Radiation Therapy Modalities in Prostate Cancer

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Abstract
Definitive radiation therapy is the preferred treatment for many men with prostate cancer. Several modalities are used for radiation treatment delivery, including 3-dimensional conformal radiation therapy, intensity-modulated radiation therapy, proton beam therapy, stereotactic body radiation therapy, high-dose-rate prostate brachytherapy, and low-dose-rate prostate brachytherapy. This article reviews technologic advances that have enhanced radiation delivery and describes contemporary radiation treatment techniques for prostate cancer. (JNCCN 2013;11:414–421)

Definitive radiation therapy offers a curative treatment for localized prostate cancer without major surgery and is the preferred treatment for many men. Additionally, men with adverse pathologic features after prostatectomy benefit from the administration of postoperative radiation therapy. The 2 major categories of radiation therapy for prostate cancer are external-beam radiation therapy (EBRT), in which radiation beams generated by a machine outside the body are directed toward the cancer cells, and brachytherapy, which involves the placement of radioactive material inside the body near the cancer cells. The goal of radiation therapy is to deliver a cancer-sterilizing radiation dose to the treatment target, which may include the prostate, seminal vesicles, prostate resection bed, and/or pelvic lymph nodes, while limiting dose to surrounding normal tissue, including bladder, bowel, erectile tissue, and the femoral heads. Minimizing dose to surrounding normal tissue is critical, because the risk of toxicity from radiation therapy is a direct consequence of the amount of inadvertent radiation dose delivered to these tissues.

Technologic advances over the past 3 decades have dramatically improved radiation therapy delivery. The development of increasingly conformal EBRT techniques has decreased radiation dose to surrounding normal tissue, and the implementation of image-guided radiation therapy (IGRT) has improved treatment accuracy. These refinements permit the escalation of radiation dose without parallel increases in toxicity, and have permitted exploration of altered radiation therapy fractionation schedules, such as hypofractionated treatment regimens, which shorten the overall duration of treatment. This article reviews these advances and discusses contemporary radiation treatment modalities for prostate cancer.

External-Beam Radiation Therapy
Dose-escalated radiotherapy is the treatment standard for men receiving definitive EBRT for prostate cancer, with current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer recommending delivery of 75.6 to 81.0 Gy total cumulative dose using conventional 1.8- to 2.0-Gy daily fractions or treatments (to view the most recent version of these guidelines, visit NCCN.org). This recommendation is supported by multiple randomized trials showing improved cancer control with dose-escalation compared with the more historic standard dose of radiotherapy (≤70 Gy). Safe delivery of dose-escalated radiotherapy has been made possible by the development of treatment techniques that tailor high-dose radiation...
to the treatment target and minimize dose to adjacent organs, and the development of IGRT, which improves treatment localization accuracy.

**EBRT Techniques**

Improved visualization of patient anatomy has enhanced radiation treatment delivery. Before the 1990s, EBRT fields for prostate cancer were designed based on pelvic bony landmarks, with contrast in the bladder and rectum for visualization on plain film radiography. CT-based 3-dimensional conformal radiation therapy (3DCRT) emerged in the 1990s, revolutionizing EBRT planning. CT imaging enabled accurate visualization of the prostate and adjacent organs, resulting in better definition of the treatment target and smaller treatment fields that delivered less radiation to adjacent organs. In 3DCRT, CT imaging is used to design static radiation treatment fields (usually 4–6) that enter the patient from selected angles to converge on the prostate. The treatment fields can be weighted so that more or less radiation enters from a particular angle.

Intensity-modulated radiation therapy (IMRT) is an advanced 3DCRT technique widely adopted for prostate cancer treatment in the 2000s. IMRT uses the same CT-based imaging to define the prostate treatment target and the adjacent organs; however, it uses a different delivery technique to shape the radiation field. While the radiation is being delivered, mobile metal blocks (called multileaf collimators [MLCs]) move in and out of the radiation beam to modulate the intensity of the dose administered to an area through the radiation portal, resulting in a planned heterogeneous dose distribution within the beam path. To spare nontarget tissue (such as bowel or bladder), part of the prostate may be underdosed by a single beam. This underdosing is compensated by a different beam from a different angle. The convergence of multiple IMRT beams creates high conformity around the prostate with sharp radiation dose gradients compared with 3DCRT, thereby decreasing high dose to nontarget organs.

Although IMRT has been widely adopted, it has never been directly compared with 3DCRT for the treatment of prostate cancer in a randomized trial. Comparisons of IMRT and 3DCRT treatment plans created for individual patients show that IMRT decreases dose to the rectum and bladder during prostate radiotherapy and also decreases dose to the bowel during radiation therapy directed at both the prostate and pelvic lymph nodes. Retrospective series show that this decrease in dose to surrounding structures is associated with lower acute and late genitourinary and gastrointestinal side effects. The use of IMRT for men treated with high-dose radiotherapy is supported by a recent analysis of men treated to a total dose of 79.2 Gy on the RTOG 0126 trial, in which a prospective toxicity evaluation that found that men treated with IMRT had fewer acute genitourinary and gastrointestinal side effects and fewer late gastrointestinal side effects than those who received 3DCRT. Additionally, a recent SEER-Medicare analysis of medical claims data found that men treated with IMRT had a lower risk of a hip fracture diagnosis and diagnoses associated with gastrointestinal morbidity, and were less likely to receive procedures/medicines associated with additional cancer therapy than men treated with 3DCRT. However, men treated with IMRT were also more likely to be diagnosed with erectile dysfunction. As Medicare claims data do not contain any meaningful information about radiation dose, no conclusions can be derived from these data, and the findings cannot be considered conclusive, but rather hypothesis-generating. Although IMRT may decrease the side effects of treatment, IMRT is more complex than 3DCRT, and therefore requires more resources for treatment planning, quality assurance, and acquisition of IMRT-capable treatment equipment and software.

IMRT is the most common technique currently used to deliver EBRT and can be delivered using various treatment platforms, some of which are listed in Table 1. Several brand names are marketed as distinct platforms, whereas others are a variation on a theme, namely that radiation intensity is modulated and delivered at discrete angles or as arcs around the body. Intensity-modulated arc therapy (IMAT) is IMRT delivery as arcs around the body while MLCs are moving. Volumetric-modulated arc therapy (VMAT) is IMAT but with enhanced delivery control systems and treatment planning tools. Delivery of dose across continuous arcs decreases time required for treatment, so men spend less time on the treatment table. Considering that most men are instructed to have a full bladder for treatment, the reduced treatment time using VMAT may reduce the time patients must maintain a full bladder. Furthermore, because treatment time is shorter, more men can be treated on a machine in...
a fixed period, thereby increasing treatment efficiency and machine capacity. Therefore, VMAT is gaining popularity as a radiation modality. Additionally, compared with static-field IMRT, VMAT delivers a more conformal dose distribution (Figure 1).

Proton beam therapy (PBT) is increasingly being used for the treatment of prostate cancer. PBT uses accelerated protons, generated in a cyclotron or synchrotron, to administer radiation dose. Protons have physical properties that are distinct from the high-energy x-rays (photons) generated in linear accelerators for IMRT; the different properties result in different interactions with the tissue, and thus deposit radiation dose differently. Figure 2 illustrates the differences in how proton and photons deposit radiation dose as they travel through tissue. Radiation dose deposited where the beam enters the tissue is called an entrance dose, and where the beam exits is called an exit dose. Photons deposit the highest dose a few centimeters into tissue, followed by a linear decline in dose with depth. Multiple photon beams are required to deliver the desired dose to the target and minimize dose elsewhere. In contrast, protons deposit most of their dose over a discrete area, called the Bragg peak. Multiple Bragg peaks are stacked or spread across the target to deliver the desired dose. Although protons deposit some entrance dose before the treatment target, this dose is much lower than that deposited by photons; additionally, protons have virtually no exit dose after the target compared with photons. Because of these properties, PBT minimizes radiation dose to nontarget organs during prostate cancer treatment, as demonstrated by comparisons of PBT and IMRT prostate treatment plans created for individual patients (Figure 1).

The appeal of PBT is the decrease in unnecessary radiation dose, which may reduce acute and late treatment toxicity. The safety and efficacy of PBT are supported by multiple publications reporting outcomes of men treated with PBT for prostate cancer. However, use of PBT for prostate cancer is controversial, with opponents calling for level I evidence showing reduced side effects and equivalent cancer control to support routine use. Currently, no high-quality comparative data show superior outcome of any EBRT modality over another with respect to outcome or toxicity. Although no randomized trial has directly compared EBRT delivery techniques for prostate cancer, and the necessity/feasibility of such a trial is debatable, level I evidence will be available in the future. A multi-institutional randomized trial compared IMRT versus PBT for the definitive treatment of early-stage prostate cancer was recently activated (ClinicalTrials.gov identifier: NCT01617161).

Analogous to the evolution of IMRT from 3DCRT, intensity-modulated proton therapy (IMPT) uses active scanning proton beams to modulate the intensity of the radiation dose, further improving dose conformity around the target. IMPT is currently in development.

### Image-Guided Radiation Therapy

Appropriate alignment of the radiation path with the prostate is crucial to ensure radiation is delivered accurately. Image-guided radiation therapy (IGRT) involves the use of imaging to ensure the radiation beams are correctly aligned with the tumor. IGRT can be performed with external beam radiation therapy (EBRT) or brachytherapy. The advantages of IGRT include improved accuracy, reduced toxicity, and increased treatment efficiency. IGRT is an active area of research and development, with ongoing efforts to improve the technology and its clinical applications.
to the target while avoiding adjacent organs. If alignment is off, the radiation can fail to treat the prostate cancer and can deliver a potentially harmful dose to the adjacent healthy tissue (Figure 3). Historically, men were aligned using skin tattoos and calibrated in-room lasers. However, prostate orientation relative to skin tattoos varies from day-to-day because of prostate movement with bladder and bowel filling, and is clearly less accurate for heavier patients. To encompass the possible range of prostate positions with skin tattoo alignment, larger radiation treatment fields that encompassed more adjacent normal tissue were used. IGRT is an important advancement that has improved the accuracy of radiation delivery. IGRT involves using imaging techniques to align the radiation beams with the prostate to within a few millimeters just before treatment. With the improved positioning accuracy, smaller treatment fields can be used, which decreases the dose to adjacent normal tissues. Various imaging modalities are used for IGRT, including kilovoltage x-rays of fiducial markers placed in the prostate, CT imaging of the prostate, ultrasound of the prostate-bladder interface, and radiofrequency tracking devices (small intraprostatic transponders). Endorectal balloons are also commonly used to stabilize the prostate. A retrospective study that compared men treated with and without IGRT suggests that the improved accuracy of therapeutic radiation dose delivery to the prostate using IGRT also improves prostate cancer control. Current NCCN Guidelines (to view the most recent version of these guidelines, visit NCCN.org) state that IGRT is required for men who receive EBRT prescribed to 78 Gy or more.

Hypofractionation
Historically, the total dose of EBRT needed to effectively treat prostate cancer cannot be safely delivered in a single treatment. Instead, the radiation is divided into smaller doses of 1.8 to 2.0 Gy delivered Monday through Friday over 7 to 9 weeks in standard fractionation regimens. Treatments are delivered in an outpatient clinic, sessions usually last only 15 to 20 minutes, and men can continue to work during treatment. However, coming in every weekday for 7 to 9 weeks can be inconvenient and is often a barrier to receiving EBRT, especially for men who live far from a treatment facility.
Hypofractionated treatment regimens shorten the duration of EBRT through decreasing the total number of treatments and using a dose greater than 2 Gy for each treatment. Radiobiologic studies indicate the dose-response of prostate cancer is distinct from that of the rectal mucosa.\textsuperscript{25,26} This difference in sensitivity to radiation fraction size suggests that appropriately designed treatment schedules using larger doses per fraction may improve prostate cancer cure rates without a parallel increase in toxicity.\textsuperscript{27} Preliminary results of prospective randomized trials using various hypofractionated regimens support comparable biochemical control and morbidity compared with standard fractionation schedules.\textsuperscript{28–33}

Stereotactic body radiation therapy (SBRT) is a form of hypofractionation that involves delivering a high dose of focused radiation using multiple beam arrangements or arcs and special immobilization equipment. SBRT is typically delivered in just 5 treatments or less. Because of the high dose delivered with each treatment (up to ≈10 Gy), IGRT is an essential component of SBRT. In a typical SBRT plan, multiple static beams or rotational fields of varying degrees of complexity are used with or without beam-intensity modulation. Results with SBRT in limited numbers of patients with low-risk prostate cancer suggest that this approach is feasible, with comparable efficacy and safety to other forms of radiation therapy.\textsuperscript{34–37} Long-term results are needed before the widespread implementation of hypofractionated treatment regimens.

**Brachytherapy**

As a simple function of radiation physics, brachytherapy is the most conformal method of radiation delivery with the least amount of normal tissue exposure. Prostate brachytherapy involves the placement of radioactive sources into the prostate gland to deliver radiation directly to the prostate. Because radiation dose is inversely and exponentially related to the distance away from the radiation source, radiation dose to surrounding bladder, rectum, and connective tissue is minimized via this modality. Prostate brachytherapy is more convenient treatment option for patients compared with EBRT (ie, the procedure can be completed in a single outpatient visit). The comparative disadvantages of brachytherapy include the inherent dependence on practitioner skill level, short-term prostate edema related to multiple needles placed into the prostate for the delivery of radiation sources, the need for spinal or general anesthesia, and the concern that the sharp dose gradient provided by brachytherapy may undertreat cancer spread beyond the planned treatment area.\textsuperscript{38} Because of concerns about undertreatment, brachytherapy is often combined with EBRT and/or androgen deprivation in men with intermediate or high risk of extraprostatic spread.\textsuperscript{39,40} Prostate brachytherapy can be delivered through permanent low-dose-rate (LDR) radiation seeds or a temporary high-dose-rate (HDR) radiation source.

**LDR Brachytherapy**

During LDR brachytherapy, radioactive seeds are permanently implanted into the prostate gland through the perineum (space between the rectum and scrotum) according to a computerized treat-
ment plan (Figure 4). The prescribed radiation dose is emitted over several months until the seeds become inert. Currently, 3 isotopes are used routinely for LDR prostate brachytherapy: iodine-125, palladium-103, and cesium-131. LDR brachytherapy has similar efficacy as surgery in the treatment of low-risk prostate cancer, and may allow for improved quality of life after treatment.\footnote{41,42} LDR brachytherapy is indicated for treatment of low-risk prostate cancer and can also be used in combination with EBRT in men with intermediate- or high-risk prostate cancer.\footnote{43,44}

**HDR Brachytherapy**

To deliver HDR brachytherapy, transperineal catheters are inserted into the prostate through a template that is fixed to the perineum. A radioactive source (iridium-192) is then inserted temporarily through the catheters via a computerized system for a predefined period at several positions within each catheter. The amount of time the radioactive source dwells in each position is based on the treatment plan for each patient, but the actual treatment is typically delivered in a few minutes. Radiation treatment planning software is used to optimize the dwell times of the radioactive source to produce the desired dose distribution. Although early results using HDR brachytherapy monotherapy seem promising,\footnote{45} HDR brachytherapy has historically been delivered in combination with EBRT.

Several factors must be considered before using either LDR or HDR brachytherapy, because not all patients are suitable candidates for this modality. Patients with large prostates or symptoms of bladder outlet obstruction are at greater risk of urinary retention after brachytherapy.\footnote{46,47} The relationship between the prostate and the pelvic bones is also important for appropriate patient selection, because the pubic ramus and/or ischium bones may prevent proper placement.

**Conclusions**

Contemporary radiation therapy is a safe, efficacious, and commonly applied treatment for prostate cancer. Advancements in radiation treatment planning and delivery have improved treatment accuracy and decreased radiation dose to surrounding normal tissues, thereby decreasing the side effects of treatment. These developments have permitted radiation dose escalation without a parallel increase in toxicity. Further refinements of IGRT, IMRT, PBT, hypofractionation, SBRT, and prostate brachytherapy should focus on comparative outcomes between modalities and continue to enhance the therapeutic ratio for men with prostate cancer.

**References**


