VANGUARD AND NEXT FRONTIERS

Y-90 Radioembolization for Prostate Cancer

The potential role of yttrium-90 radioembolization in prostate radiotherapy.

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Prostate cancer is one of the most common malignancies, with almost 200,000 cases diagnosed in 2020. For the last 30 years, the mainstays of treatment for prostate cancer have been either surgery or radiotherapy (RT) depending on disease stage. For patients with clinically localized, intermediate-risk disease (> 1/2 prostate gland volume, > T2B disease) or high-risk disease (T3), RT with either transperineal implanted brachytherapy (BT) seeds and/or external beam RT (EBRT) remain standard treatment options. However, current strategies are not without their costs in terms of morbidity and detriments to quality of life (QOL). Serum prostate-specific antigen (PSA) is closely monitored following RT, with the goal of reaching a PSA nadir to indicate clinical success, which can take 18 to 36 months.[1] Biochemical recurrence (as measured by PSA response) after curative-intent RT remains an issue, affecting 30% to 50% of patients.

Although radiation dose escalation improves biochemical response and overall survival, it is associated with a significant increase in > grade 2 early and late gastrointestinal and genitourinary adverse events in up to 30% of patients.[1] These toxicities often require intervention with either medical or surgical management. Toxicities to the bladder and rectum stem from the proximity to the prostate and inclusion within the treatment field (especially for EBRT doses > 70 Gy), with symptoms seen in up to 30% of patients.[2,3] Urinary toxicities seen with current RT continue to persist despite improved radiation delivery (eg, intensity-modulated RT), leading to long-term QOL issues.[4,5] This can include lifestyle-altering hematuria and lower urinary tract symptoms (LUTS) not easily amenable to standard therapeutic options.[6] Similarly, rectal toxicities remain an issue with current approaches due to the proximity of the rectum to the prostate. Strategies to mitigate these complications have generated mixed results, without clear benefit.[7] Erectile dysfunction arises from off-target radiation deposition to the penile soft tissues and neurovascular bundle (NVB).[8] Current RT approaches are limited by poor visualization of the NVB on cross-sectional imaging.[8] Patients are therefore left with a difficult treatment decision, choosing between disease control and QOL. Treatment decisions are therefore complex and are driven by a host of factors, including risks of urinary, erectile, and bowel dysfunction after therapy.[5]

PROSTATE ARTERY EMBOLIZATION FOR PROSTATE CANCER

Prostate cancer treatment requires a novel approach to tackle these shortcomings of standard-of-care therapy. One such strategy is employing an endovascular approach. Prostate artery embolization (PAE) has emerged as a safe and efficacious treatment for LUTS secondary to benign prostatic hyperplasia (BPH).[9,10] The technical and clinical success and favorable side effect profile demonstrated in well-conducted trials in PAE for BPH have spurred interest for developing PAE as an oncologic therapy. Modern techniques including cone-beam CT and appropriate coiling have the potential to maintain a favorable side effect profile.

However, endovascular results of PAE for prostate cancer to date have been disappointing in terms of efficacy. Pisco et al examined the role of chemoembolization in 20 patients with T2N0M0 disease.[11] Chemoembolization was performed with a combination of *Chelidonium majus* extract, docetaxel, and

150–300-µm particles. Therapeutic delivery was technically successful in 80% of patients; however, biochemical success (defined as PSA < 2 ng/mL at 1 month) was achieved in only 62.5% of patients. Drawing conclusions from this early study outside technical feasibility is difficult, as the authors used definitions of biochemical success and failure distinct from standard criteria used for either surgery or RT. A subsequent study by Mordasini et al examined 12 patients with localized disease (< T2A) treated with 100-µm bland embolization prior to radical prostatectomy.[12] On explant, all 12 patients had viable cancer foci, with two patients developing bladder wall necrosis requiring resection. Although the authors of both studies demonstrate the endovascular approach is feasible, the initial attempts demonstrated that careful technique is paramount for safety, similar to PAE for BPH, and that bland and chemoembolization likely are not sufficiently tumoricidal to achieve sufficient disease control necessary to transform prostate cancer management.

YTTRIUM-90 RADIOEMBOLIZATION FOR PROSTATE

Yttrium-90 (Y-90) radioembolization offers the potential to maximize RT dose conformity to the prostate gland while minimizing off-target effects through an endovascular approach. Prostate cancer is particularly sensitive to large radiation doses delivered in the fewest possible fractions. Clinically, this has driven interest in hypofractionation and other new dosing strategies. However, these efforts have been met with the same limitations of current standard treatments, namely dose-limiting toxicities to the surrounding tissues.[13] Due to the short penetration of β radiation, Y-90 theoretically represents an ideal isotope to treat the disease as effects to adjacent organs will be markedly limited compared to other RT sources such as iodine-125, γ rays, and x-rays, which penetrate more tissues.[14] Furthermore, positron emission tomography after Y-90 may confirm the dose delivery to ensure quality control and effective patient management, which is lacking from current standard-of-care radiation therapy.

The lessons we have learned in hepatocellular carcinoma in the liver have demonstrated that standard RT considerations, such as fractionation, dose limits, adjacent organs at risk, and motion, can be overcome through vascular delivery.[15] Furthermore, Y-90 radioembolization in the liver can deliver higher and often ablative tissue doses while sparing adjacent tissue.[16,17] By leveraging our experience with both PAE and Y-90 radioembolization, we may develop the next generation of prostate RT.

TECHNICAL CONSIDERATIONS

Many questions still remain with regard to Y-90 radioembolization for prostate cancer. Is delivery technically feasible and safe? Can the prostate and adjacent structures such as the bladder, rectum, urethra, and NVBs tolerate these doses of radiation?

To study these questions, we evaluated feasibility, safety, and dose distribution in a standard canine model used for surgical and endovascular therapies.[18] In our dose-escalation study, 14 animals were treated with Y-90 radioembolization to half of the prostate gland, with the contralateral side serving as a control. Animals were followed with serial imaging and clinical evaluation to look for standard toxicities seen after RT, including radiation cystitis, proctitis, urethra strictures, and damage to the NVB. With dose escalation up to 200 Gy (equivalent to 400 Gy EBRT in EQD2 [equivalent dose in 2-Gy fractions] and approximately 5X the standard of care), we saw dose-dependent atrophy of the treated glands with no clinical toxicities across all animals. On gross examination and histopathology postradiation, tissue changes were localized to treated prostatic tissues only; all surrounding organs at risk were spared of any deleterious effects. Specifically, there was no evidence of radiation cystitis, radiation proctitis, urethral strictures, or damage to the NVB.

The concept of prostate artery radioembolization presents many exciting opportunities for disease management. Given the radiobiology of prostate cancer, Y-90 radioembolization offers the possibility of a single-session outpatient treatment for patients with localized disease. Additionally, the potential for single-session therapy obviates the need for complex modeling of current RT, which must account for patient movement, organs at risk, and various other dose constraints.[15] These limitations are an integral component of standard EBRT and are all mitigated by the application of RT using catheter-based transarterial approaches.

For patients with higher-risk disease, Y-90 radioembolization may be combined with EBRT. There is potentially a role in patients with large glands and baseline LUTS. Treatment of glands > 60 mL is currently limited due to technical constraints.[19] These patients often require androgen deprivation to shrink their gland to a "treatable" size, which is associated with a significant side effect profile. Y-90 offers the potential to treat both the cancer and LUTS without neoadjuvant hormonal manipulation. As demonstrated in the preclinical study, targeted delivery of radiation doses higher than standard-of-care RT is both feasible and safe.[18] The dose-escalation limits and toxicities currently restricting EBRT/BT efficacy in the prostate may no longer hold true.

Similar to our experience in the liver, endovascular radiation delivery with Y-90 may break the standard dogma of prostate radiation therapy, significantly increasing the radiation dose to the prostate while limiting unwanted side effects and ultimately improving QOL. ■

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