Prostate artery embolization as an effective treatment for clinically significant prostate cancer-related hemorrhage: A case report

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Abstract. A 79-year old Caucasian male with metastatic hormone refractory prostate cancer and bilateral nephrostomy was admitted to the emergency department due to 4-day bloody urethral discharge, weakness and dizziness. The patient was treated with the luteinizing hormone-releasing hormone-antagonist and abiraterone acetate plus prednisone, dabigatran 150 mg bid (for atrial fibrillation and coronary heart disease) and 5-aminosalicylic acid for the management of mild ulcerative colitis. Imaging revealed bladder overdistention and blood analysis low levels of hematocrit (HCT) and hemoglobin (HGB) (HCT, 22%; HGB, 7.1 gr/dl). A 22F, 3-way urethral catheter was placed, and blood clots were removed with a syringe. Continuous normal saline irrigation was initiated, and the dabigatran was withdrawn; however, no evidence of control of blood loss was shown. Computed tomography and urography revealed a large prostate lesion invading the bladder neck, a pelvic lymph-node block and lack of blood extravasation. Diagnostic urethrocystoscopy revealed diffuse hematuria from the prostate lesion and bladder neck. Bipolar coagulation was performed in the absence of any significant improvement. Upon withdrawal of intravesical irrigation, the oral consumption of a large water volume (a useful measure to control hematuria and avoid clot formation) could not be applied to the patient due to urine storage and normal voiding being not feasible. Subsequently, the patient was informed on the option of superselective arterial embolization (SAE). Following signing of the relevant consent form, the patient underwent bilateral SAE of prostatic and inferior cystic arteries, while he was in heparin delivery. Dabigatran was re-administered on the 5th postprocedural day and the catheter was removed following 5 days. Following a 4-month follow-up, the patient's condition was stable with no traceable hematuria. In conclusion, the minimal invasiveness of SAE is an attractive option, notably in patients with cardiovascular comorbidities. It appears to be a safe alternative with an acceptable rate of minor complications. The encouraging results and the survival outcomes warrant further evaluation with comparative prospective multicenter studies.

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Introduction

Persistent and recurrent hematuria is a urologic emergency event which is often difficult to be addressed and is related to significant morbidity and mortality. Several etiologic factors predispose to lower urinary tract hematuria with trauma and urogenital malignancy being the most frequently encountered conditions (1-3). Copious amounts of normal saline irrigations may be required to remove blood clots and maintain a macroscopically clear bladder outflow. Other measures to control intractable hematuria include cystoscopic evacuation of the bladder with electrocautery/coagulation of the bleeding vessels, silver nitrate or alum solution irrigation or, if available, bladder overdistention with a Helmstein balloon (1). Should conservative measures fail, open surgical procedures may be undertaken for ligation of the internal iliac arteries or even salvage extirpation of the bleeding organs. The latter methods, however, are frequently associated with unacceptable high morbidity and mortality rates (3,4). In 1974, Hald and Mygind (5) were the first to describe efficient control of massive hematuria originated from the bladder with methods of arterial embolization. Since then, treatment based on selective or superselective arterial embolism is gradually gaining popularity amongst physicians for the management of urinary tract hemorrhage (2,3,6-8). In the present study, the effective control of hemorrhage is reported due to a locally advanced/metastatic hormone refractory adenocarcinoma of the prostate in a patient, which was difficult to be treated.

Case report

A 79-year old Caucasian male was admitted to the Emergency Department of Konstantopouleio-Patision General Hospital of

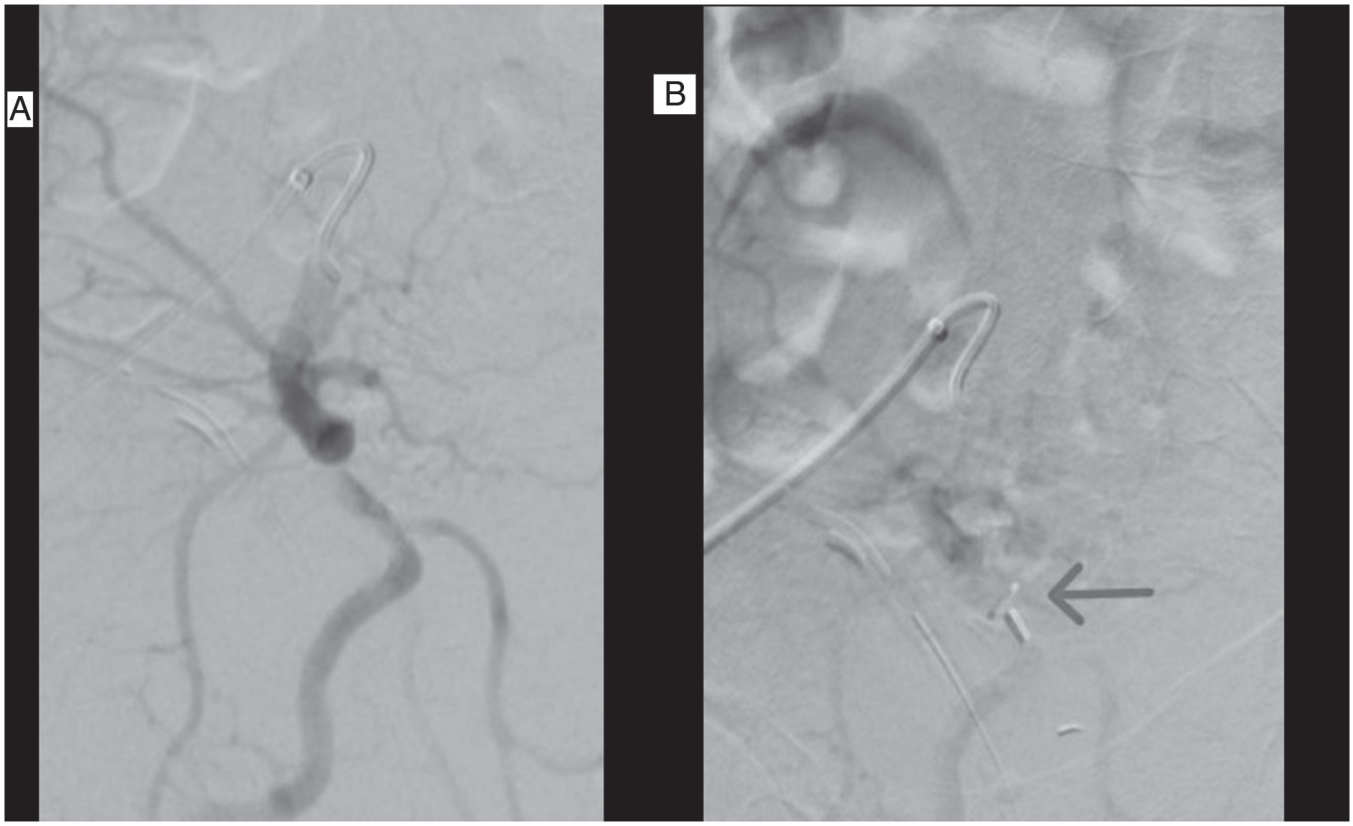

Figure 1. Digital subtraction angiography of the right blood supply of the prostate (A) before and (B) after the placement of nanoparticles (arrow).

Nea Ionia (Nea Ionia, Greece) in April 2024 due to a 4-day persistent bloody discharge from the urethra, weakness and dizziness. The patient was pale with prolonged capillary refilling time. The physical examination also revealed tachycardia, hypotension and suprapubic discomfort. Urinary ultrasonography revealed an overdistended bladder with hyperechoic content and the total blood count (TBC) revealed low levels of hematocrit (HCT) and hemoglobin (HGB) (22% and 7.1 g/dl, respectively). The patient was suffering from prostate cancer (PCa) for the last 7 years; however, a year ago the disease progressed to hormone-resistant with metastases (in pelvic lymph nodes, bones and lung). Due to an obstructive acute kidney injury which occurred 6 months ago and following the failure of placement double-j-stents, the patient underwent urinary deviation with bilateral nephrostomy and therefore the free voiding urine volume was negligible. The patient was treated with a luteinizing hormone-releasing hormone-antagonist and abiraterone acetate plus prednisone, with dabigatran 150 mg bid (for atrial fibrillation and coronary heart disease) and he also suffered from mild ulcerative colitis for which 5-aminosalicylic acid was provided on demand.

The patient was hospitalized in the Urology Department for 2 weeks overall. A 22F, 3-way urethral catheter was placed, and blood clots were removed with a syringe. Continuous normal saline intravesical irrigation was initiated and tranexamic acid was administered intravenously along with red blood cell transfusion. Dabigatran was temporarily withdrawn and bridged 2 days later with low molecular weight heparin 4,000 bid. The conservative treatment lasted for 4 days; however, hematuria reappeared every time bladder irrigation ceased. Computed tomography and urography revealed a large prostate lesion invading the bladder neck and a pelvic lymph-node block in the absence of blood extravasation. Subsequently, diagnostic urethrocystoscopy under anesthesia was performed. Active vascular bleeding could not be detected; however, only diffuse hemorrhage originating from the prostatic tumor and bladder neck were present. Due to the late stage of the disease, these two anatomic structures were fused and could be recognized as separate structures. Bipolar coagulation was performed without any significant improvement. Subsequently, the patient was referred to an interventional radiologist and he was informed on the option of superselective arterial embolization (SAE) as well as its advantages and limitations. Following signing the relevant consent form, the patient underwent bilateral embolization of the prostatic arteries and of the inferior cystic arteries with microparticles 100-300 μm and 300-500 μm (Figs. 1 and 2), while keeping the heparin delivery. With the exception of lower abdominal discomfort which lasted 3 days and treatment with on demand paracetamol administration, the convalescence period was uneventful, and hematuria did not occur on the 2nd day following SAE. Dabigatran was re-administered at the 5th post-procedural day and the catheter was removed 5 days later. The patient was discharged with HCT and HGB levels of 34% and 10.6 g/dl, respectively. Following a 4-month, follow-up, the TBC parameters were stable and there was no need for transfusion or hospitalization. No bloody urethral discharge or local pain (perineal or suprapubically) were observed. It is important to note that the prostate specific antigen (PSA) level diminished from 14 to 10 ng/ml.

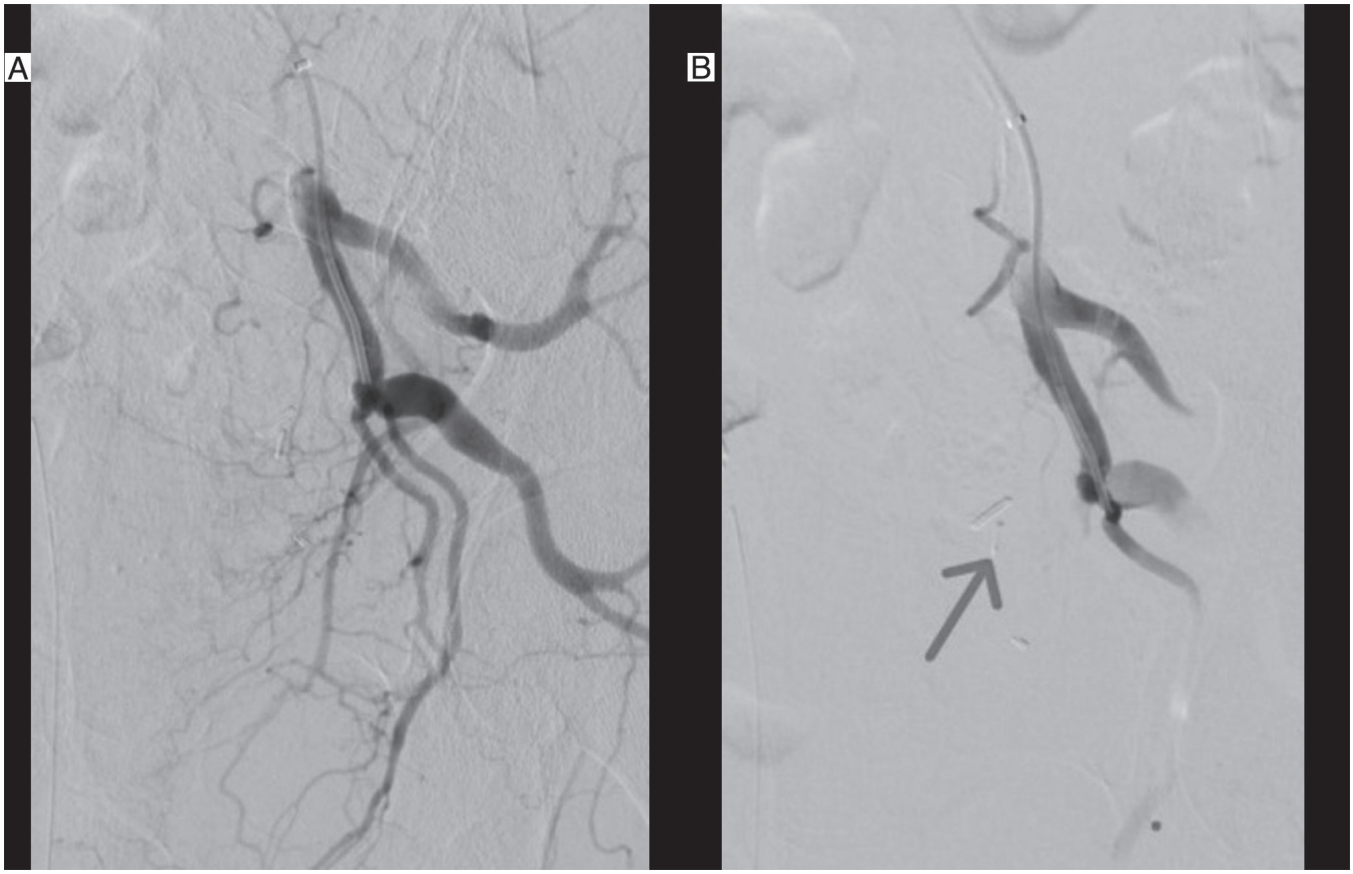

Figure 2. Digital subtraction angiography after the placement of (A) the first nanoparticle and after complete occlusion of left-sided blood supply to the prostate arteries with the placement of (B) 3 nanoparticles (arrow).

Discussion

In 1974, two Danish doctors, Hald and Mygind (5) were the first to control hematuria with arterial embolization and the method has been implemented to control cancer-related hematuria (9,10) as well as non-cancer related bleeding, such as post traumatic hemorrhage (2).

With regard to the urinary tract, significant experience with SAE has been acquired in the treatment of benign prostate hyperplasia symptoms. Pisco *et al* (11) reported a mid- and long-term success rate of 82 and 76%, respectively. Among the 630 patients treated with prostate artery embolization, only 2 experienced major complications, underscoring the safety of the method (11). A relevant systematic review with meta-regression analysis reported that SAE is a safe and effective method to treat prostate hyperplasia-related symptoms although the authors concluded that the embolization should still be considered experimental (12).

The body of evidence is limited regarding the control of PCa-related hematuria with the embolism technique. A total of ~35 relevant cases in small non-comparative retrograde case series with mixed population (comprising patients with bladder and pelvic cancer as well as non-malignant prostatic diseases) have been reported in the literature (3,6-8,13,14). However, the long-term success rate in relieving the patient from hematuria is encouraging. In a case series with 44 patients (15 with PCa), the control of bleeding was achieved in 82% following a single session while 11% required a second intervention. However, durable results were experienced by 43% of the patients (3). In another series with 18 cases, 6 of them presented with hematuria due to PCa and the technical success was noted in 16 (88%) of the patients. Hemorrhage was terminated following a maximum of 3 days and it was followed by improvement of the TBC measures after a mean follow-up of 18 months (8). Nabi *et al* (6) presented a very small series of 6 cases. Half of the cases presented with PCa. Successful embolization was performed in 5 cases and the control of hematuria was maintained following a mean follow-up of 22 months (6).

All reports demonstrated the main advantage of SAE, which was the minimal invasive nature of the procedure. Therefore, it is related with low rate of side effects which, if they occur, they are mostly minor. Nausea, vomiting, fever and abdominal pain may be experienced by the patients. They are relieved with conservative measures usually within 2-3 days (8). This constellation of symptoms resembles the post-embolization syndrome described following transarterial embolization of hepatocellular carcinoma. Post-embolization syndrome may be related with tissue necrosis, hypoxia and release of cytokines into the bloodstream. No specific methods of treatment exist; the management includes supportive therapy with analgesics, antiemetics and antipyretics. Recently, it was reported that the administration of dexamethasone and/or N-acetylcysteine may also be helpful (15). Liguori *et al* (3) after a mean of follow-up of 10.5 months, reported a post-embolism syndrome as high as 27% in a series of 39 cases with urogenital hemorrhage. They also noted external genitalia swelling in 5% of the cases.

Noteworthy, the mortality rates at 6 and 12 months were as high as 66 and 18%, respectively (3). Different studies have reported gluteal or lower abdominal pain, urgency, frequency and dysuria as potential complications of the method. The same authors published 1-, 6- and 12-month mortality rates of 0, 42 and 71%, respectively (7). The high sort-term mortality rates reported in the literature may be explained by the comorbidities and the frailty of the patients who underwent embolization, as well as the complexity and burden of disease that makes any invasive treatment to be accompanied by high rates of morbidity and mortality. Nevertheless, future comparative studies may provide an answer regarding the optimal treatment option depending on the final outcome.

Severe complications, for example tissue necrosis or sepsis, have not been reported in modern series, which are attributed to the super-selective nature of the procedure (6). The use of very small unresolvable particles, as small as 100 μm, such as those used in the present case renders superselective embolization feasible and efficient. For lower urinary tract hemorrhage, the superselective technique mandates the embolization to be performed distally to the gluteal artery avoiding complications related to gluteal muscle ischemia and perineal pain (3). Based on the experience obtained following treatment of benign prostatic hyperplasia with SAE it was shown that nanoparticles of larger sizes (300-500 μm) were equally safe and effective with those that were smaller in size (100-300 μm). The size of the particles was determined proportionally by the caliber of the branch that had to be occluded. Therefore, larger vessels were embolized with larger particles (16,17).

Previous studies that have compared different means of embolization are scarce. In one of them it is supported that liquids and small particles may have more favorable results in controlling severe bleeding compared with coils. However, this result was not significant (9); the ideal agent is yet to be determined. It should also be considered that the blood supply of the prostate stems from both sides of internal iliac artery branches. Therefore, bilateral embolization is recommended for optimal control of prostatic hemorrhage (3,8).

One of the major advantages of arterial embolization is that it can be performed under local anesthesia obviating the potential complications related to general or regional anesthesia particularly in high risk patients. It is also important that the withdrawal of antiplatelet and/or antithrombotic agents is not necessary. In one multicenter study comprising 92 patients with malignancy-related bleeding of any origin treated with selective embolization, 2 out of 3 patients (67%) received antithrombotic agents and 89% of the patients were on antiplatelet or antithrombotic treatment. Almost 11% received dual antiplatelet treatment. The clinical success rate was as high as 85% with only 14 patients experiencing re-bleeding (9). In the present case report, the antiplatelet treatment was withdrawn as one of the first measures to control bleeding. Due to the risks related with atrial fibrillation, low molecular weight heparin was administered and it was continued during the SAE procedure with a favorable outcome. Therefore, following meticulous consideration of the risks and benefits, it can be deduced that embolization could be proposed to patients with cardiovascular disorders as a measure to avoid the risks of withdrawal of antithrombotic/antiplatelet agents; concomitantly, it can be used to provide an effective treatment of severe bleeding.

It is interesting to note that a post-procedural decline of the serum PSA was recorded. The deprivation of the tumor from its blood supply may be in part beneficial in tumor control; however, the duration of this effect and long-term outcomes remain unknown. Until now, the group of patients with PCa who will experience benefit, if any, with SAE is unclear and several questions need to be addressed. For example, it remains unknown whether patients with low or intermediate-risk disease have an optimal outcome with SAE compared with those with advanced disease. In addition, it is not known whether it is preferable to use SAE in combination with other treatment (radiotherapy or hormonal therapy) or whether SAE is more efficacious as monotherapy. The combination of SAE with intraprostatic administration of chemotherapeutic agent(s), which is similar with the chemoembolization of hepatocellular cancer, requires further investigation in future studies.

Recently, unilateral super-selective embolization of the prostatic artery has been used as focal therapy in 10 patients with low risk PCa. In total, 40% of the patients had a negative post-embolization biopsy at 6 months and 30% presented with an undetectable lesion in multiparametric magnetic resonance imaging. Moreover, all 10 patients experienced a PSA decline. All cases except one continued in the active surveillance protocol (18). In a different non-comparative pilot study based on 9 patients with advanced cancer treated with SAE, a significant tumor necrosis was noted in only 1 patient (19). In a proof-of concept study from Switzerland, 12 patients with localized PCa underwent prostate artery embolization and subsequently were treated with radical prostatectomy. In the radical prostatectomy specimens, elimination of the tumor size was recorded; however, none of the patients experienced complete tumor necrosis (20). However, there are no reports on the mid- and long-term effect of bilateral embolization in the natural history of PCa.

Due to the inconclusive early results, researchers may be reluctant to design and conduct comparative studies between SAE and standard of care (surgery and radiotherapy) due to potential risks and the lack of data from reliable national or population registries, such as the Surveilance, Epidemiology and End Results database. Large registries may provide valuable preliminary data for retrograde comparative studies prior to the design of prospective clinical trials. Not surprisingly, following review of the site of clinical trial database for research in humans, it was deduced that studies comparing SAE with other methods of treatment have not been registered so far (21). Nevertheless, SAE is a new and promising concept for the treatment of patients with PCa that warrants further investigation.

The current report presents an unusual case indicating that the bloody urethral discharge and not hematuria was the symptom of intractable bleeding. Due to urinary deviation, the inability of the patient to store urine and void normally caused difficult diagnosis and treatment of hemorrhage. Bladder irrigations were applied for various days with insufficient results. Moreover, the consumption of copious amounts of water to increase urine output, which is a useful measure to relieve hematuria in patients with normal vesical storage, could not be

beneficial in the present case. In addition, even if the conservative measures were initially successful, the deprivation of lower urinary tract from the urine increased the likelihood of new blood clot formation following patient discharge, forcing the patient to readmission. Although the method is considered experimental, it has been regarded that embolization could be an option with favorable results and the patient was informed accordingly. Following a 4-month follow up, the treatment could be considered successful with regard to maintaining stable HCT and HGB levels without bloody discharge from the urethra and lack of readmission.

The results and conclusions of this single case should be generalized with caution. However, it can be assumed that this case contributes to the unmet need to determine the role of embolization in patients with intractable hematuria or lower urinary tract hemorrhage and particularly when other measures have failed. It also underscores the requirement of close cooperation between urologists and interventional radiologists on the basis of multidisciplinary medical approach targeting optimal results.

In conclusion, SAE is an attractive treatment option notably in patients with cardiovascular comorbidities, since it is a minimal invasive procedure. It appears to be an effective alternative method to control hematuria and lower urinary tract hemorrhage compared with other invasive procedures, with acceptable rate of minor complications. The encouraging results and the survival outcomes warrant further evaluation with comparative prospective multicenter studies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DK, PF and VK were major contributors in the writing of the manuscript, performed the primary treatment and consulted the patient for the novel treatment. PP, assisted by VK and AF, were responsible for the novel treatment. AZ, DB and AK analyzed the patient's data and the literature data. GH and AMK obtained the medical images. GK, KS, ER and DM advised on the patient's treatment. DK and PP confirm the authenticity of the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The treatment methods and the study were approved by the Ethics Committee of Konstantopouleio-Patision General Hospital, Nea Ionia, Greece (approval no. 26/09052024) and are in full compliance with the Declaration of Helsinki. Informed consent was obtained from the patient before treatment.

Patient consent for publication

Informed consent was obtained for publication of patient data and associated images.

Competing interests

The authors declare that they have no competing interests.

References

1. Choong SK, Walkden M and Kirby R: The management of intractable haematuria. BJU Int 86: 951-959, 2000.
2. Somani BK, Nabi G, Thorpe P and McClinton S: Endovascular control of haemorrhagic urological emergencies: An observational study. BMC Urol 6: 27, 2006.
3. Liguori G, Amodeo A, Mucelli FP, Patel H, Marco D, Belgrano E and Trombetta C: Intractable haematuria: Long-term results after selective embolization of the internal iliac arteries. BJU Int 106: 500-503, 2010.
4. Taha DE, Shokeir AA and Aboumarzouk OA: Selective embolisation for intractable bladder haemorrhages: A systematic review of the literature. Arab J Urol 16: 197-205, 2018.
5. Hald T and Mygind T: Control of life-threatening vesical hemorrhage by unilateral hypogastric artery muscle embolization. J Urol 112: 60-63, 1974.
6. Nabi G, Sheikh N, Greene D and Marsh R: Therapeutic transcatheter arterial embolization in the management of intractable haemorrhage from pelvic urological malignancies: Preliminary experience and long-term follow-up. BJU Int 92: 245-247, 2003.
7. Alarayedh A, Abdulwahab S and Mubarak M: Super-selective trans-catheter arterial embolization (TAE) of the vesical arteries in the management of intractable hematuria secondary to advanced bladder and prostate cancers. Cureus 16: e58016, 2024.
8. Korkmaz M, Şanal B, Aras B, Bozkaya H, Çınar C, Güneyli S, Gök M, Adam G, Düzgün F and Oran I: The short- and long-term effectiveness of transcatheter arterial embolization in patients with intractable hematuria. Diagn Interv Imaging 97: 197-201, 2016.
9. Minici R, Guzzardi G, Venturini M, Fontana F, Coppola A, Spinetta M, Piacentino F, Pingitore A, Serra R, Costa D, *et al*: Transcatheter arterial embolization (TAE) of cancer-related bleeding. Medicina (Kaunas) 59: 1323, 2023.
10. El-Assmy A and Mohsen T: Internal iliac artery embolization for the control of severe bladder hemorrhage secondary to carcinoma: Long-term follow-up. ScientificWorldJournal 7: 1567-1574, 2007.
11. Pisco JM, Bilhim T, Pinheiro LC, Fernandes L, Pereira J, Costa NV, Duarte M and Oliveira AG: Medium- and long-term outcome of prostate artery embolization for patients with benign prostatic hyperplasia: results in 630 patients. J Vasc Interv Radiol 27: 1115-1122, 2016.
12. Shim SR, Kanhai KJ, Ko YM and Kim JH: Efficacy and safety of prostatic arterial embolization: Systematic review with meta-analysis and meta-regression. J Urol 197: 465-479, 2017.
13. Delgal A, Cercueil JP, Koutlidis N, Michel F, Kermarrec I, Mourey E, Cormier L, Krausé D and Loffroy R: Outcome of transcatheter arterial embolization for bladder and prostate hemorrhage. J Urol 183: 1947-1953, 2010.
14. Rastinehad AR, Caplin DM, Ost MC, VanderBrink BA, Lobko I, Badlani GH, Weiss GH, Kavoussi LR and Siegel DN: Selective arterial prostatic embolization (SAPE) for refractory hematuria of prostatic origin. Urology 71: 181-184, 2008.
15. Simasingha N, Tanasoontrarat W, Claimon T and Sethasine S: Efficacy of dexamethasone and N-acetylcysteine combination in preventing post-embolization syndrome after transarterial chemoembolization in hepatocellular carcinoma. World J Gastroenterol 29: 890-903, 2023.
16. Gonçalves OM, Carnevale FC, Moreira AM, Antunes AA, Rodrigues VC and Srougi M: Comparative study using 100-300 versus 300-500 μm microspheres for symptomatic patients due to enlarged-BPH prostates. Cardiovasc Intervent Radiol 39: 1372-1378, 2016.
17. Bhatia A, Maini A and Bhatia S: Prostatic artery embolization: Technical pearls. Semin Intervent Radiol 39: 555-561, 2022.

18. Frandon J, Bey E, Hamard A, Mohammad H, Gonzalez S, Greffier J, Chevallier T, de Forges H, Beregi JP and Droupy S: Early results of unilateral prostatic artery embolization as a focal therapy in patients with prostate cancer under active surveillance: Cancer prostate embolisation, a pilot study. J Vasc Interv Radiol 32: 247-255, 2021.
19. Burkhardt O, Abt D, Hechelhammer L, Kim O, Omlin A, Schmid HP, Engeler D, Zumstein V and Müllhaupt G: Prostatic artery embolization in patients with advanced prostate cancer: A prospective single center pilot study. Cardiovasc Intervent Radiol 47: 771-782, 2024.
20. Mordasini L, Hechelhammer L, Diener PA, Diebold J, Mattei A, Engeler D, Müllhaupt G, Kim SK, Schmid HP and Abt D: Prostatic artery embolization in the treatment of localized prostate cancer: A bicentric prospective proof-of-concept study of 12 patients. J Vasc Interv Radiol 29: 589-597, 2018.
21. ClinicalTrials.gov. https://clinicaltrials.gov/search?cond=prostate%20cancer&term=Embolization&intr=Prostate%20Artery%20Embolization).