

Treatment of urethral and bladder condyloma acuminata

Abstract

Human papillomavirus (HPV) is one of the most prevalent sexually transmitted infections in the world and rarely may affect the urethra and bladder. This article describes two cases of bladder HPV infection managed at our institution and summarizes literature describing the management of lower urinary tract HPV lesions published in PubMed (MEDLINE) since 2010. Articles were selected after performing a scoping literature review using the search terms “human papillomavirus”, “condyloma”, “bladder” and/or “urethra”. Thirty-five articles were included in the review with treatment options including surgical excision, ablative therapy, photodynamic therapy, and topical agents.

Keywords: bladder, urethra, HPV, condyloma, treatment, photodynamic therapy, ablative therapy

Volume 11 Issue 1 - 2023

Nishita Patel, Joanna Marantidis, Abigail Davenport, Olivia Casas Diaz, Michael Markel, Lee Ann Richter

MedStar Washington Hospital Center, Georgetown University School of Medicine, USA

Correspondence: Abigail Davenport, MD, MedStar Washington Hospital Center, Georgetown University School of Medicine, Washington, Tel 321-271-7716, Email Abigail.patricia.davenport@medstar.net

Received: February 22, 2023 | **Published:** March 08, 2023

Abbreviations: HPV, Human papillomavirus; CA, condyloma acuminata; MeSH, medical subject heading; VIN, vulvar intraepithelial neoplasia; UTIs, urinary tract infections; PDT, photodynamic therapy

Introduction

The Human Papilloma Virus (HPV) is one of the most common sexually transmitted infections in the world. In the United States alone, approximately 14 million people acquire HPV each year.¹ The infection is usually asymptomatic and effectively cleared by the host's immune system. However, some infections result in condyloma acuminata (CA) or warty growths. Infection involving the bladder and/or urethra is rare and primarily occurs in immunocompromised individuals.¹ Symptoms of CA of the lower urinary tract include frequency, urgency, weak stream, and a feeling of incomplete emptying.²

CA often resolves on its own. However, approximately 30% of all genital lesions recur leading to increased frequency of clinic visits, increased cost to the healthcare system, and psychosocial consequences for patients.¹ The oncogenic properties of HPV also lead to an increased risk of malignancy, particularly squamous cell carcinoma. The relationship between HPV and bladder cancer is not yet fully understood. Current data describes an association between urothelial carcinoma and HPV with one study reporting an odds ratio of 4.24 for the development of urothelial carcinoma in patients with HPV infection.^{3,4}

Treatment of urethral and bladder CA varies depending on patient factors and the number, size, and site of the lesions involved. Additionally, given the rare nature of urethral and bladder CA lesions, a consensus on appropriate treatment does not exist. The purpose of this article is to describe our experience with two cases of bladder CA and provide a narrative review of current treatment options for bladder and urethral CA described in the literature since 2010.

Materials and methods

Cases

Two women treated at our institution for bladder CA were retrospectively analyzed through chart review. Demographic and clinical characteristics including age, gender, past medical history, presentation of CA, and treatment(s) performed were documented.

Operative reports and intraoperative pathology reports were additionally reviewed where appropriate.

Literature review

A scoping review of world literature on urethral and bladder HPV/CA was conducted by two researchers to identify articles utilizing any treatment modality for urethral or bladder HPV between 2010 and 2021. This search was completed using PubMed (MEDLINE). A Boolean search was conducted using the Medical Subject Heading (MeSH) terms “urethra” and “bladder” followed by the operator “AND” and the additional MeSH terms “condyloma” and “human papillomavirus”.

Thirty-five studies were identified and reviewed for study design, number of patients, treatment method, and clinical outcomes. Urethra and bladder CA lesions are rare which is generally limiting to the performance of high-quality studies requiring larger sample sizes. Thus, studies of varying quality (including case reports) were considered for inclusion in this review. No specific outcome measures were required for study inclusion. Articles were excluded if they were not in English or if the full article was not available. Table 1 includes a summary of select studies included in this review. Small case series are considered exempt by the institutional review board (IRB) at our institution.

Case series

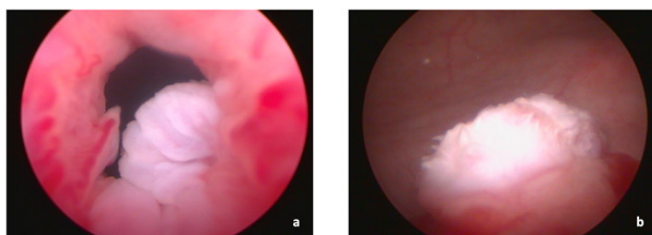
Case 1: This is a 36-year-old female with type 1 diabetes mellitus status post pancreatic and renal transplant and vulvar intraepithelial neoplasia (VIN) presenting with symptoms of stress urinary incontinence, recurrent urinary tract infections (UTIs), and a prolapsing urethral lesion. Examination in the office was consistent with a prolapsing urethra and cystourethroscopy was performed which additionally identified a small urethral polyp near the bladder neck at 6 o'clock (Figure 1a). She subsequently underwent surgical excision and repair of her urethral prolapse 10 weeks later. Repeat cystourethroscopy at the time of surgery identified diffuse white, frondular lesions within the urethra with a normal bladder survey. Exam under anesthesia revealed a peri-clitoral lesion which was excised. Pathologic examination of the urethral tissue demonstrated high-grade squamous dysplasia arising from condyloma with p16 and ki67 positivity.

Table 1 Select studies describing CA treatment

Study	Treatment protocol	Complete response	Recurrence rate	Follow up	Side effects/ complications
Surgical excision					
Chae et al, ⁵	Excision of visible CA	1/1 (100%)	0/1 (0%)	6mos	Not reported
Nordsiek et al, ²	Excision of CA similar to urethroplasty	1/1 (100%)	0/1 (0%)	Not reported	Not reported
Jeje et al, ¹⁰	Surgical resection with a 2 cm margin with a primary closure	1/1 (100%)	Not reported	Not reported	Not reported
Samarska et al, ⁷	TURBT	38/38 (100%)	7/38 (18%)	15mos to 20yrs (median 6 yrs)	Not reported
Hamano et al, ⁹	TUR followed by imiquimod	1/1 (100%)	1/1 (100%)	Recurrence at 6mos with repeat resection; no recurrence after 1 yr	Not reported
Yavuzcan et al, ¹¹	Excision with harmonic scalpel	1/1 (100%)	0/1 (0%)	12mos postpartum	Not reported
Laser ablation					
Calderón-Castrat et al, ²¹	CO2 laser continuous mode and repeated pulse in 2 passes. Base of periurethral wart coagulated.	1/1 (100%)	0/1 (0%)	13mos	None reported
de Lima, ²⁰	5-15 s per lesion with diode laser with 1.2 W/cm2 continuous wave	4/4 (100%)	19.6% (for all lesions, not just urethral)	12wks	Pain, oozing, edema, scaling
Blokker et al, ¹⁹	Nd:YAG vs thulium laser; both 550 um, continuous wave mode	115/115 (100%)	39/115 (33.9%) including lesions of external genitalia	1mo to 12yrs	5 meatal stenosis, 1 urethral stricture
Ge et al, ³⁷	TUR using Holmium/YAG laser ablation. One week later, installation of 1% fluorouracil and 1% tetracaine hydrochloride gel, performed as qwk treatment x 6 with 6wks rest for 7 cycles	100%	6/25 (24%)	2-5wks and 6mos	None from resectoin, dysuria following instillation
Photodynamic therapy					
Xie et al, ²²	ALA x 4 hr followed by PDT with frequency of PDT based on viral load changes	12/12 (100%)	Not reported	Not reported	Not reported
Shan et al, ²⁴	20% ALA x 3 hr followed by PDT x 20 min, performed qwk x 4wks	76/76 (100%)	5/76 (6.6%)	3mos	Mild burning/ stinging sensation during irradiation then for 1-2 days; moderate pain
Sun et al, ²³	19.09% ALA x 3 hours, then 635 nm laser fiber was inserted into distal urethra for 20 min at 100J, performed qweek x 3	86/86 (100%)	14/86 (16.3%)	3mos	Mucosal hyperemia, pain, edema, erosion, exudate
Zhang et al, ²⁵	Excision using CO2 laser on continuous wave mode. 20% ALA x 3h followed by PDT for 30 mins, repeat for 3 courses	6/6 (100%)	0/6 (0%)	6mos	Burning pain, stinging
Mi et al, ²⁸	Cryotherapy + ALA-PDT vs. cryotherapy alone, performed qwk up to 3 cycles	32/32 (100%) for combined group	3/32 (9%) for combined group	12wks	Pain, edema, erosion, hypopigmentation
Topical agents					
Behtash et al, ³²	5-FU applied nightly x 1mo	1/1 (100%)	0/1 (0%)	1mo	Not reported
Zayko et al, ³⁴	5- FU qweek x 6wks with 6 wk rest for 2 cycles, then qweek x 8wks	0/1 (0%)	Never cured	2yrs	Not reported
Mestrovic et al, ³⁵	5% 5-FU formulation used 3 times per wk x 6wks	2/2 (100%)	0/2 (0%)	6mos	Dysuria with first 2 applications
Mestrovic et al, ³⁵	Alternating 36% polycresulen solution and 5% imiquimod cream, performed 3 times per wk x 6wks	1/1 (100%)	0/1 (0%)	6mos	None
Martinez-Domench et al, ³⁹	Case 1: topical high dose ingenol mebutate gel with two applications one month apart. Case 2: one application of high dose ingenol mebutate gel.	2/2 (100%)	0/2 (0%)	2mos to 2yrs	Local inflammatory response with moderate pain lasting 5 d
Florin et al, ⁴⁰	0.5% cidofovir cream applied after resection/lasering	1/2 (50%)	1/2 (50%)	6mos to 3.5yrs	None

A surveillance cystoscopy was performed six months postoperatively and demonstrated a well-healed urethra with a new CA lesion near the bladder neck at 5 o'clock. The patient was also evaluated by gynecologic oncology who performed a repeat biopsy of the peri-clitoral lesion and recommended a wide local excision when the pathology returned as high-grade dysplasia. The ongoing plan was to perform a resection of the bladder neck lesion as a combined case with oncology.

Case 2: This is a 32-year-old female with a history of systemic lupus erythematosus (SLE), end-stage renal disease requiring two renal transplants, and anogenital CA status post partial vulvectomy who presented with recurrent UTIs, dysuria, frequency and urge incontinence. Cystourethroscopic examination demonstrated a polypoid lesion emanating from 11 o'clock at the proximal urethra. There was also a 1 cm broad-based growth at the right trigone with fluffy white spicules and a second smaller lesion at the left lateral sidewall of a similar appearance (Figure 1b). Her implanted ureteral orifice was normal in appearance. Cystourethroscopy under anesthesia was performed and three <1 cm raised sessile lesions were noted: left lateral bladder wall, midline trigone, and at 11 o'clock position at the proximal urethra. Transurethral resection of the lesions was successfully performed. Pathologic evaluation demonstrated positivity for p16 with ki67 staining consistent with HPV. A repeat cystoscopy three months later did not show evidence of recurrent disease.



Images of lower urinary tract CA: (a) urethral CA at the bladder neck as described in case 1 and (b) bladder CA as described in case 2.

Figure 1 Urethral and bladder condylomata acuminata (CA).

Discussion

The most common treatment modalities for bladder CA included resection, ablation, photodynamic therapy, topical agents, and vaccination. The breakdown of studies that employed each treatment modality is as follows: resection (n=15), ablation (n=7), photodynamic therapy (n=10), topical agents (n=10), and vaccination (n=1). Several studies described the use of multiple treatment modalities as CA lesions are notoriously difficult to treat and recurrence is common.

Surgical excision

Surgical excision is the most common treatment option for the management of bladder and urethral CA with the various techniques described.⁵⁻¹¹ Additionally, surgical excision or cryotherapy is the only recommended treatment options for lesions of the urethral meatus according to the Centers for Disease Control.¹² Currently, there are no Centers for Disease Control (CDC)-supported recommendations for the treatment of intraurethral or intravesical CA.

Surgical techniques vary based on the characteristics and location of the lesion. Open techniques are often chosen when endoscopic excision or ablation either fail or the lesions are so large that these modalities would be unsuccessful.¹³ Endoscopic techniques such as transurethral resection (TUR) have been increasingly used in recent years, particularly for internal lesions.^{7-9,14-17} Monopolar or

bipolar electrocautery may be used for endoscopic lesion resection. Regardless of the technique used, visual eradication of CA and sufficient resection depth are essential, especially given the increased risk of carcinoma.¹⁸

For the treatment of distal urethral lesions, an open technique may be appropriate. Nordsiek et al² described the resection of a urethral mass performed in a similar fashion to urethral caruncle excision. In the event that primary closure is not possible, several skin flap techniques have been described including the Cohnsey, Blandy-Tresidder, Brannen, and De Sy.¹³ Surgical devices such as the harmonic scalpel may also be used for open CA resection.¹¹ For all surgical methods, the most concerning complications are urethral stricture and scarring and thus close follow-up is warranted.

Ablative therapy

Laser therapy is a less invasive option for the treatment of CA when compared to surgery and has been described for nearly 50 years. While many laser types are available, the Nd:YAG laser has been most frequently described in the treatment of bladder and urethral CA, perhaps because it has a deeper penetration effect than Thulium or other commonly used lasers. Lesion location also influences laser selection, as all lasers with the exception of CO₂ easily pass through an endoscope, thus limiting the application of the CO₂ laser to external lesions.

Blokker et al. conducted a retrospective analysis comparing treatment with Nd:YAG to Thulium laser in 115 male patients with genital or urethral CA. All subjects were successfully treated and recurrence rates were comparable (33 vs 34%, respectively) in both groups.¹⁹ A prospective study of 92 patients assessing the efficacy of diode laser vaporization in genital lesions described a 70% response rate and an 18% recurrence rate. However, only four of the lesions described in this study involved the urethra.²⁰ One case report described the successful use of the CO₂ laser on a large periurethral CA lesion.²¹

In addition to laser ablation, cryotherapy has been used in the treatment of CA. This therapy is performed with the use of a metallic cryoprobe or topical application of liquid nitrogen. The low boiling point of the liquid nitrogen results in rapid heat transfer, thus destroying the cells to which it is applied. Few studies published in PubMed since 2010 have used cryotherapy as a treatment modality for bladder or urethral HPV. We describe one study evaluating cryotherapy as part of combination therapy below. Frequently described complications associated with laser therapy include urethral strictures, meatal stenosis, edema, and scarring. Cryotherapy may result in skin irritation and pigmentation changes.

Photodynamic therapy

Photodynamic therapy (PDT) is a two-step treatment modality consisting of the application of a photosensitizing agent followed by light exposure. 5-aminolevulinic (ALA) is an amino acid photosensitizer commonly used in PDT that functions by creating reactive oxygen species with subsequent cellular apoptosis when exposed to a specific wavelength of light.¹³

Generally, one cycle of treatment consists of the application of a 20% ALA solution to the lesion for 3 hours followed by 20 to 30 minutes of PDT. The number of cycles and frequency of treatment are determined by the severity of the disease. Xie et al used ALA-PDT in 21 patients with urethral CA and achieved 100% remission after four cycles.²² Additional studies support that ALA-PDT has success rates approaching 100% when two or more cycles are performed.^{23,24}

Recurrence rates were low with most patients achieving complete remission after additional PDT was performed.

Ablative techniques have been described as an effective adjunct to ALA-PDT. One case series described the utilization of the CO₂ laser for lesions of the distal urethra and urethral meatus with no recurrence at a 6-month follow-up.²⁵ Another case study described a male patient with intraurethral CA in whom the ALA solution was dissolved in a gel and administered intraurethral via a catheter. >95% of his lesions were cleared with PDT and the remaining lesions were treated with the Holmium laser.²⁶ Another case study described CA lesions removed with radiofrequency cauterization followed by PDT.²⁷

Cryotherapy has also been described in conjunction with ALA-PDT. Mi et al performed a randomized clinical trial comparing ALA-PDT with cryotherapy versus cryotherapy alone in lesions of the anus, genitalia, and urethra.²⁸ In their protocol, combined therapy consisted of an 8-second topical application of liquid nitrogen to the CA lesions for two rounds followed by ALA-PDT. Combined therapy was statistically superior to cryotherapy alone with 100% of urethral CA lesions responding to combined therapy after two treatments. Recurrence rates were also statistically significantly lower in the combined therapy group (9.4% vs 39.4%, $p < 0.05$) at 12 weeks. Another case report by Chen et al had similar findings.²⁹

Side effects of PDT include burning at the treatment site, edema, and dysuria.^{23,24,30} One study reported two patients who went into urinary retention and required short-term catheterization likely secondary to periurethral edema.³⁰

Topical agents

5-fluorouracil (5-FU) is an anti-metabolite drug that works by inhibiting the normal function of DNA and RNA.³¹ Weekly application of a 1-5% solution or gel for six weeks followed by a 6-week holiday was the most common protocol described prior to 2010.¹³ More recent data were primarily case reports with protocols ranging from once a nightly application for one month to once weekly for eight weeks and variable response rates were reported.³²⁻³⁵ Regimens included in-office and at-home topical applications. Side effects included mild irritative symptoms and dysuria.

5-FU has been examined as an adjunct to surgical and laser therapy.^{36,37} One case series described Holmium:YAG laser ablation followed by two 6-week cycles of 5-FU in the treatment of intraurethral CA in 25 male patients.³⁷ Although three participants required a repeat cycle of treatment, the response rate was 100% without relapse over an average follow-up of six months. Poliresulen is a polymolecular organic acid that stimulates regeneration and re-epithelialization while imiquimod is an immune system activator that stimulates the targeting of tumor cells. One case report described alternating intraurethral application of a 36% poliresulen solution and 5% imiquimod cream used over a 6-week period with no recurrence after six months.³⁵

Ingenol mebutate (IM) is a component of milkweed (*Euphorbia peplus*) sap and is Food and Drug Administration (FDA) approved for the treatment of actinic keratosis. It is thought to function by mediating immune responses that rapidly induce cell death. Low and high-dose topical application methods have been described. Two case reports including a total of four male patients with lesions of the urethral meatus described the complete resolution of the lesions within a matter of two to three weeks after IM therapy initiation.^{38,39}

Cidofovir is an antiviral intravenous solution FDA-approved for the treatment of cytomegalovirus retinitis. Its mechanism of action is the suppression of viral replication through the inhibition of DNA polymerase. One case series included two male patients with

intraurethral CA and utilized a 0.5% cidofovir cream which was delivered intraurethral via catheter over 28 sessions.⁴⁰ One patient had complete resolution of his urethral CA while the other had two recurrent lesions six months after discontinuing therapy.

Vaccination

The 9-valent HPV vaccine is prepared from purified virus-like particles and is intended to provide protection from HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 and is currently the only option available in the United States. The CDC recommends routine vaccination at age 11 or 12, with catch-up vaccination through age 26. Earlier vaccination is recommended as the vaccine is intended primarily as a preventative measure rather than for treatment of active infection. One study described vaccination as a treatment modality for genital lesions although only one subject in this study had urethral CA while one case report used vaccine administration as an “immunomodulator” in a patient who underwent surgical resection.^{6,41}

Limitations

This is a scoping review of studies only available through PubMed (MEDLINE) published and therefore is not intended to be a comprehensive review of all literature published on the management of bladder or urethral CA. Additionally, we only included treatment modalities utilized since 2010, therefore all possible modalities used for the treatment of bladder and urethral CA are not included in this review. Review articles are limited by the quality of literature considered for inclusion. As >50% of the studies included in this review were case studies or case series, further research is necessary to draw any meaningful conclusions regarding the efficacy or safety of the therapies described.

Conclusion

Early and effective treatment may lead to the eradication of bladder and urethral CA and reduce the risk of progression to malignancy. Utilization of several treatment modalities or repeat therapy may be necessary as recurrence is common. Surgical resection is the most frequently described treatment for bladder and urethra CA in the literature and may be used for the treatment of internal and external lesions. Laser ablation may be used internally or externally depending on the laser available and has promising response rates. PDT may also be utilized in lesions involving the external and internal urethra but is not viable for use within the bladder. While topical solutions have been extensively used for anogenital lesions, newer evidence supporting their use in urethral and bladder CA is generally of poor quality. Vaccination may provide protection against the development of CA if administered early, although patients should be counseled that vaccination is a preventative rather than a therapeutic measure.

Acknowledgements

None.

Conflicts of interest

The authors declared that there are no conflicts of interest.

Funding

None.

References

1. Dunne EF, Park IU. HPV and HPV-associated diseases. *Infect Dis Clin North Am.* 2013;27(4):765–778.

2. Nordsiek M, Ross C, Metro M. Successful surgical management of giant condyloma acuminatum (Buschke Lowenstein Tumor) in the urethra of a female patient: A case report. *Curr Urol*. 2015;8(1):49–52.
3. Sarier M, Ceyhan AM, Sepin N, et al. HPV infection in urology practice. *Int Urol Nephrol*. 2020;52(1):1–8.
4. Sarier M, Sepin N, Keles Y, et al. Is there any association between urothelial carcinoma of the bladder and human papillomavirus? A case-control study. *Urol Int*. 2020;104(1-2):81–86.
5. Chae JY, Bae JH, Yoon CY, et al. Female urethral condyloma causing bladder outlet obstruction. *Int Neurourol J*. 2014;18(1):42–44.
6. Khambati A, Bhanji Y, Oberlin DT, et al. Progression of intravesical condyloma acuminata to locally advanced poorly differentiated squamous cell carcinoma. *Urol Case Rep*. 2016;7:61–63.
7. Samarska IV, Epstein JI. Condyloma acuminatum of urinary bladder: relation to squamous cell carcinoma. *Am J Surg Pathol*. 2019;43(11):1547–1553.
8. Lazarus J, Kaestner L. Intravesical condylomata acuminata in HIV positive patient. *Can J Urol*. 2011;18(2):5663–5665.
9. Hamano I, Hatakeyama S, Yamamoto H, et al. Condyloma acuminata of the urethra in a male renal transplant recipient: A case report. *Transplant Proc*. 2018;50(8):2553–2557.
10. Jeje EA, Ogunjimi MA, Alabi TO, et al. Condyloma acuminata of the bladder in benign prostatic obstruction: Case report and review of literature. *Niger Postgrad Med J*. 2015;22(3):189–193.
11. Yavuzcan A, Çağlar M, Turan H, et al. The treatment of giant periurethral condyloma in pregnancy using an ultrasonic thermal scalpel: a case report and new single session treatment option. *Case Rep Obstet Gynecol*. 2015;2015:792412.
12. Centers for disease control sexually transmitted infections treatment guidelines, 2021: Anogenital Warts. USA: 2022.
13. Kim CJ, Campbell SP, Allkanjari A, et al. Update on the medical and surgical management of urethral condyloma. *Sex Med Rev*. 2022;10(2):240–254.
14. Murray AJ, Bivalacqua TJ, Sopko NA. Innumerable condyloma acuminatum tumors of the bladder. *Urol Case Rep*. 2017;12:76–77.
15. Nakazaki N, Zaitzu M, Mikami K, et al. Coincidence of hpv11-positive urethral condyloma acuminatum and hpv-negative multiple bladder papillomas in a female. *Case Rep Med*. 2012;2012:602819.
16. Sarier M, Ozel E, Duman I, Yuksel Y, Demirbas A. HPV type 45-positive condyloma acuminata of the bladder in a renal transplant recipient. *Transpl Infect Dis*. 2017;19(2).
17. Kawaguchi S, Shigehara K, Sasagawa T, et al. A case study of human papillomavirus-associated bladder carcinoma developing after urethral condyloma acuminatum. *Jpn J Clin Oncol*. 2012;42(5):455–458.
18. Navia N, Dinney, C. Surgical Management of Bladder Cancer: Transurethral. Open and Robotic. In Partin A, Dmochowski R, Kavoussi L, et al, editors. 12th ed. *Campbell-Walsh-Wein Urology*. Elsevier; 2021.
19. Blokker RS, Lock TM, de Boorder T. Comparing thulium laser and Nd:YAG laser in the treatment of genital and urethral condylomata acuminata in male patients. *Lasers Surg Med*. 2013;45(9):582–588.
20. de Lima MM Jr, de Lima MM, Granja F. Treatment of genital lesions with diode laser vaporization. *BMC Urol*. 2015;15:39.
21. Calderón Castrat X, Blanco S, Santos Durán JC, et al. Giant periurethral condyloma acuminata in a 2-year-old girl: Successful treatment with carbon dioxide laser. *Actas Dermosifiliogr*. 2017;108(4):385–387.
22. Xie J, Ao C, Li J, et al. 5-aminolevulinic acid photodynamic therapy for condyloma acuminatum of urethral meatus. *J Dermatolog Treat*. 2019;30(7):714–717.
23. Sun Y, Ma YP, Wu Y, et al. Topical photodynamic therapy with 5-aminolevulinic acid for condylomata acuminata on the distal urethra. *Clin Exp Dermatol*. 2012;37(3):302–303.
24. Shan X, Wang N, Li Z, et al. An open uncontrolled trial of topical 5-aminolevulinic acid photodynamic therapy for the treatment of urethral condylomata acuminata in male patients. *Indian J Dermatol Venereol Leprol*. 2016 Jan-Feb;82(1):65–67.
25. Zhang L, Li X, Liu X, Gao Y, Tang Q. Treatment of multi-position condyloma acuminatum using topical CO2 laser combined with photodynamic therapy- Report of 6 cases. *Photodiagnosis Photodyn Ther*. 2019;25:436–439.
26. Chang R, Xu C, Liu Y, et al. 5-aminolevulinic acid photodynamic therapy and holmium laser treatment for intraurethral condylomata acuminata in a renal transplant patient. *Photodiagnosis Photodyn Ther*. 2021;36:102496.
27. Che Q, Li J, Jiang L, et al. ALA-PDT combined with cystoscopy: A method to eliminate refractory HPV infection in a patient with condyloma acuminata. *Photodiagnosis Photodyn Ther*. 2020;31:101763.
28. Mi X, Chai W, Zheng H, et al. A randomized clinical comparative study of cryotherapy plus photodynamic therapy vs. cryotherapy in the treatment of multiple condylomata acuminata. *Photodermatol Photoimmunol Photomed*. 2011;27(4):176–180.
29. Chen N, Cheng Q, Zeng Q, et al. Successful treatment with ALA-PDT of Refractory condyloma acuminatum of the whole anterior urethra. *Photodiagnosis Photodyn Ther*. 2020;31:101918.
30. Wang HW, Zhang LL, Song XD, Huang Z, Wang XL. Acute urinary retention in elderly female patients after photodynamic therapy of urethral condyloma-report of two cases. *Photodiagnosis Photodyn Ther*. 2013;10(2):203–205.
31. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. *Nat Rev Cancer*. 2003;3(5):330–338.
32. Behtash N, Aghamir SMK, Tamehri Zadeh SS, et al. A case of condyloma acuminata after about 30 years of urinary obstructive symptoms. *Urol Case Rep*. 2020;31:101200.
33. Timm B, Connor T, Liodakis P, et al. Pan-urethral condylomata acuminata - A primary treatment recommendation based on our experience. *Urol Case Rep*. 2020 Feb 29;31:101149.
34. Zayko MO, Velilla RE, Shurbaji MS. Condyloma acuminata presenting as isolated papillary lesions in the prostatic urethra. *Am J Case Rep*. 2018;19:1522–1525.
35. Mestrovic T, Sviben M, Zember S, et al. Topical medication as an initial therapeutic option for protruding and non-protruding condylomata acuminata of the distal urethra. *BMJ Case Rep*. 2021;14(9):e243618.
36. Nambirajan A, Shukla AK, Mathur SR, et al. Condyloma acuminatum of urinary bladder in a male renal transplant recipient - A diagnostic and therapeutic challenge. *Clin Genitourin Cancer*. 2017;15(4):e739-e742.
37. Ge CG, Jiang J, Jiang Q, et al. Holmium:YAG laser ablation combined intraurethral fluorouracil perfusion as treatment option for intraurethral Condyloma acuminata in men. *Minerva Urol Nefrol*. 2014;66(1):77-81.
38. Braun SA, Barsch M, Gerber PA. Fast ablation of anogenital warts of the urinary meatus by low-dose ingenol mebutate gel. *Sex Transm Dis*. 2018;45(10):e80-e82.
39. Martinez Domenech A, Magdaleno Tapial J, Garcia Legaz Martinez M, et al. Successful treatment of condylomata acuminata at the urethral meatus with high-dose ingenol mebutate gel: Report of two cases. *Int J STD AIDS*. 2019;30(8):817–819.

40. Florin HJ, Snoeck R, Van Cleynenbreugel B, Albersen M. Treatment of intraurethral condylomata acuminata with surgery and cidofovir instillations in two immunocompromised patients and review of the literature. *Antiviral Res.* 2018;158:238–243.
41. Choi H. Can quadrivalent human papillomavirus prophylactic vaccine be an effective alternative for the therapeutic management of genital warts? An exploratory study. *Int Braz J Urol.* 2019;45(2):361–368.