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Prostatic Artery Embolization: A Potential Treatment Option for Localized Prostate Cancer

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Editorial

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are two common problems in aging men, and pose increasing concerns in health care and social burden as the population ages. In the United States, PCa accounts for over one-quarter of newly diagnosed cancers in men and ranks as the second leading cause of cancer-related death; it is estimated that one in twelve men died of cancer is due to PCa in 2016 [1]. During the past decades, numerous emerging techniques characterized by minimal invasion in the management of BPH and/or PCa have gained in popularity worldwide, including cryosurgery, high-intensity focused ultrasound (HIFU), radiofrequence ablation, microwave therapy , IRE, and photodynamic therapy etc. More recently, prostatic artery embolization (PAE) has showed promising results in animal experiments and clinical practice in relieving lower urinary tract symptoms (LUTS) in patients with BPH. Transcatheter arterial embolization of the prostate has long been used since 1970s to stop bleeding after prostate needle biopsy or transurethral prostatectomy and for intractable gross hematuria of prostatic origin [2]. In 2000, DeMeritt et al. [3] first reported superselective PAE by the use of coaxial microcatheter and polyvinyl alcohol particles to embolize prostatic artery in a BPH patient with severe gross hematuria, requiring a blood transfusion. Not surprisingly, bleeding was immediately terminated even though PAE had been performed only on one side of the prostatic artery; however, the patient reported significant relief in LUTS, the prostate shrank and PSA decreased remarkably during 6-month follow ups. The anecdotal findings revealed a potential therapeutic option in the management symptomatic BPH. Ever since Sun et al. first published an animal experimental study that confirmed the technical feasibility, efficacy, and safety of PAE for the treatment of BPH in 2008 [4], PAE attracted much academic attention and underwent its rapid translation from bench research into clinical practice [5]. In 2010, Carnevale et al. [6] reported successful application of PAE as primary treatment in 2 patients with acute urinary retention due to BPH. Subsequently, Pisco et al. [10] published their clinical series of PAE in the management of symptomatic BPH [7]; in the same year, Sun et al. [8] reported their animal experiments in a canine model revealing technical efficacy of PAE and suggesting its potential application in patients with localized PCa. Up to now, approximately 2000 patients with BPH have undergone PAE worldwide. As indicated in an official position statement of Society of Interventional Radiology, PAE for BPH is a novel and promising therapy that appears safe and efficacious with high patient satisfaction and low repeat intervention rates [9]. The major rationale of PAE behind its therapeutic effects is to destroy targeted tissue in the prostate by creating local devascularization. During the procedure of PAE, a microcatheter is selectively inserted into the prostatic arteries, through which micro particles are injected to occlude small precapillary arterioles, thus inducing irreversible ischemic injury. This peripheral embolization yields extensive and complete intraprostatic ischemia (anoxia), directly resulting in ischemic necrosis or infarction and associated inflammatory reactions, including cytotoxic edema and leukocytic infiltration [2]. Apart from ischemic necrosis, apoptosis is another important pathologic mechanism behind PAE-induced prostate ablation. In general any event that can result in necrosis by cell destruction can induce apoptosis. The hypothesis of ischemia-induced apoptosis is supported by previous experiments in rats and dogs, and clinical observation in BPH patients during follow-ups after PAE [2]. More importantly, androgen-related apoptosis behind PAE is of great clinical implications. The pivotal effects of androgens to development and growth of the normal prostate, as well as pathogenesis of BPH or prostate cancer, depend on a functional androgen-signaling axis. The major components of the axis include: 1) testosterone synthesis, 2) conversion of testosterone to DHT outside and inside of the prostate, 3) transport of testosterone and DHT to target tissue, and 4) binding of DHT to androgen receptor with consequent modulation of the expression of genes and secretion of growth factors that control cellular proliferation and apoptosis [2]. Therefore, interventions in blockage of the androgen-signaling axis at any point would

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yield substantial biological effects. PAE may terminate blood supply to prostate and devascularize the gland tissue. Hence the functional androgen-signaling axis is interrupted by blocking the transport of testosterone and DHT to the prostate, so that the intraprostatic testosterone and converted DHT would be at extremely low levels, thereby achieving apoptosis and subsequent therapeutic responses, similarly to other clinical therapies, such as finasteride and surgical/chemical castration. However, the "intraprostatic castration effects" remains to be tested in both animal experiments and clinical trials. While PAE in the management of BPH is for the purpose of relieving LUTS, its application in PCa is relatively simple and straightforward, just for tissue (tumor) ablation. This is because, in the treatment of BPH, the amount of tissue ablated or prostate volume reduction following PAE is not always correlated with clinical relief in either severity of bladder outlet obstruction (BOO) or LUTS. The latest data in clinical trials highlight promising efficacy and safety of PAE in the management of BPH. To evaluate efficacy of PAE in BPH patients with prostate volume (PV) > 100 cm^3, Pisco et al. [10] reported 152 patients 48-87 years old with mean PV of 134.2 cm^3 ± 41.8. PAE was technically successful in 149 patients (98.0%). Symptom control was achieved for a median of 18 months ± 15.5. Of interest, among 140 patients whose data were available during follow-ups, 135 (95.4%) patients showed decreased PV. The mean PV decreased by approximately 40% at 18-month follow-up compared with baseline data. PSA decreased from 8.90 ng/mL ± 10.98 before PAE by 3.94 ng/mL ± 10.19 (44%) at 12 months. Furthermore, there was no case reported of erectile dysfunction, retrograde ejaculation, or urinary incontinence after PAE [10]. More recently, during the 41st Annual Scientific Meeting of Society of Interventional Radiology (SIR 2016), Pisco et al. [10] reported a series of 291cases of BPH treated by PAE, young wives of 6 patients had successful pregnancy with alive newborns [11]; Kuang et al. [12] reported a meta-analysis of PAE in total 788 patients with 3 major complications, including vesicular artery dissection during catheterization (0.13%), persistent UTI (0.13%), and focal bladder wall ischemia (0.13%). Taken together, PAE has proved to be effective to ablate prostate tissue, indicated by considerable decrease in serum PSA levels, particularly in patients with large size of prostate volume (PV > 80-100 cm^3). Besides, one striking feature in regard of safety of PAE is related to satisfying quality of life without compromising sexual function or urinary incontinency after PAE.

Currently, minimally invasive therapies, such as cryosurgical ablation of the prostate (CSAP) and HIFU, are recommended as alterative therapeutic options in low-risk or intermediate-risk localized PCa patients who are unfit for radical prostatectomy and radiation therapy. However both CSAP and HIFU have numerous clinical limitations or disadvantages when comparing with PAE. CSAP and HIFU are performed under spinal or general anesthesia, whereas PAE is a typical outpatient procedure performed under local anesthesia. Since the most optimally sized prostate is less than 40 cm^3 for CSAP and HIFU, patients with larger prostate need neoadjuvant androgen ablative therapy lasting several months to downsize the prostate before CSAP or HIFU; PAE has not such a sized limitation, moreover, patients with larger sized prostate have shown promising outcomes as described earlier in the management of symptomatic BPH. Erectile dysfunction is a common complication ranging from 84 to 94% after CSAP [13], and up to 63.7% after HIFU [14]. Urinary incontinence after CSAP was previous reported as high as 15 to 27%, which has dropped to around 7.5% when the third-generation cryosurgery has been applied in clinical practice [15]. In a recent report on HIFU, however, incontinence remained in 30.9% during whole follow-up period [14]. Apparently, PAE has remarkable advantages over CSAP and HIFU in regard of technical safety in this context.

It is a common notion in interventional oncology that the hypervascular tumors are more sensitive to embolization-induced ischemia. PCa is characterized by increased vascularity in pathology. In a study comparing microscopic vascularity in benign and malignant prostate tissue, 14 of 15 radical prostatectomy specimens demonstrated significantly higher vascular density in the areas of carcinoma than in the benign tissues; the carcinoma was associated with an approximately twofold increase in the total number of vessels seen on histology sections [16]. It's reasonable to hypothesize that PAE has potential to ablate index lesion of the localized PCa. Technically, PAE is readily performed by in combination with local infusion of anti-cancer chemicals, such as docetaxel, thus enhancing its therapeutic effects. The concept of the modified prostatic artery chemo-embolization (PACE), together with previously described "intraprostatic castration effects" provides a plausible support to PAE as an alternative therapeutic strategy for localized PCa or even advanced PCa, and needs further address in the future research.

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