses between 78 to 81 Gy compared with 68 Gy to 70 Gy have supported these results.<sup>1,5,6,18-20</sup>

Although enhancing biochemical control, the delivery of higher doses using 3D CRT for prostate cancer has not come without costs. Despite the use of a more conformal treatment, normal tissue toxicities, specifically rectal toxicity, have been found to be higher. The M.D. Anderson Cancer Center trial found that late grade 2 rectal toxicities significantly increased from 11% to 19% and late grade 3 toxicities increased from 1% to 7% with the use of 78 Gy compared with 70 Gy.<sup>17</sup> Dearnaley et al<sup>1</sup> found late grade 2 and 3 rectal toxicity to increase from 14% and 4% to 20% and 6% in patients randomized to 64 Gy vs 74 Gy. Furthermore, Zelefsky et al<sup>4</sup> reported that patients who were treated with 3D CRT at 75.6 or 81 Gy compared with those receiving 70.2 or 64.8 Gy had an increased late rectal toxicity of 17% vs 7% favoring lower doses. Though increases in rectal toxicity are evident with higher doses using a 3D CRT technique, whether there is an associated increase in GU toxicity is less clear. Dearnaley et al<sup>1</sup> demonstrated a significant increase in late grade 2 and 3 GU toxicity with use of 74 Gy. Moreover, Zelefsky et al<sup>4</sup> demonstrated a significantly higher rate of late grade 2 or higher GU toxicity of 15% vs 8% in patients who received doses > 75.6 Gy. However, several other randomized trials did not report a significant increase in late GU toxicity with increased doses using 3D CRT.<sup>1,5,21-24</sup>

## Intensity-Modulated Radiation Therapy

IMRT is a high-precision radiation delivery system that evolved as the next generation of 3D CRT. It improves the ability to conform the treatment volume to concave target shapes (Fig 1). The radiation dose is consistent

with the 3D shape of the target by controlling, or modulating, the intensity of the radiation beam. Central to this technique is the integration of multileaf collimators, which are composed of individual “leaves” of a high atomic numbered material, usually tungsten, that can move independently in and out of the path of the radiation beam in order to block it. With IMRT, the intensity of the radiation beam is modulated by the leaves of a multileaf collimator moving across the field dividing the beam into individual beamlets. The intensity of these beamlets can be varied to create sharp radiation dose gradients that can reduce doses to surrounding tissues.

IMRT has been demonstrated to reduce normal tissue toxicities despite the use of higher radiation doses in the treatment of prostate cancer. Zelefsky et al<sup>10</sup> published the initial study implementing the use of IMRT in prostate cancer. This study compared 132 nonrandomized patients treated to a dose of 81 Gy with either 3D CRT (n = 61) or IMRT (n = 171). They found a reduced number of GU toxicities and a significantly reduced number of GI toxicities in the patients treated with IMRT. Since that report, several studies using IMRT with doses ranging from 76 to 86.4 Gy have shown late grade 2 and 3 GI toxicity from 1.5% to 3% and < 1% to 3%, respectively.<sup>11,25,26</sup> Late grade 2 and 3 GU toxicity

ranged from 9% to 19% and 3% to 4%. Additionally, these decreases in late toxicity have translated into improved quality of life (QOL) outcomes. Lips et al<sup>27</sup> demonstrated that the QOL outcomes of patients treated with IMRT to 76 Gy are superior to those treated to 70 Gy using 3D CRT. These data have been further supported with evidence from Japan.<sup>28</sup>

In addition to reduced normal tissue toxicity, there are emerging data that the ability to escalate doses to the prostate with IMRT results in improved bFS. Vora et al<sup>29</sup> has recently reported on biochemical control and toxicity on 272 patients treated with 3D CRT to 68.4 Gy compared with 145 patients treated with IMRT to 75.6 Gy. The use of higher-dose IMRT resulted in a 14% improved bFS ( $P < .0001$ ) with no difference in toxicity despite the increased dose. Investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) published a large cohort study of 561 patients treated to 81 Gy with IMRT.<sup>11</sup> In this analysis, patients were stratified into low-, intermediate-, or high-risk groups based on prostate-specific antigen (PSA) level, Gleason score, and T stage. Using the American Society for Therapeutic Radiology and Oncology definition of PSA relapse, they reported that 8-year actuarial PSA relapse-free survival rates for patients in favorable, intermediate, and unfavorable risk groups were 85%, 76%, and 72%, respectively ( $P = .025$ ). More recently, the MSKCC group updated their dose escalation protocol by evaluating patients treated with Gy levels of 86.4, 81, 75.6, and 70.2 or less.<sup>30</sup> Although no differences in bFS were noted among low-risk patients for the various dose groups, significant improvements were observed with higher doses for patients with intermediate- and high-risk features. Specifically, for intermediate-risk patients, radiation dose was found to be an important predictor of improved PSA relapse-free survival ( $P < .0001$ ), particularly for doses  $> 75.6$  Gy. In high-risk patients, higher dose levels also were associated with improved biochemical outcomes. Five-year PSA relapse-free survival outcomes for patients who received 86.4, 81, 75.6, and  $\leq 70.2$  Gy were 71%, 66%, 61%, and 40%, respectively. The influence of dose level on improved distant metastatic disease-free survival was most apparent for patients who received 81 Gy or greater compared with those who received 75.6 Gy ( $P = .035$ ), whereas no significant differences were observed among the other dose levels.

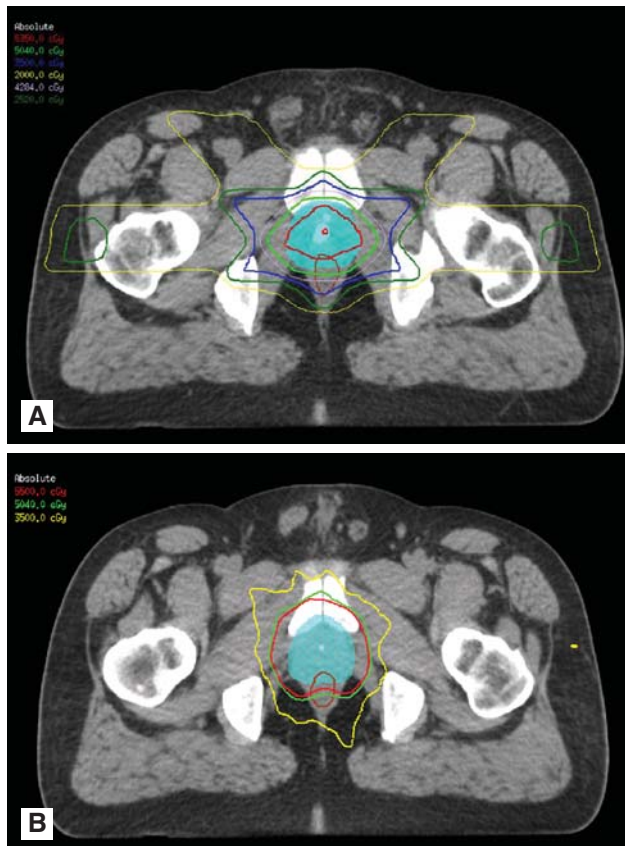


Fig 1A-B. — A 3D CRT (A) and IMRT (B) plan demonstrating much better dose conformity with IMRT. Red line equals 100% of dose, with blue line in Fig A and yellow line in Fig B equaling 63% of dose.

## Proton Therapy

Standard radiation therapy techniques such as 3D CRT and IMRT use accelerated photons to deliver radiation dose to the prostate. The development of particle accelerators resulted from the technological advancements in particle physics in the 1950s. This could accelerate heavier particles that could be employed for clinical use in the treatment of cancer. Among the first particles used for this purpose were protons. The Cyclotron Lab-

oratory at Harvard University began treating patients with protons in 1961 and treated approximately 9,000 patients before its closing in 2002 and subsequent replacement by the Francis H. Burr Proton Therapy Center at Massachusetts General Hospital. Proton therapy is an attractive alternative to photon therapy since the behavior of a proton beam has three distinct physical differences in its behavior as it interacts with tissue: (1) In contrast to photon beam, a single proton beam deposits very low amounts of dose as it enters the body, (2) the proton beam has a maximal peak dose delivery (known as a Bragg's peak) that can be defined at a specific depth in tissue by a user depending on the energy of the protons, and (3) there is no exit dose behind the peak of a proton beam. These characteristics offer a possible advantage over standard photon therapy in that theoretically, they make it possible to substantially reduce the dose delivered to normal tissue. Despite the theoretical advantages of proton therapy, it has the major disadvantage of cost. Building a hospital-based proton accelerator is prohibitively expensive. The cost of building a proton facility is estimated to be up to \$150 million (US). Construction costs at two recently built facilities at the University of Pennsylvania in Philadelphia and the University of Florida in Jacksonville were \$140 million and \$125 million, respectively. This expense equates into a price of treatment delivery for an individual prostate patient that is greater than twice that of a standard IMRT prostate treatment. This is supported by analysis by Konski et al,<sup>31</sup> who demonstrated that at 15 years, the expected mean costs of proton beam therapy and IMRT are \$63,511 and \$36,808, respectively, for a 70-year-old man and \$64,989 and \$39,355 for a 60-year-old man. The quality-adjusted survival is 8.54 and 8.12, respectively, and 9.91 and 9.45 quality-adjusted life-years.

Currently, the only tumors for which there is any evidence for the superiority of protons on the basis of clinical results are in the treatment of base of skull chordomas and ocular tumors.<sup>32</sup> Despite the fact that protons have been in clinical use for half a century, published clinical results for prostate cancer are limited. Investigators at Loma Linda Medical Center, who began treating prostate cancer patients with proton therapy in 1991, published their initial experience of 1,255 men.<sup>33</sup> In their study, 731 patients were treated with 45 Gy using photons followed by a 30-Gy equivalent (GyE) dose boost with protons, while the other 524 patients were treated with protons only to a dose of 74 GyE. Though the risk factors of these patients were heterogeneous, the majority of patients had pretreatment PSA levels of < 10 ng/mL and Gleason scores of ≤ 7. The 8-year bFS rate for the entire group was 73%. When stratified based on initial PSA, the 5-year bFS rates for PSA levels of < 4, 4–10, 10–20, and > 20 ng/mL were 90%, 84%, 65%, and 48%, respectively. Zietman et al<sup>5</sup> published

results from a randomized trial in which 393 patients were randomized to receive a proton boost of either 19.8 GyE or 28.8 GyE after receiving 50.4 Gy via traditional photons. The bFS rate at 5 years was 61.4% for conventional-dose therapy and 80.4% for high-dose therapy ( $P = .001$ ), a 49% reduction in the risk of failure. The advantage to high-dose therapy was observed in both the low-risk and the higher-risk subgroups. In the high-dose arm, grade 2 or higher acute GU and GI toxicity rates were 51% and 57%, respectively. Additionally, late grade 2 or higher GU and GI toxicity rates were 21% and 18% in the high-dose arm. A pilot protocol at the Massachusetts General Hospital and Loma Linda University Medical Center has been completed that delivered 82 GyE at 2 GyE per fraction, but the results have not yet been published. More importantly, currently there is no randomized data comparing IMRT and proton therapy for prostate cancer; thus, questions on whether the theoretical benefit results into any real clinical benefit — and whether the benefit justifies the cost — remain unanswered.

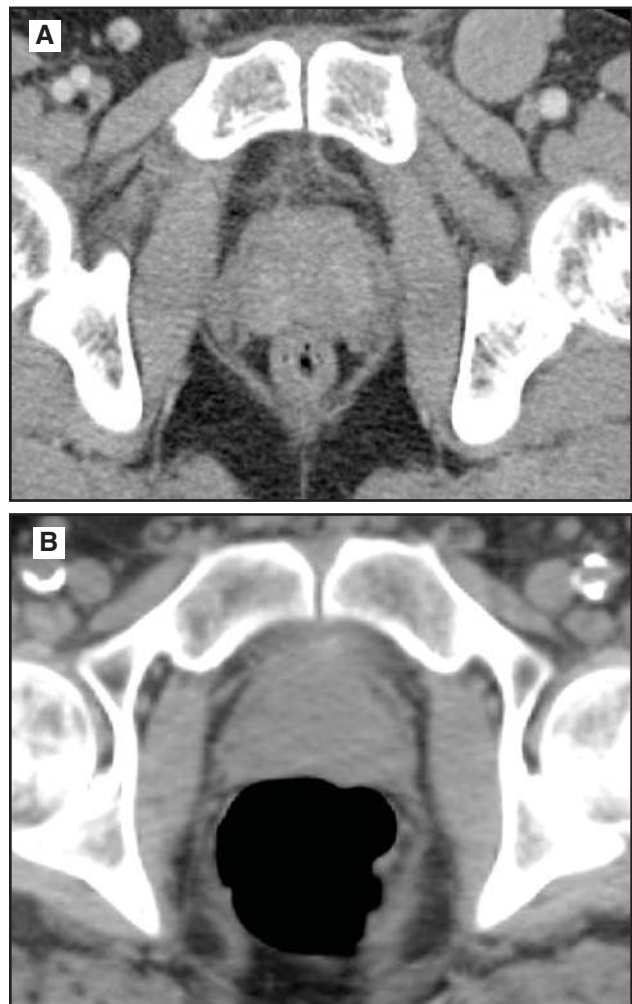


Fig 2A-B. — (A) Initial planning CT scan demonstrating empty rectum, and (B) CT just prior to treatment delivery demonstrating prostate displacement from gas in rectum.

## Prostate Motion and Image-Guided Radiation Therapy

Integration of more conformal radiation techniques with smaller radiation fields into the clinical setting has necessitated a better understanding of the location of the prostate during treatment. A multitude of imaging and localization techniques have been investigated to explore these issues. Although a typical margin of 0.4 cm to 1 cm is created around the prostate to generate a target for IMRT treatment, evidence has shown that the prostate can move as much as 1 to 2 cm on a day-to-day basis (Fig 2).<sup>34,35</sup> Cine-magnetic resonance imaging (cine-MRI) has demonstrated that this prostate motion is mostly due to varying degrees of rectal filling,<sup>36</sup> although bladder filling can contribute as well.<sup>37</sup> Thus, radiation oncologists must design a treatment strategy that will account for motion that occurs between daily treatments (interfraction motion) and that which occurs during the treatment itself (intrafraction motion). The fact that prostate motion could result in potential geographical misses and lead to worse clinical outcomes was demonstrated by de Crevoisier et al.<sup>38</sup> They found that patients who had a distended rectum at the time of treatment planning CT had > 30% worse PSA outcomes compared with those who did not.

In the era prior to advanced treatment technologies, large margins around the prostate were employed using skin markers and bony landmarks to align radiation fields. Studies using repeated CT scans or implantable markers showed that the prostate location poorly correlated with these landmarks.<sup>34,36,39,40</sup> It was quickly realized that other imaging modalities needed to be deployed during daily radiation delivery in what is now known as IGRT. One of the first imaging types used was abdominal ultrasound. Each day prior to treatment, a technologist performed an abdominal ultrasound to localize the prostate and make shifts in the patient's position in relation to the radiation field. However, this technique is user-dependent, and the ultrasound probe can displace the prostate, thus questioning its clinical accuracy.<sup>41-43</sup>

Because the use of abdominal ultrasound generated significant controversy regarding its accuracy, other imaging modalities have been explored. Metallic markers known as fiducials inserted interstitially into the prostate under rectal ultrasound have been used as a surrogate target for the prostate because of their easy visibility with x-ray imaging (Fig 3). Verification of the prostate position using fiducial markers, along with kilovoltage or megavoltage x-ray systems built into the treatment machine, has significantly improved the accuracy of prostate radiation therapy by reducing treatment setup and organ motion errors and eliminating user dependency.<sup>44,45</sup> To further improve the accuracy of treatment delivery, verification of fiducial marker location using CT was investigated since CT images

acquired in the treatment room allow definition of position and shape of the prostate relative to the surrounding normal tissue not visible on x-ray imaging. One of the first available in-room CT systems is known as CT on rails. This system requires that the patient be moved between the CT scanner and the treatment machine on a track while remaining in the treatment position. Though conceptually strong, CT on rails has been compared with fiducial markers imaged with x-rays. Significant disagreement was found between the two systems that contributed to the lag time between image acquisition.<sup>46</sup> To overcome this problem, work was done to create a CT system built into the treatment machine that does not require patient movement and decreases acquisition time, resulting in the development of cone beam CT (CBCT). CBCT of the treatment area can be obtained just prior to treatment delivery, and alignment can be performed on the prostate and surrounding tissue. However, several investigators have reported considerable inter-user variability with this method of anatomical alignment, and the use of fiducial markers with CBCT is recommended.<sup>47,48</sup>

Though the study of prostate positional variation between daily fractions has resulted in improved accuracy of radiation delivery to the prostate, the above techniques do not take into account intrafraction variations that can occur during the actual radiation deliv-

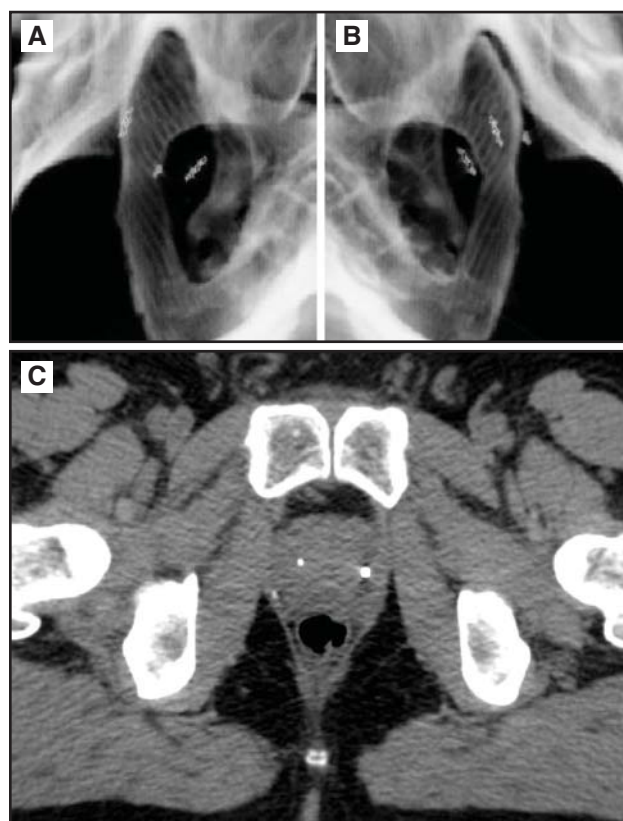


Fig 3A-C. — (A-B) Implantable fiducial markers as seen on orthogonal kV x-rays just prior to treatment, and (C) with kilovoltage x-ray systems built into the treatment machine.

ery. IMRT treatments to the prostate can take 10 to 25 minutes to deliver depending on the system used. Gas or stool that moves into the lower rectum during treatment delivery can potentially cause overdosing of the rectum and subsequent underdosing of the prostate.

The Calypso system (Calypso Medical Technologies, Inc; Seattle, WA) is a 4D radiation target positioning device that continuously monitors the location of three implanted electromagnetic beacon transponders at the rate of 10 Hz and permits 3D tracking. This system allows for continuous determination of prostate motion during the delivery of radiation in which treatment can be halted if the prostate moves outside of a set threshold distance for a predetermined period of time. Kupelian et al<sup>49</sup> were the first to report on the clinical use of this system in the context of a multi-institutional study for the treatment of prostate cancer. In the 41 patients evaluated, they found that continuous prostate motion was unpredictable. Prostate displacements of  $\geq 3$  and  $\geq 5$  mm for cumulative durations of at least 30 seconds were observed during 41% and 15% of treatments, respectively. Among individual patients, the number of treatments with prostate displacements of  $\geq 3$  and  $\geq 5$  mm ranged from 3% to 87% and 0% to 56%, respectively. This initial study demonstrated that prostate motion during treatment can be significant. Further investigation is needed to evaluate whether its active monitoring can result in improved outcomes.

## Interstitial Prostate Brachytherapy

Compared with external beam forms of radiation therapy, interstitial prostate brachytherapy (IPB), in skilled hands, represents the superior form of conformal radiation therapy permitting dose escalation beyond other current modalities. The major advantage of IPB over external beam approaches is that radiation is delivered internally, allowing for greater sparing of normal tissue and negating concerns of prostate motion. The growing popularity of prostate brachytherapy in the late 1980s and early 1990s was fueled by an evolution in transrectal ultrasonography, the development of a closed transperineal approach, and more sophisticated computer treatment planning software. Currently, there are two major approaches to prostate brachytherapy: the initial low-dose-rate (LDR) permanent radioactive seed implant and the temporary catheter-based high-dose-rate (HDR) implant. Both of these forms have been utilized alone as monotherapy and in combination with external beam radiation therapy (EBRT).

Although not all patients are appropriate candidates for brachytherapy, clear criteria to predict implant-related morbidity are not available. The American Brachytherapy Society currently recommends IPB monotherapy for patients with clinically staged T1-T2b disease, PSA level of  $< 10$  ng/mL, and Gleason score of  $\leq 6$ .<sup>50</sup> For patients with clinically staged T2c and high-

er disease or Gleason score  $\geq 7$  or PSA of  $> 10$  ng/mL, supplemental EBRT is recommended. However, an increasing body of literature reports that EBRT can be omitted in certain patient populations with high-quality implants.<sup>51-53</sup> Additionally, other relative contraindications include International Prostate Symptom Score (IPSS)  $> 15$ , prostate volume  $< 20$  mL or  $> 50$  mL, seminal vesicle invasion, and a tight pubic arch that could interfere with seed or catheter placement.<sup>50</sup>

Large prostate size is widely believed to be a relative contraindication for IPB due to technical concerns regarding pubic arch interference and concern regarding higher urinary morbidity. For these reasons, patients with prostate volumes greater than 50 mL are frequently counseled not to undergo IPB or be placed on cytoreductive hormonal therapy. However, contrary to this perception, there are data to support that large prostates can be implanted with acceptable morbidity.<sup>54,55</sup> Alternatively, reports have also demonstrated that prostates  $< 20$  mL can also be implanted with no increased urinary morbidity.<sup>54,56,57</sup> Also related to size, pubic arch interference may represent a technical issue, particularly in patients with a larger-sized prostate. However, with the use of extended lithotomy positioning and guiding needles around the arch, almost all patients can undergo implantation successfully.

Patients with urinary obstructive symptoms prior to implant are at a higher risk of postimplant urinary retention. However, this relationship is somewhat controversial. Terk et al<sup>58</sup> reported that preimplantation IPSS predicted postimplantation urinary retention. Conversely, with the use of prophylactic and prolonged alpha-blockers, Merrick et al<sup>57</sup> found no correlation with preimplant IPSS and urinary retention. Additionally, in a prospective study, Landis and Landis et al<sup>59</sup> found little correlation with preimplantation IPSS and either acute urinary retention or long-term urinary function.

## Low-Dose Rate Permanent Radioactive Seed IPB

In patients with low-risk features (Gleason score  $< 6$ , PSA  $< 10$  ng/mL, T1c/T2b), LDR IPB has resulted in high rates of biochemical control. Stock and Stone<sup>60</sup> found disease-specific survival to be 98% in patients with Gleason 6 score. In a prospective study, Khaksar et al<sup>61</sup> found a 96% bFS rate at 5 years for those patients with low-risk disease. Furthermore, Potters et al<sup>62</sup> evaluated 1,449 patients who underwent IPB and found a 12-year bFS rate of 89% among low-risk patients. The RTOG 98-05 prospective study performed at 27 institutions demonstrated that favorable results can be achieved among a multitude of users.<sup>63</sup> The 5-year bFS rate was 94%. However, physician skill with IPB is likely a more important factor than with other radiation modalities. In a review of 2,693 patients, Zelefsky et al<sup>64</sup> published an 8-year bFS rate of 93% in patients with quality

implants. Yet, in the same population with lesser-quality implants, the 8-year bFS rate was 76% ( $P = .001$ ), underscoring the importance of physician technical skill. Additionally, Grimm et al<sup>65</sup> reported on the issue of learning curve, demonstrating a significant difference in progression-free survival among patients implanted between 1986 to 1987 vs 1988 to 1990.

IPB in patients with intermediate- and high-risk disease is typically performed in combination with EBRT to a dose of 45 to 50.4 Gy. The reasons for this combined approach are to enhance the coverage to periprostatic tissue, to escalate dose to intraprostatic tumor, and to supplement inadequate tumor coverage from the implant. Intermediate- and high-risk patients treated with this approach have had favorable results. Critz et al<sup>66</sup> published their retrospective results on 689 intermediate- and high-risk patients. With a 7-year follow-up, they found a dFS rate of 88%. Similarly, long-term outcome data from Sylvester et al<sup>67</sup> showed a 15-year bFS rate of 80.3% for intermediate-risk patients and 67.8% for high-risk patients. Additionally, in a separate multi-institutional study of 179 patients, a bFS rate at 3 years was 79% among these risk groups combined.<sup>68</sup> Another multi-institutional study at six centers has been reported by Stone et al.<sup>69</sup> Among 5,889 patients, 1,078 had Gleason score 7 ( $n = 845$ ) or Gleason score 8–10 ( $n = 233$ ) prostate cancer. With a median follow-up of 46 months, the bFS rate was 83.7% for patients with Gleason score 7 and 68.7% for those with Gleason score 8–10. However, in those patients treated with a higher brachytherapy dose, the bFS rate was 89.5% for Gleason score 7 and 85.7% for Gleason score 8–10, paralleling dose escalation results found with EBRT. The beneficial role of escalating dose with IPB has been further validated with postimplant biopsies.<sup>70</sup>

Despite these excellent results with a combined approach, the usefulness of supplemental EBRT has come into question for intermediate-risk patients who have had favorable results with IPB alone. Pathological studies indicate that the radial extension of extraprostatic cancer is almost always 5 mm or less, which is within the coverage of a monotherapy IPB implant. Blasko et al<sup>51</sup> reported a 9-year bFS rate of 82% for patients treated with IPB as monotherapy. Additionally, Taira et al<sup>71</sup> demonstrated bFS, cause-specific survival (CSS), and overall survival (OS) rates of 96.4%, 100%, and 74%, respectively. Other reports have demonstrated bFS rates of 74% to 77% with IPB as monotherapy in intermediate-risk patients.<sup>52,53</sup>

### High-Dose-Rate IPB

HDR IPB was first introduced in 1986 at Kiel University in Germany. As opposed to LDR IPB, whereby radioactive seeds are permanently implanted into the prostate, HDR IPB involves the temporary transperineal placement of catheters into the prostate where a

radioactive iridium-192 source is moved in and out of each of the catheters over the course of 5 to 10 minutes. HDR IPB has several potential advantages over LDR IPB. HDR IPB does not have the any radiation safety issues associated with LDR IPB. Additionally, alterations in the position of the iridium source can overcome suboptimal intraoperative catheter placement. Also, it allows for potential increased dose to the periprostatic tissue and seminal vesicles with gross disease or at risk for microscopic spread. In addition, it permits dose escalation to areas of the prostate harboring tumor as well as easier reduction of dose to urethra and rectum.

As with LDR IPB, HDR IPB has been used alone as monotherapy for low-risk prostate patients and in combination with EBRT for intermediate- and high-risk patients. Because HDR IPB as monotherapy without supplemental EBRT did not emerge as a therapeutic option until the mid-1990s, long-term data are limited. However, like LDR IPB, when used as monotherapy for low-risk patients, results have been favorable thus far. Demanes et al<sup>72</sup> evaluated 298 patients treated with HDR IPB as monotherapy and found 5-year bFS and CSS rates of 94% and 100%, respectively. Similarly, 3-year results from the University of Utah of 209 low-risk patients showed a bFS and CSS of 99% and 100%.<sup>73</sup> Additionally, Mark et al<sup>74</sup> published 8-year results among 278 patients demonstrating a bFS rate of 88.5%. These promising findings warrant further investigation.

For patients with intermediate- and high-risk disease, HDR IPB is typically combined with supplemental EBRT and has been performed not only longer, but also on a greater scale than HDR IPB monotherapy. A retrospective analysis of three of the initial prospective studies performed at the Seattle Prostate Institute, William Beaumont Hospital, and Kiel University has been published involving 188 intermediate-risk patients and 359 high-risk patients.<sup>75</sup> The 5-year bFS and CSS rates for intermediate-risk patients were 88% and 99%, respectively. Likewise, for high-risk patients, bFS and CSS rates were 69% and 95%. Additionally, the California Endocurietherapy group found the 8-year bFS rates for 146 intermediate- and high-risk patients to be 87% and 69%, respectively.<sup>76</sup> Bachand et al<sup>77</sup> recently published their results on 153 patients treated in Quebec, of which 88% were either intermediate- or high-risk. Of the entire group, the 5-year bFS rate was 96%. Additionally, 94 of these patients consented to re-biopsy at 24 months after treatment with a negative biopsy rate of 92%. Unfortunately, patients were not stratified by risk group, so it is unclear if these data are biased by a disproportionate representation of intermediate-risk patients. Long-term results analyzing only high-risk patients have been published. Researchers at Kiel University found an 8-year bFS rate of 73% and a dFS rate of 82.6%.<sup>78</sup> Similarly, Swanson et al<sup>79</sup> evaluated 1,697 patients from three institutions and found a 10-year bFS and dFS rates of 67%

and 80%. These data likely represent the best clinical result of any modality for high-risk patients; however, randomized studies are needed.

## Stereotactic Body Radiotherapy

Stereotactic radiosurgery is the delivery of a very high dose of radiation in a single treatment referred to as a fraction. This is essentially a form of ablative therapy. The first widely accepted clinical application of stereotactic radiosurgery was in the brain using the Gamma Knife system (Elekta AB, Stockholm, Sweden) and was developed by Lars Leksell, MD, at the Karolinska Institute. The Gamma Knife system uses 201 Cobalt-60 sources located in a ring around a central treatment point (“isocenter”) and is capable of accuracies of greater than 1 millimeter. The Gamma Knife system requires a head frame bolted onto the skull of the patient and is capable of treating only cranial tumors. In order to prevent significant toxicity, radiosurgery can treat only small volumes of disease.

In the 1990s, technology advanced to allow the application of intracranial stereotactic techniques to body sites with the integration of strategies in order to define and minimize respiratory motion. With the advent of 4D CT scans, radiation oncologists had the ability to measure the motion of the tumor through all phases of a patient’s breathing cycle. Body immobilization cradles were designed to keep the patient in the same position throughout treatment. These advances led investigators to begin pioneering SBRT, which is defined as the precise delivery of high-dose extracranial radiation in 1 to 5 treatment fractions. Timmerman et al<sup>80</sup> demonstrated that SBRT could be safely used in sites outside of the brain.

The concept of treating prostate cancer with higher doses per fraction over a shorter course is not new. Kupelian et al<sup>81</sup> reported on delivering 70 Gy in 2.5 Gy fractions using IMRT with acceptable toxicity. More interesting, for over 22 years beginning in 1962, Lloyd-Davies et al<sup>82</sup> described treating patients without the benefit of CT-based planning to a dose of 36 Gy in 6 fractions over 6 weeks. They demonstrated long-term safety and possible effectiveness, the latter being difficult to assess given the lack of modern staging and risk stratification. Regardless, this has generated a significant interest in SBRT for the treatment of low- to intermediate-risk prostate cancer, given the abbreviated treatment time without the invasiveness of brachytherapy.

To date, only two reports evaluating SBRT in prostate cancer are available. The first, from Madsen et al<sup>83</sup> at the Virginia Mason Medical Center, involved the treatment of 40 patients to a dose of 33.5 Gy at 6.7 Gy per fraction, equivalent to a standard dose of 78 Gy. They used a modified standard treatment machine with fiducial marker-based IGRT. With a median follow-up of 41 months, they reported biochemical freedom from

relapse of 90% based on one definition of PSA failure. Late grade 2 and 3 GU and GI toxicity rates were 20% and 7.5%, respectively. King et al<sup>84</sup> from Stanford University recently published their initial results from a phase II trial evaluating 41 patients treated with the CyberKnife System (Accuray Inc, Sunnyvale, CA) to a dose of 36.25 Gy at 7.25 Gy per fraction, now with a median follow-up of 33 months. They reported no PSA failures, with 78% of patients achieving a PSA nadir of  $\leq 4$  ng/mL. Late grade 2 and 3 GU and GI toxicity rates were 29% and 15%, respectively, with no grade 3 GI toxicity. Using the International Prostate Symptom Score (IPSS) to assess GU toxicity and the Expanded Prostate Cancer Index Composite (EPIC) to assess GI toxicity, they noted GU and GI QOL scores of 2 or 3 (ie, small problem) to be 8% and 45%, respectively, and 9% for a GI QOL score of 4 (ie, moderate problem).

These initial SBRT results are promising, with excellent PSA control rates. However, given the need for 8- to 10-year follow-up with prostate cancer and the relatively small number of patients in these two studies, further investigation and longer follow-up are needed. Additionally, large doses per fraction have the propensity to result in late toxicity that may take years to arise and is suggested by the rate of over 50% small to moderate GI problems from the Stanford QOL assessments. For these reasons, prostate SBRT should not yet be considered a standard of care. Because of the increasing interest in prostate cancer SBRT without significant supportive evidence, the American Society for Therapeutic Radiology and Oncology recently released the following statement regarding its use:

*“There is not sufficient or mature data to demonstrate equivalency to existing standard treatment modalities and, in our view, SBRT for prostate cancer patients does not represent a ‘standard of care.’ SBRT for early-stage, low-intermediate risk prostate cancer should be further tested within the context of appropriately designed clinical trials.”*

## Conclusions

Significant technological advances have been made in the field of radiation oncology over the past 20 years. The development of more conformal treatments, initially with 3D CRT followed by IMRT, has resulted in reduced normal tissue toxicity and allowed for safe dose escalation up to 86.5 Gy. Currently, the optimal radiation dose needed for maximal tumor control remains unknown. However, multiple randomized trials have shown that doses of 76 Gy or greater are superior to the previous standard dose of 70 Gy. While recent reports suggest that different risk strata may require different doses with higher-risk cancers requiring higher doses, randomized trials are needed.

In the last decade, the development of better IGRT technologies have improved our understanding of day-to-day positional variations as well as variations that can occur during treatment delivery. Further adoption of IGRT techniques will likely result in a reduction of treatment toxicity and expansion in the ability to further escalate dose. Additionally, prostate brachytherapy represents a minimally invasive procedure that is an alternative to the typical 8-week course of EBRT. Both LDR and HDR IPB have better rectal sparing and, when combined with EBRT, may represent a superior form of therapy for intermediate- and high-risk patients, although further randomized trials are needed. Lastly, the recent introduction of SBRT for the treatment of low- to intermediate-risk prostate cancer presents an attractive alternative to standard radiation treatments. Further study is required to delineate long-term toxicity and efficacy before it can be accepted as another potential standard of care.

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