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Emerging Technologies and Techniques in Radiation Therapy

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The past decade has brought an improved ability to precisely target and deliver radiation as well as other focal prostate-directed therapy. Stereotactic body radiotherapy (SBRT), proton beam radiation, high-dose-rate (HDR) brachytherapy, as well as nonradiotherapy treatments such as cryoablation and high-intensity focused ultrasound are several therapeutic modalities that have been investigated for the treatment of prostate cancer in an attempt to reduce toxicity while improving cancer control. However, high-risk prostate cancer requires a comprehensive treatment of the prostate as well as areas at risk for cancer spread. Therefore, most new radiation treatment (SBRT, HDR, and proton beam radiation) modalities have been largely investigated in combination with regional radiation therapy. Though the evidence is evolving, the use of SBRT, HDR, and proton beam radiation is promising. Nonradiation focal therapy has been proposed mainly for partial gland treatment in men with low-risk disease, and its use in high-risk prostate cancer patients remains experimental.
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Introduction

The past 10 years has brought an improved ability to precisely target and deliver radiation and other nonsurgical treatment to the prostate. For prostate cancer that has a high likelihood of being confined to the prostate, more precise radiotherapy techniques attempt to spare normal tissue surrounding the prostate from excess radiotherapy treatment. Stereotactic body radiotherapy (SBRT), proton beam radiation, high-dose-rate (HDR) brachytherapy, as well as nonradiotherapy treatments such as cryoablation, high-intensity focused ultrasound (HIFU), and radiofrequency ablation (RFA) are therapeutic modalities that have been investigated for the treatment of prostate cancer in an attempt to reduce toxicity while improving cancer control.

However, for high-risk prostate cancer, in addition to sparing normal tissue, there are additional clinical issues to consider. High-risk prostate cancer may have a greater likelihood of local prostate recurrence after standard radiation treatment because of greater resistance to current doses of fractionated radiation,[1] and therefore may benefit from emerging technologies that aim to escalate dose locally. Balancing this need for local dose escalation is the greater likelihood of extraprostatic and more distant disease with high-risk disease. This greater likelihood of extraprostatic and disseminated disease may limit the utility of extreme dose escalation and locally targeted therapy. Furthermore, locally intensified therapy may increase the possibility of treatment-related toxicity. Therefore, the risks and benefits of any locally directed treatment must be considered.

In light of the required balance between treatment intensification and treatment-related toxicity, a review of new radiation and nonradiation technologies for the treatment of high-risk disease is needed.

Moderate Hypofractionation and SBRT

Altered fractionation (generally, larger fractions per treatment) has been hypothesized to deliver greater radiobiologic dose to the prostate and prostate cancer.[2] Generally, 2 methods of external beam radiotherapy have been proposed—moderate hypofractionation (delivering doses of radiotherapy between 2.2 and 4 Gy per fraction), and SBRT (generally delivering doses >5 Gy per fraction).

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Though generally investigated for low- and intermediate-risk disease, an Italian study randomized 168 high-risk patients to conventionally fractionated radiotherapy vs moderately hypofractionated therapy (3.1 Gy per fraction × 20 fractions).[3] There was no statistically different difference between the 2 regimens in terms of cancer outcomes. A prior analysis of toxicity in this trial indicated a trend toward greater grade 2 or higher toxicity for hypofractionated radiotherapy though the difference did not reach statistical significance ($P = 0.07$).[4]

Other studies have reported on quality of life and toxicity, though we await cancer-related efficacy results. The conventional or hypofractionated high–dose intensity-modulated radiotherapy in prostate cancer (CHHiP) trial recently reported on a cohort that included some high-risk patients (roughly 11%-13% of the cohort) and reported that toxicity seems equivalent between moderate hypofractionation and conventional radiotherapy.[5] In contrast, the Dutch HYPRO trial recently reported that late toxicity results could not confirm noninferiority of hypofractionation to conventional radiotherapy—raising caution that moderate hypofractionation may be more toxic.[6] This study randomized intermediate-risk and high-risk patients to conventional fractionation vs 3.4 Gy × 19 fractions (delivering 3 fractions a week). We await the efficacy results of these large randomized trials before we can make more definitive judgment regarding the role of moderate hypofractionation for high-risk disease.

SBRT, also known as stereotactic ablative radiotherapy, attempts to deliver greater doses per fraction to the prostate, to take advantage of the potentially low alpha/beta of prostate cancer[7,8] (though the concept of a uniformly low alpha/beta of prostate cancer is being revisited[9,10]). To safely deliver high doses of radiation, SBRT uses more intensive prostate tracking and patient immobilization than standard intensity-modulated radiation therapy (IMRT). Treatment for low-risk prostate cancer is promising, and the American Society of Radiation Oncology notes that data support the use of SBRT as an appropriate alternative treatment for "select patients with low- to intermediate-risk disease." The use of SBRT for high-risk prostate cancer is more controversial. In this group of patients, SBRT has been investigated both as primary treatment (monotherapy) and as boost therapy after whole pelvic radiation.

Monotherapy

Perhaps the largest experience investigating the use of SBRT for prostate cancer was published in 2013 by King et al[11] with data encompassing 1100 patients with clinically localized prostate cancer. This included 125 high-risk patients (here defined as prostate-specific antigen [PSA] > 20, Gleason score of 8-10, or clinical stage T2c-T3) who were treated using doses of 35-40 Gy in 5 treatments of 7-8 Gy. The 5-year biochemical recurrence-free survival of 81% compares well to historical rates, and treatment was well tolerated. The authors noted that the number of patients in the high-risk group with 5 year follow-up was small, and so some caution should be taken when interpreting these findings.

Kang et al reported on 29 high-risk patients (among 44 patients overall) who were treated with SBRT to a dose of 32-36 Gy in 4 fractions[12] with a 5 year biochemical failure-free survival of 90.8%, though follow-up was short (median of 40 months) and details of androgen suppression are unknown. Others have investigated the use of SBRT in cohorts that included too few high-risk patients to draw firm conclusions from.[13,14]

Notably, one analysis found a potential benefit to higher (37.5 Gy in 5 fractions) compared with lower (36.25-35 Gy in 5 fractions) doses in terms of biochemical disease-free survival,[15] though the difference in biochemical disease-free survival was not confirmed as prostate-specific failure (vs distant). Therefore, the authors noted that conclusions regarding dose response are difficult to draw.

Notably, investigation into even higher fractionation schemes (albeit for low- and intermediate-risk patients) have shown that doses above 47.5 Gy in 5 fractions leads to unacceptable toxicity.[16] Additionally, though Fuller et al[17] has investigated 9.5 Gy × 4 in a group of low and intermediate-risk patients with good biochemical outcomes, the overwhelming majority of patients undergoing SBRT receive a dose of 35-36.25 Gy in 5 fractions.[11]

The HYPO-RT-PC trial, which completed accrual in 2015, included intermediate-risk patients with the primary outcome of freedom from PSA failure at 5 years posttreatment.[18] It is hoped that this study will shed further light on the relative risks and benefits of SBRT in higher-risk patients.

Whole-Gland Boost Therapy

The use of SBRT as a method of delivering a "boost" of radiation to the prostate after more regional radiotherapy has also been investigated in patients with intermediate- and high-risk disease. Investigators have used 2 fractions of 9.5-10.5 Gy directed to the prostate after 45 Gy of pelvic radiation[19] or 19.5-21 Gy in 3 fractions in prostate radiation after 45-50.4 Gy delivered to the pelvis.[20,21] Generally, these treatments have been well tolerated with little to no reported acute Grade 3 or higher toxicity. For example, a study from University of California, San Francisco investigating 45 patients (44% of whom had Gleason 8-10 disease) reported an estimated 5 year recurrence-free survival of 83% (95% CI: 62%-93%). Notably, one patient experienced a late grade 3 urinary tract obstruction according to CTCAE v4 criteria. Patient reported outcomes have been favorable, with expanded prostate cancer index composite scores returning to baseline by 6 months posttreatment.[21]

Focal Boost of Dominant Intraprostatic Lesion

SBRT has been investigated as a method of delivering a focally escalated dose to the dominant intraprostatic lesion. In low- and intermediate-risk prostate cancers, it was shown feasible to deliver a whole-gland treatment of 9.5 Gy × 4 fractions with a simultaneous dominant lesion boost of an additional 1.5 Gy per treatment (for a total of 11 Gy × 4 fractions), though the median follow-up of patients in this study was only 23 months, limiting long term conclusions regarding toxicity.[22] Another study by Kotecha et al[23] recently investigated 24 patients with

intermediate- and high-risk prostate cancer who were treated with SBRT to a dose of 7.25 Gy for 5 fractions with a simultaneous integrated boost of the dominant intraprostatic lesion with 10 Gy for 5 fractions (an additional dose of 2.75 Gy per fraction). Overall, 9 (38%) experienced acute grade 2 genitourinary (GU) toxicity, and there were no cases of acute gastrointestinal (GI) toxicity. Overall, 2 (8%) patients experienced late grade 2 GU toxicity and 2 patients experienced late grade 2 GI toxicity with 25 months of median follow-up. Two-year PSA relapse-free survival was 95.8%. As with the prior study, further follow-up is needed before conclusions can be made.

Technique

Radiotherapy technique for delivering a prostate SBRT should ideally use prostate localization via continuous (radiofrequency tracking of implanted markers) or near-continuous tracking (orthogonal x-rays every 30 seconds) with implanted fiducial markers. If tracking is unavailable, care should be taken to ensure that the periodic monitoring of the patient's position be performed at least every 5-7 minutes. Should tracking not be used, repeat localization images after the end of each treatment should be obtained. If a significant prostate or patient shift be detected, more frequent correction and localization of the patient and prostate is recommended. Though allowed for some multi-institution protocols such as RTOG 0938,[24] and prostate movement can be minimized with rigorous immobilization along with careful bladder and bowel preparation, sudden movement cannot be detected without continuous tracking of the prostate.[25] Therefore, though possible to perform prostate SBRT with standard cone beam computed tomography (CT) before and after treatment (with fiducial marker, as soft tissue based target alignment without fiducial marker is too imprecise for SBRT), caution and care is required to educate, immobilize, and treat the patient appropriately.

Care should be taken to ensure the rectum receives less than the prescribed radiation dose. Two methods of rectal protection have been investigated: the use of an inflatable endorectal rectal balloon to immobilize and distend the rectum, and an injectable hydrogel spacer that is implanted into the rectoprostatic space. The endorectal balloon has been criticized for distending the rectum and exerting an anterior-driving force on the prostate, potentially deforming the prostate as well as pushing the rectal wall anteriorly toward the prostate.[26] Dosimetrically, the endorectal balloon has been theorized to actually increase the absolute volume of rectum receiving high-dose therapy.[27] Clinicians wishing to involve an endorectal balloon in prostate SBRT should proceed with caution.

The implanted hydrogel spacer on the other hand holds promise in terms of reducing the dose of radiotherapy delivered to the rectum. In studies using conventional fractionation, a hydrogel spacer has been shown to result in a significant decrease in rectal dose[28-33] with encouraging acute and late toxicity profiles.[34,35] The first multi-institutional randomized trial assessing the safety and efficacy of this hydrogel was recently published, demonstrating a 99% placement success rate, significant reduction in mean rectal V70 (12.4%-3.3%), and a significant reduction in late rectal toxicity severity, with no GI toxicity greater than Grade 1 in the spacer group.[36] Insertion of a perirectal spacer has also been shown to significantly decrease rectal dose in prostate SBRT plans.[37]

Finally, care should be taken to ensure the dose through the prostate is as homogeneous (ideally with maximal dose inhomogeneity of less than 107% of the prescription dose within the prostate) as possible given difficulty localizing and visualizing the prostatic urethra. If the dose within the prostate exceeds 107%, visualization of the prostate should be performed via urethrogram, foley catheter, or magnetic resonance imaging (MRI). MRI imaging may also be beneficial to help define the prostate and surrounding tissue,[38] in combination with the planning computed tomography simulation.

Proton Beam

Proton beam radiation therapy (PRT) aims to deliver radiotherapy to the prostate whereas taking advantage of the physical property of protons to minimize dose to surrounding tissue and organs at risk such as the rectum, bladder, small bowel, and femoral heads.[39-41] Early research has focused mainly on early (low risk) prostate cancer.[41,42] Few studies have assessed the use of PRT alone in high-risk prostate cancer, as most studies use PRT in combination with other treatment modalities.[43,44] Moreover, the dose distribution of PRT in high-risk prostate cancer has been investigated in silico through dosimetric studies[45-47] generally showing a reduction in low- and medium-range radiation dose to organs at risk.

A 2013 prospective study by Mendenhall et al[40] may provide the best available data for clinically localized high-risk prostate cancer treated with image-guided proton therapy. Investigators identified 40 high-risk prostate cancer patients (here defined as Gleason score $\geq$ 8, PSA $\geq$ 20, or Clinical Stage $\geq$ T3) who were treated using doses of 78 CGE in daily doses of 2 CGE. All patients were also given weekly concomitant docetaxel therapy followed by androgen deprivation therapy (ADT) for 6 months. Two patients refused ADT. Investigators reported excellent outcomes and minimal toxicity. The 5-year biochemical recurrence-free survival was 76% and the overall 5-year survival was 86%. GI and urologic grade 3 toxicities were 0.5% and 1.0%, respectively. Patient reported outcomes as measured by the expanded prostate cancer index composite survey (EPIC) showed stable bowel, urinary irritative or obstructive, and urinary incontinence domains, as well as nonsignificant changes in sexual function. These outcomes were validated via a retrospective analysis from the same institution that included 229 high-risk patients and reported 76% 5-year freedom from biochemical progression, and grade 3 or higher GI and GU toxicity of 0.6% and 2.9%,respectively, roughly equivalent to existing photon based literature.[48]

On the contrary, Slater et al[41] identified 133 patients with a PSA $\geq$ 20 and 86 patients with a Gleason score $\geq$ 8. Patients were treated using doses of 74 CGE to the isocenter by opposed lateral means in daily doses of 2 CGE and found a relatively poor 5-year biochemical recurrence-free survival of

48% and 50%, respectively. In multivariate analysis, PSA and Gleason score were independent factors of treatment outcome.

In silico Dosimetric Studies

Proton radiotherapy, in addition to potentially escalating dose to the prostate with fewer side effects, also has been proposed to treat pelvic lymph nodes while minimizing dose to organs at risk such as the bladder, rectum, and small bowel. Overall findings suggest that PRT has optimal clinical target volume coverage and reduced irradiation to organs at risk when treating the prostate and pelvic lymph nodes for high-risk prostate cancer.[45-47] Chera et al[45] stated that 3D-PRT may "improve the therapeutic ratio beyond what is possible with IMRT" because of the potential for dose escalation to pelvic lymph nodes with protons. Furthermore, normal tissue complication probability models indicate that intensity-modulated proton therapy using pencil beam scanning will significantly reduce irradiation to surrounding tissue compared with intensity-modulated x-ray beams, volumetric-modulated arc therapy, and helical tomotherapy.[46,47]

Further evidence is required to determine the relative efficacy of PRT in high-risk prostate cancer and its potential for dose escalation and the treatment of lymph nodes. Caution should be taken interpreting the findings above as sample sizes were small and the number of studies investigating proton beam radiation as monotherapy for high-risk disease is scarce. Further, proton range uncertainty[49] and other technical and clinical issues associated with proton radiotherapy to the pelvic lymph nodes (such as difficulty with complex inhomogeneities such as rectum and small bowel, difficulty dealing with organ motion, and lack of strong clinical evidence)[50] limit our ability to assess this treatment. Specifically, errors and variation patient and prostate positioning may result in greater errors for proton beam radiation compared with photon beam therapy because of sharper dose gradients, as well as greater sensitivity to the traversed tissue density.[51] Additional prospective clinical trials are crucial to compare PRT with other treatment modalities when treating the pelvis. In particular for a time when any pelvic radiation (regardless of particle used—photon or proton) remains an area of investigation and uncertainty.[52]

HDR Brachytherapy

Even with the most modern techniques, the normal tissue tolerance of the bladder and rectum limit the dose to which patients can be safely treated with external beam radiotherapy (EBRT). The use of intensity-modulated, image-guided HDR brachytherapy allows for a degree of conformality and dose escalation that is difficult to achieve with EBRT. By definition, HDR brachytherapy delivers radiotherapy at a dose rate of >12 Gy/hour and Iridium-192 is the most commonly used isotope. The treatments are either performed as an outpatient (single fraction) or require a short hospitalization (single implant and multifraction).

At most centers, fiducials and HDR catheters are placed with an epidural and under conscious sedation, using transrectal ultrasound (TRUS) guidance. Once the catheters are in place, computed tomography, TRUS, or MRI is obtained to ensure proper placement and for treatment planning purposes. The Groupe Europeen de Curietherapie European Society of Therapeutic Radiation Oncology (GEC-ESTRO) recently published dosimetric constraints for both target coverage and organs at risk.[53] The recommendations for target coverage include $V_{100} > 95\%$ and $D_{90} > 100\%$. The normal tissue constraints set forth include limiting dose to 2 cc of the rectum to <75 Gy (EQD2), dose to 2 cc of the bladder < 85 Gy (EQD2), and dose to 0.1 cc of the urethra < 120 Gy (EQD2).

Although HDR and low-dose-rate (LDR) brachytherapy are excellent treatment modalities, there are many advantages to HDR brachytherapy. HDR brachytherapy plans are optimized and administered with the catheters in place, thereby giving a more accurate reflection of the actual dose delivered. Conversely, LDR brachytherapy is susceptible to seed migration and seed misplacement. Additionally, the highly conformal dose distributions that can be achieved with HDR brachytherapy allows for more reliable coverage of extraprostatic disease, which is particularly important when treating patients with high-risk prostate cancer. In an analysis of 454 patients treated with brachytherapy (248 HDR and 206 LDR), HDR brachytherapy was associated with less acute grade 1-3 dysuria, urinary frequency or urgency, rectal pain, chronic urgency or frequency, chronic dysuria, and erectile dysfunction compared with LDR brachytherapy with no difference in biochemical disease-free survival.[54]

From a radiation biology perspective, HDR brachytherapy may be ideally suited for the treatment of prostate cancer. Although the true alpha/beta ratio of prostate cancer is unknown and controversial, it is theorized to be between 1 and 3 Gy,[55] and therefore it has been hypothesized that larger doses per fraction may be optimal for tumor control.[56]

Although HDR brachytherapy is generally well tolerated, there are patients who are not suitable candidates because of preexisting conditions that may increase the probability of toxicity or result in suboptimal patient outcomes. Specifically, the American Brachytherapy Society guidelines for HDR brachytherapy list prior rectal surgery, prior pelvic radiotherapy, inflammatory bowel disease, prior transurethral resection of the prostate, large prostate volume (>50 cc) and significant urinary symptoms (international prostate symptom score > 20) as relative contraindications.[57]

Boost

HDR brachytherapy is most commonly used as a form of dose escalation with EBRT to treat patients with high-risk and intermediate-risk prostate cancer. Although there is a wide range of HDR brachytherapy boost schedules found in the literature, the National Comprehensive Cancer Network recommends 9.5-11.5 Gy $\times$ 2 fractions, 5.5-7.5 Gy $\times$ 3 fractions or 4-6 Gy $\times$ 4 fractions. Conversely, recent NRG or Radiation Therapy Oncology Group trials mandate a single fraction of 15 Gy if they are to receive an HDR boost. Owing to

the concern of increased toxicity that may be seen with larger fraction sizes, most of the earlier series of HDR brachytherapy delivered multiple fractions with one or more implant. More recently, for resource allocation and patient convenience, the trend has been toward fewer fractions and a single implant with favorable results.[58,59]

Investigators at Memorial Sloan Kettering Cancer Center retrospectively reviewed the outcomes of patients treated with dose escalated IMRT (86.4 Gy; $n = 470$) to those treated with HDR brachytherapy (21 Gy in 3 fractions) followed by IMRT (50.4 Gy; $n = 160$).[60] At a median follow-up of 53 months, the 5-year biochemical disease-free survival for patients with high-risk prostate cancer was 93% in patients who received an HDR boost followed by IMRT vs only 71% in patients treated with IMRT alone ($P < 0.01$). Though these groups (IMRT and HDR) were compared within each risk group strata, the IMRT cohort overall appeared to be higher risk than the HDR cohort. Further study is needed before definitive conclusions can be made.

More recently, the Androgen Suppression Combined With Elective Nodal and Dose Escalated Radiotherapy (ASCENDE-RT) trial randomized 400 patients (276 high risk and 124 intermediate risk) to whole pelvis radiotherapy (46 Gy in 23 fractions) followed by Iodine-125 LDR brachytherapy boost (115 Gy) vs whole pelvis radiotherapy (46 Gy in 23 fractions) followed by a conformal EBRT boost (32 Gy in 16 fractions).[61] All patients were treated with twelve months of ADT with a leutenizing hormone releasing hormone agonist plus a non-steroidal antiandrogen for at least one month. With a median follow-up of 6.5 years, patients receiving brachytherapy boost were half as likely to have biochemical recurrence at 9 years (17% vs 37%; $P < 0.01$). Unfortunately, those randomized to LDR brachytherapy boost had a higher prevalence of late grade 3 or higher toxicity (8% vs 2%; $P < 0.01$). Theoretically, with HDR brachytherapy, lower rates of late toxicity could be hypothesized given the potential dosimetric advantages mentioned above.

Monotherapy

Historically, the primary role of HDR brachytherapy in patients with high-risk prostate cancer has been as a boost after the completion of EBRT. This is because many physicians believe that patients with high-risk disease may warrant pelvic EBRT and have extraprostatic disease that may not be adequately covered with brachytherapy. However, some investigators suggest that with plan optimization and inverse planning, HDR brachytherapy can provide adequate coverage for lesions with extraprostatic extension.[62-64]

In the largest series of HDR brachytherapy monotherapy in the literature, 718 patients (55% low risk, 25% intermediate risk, and 20% high risk) were treated with TRUS-guided HDR monotherapy using the following schedules: 9.5 Gy × 4 fractions (2 implants) or 11.5 Gy × 3 fractions (3 implants).[63] In the entire cohort, 21% received ADT (median duration of 9 months). With a median follow-up of 52 months, the 8-year bDFS was 90% and the rates of acute GU and GI toxicity was 5.4% and 0.2%, respectively. The rates of late grade 3 GU and GI toxicity was 3.5% and 1.6%, respectively. Additionally, 81% of patients reported erectile function suitable for intercourse (with or without the use of erectile aids). In the high-risk cohort, ADT was administered to 56% of patients and the 8-year bDFS was 82%.

More recently, Yoshioka et al[65] published the results of 190 patients (111 high risk and 79 intermediate risk) treated with a single HDR implant and the following schedules: 48 Gy/8 fractions, 54 Gy/9 fractions, or 45.5 Gy/7 fractions. Overall, 73% of all patients received ADT (median duration of 2 years). With a median follow-up of 92 months, the 8-year bDFS was 91% for the entire cohort and the cumulative incidence of late grade 2-3 GU and grade 2-3 GI toxicity at 8 years was 10% and 4%, respectively. In this cohort of 190 intermediate- and high-risk patients who did not receive pelvic EBRT, only 3 (1.5%) failed in the pelvis. In patients with high-risk prostate cancer, ADT was administered to 94% of patients and the 8-year bDFS was 77%.

Focal Boost of Dominant Intraprostatic Lesion

HDR has been investigated for focal boosting of MRI detected dominant intraprostatic lesions (DILs), and has been shown to be feasible[66-68] in combination with ADT.[69] Generally, HDR appears to be superior to external beam treatment in terms of dosimetry.[70] The largest report involves 15 patients with intermediate-high–risk prostate cancer with a median follow-up of 18 months.[71] Early biochemical response was "good in all patients" though not reported. Of 15 patients, 3 experienced acute grade 2 GU toxicity and 2 had acute grade 2 GI toxicity. Robust and long term information regarding clinical outcomes are therefore still lacking.

In conclusion, HDR brachytherapy is a safe and effective treatment modality for dose escalation, either as a boost after EBRT or as monotherapy. Recent technological advances have allowed for improvements in plan optimization and inverse planning, resulting in highly conformal dose distributions that maximize dose to the target whereas minimizing dose to the urethra, bladder, and rectum. Whether HDR brachytherapy is superior to other treatment modalities that attempt to boost dose to the prostate should be the subject of further clinical research.

Nonradiotherapy and Nonsurgical Options

Alternative therapies to radiation and surgery continue to be investigated for the treatment of high-risk disease with the intent of delivering treatment focally. The most widely studied include HIFU and cryoablation. Both of these technologies aim to deliver prostate ablative treatment in a minimally invasive manner and in particular are being investigated as a middle ground alternative to active surveillance and whole-gland treatment. Unfortunately, long term data remain lacking, and the utility of a focal therapy for high-risk disease remains unclear and controversial.[72] Furthermore, most investigation of focal therapy has centered on low-risk disease.[73]

High-Intensity Focused Ultrasound

HIFU therapy attempts to deliver thermal energy to the prostate, causing coagulative necrosis, and has largely been investigated for low-risk disease. However, some data on intermediate and high-risk disease do exist. A German study retrospectively investigated 704 patients, of whom 78% had intermediate- or high-risk disease. Notably, 1440 cases were initially identified but 736 were excluded from analysis for one reason or another. In this highly selected cohort, there was a striking 19%-24% risk of bladder neck scar or stenosis, and a likelihood of urinary incontinence of 3.26%. Rectourethral fistula, chronic perineal pain, and other toxicities were noted—though at a rate of less than 1%. The need for salvage therapy was required in 32% of high-risk patients.[74] The type of salvage therapy required was not specified (though typically local salvage therapy involves radical prostatectomy or radiotherapy). Notably, salvage radical prostatectomy post-HIFU are suggested to have more significant toxicity and worse biochemical control compared with salvage radiotherapy,[75] though comparative studies do not exist.

Though the above German study was considered encouraging data by urology editorialists[76,77] these findings do indicate a treatment that is reportedly more toxic and potentially less efficacious than modern radiotherapy treatments. Other investigators have also noted the possibility of a rectourethral fistula after HIFU.[78] Therefore, in light of existing radiation technology that is arguably more comprehensive and less toxic, the role of HIFU in high-risk prostate cancer patients is likely limited, and will be reserved for low-risk patients or those patients who require focal salvage therapy after radiation.[79] Even in these patients, further data are needed before appropriate efficacy and toxicity can be proven.

Cryoablation

Cryotherapy (otherwise known as cryoablation) attempts to create focal areas of freezing (to below negative 30°C) and thus causing cell death. As freezing the entire prostate is obviously problematic, most studies have focused on hemiablation or focal (lesion targeted) therapy. The largest hemiablation cryotherapy study found that of 73 patients, continence was maintained in 100%, and 86% had potency sparing.[80] All of these patients, however, had unilateral and low-intermediate–risk disease. Cryoablation has been also investigated as focal salvage therapy after recurrence of disease post-radiation.[79] However, the use of cryotherapy for high-risk disease has not been investigated and should be considered highly experimental.

Other Focally Delivered Therapies

Other focally directed therapy,[72] such as photodynamic therapy, photothermal ablation and RFA have been proposed for the treatment of prostate cancer. Though most series are small, there are multiple ongoing clinical trials that can hopefully shed light on the utility of these experimental therapies.[72]

Photodynamic therapy uses transperineally inserted fiber optic catheters that deliver light to the prostate. This light, in combination with a photosensitizing agent (that would ideally preferentially locate to the prostate and prostate cancer) attempts to cause cancer death via vascular damage and cellular injury. Very little data exist to support the use of photodynamic therapy in prostate cancer. In a recent systematic review of focal therapy for prostate cancer[81] only two studies were found that used photodynamic therapy as primary treatment.[82,83] Neither of these studies included high-risk patients. No studies are ongoing for the use of photodynamic therapy in high-risk patients.[81]

Photothermal ablation, also known as laser interstitial thermal therapy (LITT) has been readily embraced for the treatment of intracranial disease.[84] However, given its potential ability to deliver thermal energy in a more controlled and image-guided manner, LITT is also being investigated for prostate cancer.[85] The largest series is a phase I trial which indicated reasonable toxicity in a group of low-risk men.[86] As with other focally directed non–whole gland treatment, its utility for high-risk disease may be limited. In contrast, LITT may be a promising therapy for cases of local recurrence after radiotherapy for high-risk prostate cancer. Limiting its use is the required presence of an MRI within the operating suite. Further study is obviously needed.

RFA delivers electrical current to the target through an interstitial electrode to cause cell death via thermal damage. A pilot study was completed in 2013[87] but has yet to publish its results despite enrolling only 5 patients. A second study reported almost 20 years ago was performed to demonstrate the potential feasibility of RFA in patients who were scheduled for prostatectomy.[88] "Extensive" coagulative necrosis was reported in this study, and only one patient who underwent the RFA procedure did not subsequently undergo surgery. Therefore, given the lack of data concerning RFA and the treatment of any prostate cancer, the use of RFA for prostate cancer remain experimental.

Conclusion

The treatment of high-risk prostate cancer continues to evolve. Not only treatment-related toxicities are of critical importance, but high-risk disease prostate cancer still requires the comprehensive treatment of the prostate. Escalating dose to the prostate using HDR, SBRT, or proton radiotherapy may improve disease control, though further study is needed. Most new radiation therapy (SBRT, HDR, and proton beam radiation) has been largely investigated in combination with regional radiation therapy. Though the evidence is evolving, the use of SBRT, HDR, and modern proton beam radiation is promising. Nonradiation focal therapy has been proposed mainly for partial gland treatment, and its use in high-risk patients remains experimental.

Future directions in the treatment of high-risk prostate cancer require further evidence as to the risks and benefits of SBRT and HDR boost therapy. The optimal doses, treatment volumes, and technique remain to be elucidated before SBRT

and HDR boost can been routinely incorporated into standard therapy. Given randomized evidence supporting earlier chemotherapy in the metastatic setting and potentially in the very high-risk setting,[89] how to incorporate systemic therapy and new focal technologies should be an area of further investigation.

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