Radiation therapy is a well-established treatment option for patients with localized and locally advanced prostate adenocarcinoma. External beam radiation therapy (EBRT) has been the traditional method for delivering radiation treatments to patients. Technologic advancements have resulted in dramatic changes in planning and delivery techniques over the past 10 to 15 years from conventional radiation therapy to 3-dimensional conformal techniques (3-DCRT) to intensity-modulated radiation therapy (IMRT). Improvements in imaging and radiation delivery techniques have allowed continued escalation of radiation doses without increased morbidity. Interstitial brachytherapy (aka, radioactive implants) also has emerged as a highly effective radiation treatment option for select patients with localized prostate cancer. This method typically involves the permanent implantation of radioactive seed directly into the prostate; however, newer techniques are using temporary high-dose rate sources to deliver local radiation dose.

**BACKGROUND AND MECHANISM OF ACTION**

Ionizing radiation kills cancer cells by a variety of mechanisms, but the most important mechanism involves the interaction of ionizing radiation with water molecules to form free radicals. These free radicals subsequently cause irreparable double DNA strand breaks resulting in chromosomal aberrations and reproductive cell death. Apoptotic cell death also occurs after radiation but is varied in prostate adenocarcinomas. Absorbed radiation dose is measured in gray (Gy) or centi-gray (100 cGy = 1 Gy) and represents energy (in joules) absorbed per unit mass (in kilograms). Radiation is usually delivered in multiple smaller daily doses or fractions. The basic purpose of fractionating radiation dose is to maximize tumor cell kill while allowing normal tissue to repair between fractions. A typical prostate radiation prescription may read as 1.8 Gy per fraction × 40 fractions for a total dose of 72 Gy.
External beam radiation for prostate cancer typically involves the use of high-energy photons or x-rays, although other forms of radiation such as neutrons and protons have been used in specialized centers. The clinical target volume (CTV) is usually defined as the entire prostate (including any extraprostatic tumor extension) with some portion of the seminal vesicles. Because of daily variability in patient setup and potential prostate positional changes secondary to variations in rectal and bladder filling, a margin is added to the CTV to ensure target coverage. This larger volume is known as the planning target volume (PTV). A sufficient PTV margin is needed to make certain that the tumor is covered, but increasing this margin also increases the amount of normal tissue in the radiation field, which may result in increased toxicity. The surrounding normal tissue (ie, rectum and bladder) also limits the maximum dose that can be delivered to the tumor without significant morbidity.

**CONVENTIONAL, 3-DIMENSIONAL CONFORMAL, AND INTENSITY-MODULATED RADIATION THERAPY**

Conventional radiotherapy, 3-DCRT, and IMRT are often described as different types of radiation when in fact they all use high energy x-rays delivered to a target. The main difference among these types of radiation involves the method of planning the radiation delivery. Conventional radiotherapy planning relies on 2-D fluoroscopic images to design the radiation fields or ports. For soft tissue targets such as the prostate, correlative bony anatomy is used to guide the field borders and block design. Contrast in the rectum or bladder may be used to delineate these structures and approximate the position of the prostate. Multiple beam arrangements are used to maximize the dose to the target and minimize dose to normal tissue. A typical set of beam arrangements would include an anterior, posterior, right lateral, and left lateral field (ie, four-field box technique) (Fig. 1). Conventional techniques are relatively easy to plan but are considered antiquated for prostate radiation therapy for the
following reasons: It does not allow direct visualization of 3-D pelvic anatomy, large treatment margins are needed to ensure adequate dosimetric coverage, the resulting total dose is limited, and radiation dose to the target and normal tissue is not actually visualized. The limitations of conventional radiation therapy, especially overdosing the rectum, have generally limited the doses to 70 Gy or less for prostate cancer.

The incorporation of computed tomography (CT) into radiation treatment planning was a major advancement in prostate cancer radiotherapy. Pelvic anatomy can be contoured or outlined on a slice-by-slice basis and subsequently reformatted into a 3-D volumetric image. These 3-D images can be used to design multiple customized fields with beam’s-eye-views that closely conform to the target while minimizing dose to surrounding normal tissues. Since CT-based target and normal tissue delineation is more accurate, smaller treatment margins can be used and this in turn allows the delivery of higher radiation doses. Another component of 3D-conformal radiotherapy is the generation of volumetric radiation dose maps (ie, isodose distributions) within the patient. These isodose maps provide a more detailed and precise estimate of the actual dose to specific tissues and also provide the basis for the calculation of dose-volume histograms (Fig. 2). Dose-volume histograms display how much radiation is being delivered to a specific volume of tissue and provide a quantitative evaluation of target coverage as well as dose to normal tissues (eg, rectum). These dose-volume metrics have been correlated with subsequent

![Dose-volume histogram](image)
post-treatment outcomes and toxicities. Because 3-DCRT makes it easier to plan with multiple fields (eg, six to eight intersecting fields), the dose conformality around the target can be further improved with relatively sharp dose fall off beyond the target volume. Three-dimensional conformal radiation therapy has allowed doses in excess of 75 Gy; however, there is an increased risk for rectal toxicity at these higher dose levels [1–4].

The most influential technologic advancement in prostate radiotherapy in the past 10 years has been IMRT. Similar to 3-DCRT, IMRT uses a 3-D image set (usually CT) to plan the treatment. However, unlike 3-DCRT, IMRT has two important differences: the use of dynamic fields that allow varying radiation intensities within a given field and inverse treatment planning. In most cases, a traditional field will be split into a series of smaller beamlets, and the intensity of the radiation is modulated using multi-leaf collimation. Multi-leaf collimators are essentially multiple small blocks that can be placed in or out of the field under computer control (Fig. 3). One can specify the size of a given radiation beamlet by combining multiple multi-leaf collimators. Furthermore, varying how long the port stays open can control the intensity of the radiation within the beamlet. Combining multiple beamlets of varying intensities through multiple gantry angles results in extremely conformal dose distributions with sharp dose fall off beyond the target volume (Fig. 4).

The second important aspect of IMRT is the integration of “inverse” radiation treatment planning. Three-dimensional radiation therapy typically involves “forward” planning, which involves designing a field and then reviewing the resulting isodose distributions. If the specified dose line does not adequately cover the target, then increasing the margins or prescribing the dose to a different isodose line usually will result in better coverage. Conversely, if too much of a normal structure is receiving excess radiation dose the margins may be decreased or the prescription line can be changed. After any changes, the plan is recalculated and the resulting dose distributions are

Fig. 3. Multi-leaf collimators in head of treatment gantry.
reevaluated. For complicated plans this iterative process may take several trials before an acceptable plan is achieved. Inverse planning allows the planner to specify dosimetric goals before the generation of the radiation plan. For example, the dose goal for the prostate target may be specified as 100% of the volume to receive a minimum of 75 Gy and the rectal goal will be for less than 20% of the volume to receive greater than 70 Gy. The planning software will perform the iterative process to design a radiation plan to achieve these dosimetric goals. In actual practice many dosimetric goals beyond just two constraints are used in the formulation of prostate IMRT plans.

**RATIONALE FOR 3-DCRT AND IMRT FOR DOSE ESCALATION**

The primary reasons to consider 3-DCRT or IMRT are to escalate the total radiation dose that will improve clinical outcomes and to decrease radiation-related toxicity. Directly comparing the efficacy of conventional radiation therapy and 3-DCRT for prostate cancer is difficult. Historical comparisons between conventional radiation and 3-DCRT may not be valid because of differences in the total doses that were used and the imbalance in the clinical characteristics of the patients treated. No randomized studies have shown
a convincing superiority of one versus the other in terms of disease control [5]; however, for a given dose 3-DCRT has been shown to result in less toxicity. Dearnaley and colleagues [6] randomized 225 men with T1-4 prostate cancer to 64 Gy (2 Gy per fraction) with either a three-field conventional technique or 3-DCRT. The conventional technique used rectangular fields, whereas the conformal technique used customized blocks. With a median follow-up of 3.6 years (range 2 to 8 years), no significant difference was noted in biochemical or local control between the two different arms, but the conformal arm had a significant reduction in Radiation Therapy Oncology Group (RTOG) Grade 2 or higher proctitis and rectal bleeding (5% versus 15%, \( P = .01 \)). No difference was seen in RTOG Grade 2 or higher bladder toxicity (23% versus 20%, \( P = .61 \)). The increased rectal toxicity was presumably from a larger volume of rectum receiving a higher dose in the conventional treatment arm that used larger margins or from inaccurate delineation of the target.

Despite the improvement in post-treatment toxicity, 3-DCRT did not show a significant improvement in disease-specific outcomes when similar doses were used. However, the decreased toxicity of this technique has allowed an escalation of the total dose, which has translated into improved clinical outcomes. A number of retrospective studies have shown that higher doses of radiation improve biochemical control in a wide range of prostate cancer patients [3–5, 7–12]. One of the first randomized trials in the prostate specific antigen (PSA)-era showing a clinical benefit to dose-escalation over standard dose radiation therapy was conducted at the M.D. Anderson Cancer Center. Pollack and colleagues [1,13] randomized 305 men with stage T1-3 prostate cancer to either 70 Gy or 78 Gy at 2 Gy per fraction prescribed to isocenter (center of intersecting beams). The clinical target volume was the prostate and seminal vesicles. The 70-Gy arm was planned using a conventional 4-field technique (AP, PA, right lateral, left lateral) to a dose of 46 Gy with a typical field size of \( 11 \times 11 \) cm for the AP and PA fields and \( 11 \times 9 \) cm for the lateral fields. The fields were reduced (typically \( 9 \times 9 \) cm) and treated to an additional 24 Gy using similar beam arrangements. The 78-Gy arm was treated with the identical technique as for the initial 46 Gy, but a 3D-conformal six-field boost was used for the remaining 32 Gy.

Patients were balanced between the two arms in terms of presenting PSA, Gleason score, and T-stage. With a median follow-up of 60 months, the 6-year freedom from failure (FFF) rates for the 70- and 78-Gy arms were 64% and 70% (\( P = .03 \)). This benefit was preferentially seen in patients with pretreatment PSAs greater than 10 ng/mL with 6-year FFF rates of 43% and 62% (\( P = .01 \)) in favor of the 78-Gy arm (Fig. 5). A trend for improvement in distant metastasis–free survival also was seen in this subgroup (98% versus 88%, \( P = .056 \)). There was no significant difference in FFF between the two dose groups for patients with PSA 10 ng/mL or less.

Side effects were graded using a modified RTOG scale [2,14] and a modified Late Effects Normal Tissue Task Force scale [15,16]. The 78-Gy arm had substantially increased Grade 2 or higher late rectal side effects when compared
with the 70-Gy arm (12 versus 26%, \( P = .001 \)). Further analysis of the 78-Gy arm showed that patients who had more than 25% of the total rectal volume (defined as the entire rectum and contents from the anus to the anterior flexion of the sigmoid colon) irradiated to at least 70 Gy had significantly higher rates of Grade 2 or higher late rectal side effects [2]. The 6-year freedom from Grade 2 or higher late rectal side effects for patients receiving 70 Gy or more to less than or equal to 25% and greater than 25% of the rectal volume were 84% and 54% (\( P = .001 \)).

Similar correlations between rectal toxicity and dose volume histogram (DVH) have been reported in retrospective and prospective studies [4–6,17]. There was no significant difference between the two arms regarding Grade 2 or higher bladder toxicity (approximately 10% for both arms). This study showed that the improvements in disease control seen with higher radiation doses come with the potential for added morbidity as more normal tissue receives higher radiation doses.

Zelefsky and colleagues [3,4] have shown an improvement in biochemical failure free survival for escalating radiation doses (>75Gy) with 3-DCRT or IMRT even among patients with favorable features. In a retrospective series from Memorial Sloan Kettering Cancer Center, men with favorable- (T1-2, Gleason score \( \leq 6 \), and PSA \( \leq 10 \)), intermediate- (elevation of one factor), and unfavorable- (elevation in 2 to 3 factors) risk prostate cancer all showed a PSA failure free survival (PSA-FFS) benefit with higher radiation doses. The 5-year PSA-FFS for favorable patients treated with 64.8 to 70.2 Gy versus 75.6 to 86.4 Gy were 77% versus 90% (\( P = .05 \)), for intermediate patients the corresponding rates were 50% versus 70% (\( P = .001 \)), and for unfavorable risk patients they were 21% versus 47% (\( P = .002 \)) [3]. However, patients treated with doses greater than 75 Gy had a 5-year actuarial grade 2 rectal toxicity
rate of 14% versus 5% for those patients treated with doses less than 70 Gy despite the use of 3-DCRT in both subgroups.

IMRT significantly reduced the incidence of late rectal toxicity even at doses greater than 81 Gy in this series. For patients treated to a dose of 81 Gy at 1.8 Gy per fraction, the 3-year actuarial incidence of grade 2 rectal toxicity was 2% and 14% (P = .005) among patients treated with IMRT versus 3-DCRT. The benefit of IMRT compared with 3-DCRT likely is related to its ability to produce concave dose distributions that avoid the rectum and to have rapid dose fall-off near critical structures (eg, rectum). The incidence of any grade 3 to 4 toxicity was extremely low (< 2%) regardless of the dose or the treatment technique. The total dose also affected the incidence of late grade 2 urinary toxicity at 13% and 4% for men treated to more than 75 Gy and 70.2 Gy or less; however, IMRT did not significantly change the incidence of late urinary toxicity. In a subsequent publication, this group reported a 3-year Grade 2 or higher late urinary toxicity incidence of 15% for 772 men treated with IMRT (90% 81.6 Gy, 10% 86.4 Gy) [4]. IMRT may not improve urinary toxicity because of a potential lack of correlation between bladder DVH and urinary toxicity. The bladder neck may be an important structure for determining urinary toxicity and this likely receives a substantial dose with either 3-DCRT or IMRT. Furthermore, the dose to the prostate needle rather than bladder may be a better correlate of urinary toxicity [18–20], and the urethra may actually receive a higher dose with IMRT due to the dose heterogeneity within the target. IMRT results in tight dose conformality, but it may come at the cost of islands of increased dose within the target volume, which results in a higher mean dose. Despite this shortcoming, IMRT does allow dose escalation beyond 75 Gy with relatively low morbidity compared with 3-DCRT or conventional therapy.

**IMAGE-GUIDED RADIATION THERAPY**

The prostate target may move from one day to the next or even from one minute to the next depending on variations in patient setup and internal target motion because of rectal and bladder filling. These variations are usually taken into account when designing the PTV (planning target volume) margin. This extra margin around the target ensures adequate dosimetric coverage in the event of interfractional and intrafractional shifts. A large PTV margin will likely cover the target, but at the cost of potentially overdosing adjacent normal tissues (eg, rectum, bladder, penile bulb). Image-guided radiation therapy describes the adaptation of daily radiation treatment based on imaged anatomic changes. The rationale for using image-guided radiation therapy is to improve overall treatment accuracy, which allows the use of tighter PTV margins that subsequently irradiate less normal tissue. In its simplest form, image-guided radiation therapy (IGRT) is performed when a verification portal image is taken of the patient’s setup. The daily bony anatomy is correlated with the bony anatomy at the time of treatment planning to check if the field is properly aligned. Bony alignment may correct patient setup error, but it does little to correct for internal prostate motion that may exceed 1 cm in certain directions [21–23].
Several methods are currently used to target daily prostate motion or minimize its motion to reduce the PTV margin. Transabdominal ultrasound is one popular technique to target the prostate on a daily basis. Special ultrasound units that are calibrated to the geometric center of the treatment machine are used to image the prostate and find its relative location in 3-D space. These images are then compared with the prostatic contours from the original planning CT and a manual shift is made to more accurately target the prostate. This system has the advantage of being reasonably accurate, is noninvasive, does not require extra radiographic imaging, and is well established [24–27]. Potential disadvantages include mixed results regarding accuracy, inter-user variability, does not provide true 3-D images, and certain patient anatomy (eg, thick patients) may be difficult to image [28].

Because of uncertainties with ultrasound-based prostate localization, intra-prostatic fiducial markers are being used with increasing frequency. These systems usually involve the transrectal implantation of 3 to 4 metallic markers directly into the prostate. These markers are radio-opaque (usually gold) and can be imaged on a standard portal film. The positions of these markers are then used to make subsequent daily shifts. This system has the advantage of being accurate and less prone to inter-user variability because the markers are relatively easy to visualize. An obvious disadvantage is that implantation of the markers is invasive similar to a transrectal ultrasound-guided prostate biopsy. Other potential disadvantages include possible migration of the markers, which may make the alignments inaccurate. However, manufacturers typically modify the markers by roughing the surface to decrease the probability of migration, and most studies have reported good positional stability beyond 5 days after implantation [29–34]. Fiducial-based alignments give the mean shift of all the markers and do not offer detailed volumetric information to account for prostate surface deformation, but the impact of organ deformation is relatively minor compared with translational shifts [35].

Newer localization techniques use daily 3-D images to align the target. This requires a 3-D imager (eg, CT scanner) inside the treatment room. Several facilities have specialized treatment units that combine a linear accelerator and a diagnostic quality CT scanner in the same room. These units allow a CT to be obtained before each treatment, which is then used to make shifts using CT versus CT image correlation [22,36,37]. A slightly different technique involves the use of cone-beam CT, which is obtained using an onboard kilo-volt-age x-ray source and an amorphous silicon flat panel imager that are mounted to the treatment gantry. Unlike a conventional CT scanner that uses a small beam rotated in a spiral fashion, a cone-beam CT uses a large field of view with a single revolution to capture the image set [38,39]. This may produce inferior image quality compared with a diagnostic CT, but it may be adequate to perform anatomically based alignment for radiation therapy [40].

These localization techniques offer a multitude of options for localizing the prostate on a day-to-day basis, but they do not account for potential intrafractional motion of the prostate. A typical IMRT fraction may take as long as 15
to 20 minutes when one considers setup time and the delivery of all the individual beam segments. This interval is long enough to see prostate motion from transient rectal volume changes as a result of gas; however, for most patients the impact of intrafractional motion is relatively small when compared with interfraction variations [40–43]. One method to proactively reduce inter- and intrafraction prostate motion is the use of an endorectal balloon to fix the prostate position [44–47]. This technique minimizes prostate motion secondary to variable rectal filling and also physically displaces the posterior rectal wall away from the high-dose radiation regions resulting in improved rectal dosimetry [48–51].

**HYPOFRACTIONATED RADIATION THERAPY**

The $\alpha/\beta$ ratio is a radiobiologic parameter that describes how cells respond to changes in radiation fraction size. Specifically, cells with a high $\alpha/\beta$ ratio (eg, most tumors) tend to be less sensitive to changes in fraction size (ie, a smaller or a larger dose per fraction will have result in similar cell killing). Conversely, cells with a low $\alpha/\beta$ ratio (eg, normal tissue) are more sensitive to changes in fraction size and larger fractional doses result in increased cell killing compared with cells with higher $\alpha/\beta$ ratios. Hypofractionated radiation therapy refers to the use of larger fractional doses (typically $>2$ Gy) to deliver a total dose in fewer fractions. The rationale for considering hypofractionated regimens for prostate cancer is based on the hypothesis that prostate cancer cells may actually have relatively low $\alpha/\beta$ ratios ($<3$) compared with adjacent normal tissues such as the rectum and bladder [52–54]. If this is the case, then treating prostate cancer patients with larger fraction sizes to a lower total dose may result in improved tumor control without increased toxicity.

A Canadian study randomized 936 men with T1-2 prostate cancers to 66 Gy delivered in standard fractionation of 2 Gy versus a hypofractionated schedule of 52.5 Gy (2.625 Gy x 20 fractions) both treated with 3-DCRT [55]. The study was designed as a “noninferiority” trial. The median follow-up was 5.7 years (range 4.5 to 8.3 years) and showed a 5-year biochemical or clinical failure rate of 52.95% for the “standard” 66-Gy arm and 59.95% for the experimental 52.5-Gy arm. The investigators concluded that the hypofractionated regimen could be inferior; however, critics have contended that the total dose used for the hypofractionated arm was insufficiently low.

Kupelian and colleagues [56] reported one of the largest series of hypofractionated radiation therapy in the modern era using IMRT. One hundred men with localized prostate cancer were consecutively treated to a total dose of 70 Gy at 2.5 Gy per fraction using IMRT. If one assumes an $\alpha/\beta$ ratio of 1.5 for prostate cancer cells, then this regimen would approximate a total dose of 85 Gy at 1.8 Gy per fraction. With a median follow-up of 66 months, the 5-year biochemical failure free survivals were 85% for the entire cohort and 97%, 88%, and 70% for men at low (T1-2a, Gleason score $\leq 6$, and PSA $\leq 10$), intermediate (T2b, Gleason 7, or PSA 10.1–20), and high (T2c, Gleason $\geq 8$, or PSA $> 20$) risk of post-treatment PSA failure. Seven patients developed
grade 2 late rectal toxicity and three had grade 3 toxicity. The late urinary toxicity was also low (11 grade 2, 1 grade 3). The authors concluded that hypofractionated radiation therapy was a reasonable alternative to standard dose-escalation for prostate cancer when conformal techniques such as IMRT are used. Multiple single institution trials are accruing patients with various hypofractionated schedules, and the RTOG is planning a multi-institutional randomized study to further investigate this issue.

HORMONE THERAPY AND RADIATION THERAPY

The addition of hormone therapy to radiation therapy has been established to provide a clinical benefit in randomized trials over radiation therapy alone for patients with bulky, locally advanced, and unfavorable prostate cancers (Table 1) [57–62]. Hormone therapy should begin before radiation therapy and continue at a minimum through the radiation course for optimal effect. Long-term adjuvant hormonal therapy after radiation also has shown an overall survival benefit in trials from the RTOG and EORTC [58,62].

More recent studies have investigated the use of hormone therapy with radiation for more favorable risk disease. D’Amico and colleagues [63] randomized 206 men with clinically localized intermediate and high-risk prostate cancer to either 70 Gy or the same radiation with 6 months of total androgen blockade (goserelin/leuprolide with flutamide) beginning 2 months before radiation. With a median follow-up of 4.52 years, the combined hormone and radiation therapy group compared with the radiation alone group had significantly better 5-year freedom from salvage therapy (82% versus 57%, \(P = .002\)), prostate cancer specific mortality (0% versus 5%, \(P = .02\)), and overall survival (88% versus 78%, \(P = .04\)). These studies are providing the foundation for consideration of hormone therapy with radiation therapy for earlier stage disease as another method to improve the therapeutic ratio; however, the additional benefit of hormone therapy to dose-escalation radiation therapy has not been demonstrated in a randomized trial.

PROSTATE BRACHYTHERAPY

“Brachy” means short distance in Greek. In the 1970s and early 1980s, prostate brachytherapy involved open surgery where the prostate was exposed, and radioactive seeds were inserted into the prostate gland by a retropubic approach with “finger-guidance.” This retropubic approach resulted in poor radiation coverage of the gland and was used for unfavorable patients. Given the relatively dismal results, the procedure was largely abandoned in the United States. In the late 1980s and early 1990s, new minimally invasive techniques with ultrasound image guidance were developed in Sweden and further advanced in the United States under the direction of Dr. John Blasko.

Prostate brachytherapy is another form of image-guided radiotherapy (IGRT) that typically uses ultrasound and in specialized centers, MRI, to guide placement of radioactive sources into the prostate. The most common form of prostate brachytherapy uses a transrectal ultrasound probe with a template that
<table>
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<th>Trial</th>
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<th>ARMS</th>
<th>Distant Mets (%)</th>
<th>bNED (%)</th>
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<td>RTOG 85–31</td>
<td>T3 (15%) or T1-2, N+ or path T3 and (+) margin or (+) SV</td>
<td>XRT (HT at time of failure) vs XRT + indefinite AHT</td>
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<td>EORTC 22863</td>
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<td>XRT vs XRT + CAHT 3 years</td>
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<td>Bulky T2b, T3-4, N+ allowed</td>
<td>XRT vs XRT + NHT (TAB) 3.7 mo</td>
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<td>3 vs 16</td>
<td>69 vs 77</td>
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<td>RTOG 92–02</td>
<td>T2c-4 w/ PSA &lt; 150, N+ allowed</td>
<td>XRT + NHT (TAB) 4 mo vs XRT + NHT + AHT 28 mo</td>
<td>5-year</td>
<td>45.5 vs 72</td>
<td>28.1 vs 46.4</td>
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Abbreviations: AHT, adjuvant HT; ARMS, treatment arms; bNED, biochemical failure free survival; CAHT, concurrent-adjuvant HT; DFS, disease-free survival; HT, hormone therapy; mets, metastasis; NHT, neoadjuvant HT; N+, node positive; OS, overall survival; PSA, prostate specific antigen; SV, seminal vesicle; TAB, total androgen blockade; WHO, World Health Organization; XRT, radiation therapy.
overlies the perineum (Fig. 6). With the patient under general or local anesthesia, needles are inserted through the perineum via the perineal template and radioactive seeds (usually I-125 and Pd-103) are deposited into the prostate to achieve a conformal dose distribution. The seeds are the size of a grain of rice ($4.5 \times 0.8 \text{ mm}$) and typically 75 to 100 seeds are needed depending on gland size. These radioactive seeds emit low-energy radiation over a discrete volume for several months and kill prostate cancer cells through its interaction with DNA. Image guidance with transrectal ultrasound allows precise placement of the radioactive seeds with millimeter accuracy. This radiation technique has resulted in high cure rates comparable to those obtained with radical prostatectomy or external beam radiation therapy for appropriately selected patients.

**Patient Selection and Outcomes**

Current guidelines from the American Society of Therapeutic Radiology and Oncology (ASTRO), American Brachytherapy Society (ABS), and the American College of Radiology (ACR) for the treatment of prostate cancer by an implant alone include patients with low risk features (ie, pretreatment PSA $\leq 10 \text{ ng/mL}$, Gleason score $\leq 6$, and clinical stage T1c to T2a). Generally, patients with more advanced localized disease (eg, Gleason 7 or PSA $> 10$) are at increased risk of extraprostatic extension of tumor and upfront external beam radiation will supplement the brachytherapy with good results [64].

With favorable data maturing out to 10 to 15 years, prostate brachytherapy has emerged as another nonsurgical option for prostate cancer patients [65]. The outcomes for patients treated with interstitial implant have been favorable compared with surgery or external beam radiation therapy [66]. The biochemical progression-free survival for patients at low risk (PSA $\leq 10$, Gleason score

**Fig. 6.** Trans-rectal ultrasound guided brachytherapy setup. (Courtesy of Peter Grimm, DO, Seattle Prostate Institute, Seattle, WA.)
≤ 6, and clinical stage ≤ T2a) for failure has exceeded 85% to 90% in select series [65,67]. The expectations for cure should be approximately 85% to 90% for low-risk patients and approximately 75% to 80% for intermediate-risk patients, regardless of brachytherapy modality [68].

Prostate cancer patients considered at intermediate risk (PSA 10–20, Gleason score 7, or clinical stage T2b) for post-treatment biochemical failure traditionally have had inferior disease control with brachytherapy alone compared with either radical prostatectomy or external beam radiation therapy [69]. However, Merrick and colleagues [70] reported a 96% biochemical progression-free survival in patients with intermediate-risk disease treated with permanent prostate brachytherapy. These results compare favorably to the best-published results from hormone naïve patients treated with radical prostatectomy or 3-DCRT. High-quality implants with appropriate treatment margins are critical to achieve these results. Treatment must be individualized for specific patients to account for potential pathologic extracapsular extension, which may as low as 5% in low-risk patients and as high as 80% in some intermediate-risk patients [71].

Toxicity

Following a brachytherapy implant, patients generally are discharged home the same day as the procedure and resume their normal daily activities within a week. However, acute and late side effects may occur as a result of post-implant edema and hemorrhage and the radiation dose received by the urethra, rectum, and erectile tissues. Appropriate patient selection along with quality implants with judicious planning performed by experienced radiation oncologists can minimize both acute and long-term morbidity. The most common acute toxicity associated with a prostate implant is irritative urinary symptoms such as frequency and urgency that occurs commonly during the first 3 months after the procedure but usually resolves. A literature review by Vicini and colleagues [72] to assess long-term urinary and rectal morbidity associated with prostate brachytherapy revealed urinary retention, incontinence, and urethral stricture rates of less than 3% to 5% each. The reported rates of significant radiation proctitis were less than 5%, rectal bleeding less than 10%, rectal ulcer or fistula less than 2%. Post-implant erectile dysfunction may occur in up to 60% of men within 6 years after brachytherapy depending on the patient’s pre-implant erectile function and the dose received to the proximal penile bulb [73–75]. Sildenafil may still be effective in the majority of men who suffer post-implant erectile dysfunction [76–78].

Future Directions in Prostate Brachytherapy

Traditionally, patients with intermediate-risk prostate cancer treated with brachytherapy also received initial external beam radiation therapy to a dose of 40 to 50 Gy that was followed by a brachytherapy boost. However, single institution retrospective data seem to indicate that select patients with unfavorable features may be effectively treated with implant monotherapy [64,79–82]. Currently, a multi-institutional randomized equivalence trial is being conducted by
the Radiation Therapy Oncology Group (RTOG) to compare external beam radiation therapy with brachytherapy versus brachytherapy alone for patients who present with intermediate-risk prostate cancer.

Another modern prostate brachytherapy option involves the use of temporary high-dose rate (HDR) sources. This procedure involves transperineal placement of catheters into the prostate under image guidance, which subsequently are used to deliver radiation through a high-dose rate source such as iridium 192. Rather than emitting therapeutic radiation over a period of weeks to months, these HDR sources deliver radiation in minutes, but may require more than one insertion. Furthermore, the radiation oncologist can tailor the dose by increasing or decreasing the dwell time (i.e., how long the source remains in one position) inside the individual catheters. This allows further dose customization depending on the patient’s anatomy and the catheters’ positions on that day. The primary advantages of HDR over LDR (low-dose rate) include the combination of planning and treatment occurring in the operating room with optimized dose conformality achieved during each fraction of treatment. Additionally, the implant is temporary and no permanent seeds are left in the prostate and, therefore, no radiation is emitted from the patient after the procedure and there is no chance of seed migration. Grills and colleagues reported similar biochemical control rates and potentially less toxicity with HDR monotherapy (iridium 192) when compared with LDR monotherapy with palladium-103 for men treated at William Beaumont Hospital. HDR brachytherapy was associated with decreased rates of acute urinary frequency, urgency, dysuria, and rectal pain compared with LDR. The principal advantages over external beam radiation therapy are reduced overall treatment times and no additional technological requirements to account for treatment setup uncertainties and organ motion.

**PROTON THERAPY**

Proton therapy is another type of external beam radiation that uses high-energy protons rather than x-rays (photons) to deliver radiation dose. Unlike x-rays that continue to deposit radiation beyond the target, proton therapy can deliver radiation at depth with a sharp distal dose gradient. As protons travel through tissue they deposit virtually all their energy over a finite range with almost no radiation dose beyond that point. This ability of protons to stop in tissue is characterized by the Bragg-Peak (Fig. 7). The physical characteristics of proton beam therapy allow fewer beams to be used to achieve similar conformal radiation plans as more complicated arrangements with x-rays (Fig. 8). Using fewer beams and the sharp distal dose gradient also may result in a decrease in the integral dose (total dose to all exposed tissue) to the patient. Early studies using research-based cyclotrons for advanced prostate cancer did not show a clinical benefit to protons over conventional techniques; however, only a portion of the treatments were delivered with protons and the technique was not optimal by modern standards. The largest series for prostate proton therapy was reported by Slater and colleagues.
involved 1255 men with prostate cancer treated with either combination protons and x-rays (731) or protons alone (524) at Loma Linda University Medical Center. Patients typically received 74 to 76 Gy with the proton portion being delivered by a single alternating lateral beam. At a median follow-up of 62 months, Slater and colleagues reported an 8-year PSA failure free survival (FFS) rate of 73% for the entire cohort, which contained a heterogeneous group of patients. Disease-free survival was dependent on Gleason score and pretreatment PSA with patients presenting with PSAs of 10 ng/mL or less having PSA-FFS exceeding 80%. Acute or late RTOG grade 3 to 4 toxicity was less than 2%, and the 5-year actuarial rate of being free of grade 3 to 4 urinary or rectal toxicity was 99%. An earlier analysis from the same group reported the 3-year incidence of grade 2 urinary or rectal toxicity as approximately 5% [87].

A recently reported randomized dose-escalation proton therapy trial conducted at Loma Linda and Massachusetts General Hospital randomized 393 men with localized prostate cancer to either 70.2 CGE (cobalt gray equivalents)

Fig. 7. Dose-depth curves for x-rays (photons) versus protons.

Fig. 8. Isodose distribution for proton plan (2 lateral beams only).
or 79.2 CGE between 1996 and 1999 [88]. The initial 19.8 CGE or 28.8 CGE was delivered to the prostate using protons, which was then followed by a dose of 50.4 Gy using x-rays for both arms. With a median follow-up of 5.5 years, the higher dose arm had significantly better 5-year biochemical FFS (61.4% versus 80.4%, \( P < .01 \)) and local control (47.6% versus 67.2%, \( P < .01 \)). This clinical benefit was seen in the intermediate/high-risk patients as well as among the low-risk patients. Grade 2 late rectal toxicity was seen in 8% versus 17% (\( P = .005 \)) among the standard and high-dose arms. Grade 2 late urinary toxicity did not significantly differ between the two arms (18% versus 20%). The incidence of any grade 3 late toxicity was 2% or less. These studies show that proton therapy can deliver dose-escalation radiation therapy with modest side effects even when only the simplest beam arrangement is used. Current proton therapy trials are escalating the total dose to 82 CGE with protons alone. Several centers also are developing intensity modulated proton therapy, which will further maximize the conformality of this modality beyond current IMRT techniques. Beyond dose escalation, this modality also may provide an improved method for further hypofractionated prostate radiotherapy. Two new US proton therapy centers will be opening in the near future at M.D. Anderson Cancer Center and the University of Florida.

**SUMMARY**

Higher doses of radiation result in improved clinical control of prostate cancer, and the recent advances in prostate cancer radiotherapy are designed to escalate dose while minimizing toxicity. To achieve this goal, tighter treatment margins are needed, which require more accurate delineation of the prostate target and normal tissue at the time of treatment planning and before actual daily treatments. Modern radiation therapy techniques can deposit conformal dose virtually anywhere in the body; however, this precise therapy is of no value if it is not accurately hitting the target. Whether dose escalation is achieved by external beam techniques (eg, IMRT, protons) or brachytherapy, these basic planning and delivery considerations are essentially the same. Future directions in prostate radiation therapy will use even higher radiation doses, alternative fractionation patterns, intraprostatic targets (eg, prostate tumor seen on MRI), and improved patient selection regarding which patients will benefit the most from these advanced techniques.

**References**


