Prostatic Artery Chemoembolization: The Next Frontier in Prostate Cancer Therapy?

Transarterial embolization techniques for treating liver malignancy are ready for adaptation to prostate cancer applications.

BY RAJ AYYAGARI, MD

Prostate cancer is the second most common cancer in men and the fifth leading cause of cancer death in men worldwide.[1,2] In the United States, approximately 165,000 new cases of prostate cancer will be diagnosed and 29,000 patients with prostate cancer will die in 2018. Approximately 80% of all men will develop prostate cancer in their lives, so effective diagnosis and treatment are immensely important goals for our health care system.[1]

Unfortunately, the detection of prostate cancer can be challenging, and once it is detected, the indolent nature of the disease can make management decisions difficult. With any cancer screening, the risks of overdiagnosis and overtreatment play a prominent role in decision-making, and overly aggressive treatment of prostate cancer has been shown to expose patients to significant risk.[3] Once significant suspicion for prostate cancer is raised, patients typically undergo a biopsy. Classically, this is a random ultrasound-guided transrectal needle biopsy, which is prone to sampling error, but some centers offer MRI-guided prostate biopsies that improve detection rates of clinically relevant cancers.

CURRENT PROSTATE CANCER TREATMENT PARADIGM AND ITS CHALLENGES

After prostate cancer is detected, a complex individualized management decision must be made based on the severity of the detected disease, the health and life expectancy of the patient, and the potential risks and side effects of any proposed treatment strategy. Patients are stratified into risk groups based on prostate-specific antigen (PSA) level, biopsy specimen pathologic grading, and disease extent. Patients with localized, unfavorable, intermediate- or high-risk disease are offered definitive radical prostatectomy or radiation therapy, and those with localized very high-risk disease or locally advanced disease may be offered extended lymph node dissection with surgery or androgen deprivation therapy (ADT) with radiation.[4] Patients with metastatic disease are offered ADT and possibly radiation. However, patients diagnosed with localized, favorable, intermediate- or low-risk cancer are offered active surveillance in addition to definitive treatment options, and for patients with very low-risk cancer, active surveillance is the primary recommendation.[5] Active surveillance consists of repeat PSA level testing every 6 months, repeat digital rectal exam yearly, and yearly follow-up biopsy or possibly MRI to rule out any new or previously missed higher-grade disease.

For lower-risk patients, the binary choice between active surveillance and definitive therapy is currently the best we can do to fit patients with a spectrum of disease into the two available management "bins," a strategy which, unfortunately for many patients, risks mismatching the relative severity of their disease with a chosen level of treatment. A certain proportion of undertreating or overtreating patients is tolerated so as to strike an optimal overall therapeutic balance for the population as a whole. This is where the minimally invasive image-guided endovascular techniques of interventional radiology could play a major role, to perhaps bring about a paradigm shift in prostate

cancer treatment by offering more intermediate treatment options.

LOCOREGIONAL THERAPY MODEL: MORE GRANULAR TREATMENT OPTIONS

For many years, imaged-guided transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) techniques have played a dominant role in the management of hepatocellular carcinoma (HCC). For cancers too large, diffuse, or difficult to ablate percutaneously or resect surgically, TACE and TARE procedures have shown great success in providing significant improvement in overall survival, disease-free survival, and recurrence rates.[6] Although TACE and TARE are not considered curative, such interventions are often quite successful at bridging a patient to definitive liver transplantation. These procedures are the mainstay of the locoregional therapy model that provides a granular array of treatment options that can be readily tailored to an individual patient's disease severity and overall health. Furthermore, such procedures are widely available and technically straightforward, are performed on an outpatient or overnight stay basis with short recovery times and minimal side effects, and can be easily and safely repeated as needed.

Can a locoregional therapy model be successfully applied to prostate cancer to provide less invasive, better-tailored, lower-risk treatment options for those with lower-grade disease or those too sick to tolerate more aggressive treatments? Prostate cancer is a fundamentally multifocal disease, so existing focal percutaneous ablative therapies designed to treat discrete lesions characterized by MRI have limitations—no imaging modality can reliably detect all foci of bona fide histopathologic disease.[7] Interestingly, more aggressive tumors have been shown to be more susceptible to ischemia that disrupts their metabolism.[7] This observation has led many to wonder if transarterial embolization could play a role in treating prostate cancer as it does in HCC.

PROSTATIC ARTERIAL EMBOLIZATION: FOR BPH OR PROSTATE CANCER?

Perhaps the most exciting advances foretelling such a paradigm shift in prostate cancer treatment have been in the realm of prostatic artery embolization (PAE), which has to date been used to treat symptoms related to benign prostatic hyperplasia (BPH). The procedure works by causing irreversible necrosis of prostatic adenomatous tissue, which causes the gland to shrink and soften, especially in the central periurethral tissue, thereby relieving pressure on the prostatic urethra and diminishing obstruction to urinary outflow. PAE was initially described in 2000 to treat severe prostatic arterial bleeding in a patient with massive BPH.[8] Subsequently, pioneering groups led by Dr. João Pisco in Portugal and Dr. Francisco Carnevale in Brazil forged forward with numerous studies demonstrating safety and remarkable efficacy of the PAE technique for treating BPH. Many more groups throughout the world have since built upon this foundation, replicating their results, comparing PAE with transurethral prostate resection, and making numerous refinements in the technique and how it can be used to manage lower urinary tract symptoms, urinary retention, and hematuria.[9,10]

Interestingly, some authors have proposed adjunctive roles for PAE in the setting of prostate cancer treatment. Embolization used to shrink large glands prior to radical prostatectomy could allow for less blood loss during resection and perhaps allow for a smaller cystotomy, which could contribute to improved urinary continence after resection. PAE has also been successfully used to control prostatic bleeding after radiation therapy. Of course, the true paradigm shift would be the successful development of a transarterial embolization procedure capable of directly treating prostate cancer. Such a procedure would need to be technically feasible, safe, and effective at palliating or treating some subset of prostate cancer patients.

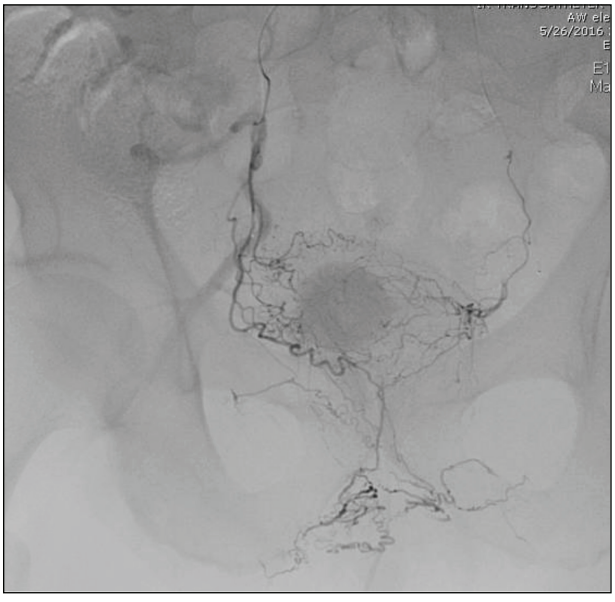

Figure 1. Coronal angiogram showing right inferior vesicular artery contrast injection with readily visualized collaterals to bilateral superior vesicular, inferior vesicular, and internal pudendal arterial branches. These collaterals need to be identified and excluded for safe and effective PAE.

PROSTATIC ARTERY CHEMOEMBOLIZATION

Technical Feasibility: Arterial Anatomy and Tumor Distribution

Although the PAE procedure is technically challenging, its fairly steep learning curve is surmountable with training and experience. To safely embolize the prostate gland and avoid nontarget embolization, many periprostatic arterial shunts and collateral connections must be protected by coil occlusion, excluded with an occlusive balloon-tipped microcatheter, or carefully avoided by taking advantage of competitive inflow and shifting flow dynamics (Figure 1).

Another potential feasibility issue for transarterial prostate cancer therapy is the observation that approximately 80% of prostate cancers arise in the peripheral zone of the prostate gland, whereas the gland infarction seen when PAE is performed to treat symptomatic BPH is primarily in the central periurethral tissues, as demonstrated by postembolization imaging studies (Figure 2).[8] However, the degree of tissue penetration with an embolic agent is significantly affected by the diameter of the embolic particle. Most studies have looked at images obtained from glands embolized with 300–500-µm Embosphere microspheres (Merit Medical Systems, Inc.), whereas TACE procedures performed in the liver typically employ LC Bead particles (BTG International) as small as 70–150 µm or a liquid embolic agent (Lipiodol, Guerbet LLC). Furthermore, it is not certain that the infarction seen in the central parts of the gland after PAE would be necessary to treat a cancer in the peripheral zone, particularly if the injected particle were not just a simple embolic agent, but rather a vehicle for a chemotherapeutic or brachytherapeutic agent. Images acquired from a prostatic perfusion mapping study by Abele et al, as well as the standard cone-beam CTA images routinely acquired during a PAE procedure (Figure 3), demonstrate that injected agents uniformly reach and reside in the periphery of the gland.[12]

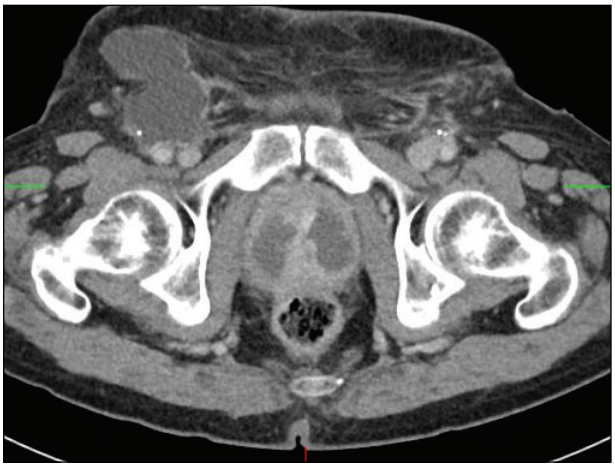

Figure 2. Axial CTA of a patient 4 months after PAE, showing bilateral avascular periurethral tissue, which is indicative of excellent bilateral necrosis corresponding to an excellent clinical result but with viable peripheral zone tissue remaining. An incidental note is made of a right groin hematoma after a vascular surgeon's attempt at placing an aortic stent graft.

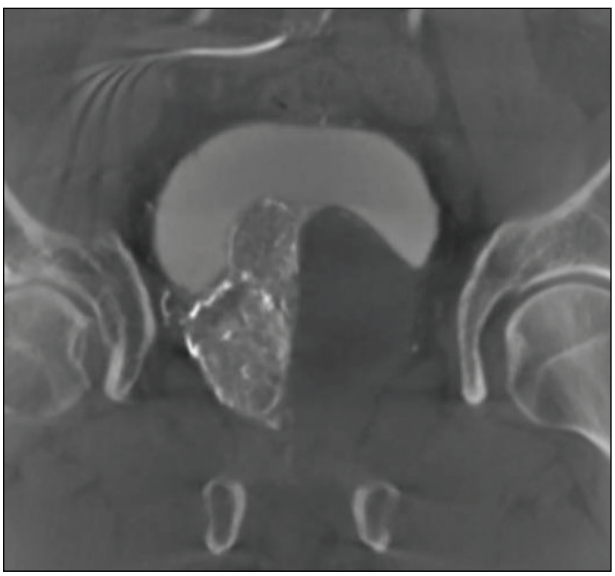

Figure 3. Coronal cone-beam CT performed during a PAE procedure demonstrating that the injected agent readily distributes throughout the entire hemigland being treated, including the central periurethral tissues and the peripheral zone.

Safety and Efficacy

Dozens of studies reporting on thousands of patients over the past decade have demonstrated that we can safely embolize the prostate gland in an outpatient setting with minimal complications and adverse side effects in patients of all relevant ages with a wide range of medical comorbidities.[9,10,13-16] Regarding the safety of TACE or TARE to treat malignancy, the scientific literature is replete with thousands of reports demonstrating the safety and efficacy of these techniques when treating tumors in the liver.

Recently, a preliminary demonstration of the technical feasibility and safety of prostatic artery chemoembolization (PACE) to treat prostate cancer was reported by Pisco et al.[17] Twenty patients with prostate cancer underwent PACE. Their mean Gleason score range was 6 to 10, and their staging was T2, N0, M0. PACE was performed with a combination of *Chelidonium majus*

extract, docetaxel, and 150–300-µm Embosphere particles. All patients were treated on an outpatient basis and discharged home the same day. Technical success, defined as bilateral PAE, was achieved in 16 of 20 patients. Biochemical failure, defined as PSA decrease to < 2 ng/mL and recurrence to > 2 ng/mL within 1 month, was seen in three of 16 patients. Biochemical success at 12 to 18 months was seen in 10 of 16 patients. Adverse events were few and mostly minor. Multiparametric prostate MRI obtained at 12 months for the 10 patients with biochemical successes showed that of the seven patients with a Gleason score of 6, no changes were seen in the lesions, whereas the three patients with a Gleason score > 7 had > 50% tumor size reduction.

Subsequently, Mordasini et al reported on 12 patients with prostate cancer who underwent PAE using 100-µm Embozene microspheres (Boston Scientific Corporation) and then radical prostatectomy 6 weeks later.[7] On pathologic evaluation of the resected specimens, two patients had complete necrosis of their index lesions, and five patients had partial necrosis of their lesions. Of note, all 12 patients had previously undetected secondary foci of viable disease. There were few adverse events.

FUTURE DIRECTIONS: PROSTATE EMBOLIZATION AS AN ANSWER TO ACTIVE SURVEILLANCE

We know that PAE is technically feasible and safe, and studies are beginning to show safety and some efficacy of chemoembolization in the treatment of prostate cancer. These pioneering studies are paving the way for more expansive and systematic trials that will further explore this potentially game-changing approach. Perhaps someday soon, we might even be able to use TARE as another means to deliver brachytherapy to the gland, if a radioisotope with favorable dosimetry parameters could be developed and appropriately packaged. Furthermore, any agents that might be developed to sensitize prostate cancers to radiation or chemotherapeutic treatments could be theoretically delivered in a transarterial fashion directly to the prostate gland.

Although these transarterial embolization techniques may never demonstrate equivalent efficacy to surgical or ablative procedures in treating prostate cancer, they show great promise in treating patients with localized lower-grade disease who many never need those more invasive procedures. Such techniques may provide sufficiently effective treatment options for patients who would otherwise have to live with the anxiety of active surveillance or the risks and side effects of definitive treatments such as urinary incontinence, erectile dysfunction, and radiation proctitis or cystitis. Moreover, these embolization procedures would still preserve a patient's options to transition to more definitive treatments as appropriate.

CONCLUSION

Endovascular techniques have tremendous future potential to bring about a revolutionary paradigm shift in the treatment of prostate cancer. ■

1. Stewart BW, Wild BW, editors. World Cancer Report 2014. Geneva, Switzerland: World Health Organization; 2014.
2. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011;61:69-90.
3. Alberts AR, Schoots IG, Roobol, MJ. Prostate-specific antigen-based prostate cancer screening: past and future. Int J Urol. 2015;22:524-532.
4. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision-making, and care options [published online December 15, 2017]. J Urol.
5. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part II: recommended approaches and details of specific care options. J Urol. 2018;199:990-997.
6. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology. 2003;37:429-442.
7. Mordasini L, Hechelhammer L, Diener P, et al. Prostatic artery embolization in the treatment of localized prostate cancer: a bicentric prospective proof-of-concept study of 12 patients. J Vasc Interv Radiol. 2018;29:589-597.
8. DeMeritt JS, Elmasri FF, Esposito MP, Rosenberg GS. Relief of benign prostatic hyperplasia-related bladder outlet obstruction after transarterial polyvinyl alcohol prostate embolization. J Vasc Interv Radiol. 2000;11:767-770.
9. Bagla S, Martin CP, van Breda A, et al. Early results from a United States trial of prostatic artery embolization in the treatment of benign prostatic hyperplasia. J Vasc Interv Radiol. 2014;25:47-52.
10. de Assis AM, Moreira AM, de Paula Rodrigues VC, et al. Prostatic artery embolization for treatment of benign prostatic hyperplasia in patients with prostates > 90 g: a prospective single-center study. J Vasc Interv Radiol. 2015;26:87-93.
11. Kisilevzky N, Faintuch S. MRI assessment of prostatic ischemia: best predictor of clinical success after prostatic artery embolization for benign prostatic hyperplasia. Clin Radiol. 2016;71:876-882.
12. Abele JT, Moore R, Tymchak W, Owen RJ. Prostate perfusion mapped by technetium-99m macroaggregated albumin after selective arterial injection. J Vasc Interv Radiol. 2015;26:418-425.
13. Carnevale FC, da Motta-Leal-Filho JM, Antunes AA, et al. Quality of life and clinical symptom improvement support prostatic artery embolization for patients with acute urinary retention caused by benign prostatic hyperplasia. J Vasc Interv Radiol. 2013;24:535-542.
14. Bhatia S, Sinha V, Harward S, et al. Prostate artery embolization in patients with prostate volumes of 80 mL or more: a single-institution retrospective experience of 93 patients [published online September 11, 2018]. J Vasc Interv Radiol.
15. Pisco JM, Rio Tinto H, Campos Pinheiro L, et al. Embolisation of prostatic arteries as treatment of moderate to severe lower urinary symptoms (LUTS) secondary to benign hyperplasia: results of short- and mid-term follow-up. Eur Radiol. 2013;23:2561-2572.
16. Pisco JM, Bilhim T, Pinheiro LC, et al. Medium and long term outcome of prostate artery embolization for patients with benign prostatic hyperplasia: results in 630 patients. J Vasc Interv Radiol. 2016;27:1115-1122.
17. Pisco J, Bilhim T, Costa NV, et al. Safety and efficacy of prostatic artery chemoembolization for prostate cancer—initial experience. J Vasc Interv Radiol. 2018;29:298-305.

Raj Ayyagari, MD
Assistant Professor of Radiology and Biomedical Imaging
Adjunct Assistant Professor of Urology
Yale School of Medicine
New Haven, Connecticut
raj.ayyagari@yale.edu
Disclosures: Paid consultant to Merit Medical Systems, Inc. and Embolx, Inc.