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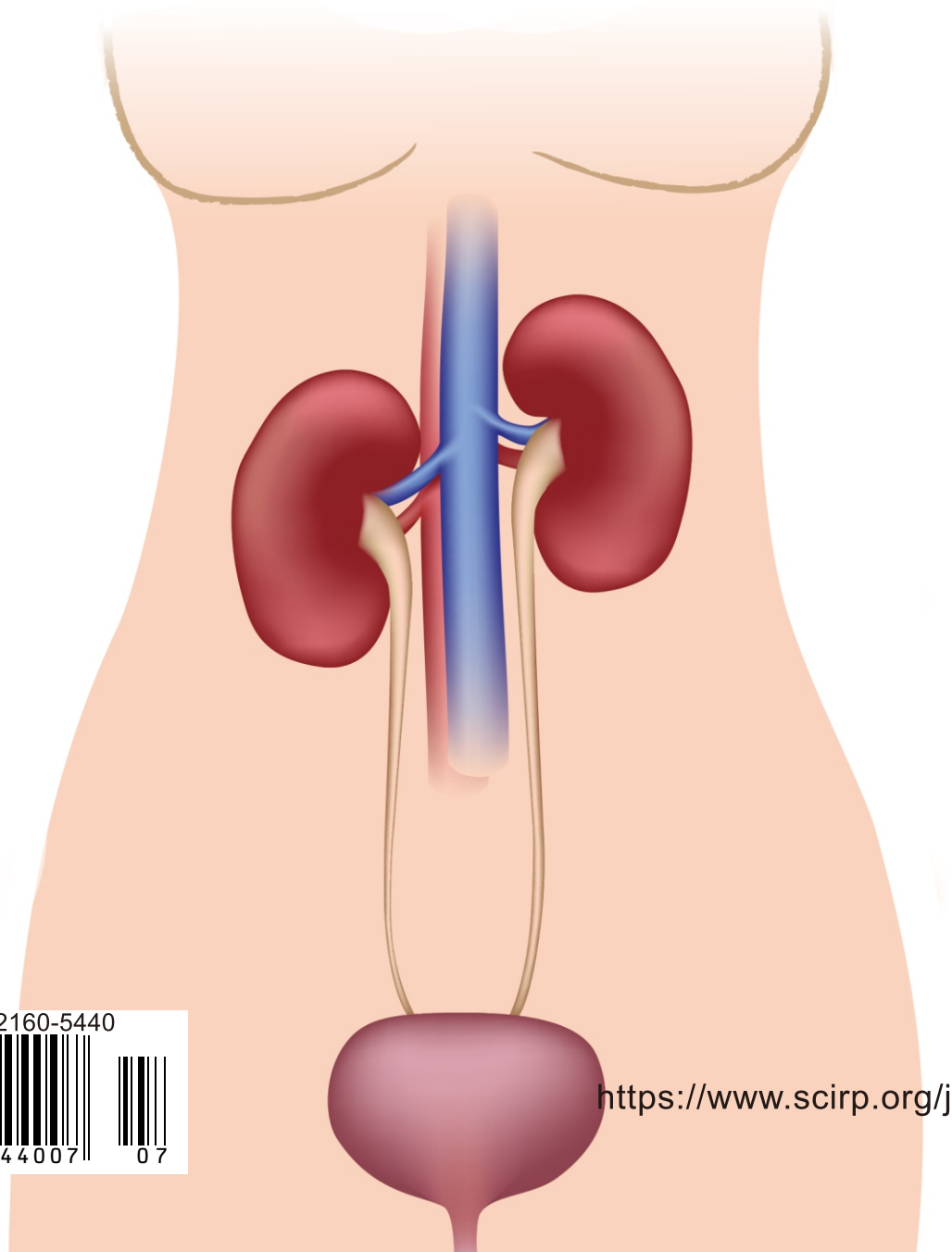

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Primary Presentation of Ovarian Cancer with Bladder Outlet Obstruction/Chronic Urinary Retention in a 12-Year Old Female

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Abstract

Urinary retention in women is rare and is more frequently described as case reports or small case series. The female/male ratio is 1:13 with about 3 cases per 100,000 women every year We report a case of a 12-year old female student. She presented with progressive weight loss, worsening lower urinary tract symptoms with distended lower abdomen of 10 weeks duration. Physical examination revealed a mobile tender firm pelvic mass, 18 centimeters (cm) × 16 cm in size. Laboratory and imaging studies showed obstructive nephropathy and uropathy respectively. She was worked up and had uneventful exploratory laparotomy with right salpingo-oophorectomy, urinary bladder diverticulectomy and pelvic lymphadenectomy. Histopathology of the pelvic mass showed ovarian dysgerminoma with lymph node metastasis. She responded very well to chemotherapy and resumed her school activities. Bladder outlet obstruction is relatively rare in females and in the index patient, ovarian dysgerminoma is the cause leading to obstructive nephropathy and uropathy.

Keywords

Bladder Outlet Obstruction, Chronic Urinary Retention, Pelvic Mass, Ovarian Dysgerminoma, Chemotherapy

1. Introduction

Urinary retention implies a difficulty in passing urine or completely emptying the urinary bladder and it can be acute or chronic. Urinary retention in women is rare with about 3 cases per 100,000 women every year [1]. The female/male ratio is 1:13 [1] [2]. In short, urinary retention in females is more frequently de-

scribed as case reports or small case series with unusual causes [2]. Two common causes of chronic urinary retention in women are detrusor dysfunction and obstruction [1]. Urinary symptoms such as hesitancy, straining, poor urinary stream and feeling of incomplete emptying of the urinary bladder are clearly suggestive of bladder outlet obstruction in women [3] [4] [5].

Anatomical non-iatrogenic causes of bladder outlet obstruction in females include pelvic organ prolapse, vaginal masses like cysts, urethral pathology like diverticulum, carcinoma, gynaecological lesions like large ovarian cysts, tumors, cervical, uterine tumors and pregnancy due to uterine displacement [4].

We present the case of a 12-year old female student with ovarian cancer who presented with lower urinary tract symptoms and chronic urinary retention with urinary tract infection (UTI) and overflow incontinence to the urologist and her successful management.

2. Case Report

Miss A, a 12-year old Nigerian student presented at the accident and emergency department with about 3 months worsening symptoms of progressive weight loss, daytime frequency, nocturia, overflow incontinence, feeling of incomplete emptying of the bladder and lower abdominal pain. There was no haematuria.

She was cachectic, clinically pale, anicteric. The chest was unremarkable. There was lower abdominal distension. A tender mobile mass 18 cm × 16 cm which was firm in consistency was palpated. A working diagnosis of bladder outlet obstruction secondary to a pelvic mass was made. She was aseptically catheterized with a size 12F (all silicone) two-way Foley catheter and 350 mililiters (mLs) of turbid offensive urine drained.

Haematological investigations, serum electrolytes, urea and creatinine, etc. are as shown in **Table 1**.

Abdominopelvic ultrasonography showed a solid pelvic mass posterior to and compressing the urinary bladder with hypoechoic and highly echogenic areas measuring 18.94 × 11.24 cm, there was also bilateral hydronephrosis with hydroureter.

Intravenous urography after normalization of serum electrolyte, urea and creatinine showed bilateral hydronephrosis and hydroureter, bladder diverticulum in keeping with bladder outlet obstruction (**Figure 1**).

The anemia was corrected by blood transfusion, the UTI treated with ceftriaxone. The patient was worked up and prepared for laparotomy. Via a mid-line abdominal incision, the peritoneum and pelvis were explored. The mass was mobilized off the posterior wall of the urinary bladder. Within the mass were embedded the right ovary and the right fallopian tube. There was pelvic and iliac lymphadenopathy. A urinary bladder diverticulum was noted. The mass with the right ovary and right fallopian tube within was resected. Pelvic and iliac lymphadenectomy was done. She had an uneventful post-operative recovery. The indwelling urethral catheter was removed on the seventh-day post-operatively. The

Table 1. Haematological and other laboratory investigations.

Parameters	Results	Range
Heamoglobin (HB)	7.2 gm/dL	11.0 - 16.0 gm/dL
Platelet count	165,000/mm^3	150,000 - 400,000/mm^3
Erythrocyte sedimentation rate	104 mm/hr.	0 - 29 mm/hr (women)
Total White Blood Cell (WBC) Count	11,800/mm^3	4000 - 10,000/mm^3
Differential	▪ Neutrophil—80% ▪ Lymphocyte—19% ▪ Eosinophil—01% ▪ Basophil—0 ▪ Monocytes—0	
1) Serum Electrolytes, Urea and creatinine (Pre-catheterization)	▪ Na^+—137 mmol/L ▪ K^+—5.6 mmol/L ▪ Cl^-—98 mmol/L ▪ HCO_3—24 mmol/L ▪ Urea—168 mmol/L ▪ Creatinine—3.2 mmol/L	(135 - 145) (3.5 - 5) (96 - 110) (22 - 30) (10 - 40) (0.4 - 1.6)
2) Serum Electrolytes 1 week post catheterization	▪ Na^+—140 mmol/L ▪ K^+—3.2 mmol/L ▪ Cl^-—100 mmol/L ▪ HCO_3^- —26 mmol/L ▪ Urea—35 mg/dL ▪ Creatinine—1.0 mg/dL	(135 - 145) (3.5 - 5) (96 - 110) (22 - 30) (10 - 40) (0.4 - 1.6)
3) LIVER FUNCTION TEST	▪ Billirubin total 0.5 mg/dl ▪ AST 20.3 IU/L ▪ ALT 6.5 IU/L ▪ Alk Phosphatase 94 IU/L	(<1) (<50) (<50) (<129)
Gamma Glutaryl Tranaminase	19 iu/L	(<40)
Lactate dehydrogenase	190 iu/L	(120 - 240)
HIV	Negative	
HBsAg	Negative	
HCV	Negative	
b-chorionic Gonadotrophin	Negative	
URINE CULTURE	Yielded heavy growth of *E. coli* sensitive to ceftriaxone	

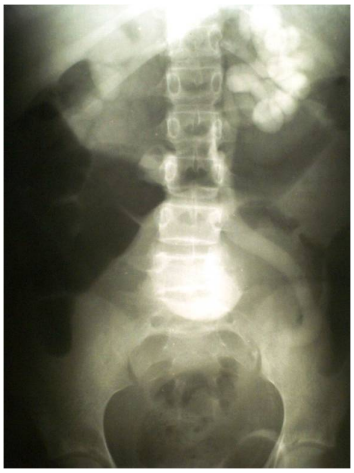

Figure 1. Intravenous urography showing hydronephrosis with hydroureter.

patient was discharged on the tenth-day post-operatively to the outpatient department. Histology report showed ovarian dysgerminoma. The sections from the ovary and retroperitoneal lymph nodes are similar and show a malignant germ cell tumour made up of broad and thin trabeculae of pleomorphic malignant cells. These cells have abundant amphophilic cytoplasm and large vesicular nuclei with a prominent eosinophilic nucleolus. Between the tumour trabeculae, there are fibrous connective tissue columns that contain many lymphocytes. Within the tumour masses, there are multinucleated giant tumour cells of trophoblastic type. Some of the blood vessels within the tumour show intravascular tumour dissemination (**Figure 2**, **Figure 3**).

Patient was referred to the oncologist for chemotherapy and she did well after the course of chemotherapy and resumed her academic activities. She was lost to follow up after 10 months.

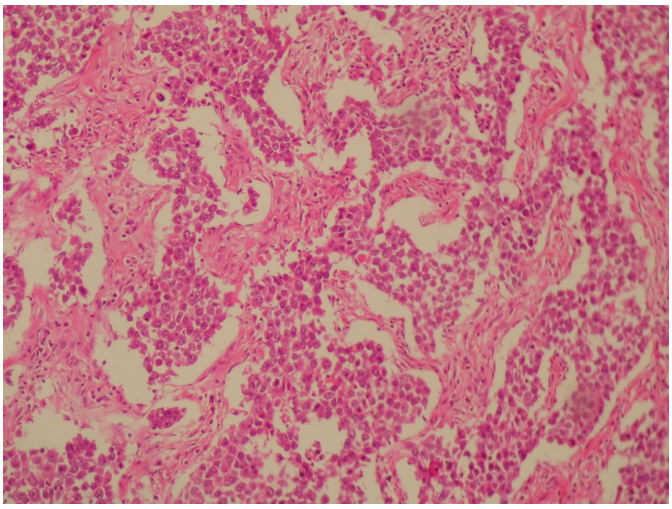

Figure 2. H&E × 150 magnification ovarian dysgerminoma. There are anastomosing trabeculas of tumor cells separated by fibrous bands that contain lymphocytes.

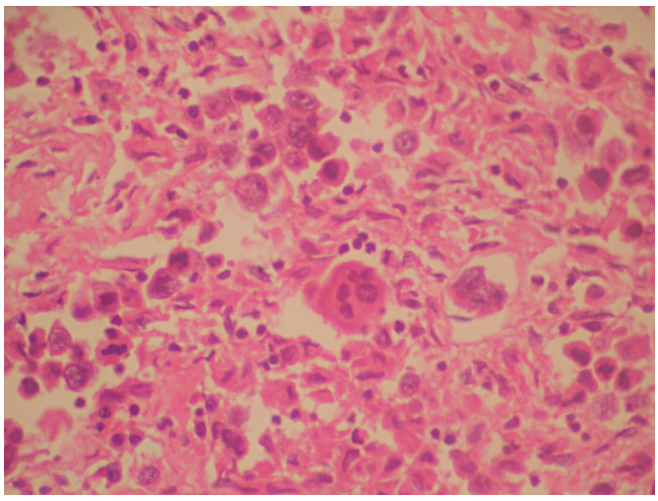

Figure 3. H&E × 300 magnification ovarian dysgerminoma. Note the frequent multinucleated tumor giant cells among the other tumor cells.

3. Discussion

Although relatively common in men, bladder outlet obstruction is relatively uncommon in women in clinical practice and the etiological factors more diverse in females than in males [3]. The mechanism of obstruction could be urethral compression, bladder neck distortion or luminal occlusion [2]. In the index patient, the ovarian tumor compressed and distorted the bladder neck causing lower urinary tract symptoms, impaired detrusor emptying with increasing residual urine volume. Furthermore, there was associated daytime urinary frequency, nocturia, urgency, poor urinary stream, intermittency, terminal dribbling and feeling of incomplete emptying of the urinary bladder. Storage and voiding symptoms can coexist in bladder outlet obstruction in females making it a challenge in clinical practice to make an accurate diagnosis and offering the best form of treatment [6]. Both urgency urinary incontinence and overflow incontinence coexisted in this patient. Urinary incontinence adversely impacts the patient, family members and the health care system with abstinence from routine activities, increased rate of depression and reduced quality of life [7]. The index patient experienced all these and dropped out of school with depression. In addition, the patient with overflow urinary incontinence has high residual urine volume with associated high pressure within the bladder which at this stage is considered as high-pressure chronic retention and can cause renal impairment [7]. The index patient at presentation, laboratory and ultrasound studies showed obstructive nephropathy and uropathy respectively. A total of 350 mL turbid offensive urine was drained from the urinary bladder on aseptic urethral catheterization and the patient was admitted and monitored for complications. The patient in the first 72 hours following catheter insertion made a daily average of 3 liters of urine which was promptly replaced with intravenous fluids to avoid dehydration and shock. Drainage of more than 300 mL of urine from the bladder after voiding suggests urinary retention [1], and the condition is best managed in a hospital setting with the patient monitored for post obstructive diuresis [7]. Imaging studies like abdominopelvic ultrasound, CT imaging have been advocated in the investigation of these patients [1] [3] [5] [6] [8] [9]. Abdominopelvic ultrasonography was utilized to unravel the etiology of this condition. Furthermore, ultrasonography could be useful in estimating the residual urine volume [3] [5] and detection of greater than 200 mL of urine in the bladder after voiding is suggestive of overflow urinary incontinence [10]. This patient did not experience acute urinary retention. Acute urinary retention in females is due to impacted pelvic masses that displace the cervix superiorly and anteriorly compressing the lower bladder leading to obstruction of the internal urethral orifice [11]. The pelvic mass was mobile in the index patient and not impacted with the internal urethral orifice partially obstructed. The lower abdominal pain the patient had was due to pressure from the mass and urinary tract infection caused by *E. coli*.

While lactate dehydrogenase (LDH) levels are known to be elevated in some patients with dysgerminoma, our patient had normal values of LDH and β-cho-

rionic gonadotrophin (βHCG). She had complete resection of the mass with right salpingo-oophorectomy followed by chemotherapy with bleomycin, etoposide and cisplatin (BEP). Even patients with incompletely resected dysgerminoma can be rendered disease-free with a combination of cisplatin, vinblastin, and bleomycin (PVB) [12]. A number of patients had one or more successful pregnancies following unilateral salpingo-oophorectomy [13]. However, our patient was lost to follow up after 10 months of having resumed her academic activities and in excellent health.

4. Conclusion

Although relatively common in men with voiding dysfunction, bladder outlet obstruction is relatively rare in women. In this patient right ovarian cancer was the cause of complications of obstructive uropathy and nephropathy, the patient and her relative concern was the disabling lower urinary tract symptoms oblivious of the underlying pathology. The onus thus lies on the attending clinician to evaluate the patient diligently and unravel the pathology and in this case, a right ovarian dysgerminoma which responded excellently to chemotherapy with the patient resuming her academic activities.

Author Contributions

Study design: Dr. Charles A. Odoemene, Dr. Mrs. Ijeoma Ezeome, Dr. Okechukwu Charles Okafor.

Data acquisition: Charles A. Odoemene, Dr. Mrs. Ijeoma Ezeome, Dr. Okechukwu Charles Okafor.

Data analysis: Charles A. Odoemene, Dr. Mrs. Ijeoma Ezeome.

Drafting of the manuscript: Charles A. Odoemene, Dr. Mrs. Ijeoma Ezeome, Dr. Okechukwu Charles Okafor.

Critical revision of the manuscript: Charles A. Odoemene, Dr. Mrs. Ijeoma Ezeome, Dr. Okechukwu Charles Okafor.

Parents Informed Consent

We attest that the patient's parents gave consent for the publication of this case.

Conflicts of Interest

The authors have no conflicts of interest.

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Penile Skin Flap Urethroplasty for Urethral Stenosis at Sominé DOLO Hospital of Mopti (MALI)

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Abstract

Introduction: Penile skin flap urethroplasty is a technique for replacing or enlarging an obstructed urethra. We aim to report our experience in the practice of this surgical technique. **Patients and method:** This was a prospective and descriptive study of penile skin flap urethroplasty indicated for urethral stenosis between January 2014 and December 2019. **Results:** A total of 21 penile skin flap urethroplasties for urethral stenosis were performed. The average age was 38.6 years old. The stenosis was of sclero-inflammatory origin in 15 cases (71.43%). It was of bulbo-perineal, penile, and penile-bulbar topography in about a third each. A history of urethral surgery was reported in 80.95% of the cases. The average length of the stenosis was 6.8 cm. Mundy circular skin flap urethroplasty about 15 cases (71.43%), and Quartey rectangular skin penile flap urethroplasty about 6 cases (28.57%) were the surgical techniques performed. The postoperative follow-up was favorable in 19 cases (90.48%). Two cases of urethral fistula (9.52%) underwent the 2nd urethroplasty. Urination at 1 year was satisfactory. No relapse has been reported to date. However, 4 patients (19.04%) reported asthenic ejaculation, and 1 patient (4.76%) a marked decrease in sexual pleasure. **Conclusion:** This surgical

technique is effective in terms of voiding when the surgical indications are well chosen. The sexual aspect must be taken into account and the intervention only offered to those who really need it.

Keywords

Urethral Stenosis, Urethroplasty, Pedicled Flap

1. Introduction

Stenosis of the urethra is a permanent decrease in the size of the urethra, due to non-neoplastic morphological changes in its wall. Its clinical translation is difficult or even an impossibility for the patient to empty his bladder. It is responsible for impaired life quality due to its complications particularly, urinary tract infection, bladder stone, fistulas, sepsis, and kidney failure [1]. A distinction is made between spongy or anterior urethral stenosis and stenosis of the posterior urethra of traumatic origin. Spongy or anterior urethral stenosis is pathology of alteration and scarring of the urethral wall, more or less long, and most often it's of sclero-inflammatory etiology. The incidence of urethral stenosis is estimated at 200 to 1200 cases per 100,000 men [1]. The therapeutic means consist of urethral dilation, urethrotomy, and reconstructive surgery techniques [2]. In the literature, it is accepted that short urethral stenosis of fewer than 2 centimeters (cm) is treated by excision of the stenosis followed by end-to-end anastomosis [3]. Urethral stenosis beyond 2 cm managed by an anastomotic urethroplasty could lead to the risk of shortening of the penis and especially of curvature of the penis for stenosis of the penile urethra [4]. Complex structures of the anterior urethra should benefit from a urethral reconstruction technique using free or pedicle autograft [5] [6]. At the end of the 1990s, urethroplasty by a buccal mucosal graft had become the reference treatment in reconstructive surgery of the urethra for long urethral stenosis because of its advantageous histological properties and especially because of its results [7]. Nevertheless, it has some drawbacks such as the double site of intervention, the intervention of another specialist for the safe harvesting of the buccal mucosa. Sometimes, complications of the sampling site occurred. Last but not least, general anesthesia is required for buccal graft sampling and urethral surgery. With a similar functional result between urethroplasty by buccal mucosal graft and urethroplasty by penile skin flap [8] [9] [10] [11] and due to the conditions of wider use due to the vascularization of the flap, our team opted for urethroplasty by a penile skin flap in the first intention to treat long and or complex shrinkage of the male anterior urethra. It is a surgical technique to replace or enlarge the urethra by a flap of the skin of the penis or of the pedunculated foreskin on the cellulovascular tissue of the penis. The main objective of this study was to report our experience in the practice of this surgical technique in our hospital.

2. Patients and Methods

This was a prospective and descriptive study of male patients who underwent penile skin flap urethroplasty for urethral stenosis between January 1st, 2014, and December 31, 2019, in our hospital. All patients with single or multiple urethral strictures greater than 2 cm without urethral fistula were included except stenoses due to atrophic lichen sclerosus. All patients underwent retrograde voiding and antegrade urethra-cystography for patients with a cystostomy, to measure the length of the stenosis, and to assess the alteration of the ureteral wall. All patients underwent a cytobacteriological urinalysis with antibiogram and the urine-born infections (UBIs) detected were treated before any surgical planning. All patients received a preoperative assessment and an explanation of the principle and procedure of the intervention as well as any possible complications and side effects after the intervention. Informed consent of all patients was obtained prior to surgery planning. In the operating room, a supine position was used for stenosis of the penile urethra and a waist position for stenosis of the bulbar urethra. Patients were under locoregional or general anesthesia, and antibiotic prophylaxis. All interventions were carried out by a team of 3 urologists including a senior present at all interventions.

We performed flap urethroplasty pedicled penile which breaks down as shown in Figure 1 into:

- Placement of a lubricated probe to locate the narrowed part;
- Incision straddling the narrowed part and dissection of subcutaneous cellular tissue and/or muscle up to the urethra;
- Release of the urethra at the level of the narrowed part all around and opening of the wall at the level of the stenosis to a healthy and flexible area;
- Measurement of the stenosis and excision of the entire pathological urethra and all neighboring pathological tissues;
- Measurement on the skin of the penis at the level of its dorsal part or of the foreskin of the length of the stenosis increased by 20%;
- First distal incision on the penis which crosses all the layers until contact with the albuginea of the cavernous bodies, then dissection continued until the root of the penis;

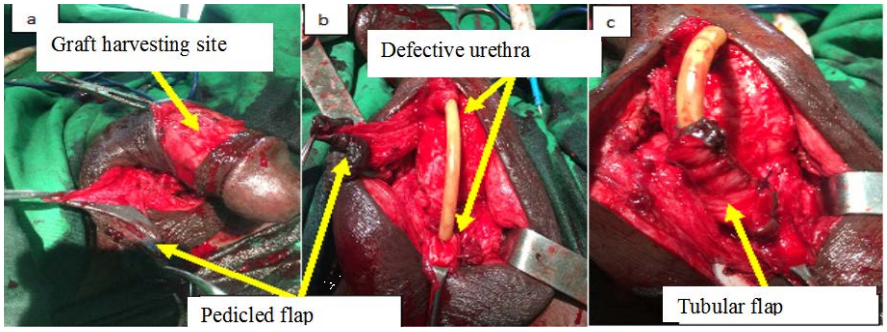

Figure 1. Pedicled penile flap urethroplasty. (a) Taking the flap from the dorsal side of the penis; (b) Flap brought back to the ventral surface of the penis; (c) Tubular flap.

- Second superficial incision taking only the skin, below the first and delimiting the width of the flap, separating the skin from the vascular subcutaneous tissue. This dissection is also continued down to the root of the penis, thus delimiting the pedicled flap (**Figure 1(a)**);
- Mobilization of the pedicle flap is brought back into contact with the penile urethra or the bulbar urethra through a peno-perineal tunnel (**Figure 1(b)**);
- Tubularization of the cutaneous part of the flap by inverting points on the dartos, around a probe of variable size depending on the size of the healthy urethra (**Figure 1(c)**);
- Spatulation of the proximal and distal part of the healthy urethra to obtain a larger anastomosis zone;
- End-to-end anastomosis of the tubularized flap to the urethra, around a catheter whose balloon is inflated in the bladder, the suture line of the flap tubularization being placed in the dorsal position;
- Layer by layer closure of donor site and the urethral pathway.

All patients received antibiotic therapy with intravenous ceftriaxone 1gramme twice daily for 3 days and oral relay therapy with cefixime 400 mg as a single dose for 10 days. Dressings, good oral hydration, and mobilization from the 3rd postoperative day constituted the bulk of postoperative care. The urethra-vesical catheters were kept for 21 days. Patients were followed every 3 months for one year, and then asked to come for a medical consultation after 1 year whenever they noticed a change in voiding comfort. This follow-up consisted of a history, physical examination, and direct assessment of urination. The intervention was considered successful if the patient had good voiding flow and had not had any other stenosis treatment procedure. Good urination was characterized by an immediate onset, a jet drawing a parabola, a frank ending without late drops and an absence of abdominal thrust.

Data were collected from the patient's medical record, and the operative reports. Epidemiological, diagnostic and therapeutic data were recorded. Data were analyzed by using SPSS software.

3. Results

In 6 years, 21 penile skin flap urethroplasties for urethral stenosis were performed. Several urethroplasty techniques have been used depending on the length of the stenosis, the presence of fistula or depending on the existence of suppuration. Among these surgical techniques, penile skin flap urethroplasty accounted for 19.44% (21/108).

Penile skin flap urethroplasty also represented 1.04% (21/2130) of all urosurgeries. The annual distribution of penile skin flap urethroplasties is shown in **Figure 2**.

The mean age was 38.6 ± 12.3 years with the extremes ranging from 11 to 59 years. The dilation with 33.33% was the most carried out treatment antecedent. The sclero-inflammatory etiology with 71.43% was the most common. The mean

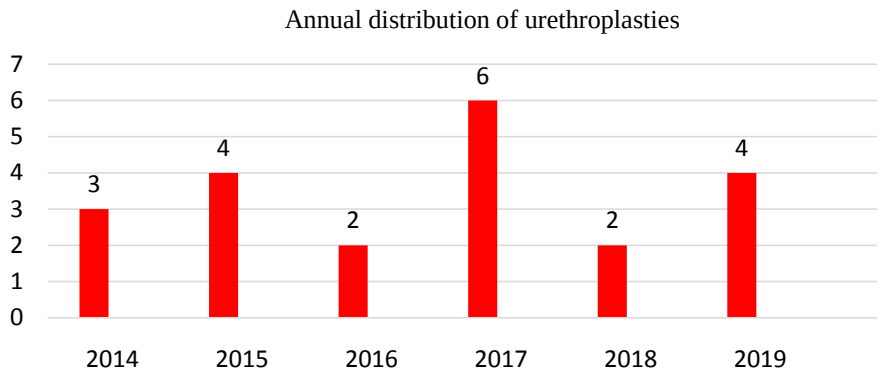

Figure 2. Annual distribution of urethroplasties.

length of the stenosis was 6.8 ± 2.1 cm with the extremes ranging from 3 to 12 cm. The topography was bulbo-perineal in 38.1% of cases. In **Table 1**, the characteristics of the stenosis before urethroplasty are highlighted.

The anesthetic mode was spinal anesthesia in 20 cases (95.24%) and general anesthesia in 1 case (4.76%). Mundy's penile skin flap urethroplasty 15 cases (71.43%), and Quartey's rectangular penile skin flap urethroplasty 6 cases (28.57%) were the surgical techniques performed. The postoperative follow-up was favorable in 19 cases (90.48%), 2 cases of urethral fistula (9.52%) underwent second urethroplasty. The mean duration of follow-up was 41.21 months. The urination at 1 year of follow-up was satisfactory. No relapse has been reported to date. However, 4 patients (19.04%) reported asthenic ejaculation and 1 patient (4.76%) a marked decrease in sexual pleasure.

4. Discussion

The anterior urethra is poor healing tissue due to the presence of spongy tissue. A wound by infectious or traumatic origin weakens the urethral mucosa and causes urine output to the spongy body which gets irritated and inflames on a larger dimension. The healing process results in an exaggeration of the scar tissue whose epicenter represents the stenosis part of the urethra. The extent of the spongy body disease is not always known, and several lesions at different stages of development can cause the stenosis to recur at another site even after proper treatment. Recurrence is also the rule in all treatment methods that leave the pathological urethra in place. Because of all these difficulties, many surgical techniques were developed without having a good efficiency until the advent of tissue transfer techniques initiated by Orandi [12] and especially Quartey for the pedicled graft [13] [14]. Since then, several modified techniques have emerged either by the shape of the graft, circular Mundy flap, or the graft harvesting area, scrotal graft for Gategno, perineal for Blandy, and penis fascia for Mac Aninch [15] [16]. These different techniques have not been able to completely suppress the phenomenon of excessive scarring at the graft-urethra junction. Ten years later, techniques using free grafts of oral mucosa and allowing such an exploit were born [17] [18]. Given that the retrospective studies have shown no significant

Table 1. Characteristics of stenosis.

Variables	Fequency	%
Age in years		
10 - 15	1	4.76
16 - 30	2	9.52
31 - 45	11	52.38
46 - 60	7	33.34
Total	21	100
Etiology		
Sclero-inflammatory	15	71.43
Iatrogenic	3	14.28
traumatic	2	9.52
Trophic	1	4.77
Topography		
Bulbar	8	38.01
Penile	7	33.33
Staged (Penile and Bulbar)	6	28.57
Total	21	100
Stenosis lenght in cm		
3 - 5	11	52.39
6 - 8	7	33.33
9 - 11	2	9.52
More than 11	1	4.76
Total	21	100
Antecedents		
Urethral dilation	7	33.33
Urethroplasty	6	28.57
Endoscopic internal urethrotomy (EIU)	4	19.05
No history	4	19.05
Total	21	100

difference between the two techniques, the choice of teams will be made according to the facilities of each.

The average age of our patients was 38.6 years. Our patients were younger than in most studies. It was 44.4 years in Burkina [19], 45 years in Tunisia [20], 45.2 in Egypt [21]. Stenosis of the urethra is pathology of young adults. Inflammatory etiology is most common in Africa [21]. Infectious urethritis contracted early in the sexual experience is responsible for urethral obstruction 10 to 15 years later. The etiology was infectious in 71.43% of the cases in our study; it was most frequent with 52% in Tunisia [20] and 42% in Egypt [21]. In developed

countries, the etiology is traumatic and iatrogenic [22] [23]. In our study, a case of trophic stenosis extending from the urethral meatus to the penoscrotal angle was diagnosed in an 11-year-old child. He had a long history of dysuria with the impossibility of probing whatever the caliber of the catheter and a threadlike urine stream. The site of postinfectious urethral stenosis is the anterior urethra. In our study, it was bulbar in about a third of the cases, penile and bulbo-penile in a third each. The site was bulbar in 90% and 3% of the penile site in Tunisian series [20] and bulbar-penile in 60.5% of cases in Egyptian series [21]. The larger bulbar urethra is a storage site for secretions after intercourse and is therefore the preferred site for postinfectious urethral stenosis. One of the particuliarities of post-infectious shrinkage is the length of the stenosis, unlike post-traumatic stenosis, which is shorter and is more treated with endoscopic internal urethrotomy (EIU) or anastomotic urethroplasty [3]. Recurrence of short stenosis after EIU or after dilation usually results in longer shrinkage due to urine entering the spongy body through the intrusion of the urethral membrane caused by the treatment. An anastomotic urethroplasty can also cause a longer recurrence due to the healing process but also insufficient excision of the pathological tissue, apparent or not. About 80% of our patients had a history of treatment for the stenosis by either anastomotic urethroplasty, urethral dilation, or EIU. This treatment history rate was 89%, including 65% of EIU for a study carried out in Tunisia [20].

The mean length of the stenosis was 6.8 cm. It was higher than the Tunisian series [20] which was 5 cm and lower than Egyptian series [21] which was 10.7 cm. Penile skin flap urethroplasty is a suitable technique to replace a pathological urethra from the navicular fossa to the membranous urethra [20]. This technique has long been used to create a missing urethra in often posterior hypospadias before finding its indication in urethral stricture. The virtual absence of hair on the skin of the penis or the foreskin has allowed the technique to supplant other flaps such as the scrotal skin of Gatégno and the perineal skin of Blandy since these flaps can be blocked by the growth of hair which in its turn could promote the lithogenesis.

The flexibility of the skin of the penis and its supporting tissue allows it to be mobilized to the level of the bulbar urethra.

The choice of surgical technique in our study depended on the length of the stenosis. Regarding a penile skin flap in all cases, Mundy's circular flap was chosen whenever the length of the stenosis was greater than 4 cm. This technique generally allows the choice of a longer and wider flap. The rectangular flap of Quartey has been indicated in stenosis less than or equal to 4 cm. These two techniques allowed us to have a success rate of 90.48% for an average follow-up of 41.21 months. However, we recorded 2 early failures by suppuration and fistulization. In these patients, antibiotic therapy was started according to the antibiogram. Also, early catheter removal and sitz baths were performed, transforming the one-step urethroplasty to a 2-step urethroplasty, the flap having played the role of an open urethra sutured to the skin.

Our result is similar to those of several studies in the literature where success rates range from 70% to 90% [9] [20] [21] [24] [25].

Our follow-up was active for 1 year with an appointment every three months. After one year, the patients were asked to seek a medical consultation when they experience a decrease in the urinary stream or in voiding comfort. Patient agreement on this method of monitoring was obtained and implemented, especially since the majority of them had a history of treatment for the same pathology. For the cured patients, no complaints regarding urination were noted; the complaints mainly concerned the sexual function of the urethra. Four patients reported drooling asthenic ejaculation with no saccade and decreased sexual pleasure, while one patient reported a marked decrease in sexual pleasure. The urethra has a sexual function; its replacement can have repercussions on ejaculation, especially in long stenosis. In urethral replacement, in order to prevent a recurrence, one is tempted to take a longer and wider flap than necessary. Such an attitude can be responsible for urethral diverticulum, urine leakage after the end of urination, and asthenic ejaculation. The size of the flap must be 20% greater than the length of the stenosis according to the formula: Flap length = (US + (US*0.2)) [26]. Notice that US stands for Urethral Stenosis. In a study conducted in Egypt [21], the pseudo diverticulum neourethra was found in 7.6% of cases and late post-voiding drops in 23% of cases.

5. Conclusion

We used tubularized penile skin flap successfully in one stage in our patients. Its indication in the treatment of long non-fistulized urethral stenoses gave very good results. Despite its good voiding result, the flap cannot fulfill the sexual function of the original urethra; therefore its indications must be strict and only intended for those who really need it.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Reponse Letter

1) Several urethroplasty techniques have been used depending on the length of the stenosis, the presence of fistula or depending on the existence of suppuration. Among these surgical techniques, penile skin flap urethroplasty accounted for 19.44%.

2) All interventions were carried out by a team of 3 urologists including a senior present at all interventions.

3) All patients with single or multiple urethral strictures greater than 2 cm without urethral fistula were included except stenoses due to atrophic lichen sclerosus.

4) We used tubularized penile skin flap successfully in one stage in our patients. Its indication in the treatment of long non-fistulized urethral stenoses, gave very good results.

5) Good urination was characterized by an immediate onset, a jet drawing a parabola, a frank ending without late drops and an absence of abdominal thrust.

6) We have made the grammatical corrections to the extent of our linguistic knowledge. We wrote the manuscript in French before translating it into English. We are at your disposal to make any correction suggests to improve the quality of work.

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Early Evaluation of PSA Response in Metastatic Prostate Cancer Treated with Abiraterone

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Abstract

Background: According to the main prostate cancer guidelines, the response to treatment with abiraterone plus prednisone (AA+P) must be evaluated by assessing prostate-specific antigen (PSA) levels at 12 weeks. Recent studies have shown that early PSA decline, at 4 weeks, maybe a surrogate marker for survival. The objective of this work was to analyze if a decline in PSA at 4 weeks correlates with a better outcome in terms of OS (overall survival) and PFS (progression-free survival). **Methods**: We evaluated 168 patients (with a median age of 71 years) with prostate cancer who had started AA+P treatment between February 2012 and July 2019. Patients were divided into three different groups according to the decline of PSA (≥30%, ≥50%, and ≥90%) at 4, 8, and 12 weeks. Statistical survival analysis was performed using the Kaplan-Meier method. **Results**: After a follow-up of 69 months, a PSA decline ≥ 30% at 4 weeks was associated with longer median OS times (28 vs. 18 months; $p = 0.027$). A decline in PSA by ≥50% was also associated with increased median OS times (36 vs. 21; $p = 0.003$). Cox univariable analysis indicated that a decrease in PSA (both by ≥30% and ≥50) were predictive of OS at 4 weeks (PSA ≥ 30%: HR = 1.568, 95%CI [1.041, 2.360], $p = 0.031$; PSA ≥ 50%: HR = 1.901, 95% CI [1.222, 2.956], $p = 0.004$); although multivariable analysis did not confirm these results. The prior administration of chemotherapy was an independent risk factor for death (HR = 2.511; $p < 0.001$) and progression (HR = 3.238; $p < 0.001$), probably because of different factors. **Conclusion**: A decrease in PSA by ≥30% or ≥50% at 4 weeks after starting treatment with AA+P correlated with longer PFS and OS, and provides clinically meaningful information guiding the physicians towards a personalized treatment.

Keywords

Prostate Cancer, Abiraterone, Prostate-Specific Antigen Decline, Survival

1. Introduction

Abiraterone acetate (AA) is a second-generation antiandrogen; it is a selective inhibitor of the enzyme 17 alpha-hydroxylase/C1,20-lyase (CYP17) [1]. Following the excellent survival results obtained in pivotal trials [2] [3] [4], the administration of abiraterone together with prednisone (AA+P) has been approved by health authorities as a treatment for pre-chemotherapy castration-resistant metastatic prostate cancer (pre-CT mCRPC), post-chemotherapy metastatic prostate cancer (post-CT mCRPC), and hormone-sensitive metastatic prostate cancer (mHSPC).

The timely identification of non-responders from among patients treated with AA+P is crucial so that they can potentially benefit from an early change in their treatment regimen. Except for PSA (prostate-specific antigen), no sensitive and accessible predictive biomarkers for the evaluation of AA+P treatment are yet available. However, the evaluation of PSA is also associated with a series of limitations such as the flare effect.

The latest recommendations from the Prostate Cancer Working Group 3 (PCWG3) [5] indicate that the first PSA measurement after the start of treatment should not be carried out before 12 weeks in order to avoid potential biases caused by these aforementioned phenomena. Thus, data on the kinetics of PSA after the first 4 weeks of treatment are limited because none of the pivotal trials performed to date evaluated the decrease in PSA before 3 months. Despite this, some recent publications have evaluated PSA at 4 weeks with promising results, suggesting that PSA could act as a surrogate marker for survival.

Until 2019, these studies had focused solely on mCRPC patients and found that a decrease in PSA by ≥30% or ≥50% was related with increased survival [6] [7] [8] [9] [10]. Recently, two studies that exclusively analyzed mHSPC patients added the variable of a decrease in PSA by ≥90% and found similar data [11] [12]. These studies suggested that professionals should consider early changes in PSA because this marker can provide information on the efficacy of treatments, the need to interrupt therapies, and their associated prognosis.

In this present work, our objective was to analyze whether a decrease in PSA greater than 30%, 50%, and/or 90% at 4 weeks in our patient groups correlated with an improvement in OS and PFS. We wanted to ascertain whether this factor could serve as an early predictive marker of a good response to AA+P therapy. Finally, we also analyzed these data at 8 and 12 weeks to compare the results with the earliest response at 4 weeks.

2. Material and Methods

This is a retrospective, multi-center study carried out at two centers attached to our health department (Consorcio Hospitalario Provincial de Castellón, Hospital Universitario General de Castellón). This work included 172 patients diagnosed with prostate adenocarcinoma who had started treatment with AA+P between February 2012 and July 2019. After more thorough evaluation, 4 patients were

excluded because insufficient data were available for them. We collected demographic and biometric data including information regarding their personal history, the histological characteristics of the tumor, staging (TNM 8th edition [13]), initial treatment, and dates of relapses and resistance to castration, if any. All these variables were selected based on previously conducted pivotal studies and were collected using an SPSS dataset.

Since this was a retrospective study we did not have an ethical protocol, but patients received the informed consent documents for treatment and we complied with the data protection law.

Patients were divided into 3 groups: patients with metastatic castration-resistant prostate cancer who had previously received docetaxel-based chemotherapy (post-CT mCRPC), patients with metastatic castration-resistant prostate cancer with no previous chemotherapy (pre-CT mCRPC) and patients with metastatic hormone-sensitive prostate cancer (mHSPC). The PCWG3 castration-resistant definition was used.

PSA figures were collected at 4, 8, and 12 weeks after the initiation of AA+P, and then every 6 months thereafter. The patients were classified considering the percentage of the decrease in PSA registered at each time point. Within each of the periods, the patients were subdivided into three groups according to whether there had been a decrease in PSA greater than or equal to 90%, 50%, and 30%, respectively.

In addition, analytical data were collected before and during the AA+P treatment. These included lactate dehydrogenase (LDH), alkaline phosphatase (AP), liver enzymes, potassium, cholesterol, triglycerides, and the neutrophil to lymphocyte ratio (neu/lym index). The time to the PSA nadir was defined as the time from the start of AA+P treatment to the date with the lowest PSA figure, quantified in months. This variable was divided into three periods: <6 months, between 6 and 12 months, and >12 months.

All the calculations were carried out using SPSS software (version24, IBM Corp., Armonk, NY). OS was defined as the time from the start of treatment to the date of death or the last update on the patient's condition. PFS was defined as the time from the start of treatment to the date of radiological progression or clinical deterioration. Both OS and PFS were calculated with the Kaplan-Meier method, and the differences between the curves were analyzed with the Log-Rank test, using $p < 0.05$ as a reference value.

A univariate COX model was used to evaluate the effect of a decrease in PSA by ≥30%, ≥50%, or ≥90% at 4, 8, and 12 weeks in terms of OS and PFS. In addition, multivariate analysis was used to analyze these variables together with other factors such as LDH, AP, neu/lym index, previous administration of chemotherapy, Gleason score at diagnosis, presence of cardiovascular factors (hypertension, diabetes mellitus, dyslipidemia), and others. Finally, Spearman correlations were used to analyze the relationship between PSA levels and their decline at 4, 8, and 12 weeks.

3. Results

Of the 168 patients, 49.4% were in the pre-CT mCRPC group, 36.9% were identified as post-CT mCRPC, and the rest (13.7%) had mCPHS. Table 1 summarizes the baseline characteristics of the overall sample, and Tables 2-4 show the baseline characteristics of these patients according to these afore mentioned subdivisions. In the mHSPC group all patients debuted as metastatic and most of them received AA as first treatment following the LATITUDE protocol criteria. On the other hand, in the mCRPC group most patients were not metastatic at the time of disease diagnosis but were included in the locally advanced stage. In

Table 1. Baseline characteristics of overall sample.

OVERALL SAMPLE (n = 168)					
Average age: 70.60 years (range = 47 - 92)					
DM	Yes: 16.7%	No: 83.3%			
PAH	Yes: 53.6%	No: 46.4%			
DLP	Yes: 37%	No 63%			
Statins	Yes: 30.3%	No: 69.7%			
Gleason	G6: 13.6%	G7: 29.9%	G8: 26.5%	G9: 24.5%	G10: 5.4%
T	T1: 0.9%	T2: 22.3%	T3: 55.4%	T4: 21.4%	
N	N0: 60.7%	N1: 29.9%	N2: 5.6%	N3: 3.7%	
M	M0: 49.1%	M1a: 5%	M1b: 46%		
Risk	Low: 2.4%	Medium: 7.1%	High: 81.5%		
1st Treatment	RT: 25.5%	PRL: 14.5%	HT: 46.1%	AA: 10.3%	CT: 2.4%

Abbreviations: DM, diabetes mellitus; PAH, pulmonary arterial hypertension; DLP, dyslipidemia; RT, radiotherapy; PRL, prostatectomy; HT, hormone therapy; AA, abiraterone acetate; CT, chemotherapy.

Table 2. Baseline characteristics of mHSPC sample.

mHSPC (n = 23)					
Average age: 68.70 years (Range = 47 - 81)					
DM	Yes: 17.4%	No: 82.6%			
PAH	Yes: 43.5%	No: 56.5%			
DLP	Yes: 35%	No 65%			
Statins	Yes: 30%	No: 70%			
Gleason	G6: 0%	G7: 4.3%	G8: 47.8%	G9: 43.5%	G10: 4.3%
T	T1: 0%	T2: 11.1%	T3: 44.4%	T4: 44.4%	
N	N0: 10.5%	N1: 47.4%	N2: 31.6%	N3: 10.5%	
M	M0: 0%	M1a: 0%	M1b: 100%		
Risk	Low: 0%	Medium: 0%	High: 100%		
1st Treatment	RT: 0%	PRL: 0%	HT: 19%	AA: 81%	CT: 0%

Abbreviations: DM, diabetes mellitus; PAH, pulmonary arterial hypertension; DLP, dyslipidemia; RT, radiotherapy; PRL, prostatectomy; HT, hormone therapy; AA, abiraterone acetate; CT, chemotherapy.

Table 3. Baseline characteristics of pre-CT mCPRC sample.

pre-CT mCRPC (n = 83)					
Average age: 73.48 years (Range = 49 - 89)					
DM	Yes: 19.3%	No: 80.7%			
PAH	Yes: 60.2%	No: 39.8%			
DLP	Yes: 47%	No 53%			
Statins	Yes: 37.3%	No: 62.7%			
Gleason	G6: 20.8%	G7: 33.3%	G8: 26.4%	G9: 15.3%	G10: 4.2%
T	T1: 1.8%	T2: 23.6%	T3: 65.5%	T4: 9.1%	
N	N0: 72%	N1: 24%	N2: 0%	N3: 4%	
M	M0: 68.4%	M1a: 7.6%	M1b: 24.1%		
Risk	Low: 3.6%	Medium: 9.6%	High: 77.1%		
1st Treatment	RT: 36.6%	PRL: 20.7%	HT: 42.7%	AA: 0%	CT: 0%

Abbreviations: DM, diabetes mellitus; PAH, pulmonary arterial hypertension; DLP, dyslipidemia; RT, radiotherapy; PRL, prostatectomy; HT, hormone therapy; AA, abiraterone acetate; CT, chemotherapy.

Table 4. Baseline characteristics of post-CT mCPRC sample.

post-CT mCPRC (n = 62)					
Average age: 67.45 years (Range = 50 - 92)					
DM	Yes: 12.9%	No: 87.1%			
AH	Yes: 48.4%	No: 51.6%			
DLP	Yes: 24.2%	No: 75.8%			
Statins	Yes: 21%	No: 79%			
Gleason	G6: 9.6%	G7: 36.5%	G8: 17.3%	G9: 28.8%	G10: 7.7%
T	T1: 0%	T2: 25.6%	T3: 46.2%	T4: 28.2%	
N	N0: 71.1%	N1: 28.9%	N2: 0%	N3: 0%	
M	M0: 42.4%	M1a: 3.4%	M1b: 54.2%		
Risk	Low: 1.6%	Medium: 6.5%	High: 80.6%		
1st Treatment	RT: 19.4%	RP: 12.9%	HT: 59.7%	AA: 0%	CT: 6.5%

Abbreviations: DM, diabetes mellitus; PAH, pulmonary arterial hypertension; DLP, dyslipidemia; RT, radiotherapy; PRL, prostatectomy; HT, hormone therapy; AA, abiraterone acetate; CT, chemotherapy.

the pre-CT mCRPC, more than 60% were staged as T3 and almost 80% belonged to the high-risk classification, according to NCCN guidelines. In the latter group (post-CT mCRPC) had a higher proportion of patients staged as T4 and it is noteworthy that approximately 7% of patients received CT as first treatment.

At 4 weeks, 52% of all the patients had presented a decrease in PSA by ≥30%, 39% had exceeded a 50% decrease, and the decrease in PSA exceeded 90% in 10.1% of the total sample. As might be expected, the proportions between these data at 8 and 12 weeks were like those from 4 weeks, although the percentages were progressively higher (see Table 5). The median PSA nadir was 6.82 ng/mL

Table 5. Percentage of patients according to PSA decline at 4, 8 and 12 weeks.

PSA decrease	≥30%	<30%	≥50%	<50%	≥90	<90%
4 weeks	52.0%	48.0%	39.2%	60.8%	10.1%	89.9%
8 weeks	56.8%	43.2%	48.7%	51.3%	13.4%	86.6%
12 weeks	62.8%	37.2%	56.2%	43.8%	26.3%	73.7%

Abbreviations: PSA, prostate-specific antigen.

(range = 0.00 - 1232) and the mean time to the PSA nadir (tPSAn) was 7.69 months. A longer tPSAn was associated with better OS and PFS, as shown in Table 6.

In addition, at 4 weeks, patients who had shown a decrease in PSA by ≥30% had a better median OS (28 vs. 19 months; $p = 0.027$) (Figure 1) and median PFS (17 vs. 6 months; $p < 0.001$). Similarly, in the subgroup whose PSA had decreased by ≥50%, we also observed significant differences in median OS (36 vs. 21 months; $p = 0.003$) (Figure 2) and median PFS (20 vs. 8 months; $p < 0.001$). Finally, a decrease in PSA by ≥ 90% at 4 weeks was related to an improvement in median PFS (31 vs. 11 months; $p = 0.006$) (Figure 3); however, the relationship was not significant between this parameter and median OS, although it did follow the same trend (57 vs. 24 months; $p = 0.063$). The results were similar at 8 and 12 weeks, with an increase in OS and PFS observed in patients whose PSA had decreased by ≥30% or ≥50%. The decrease in PSA by ≥90% was only significantly related to an improvement in PFS, not in OS.

To clarify if there were any differences that could distort the results we performed an analysis by the three subgroups that include our sample, as shown in the following Tables 7-10: in the mCRPC group a decrease in PSA ≥ 50% and ≥90% was related with a significant better outcome in terms of OS and PFS. However, when analyzing the two subgroups inside this group (pre-CT mCRPC and post-CT mCRPC) we did not find any significant results. In the last group (mHSPC), we observed a relationship between a PSA decline ≥ 30% and an improvement in OS and PFS, but not with a PSA decrease ≥ 50% and ≥90%. All these results are given as median survivals, except for the ones that refer to the PSA decrease ≥ 90% that are given as mean survival because this group of data did not achieve the fiftieth percentile.

The univariate analysis showed that, at 4 weeks, both decreases by ≥30% and ≥50% were related to increased OS (HR = 1.568, 95% CI [1.041, 2.360], $p = 0.031$; HR = 1.901, 95% CI [1.222, 2.956], $p = 0.004$) and increased PFS (HR = 2.036, 95% CI [1.371, 3.025], $p < 0.001$; HR = 2.236, 95% CI [1.465, 3.412], $p < 0.001$). However, we were unable to corroborate this result in the multivariate analysis (see Table 11). Nonetheless, it should also be noted that, in the overall sample, administration of chemotherapy prior to AA+P was a risk factor which was associated with a reduced time to progression (HR = 3.238; $p < 0.001$) or death (HR = 2.511; $p < 0.001$). Moreover, this variable remained statistically significant in the multivariate analysis.

Table 6. Relationship between time to PSA nadir and survival.

Time to PSA nadir	Time to progression (months)	*p*-value	Time to death (months)	*p*-value
<6 months	8.87		18.14	
4 - 6 months	23.76	**<0.001**	32.70	**<0.001**
>12 months	44.06		58.09	

Abbreviations: PSA, prostate-specific antigen.

Table 7. Results of survival in m-CRPC group.

	<30%	**>30%**	***p* value**
Median PFS	7	16	**0.004**
Median OS	21	26	0.83
	<50%	**>50%**	***p* value**
Median PFS	8	18	**0.001**
Median OS	21	36	**0.009**
	<90%	**>90%**	***p* value**
Mean PFS	16.10	37.22	**0.014**
Mean OS	26.44	51.33	**0.017**

Abbreviations: OS, overall survival; PFS, progression-free survival.

Table 8. Results of survival in pre-CT m-CRPC group.

	<30%	**>30%**	***p* value**
Median PFS	17	20	0.297
Median OS	29	40	0.793
	<50%	**>50%**	***p* value**
Median PFS	16	29	0.055
Median OS	28	45	0.104
	<90%	**>90%**	***p* value**
Mean PFS	21.95	40.12	0.058
Mean OS	32.46	51.33	0.066

Abbreviations: OS, overall survival; PFS, progression-free survival.

Table 9. Results of survival in post-CT m-CRPC group.

	<30%	**>30%**	***p* value**
Median PFS	4	11	0.069
Median OS	13	24	0.269
	<50%	**>50%**	***p* value**
Median PFS	4	11	0.079
Median OS	13	25	0.130
	<90%	**>90%**	***p* value**
Mean PFS	8,83	14	0.570

Abbreviations: OS, overall survival; PFS, progression-free survival.

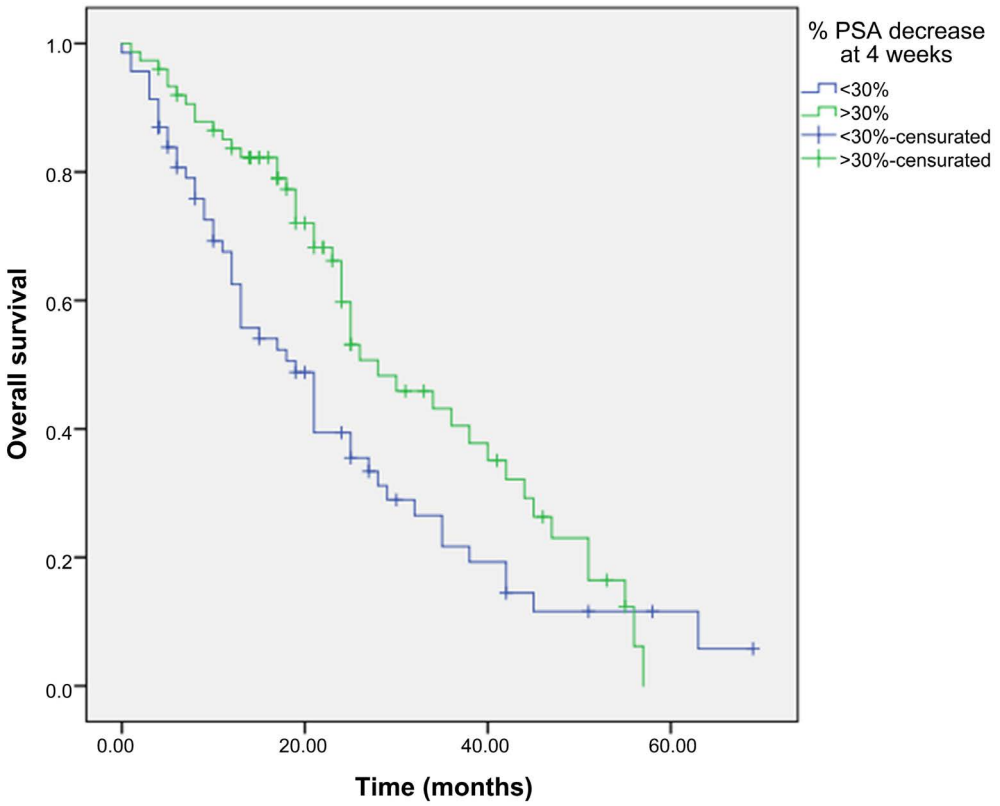

Figure 1. Overall survival curve as a function of the decrease in PSA (by >30% and <30%).

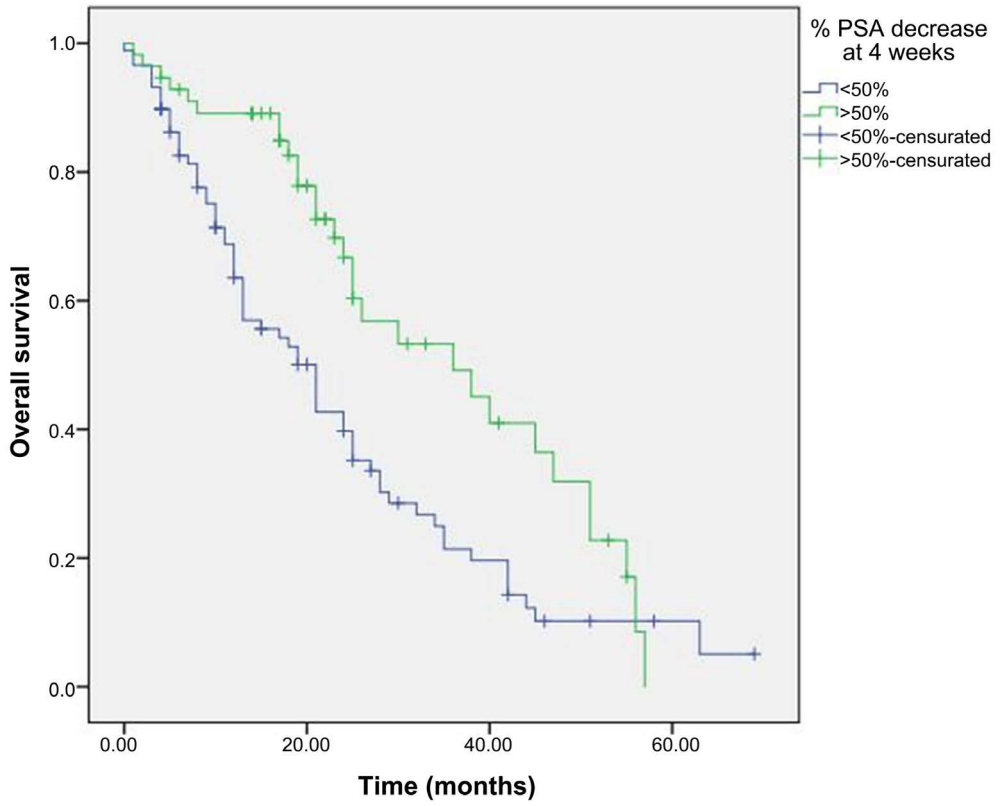

Figure 2. Overall survival curve as a function of the decrease in PSA (by >50% and <50%).

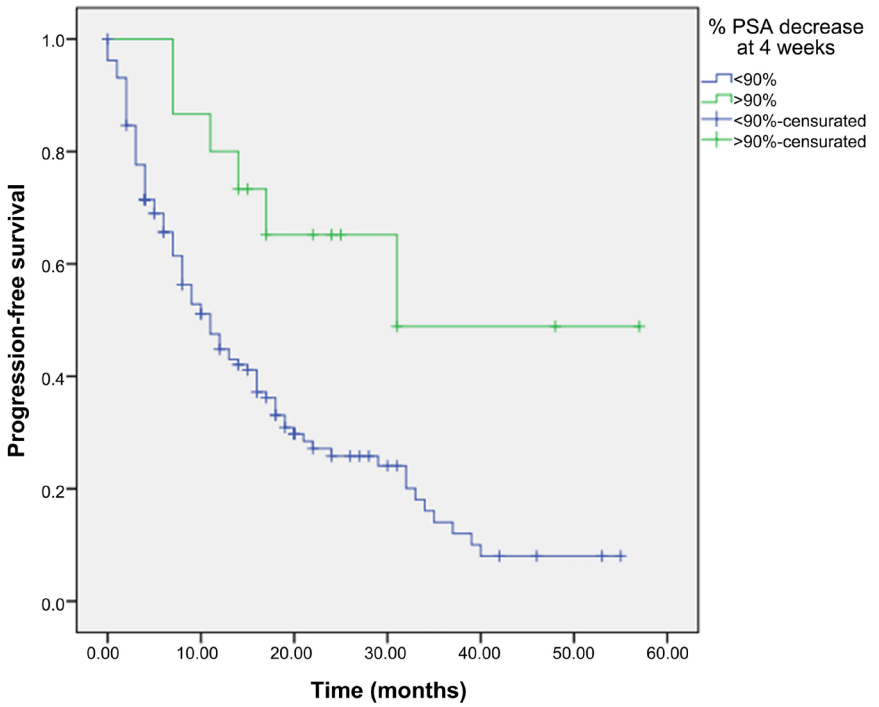

Figure 3. Progression-free survival curve as a function of the decrease in PSA (by >90% and <90%).

Table 10. Results of survival in m-HSPC group.

	<30%	>30%	*p* value
Median PFS	3	0	0.011
Median OS	5	0	0.008
	<50%	**>50%**	***p* value**
Median PFS	4	0	0.146
Median OS	9	0	0.114
	<90%	**>90%**	***p* value**
Mean PFS	17.26	19.78	0.669
Mean OS	19.73	16.17	0.381

Abbreviations: OS, overall survival; PFS, progression-free survival.

Table 11. OS results in the multivariate analysis at 4 weeks.

	Sig.	Exp(B)	95.0% CI for Exp(B)	
			Upper	Lower
PSA diagnosis	0.301	1.000	1.000	1.001
Previous CT	0.001	2.764	1.481	5.158
PSA when AA started	0.145	1.003	0.999	1.006
Decrease in PSA > 50%	0.163	1.573	0.832	2.976
Decrease in PSA > 30%	0.95	1.02	0.55	1.91
LDH	0.581	1.000	0.999	1.001
AP	0.023	1.001	1.000	1.002

Abbreviations: LDH, low-density lipoprotein; AP, alkaline phosphatase.

At 8 and 12 weeks, the results were very similar. At 8 weeks, both OS and PFS showed a significant relationship with a PSA decline > 30% (OS: 33.35 vs. 22.56 m, $p = 0.002$; PFS: 24.78 vs. 10.75 m, $p < 0.001$), >50% (OS: 37.59 vs. 23.13 m, $p < 0.001$; PFS: 25.81 vs. 12.47 m, $p < 0.001$) and >90% (OS: 28.08 vs. 39.29 m, $p = 0.005$; PFS: 15.85 vs. 36.51 m, $p = 0.002$). At 12 weeks, all the survivals found significant relationship with a PSA decline > 30%, >50% and >90% as well. However, when the multivariate analysis is performed, these variables lose statistical weigh but a trend is observed.

Regarding the analytical parameters evaluated, we saw a significant decrease in LDH and AP levels in the periods evaluated in relation to OS and PFS (except for LDH at 12 weeks). Nonetheless, given that these HRs were remarkably close to 1, these factors should be considered neutral. The neu/lym index was not statistically significant in any of the time periods we included. Moreover, these parameters were analyzed in each subgroup and the results obtained were similar. Finally, we found a strong correlation between the decrease in PSA at 4 and 8 weeks (Rho = 0.912; $p < 0.001$), 4 and 12 weeks (Rho = 0.801; $p < 0.001$), and 8 and 12 weeks (Rho = 0.948; $p < 0.001$).

4. Discussion

AA is an effective therapy for metastatic prostate cancer but not without its drawbacks such as some side effects and its cost. The study of the PSA kinetics and its early changes could serve as a tool in daily clinical practice to make a decision about discontinuing the treatment, even earlier than the actual standard.

Our analysis demonstrated a significant improvement in OS and PFS in patients with a decrease in PSA by ≥30% at 4, 8, and 12 weeks. These results coincide with those described in the multicenter study by Rescigno [9] which observed that a decrease in PSA of more than 30% at 4 weeks was associated with a better OS. Similarly, a decrease in PSA ≥ 50% was also related to an improved OS and PFS. This confirmed the data previously obtained by Schiff *et al.* [10] who analyzed PSA levels at 4 and 12 weeks, as well as the results from Facchini [7] who assessed PSA even earlier, 15 days after the start of treatment.

As also found in the post-hoc analysis of the LATITUDE study [11], in our work we observed a correlation between a decrease in PSA by ≥90% and an improvement in PFS. However, we evaluated PSA levels at three specific time points (4, 8, and 12 weeks) while the analysis in the aforementioned study was carried out when the decrease occurred, rather than at specific points in time. Nonetheless, the relationship between decreased PSA and OS followed the same trend, although it did not reach statistical significance ($p = 0.063$), perhaps because of the limited number of events in our work that achieved this early decrease. Furthermore, an inverse relationship was observed between the tPSAn and survival in both the LATITUDE study and our work, which, although not relevant as a predictive factor because of its retrospective nature, provides valuable retrospective information that can help researchers to better understand the profile of

non-responders.

Although a decrease in PSA (by ≥30% or ≥50%) initially correlated with OS in our univariate analysis, the multivariate analysis failed to confirm this. In agreement, the data published by Nakayama [6] showed that a decrease in PSA of more than 30% at 4 weeks was not a significant predictor of OS. In the univariate analysis, the decrease in PSA by ≥30% or ≥50% was statistically significant for PFS. However, the multivariate analysis only confirmed these decreases as independent prognostic factors when measured at 12 weeks. This finding may be due to several reasons. For example, our sample was heterogeneous compared to the populations studied in the previous literature, which had only included mCRPC or mCPHS patients, but not in the same group. Although we analyzed each patient subgroup separately and did not observe any notable differences between them, this may have been because of the limited sample size in our work. In any case, the data we obtained did not allow us to configure a mathematical predictive model for decreased PSA expression. Nonetheless, it did provide relevant clinical information that could help researchers to individualize the treatment and follow-up of each patient subgroup.

In contrast, our study indicated that the prior administration of chemotherapy constituted an independent risk factor for reduced survival. This finding has already been described elsewhere, such as in the work by Nakayama [6] which observed a difference in PSA response at 4 weeks between patients who had or had not received prior chemotherapy. Perhaps this could be explained by the hypothesis proposed by some authors suggesting that taxanes produce cytoplasmic sequestration of the androgen receptor (AR) and therefore, decrease AR sensitivity which can lead to cross-resistance between docetaxel and AA [14] [15] [16]. Furthermore, it is important to consider that the patient populations who have undergone chemotherapy tend to be older patients who have received numerous previous lines of treatment, a fact that may condition their poorer prognosis.

Other variables that were significant in the univariate analysis and, in some cases also in the multivariate analysis were the LDH and AP levels. However, their impact was doubtful in our study because the HR values were close to 1, thereby making them neutral variables. Thus, even though these factors have been previously studied and found to be positive prognostic markers, in this current work we could not conclude that they were significant predictive factors.

Another fact worth to mention is that in our study we confirmed the existence of a strong correlation between PSA figures at 4, 8 and 12 weeks, which means that a downward trend is observed from the first 4 weeks and continues until reaching the 12th week. This is very interesting information for physicians when interpreting the analytical results and being able to predict the most likely future behavior in terms of PSA kinetics.

Finally, we must also assume that our study had several limitations. First, it was a retrospective study. Second, the number of patients included in each subgroup was not as large as would have been desirable. Finally, we were unable to eva-

luate the PSA flare effect in this current work.

5. Conclusion

To conclude, although it cannot be considered an independent predictive variable, an early decrease in PSA could serve as a valuable tool in the early assessment of the effectiveness of second-generation antiandrogens such as AA. This would aid physicians in the timely selection of patients who are unlikely to benefit from this therapy and would thus, help intensify the drive-in current medicine towards individualized therapeutic strategies.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Endoscopic Internal Urethrotomy (EIU) for the Treatment of Ureteral Stenosis: A Review of 233 Cases

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Abstract

Background: Urethral stricture is a not uncommon pathology consisting of the narrowing of the urethra lumen with consequent reduction or cessation of urine flow. **Objective:** The objective is to retrospectively evaluate the results of treatment of urethral strictures by endoscopic internal urethrotomy in a series of 233 cases. **Patients and Methods:** It is Retrospective and descriptive study of 233 cases of urethral strictures treated by endoscopic internal urethrotomy under visual control in a private facility in Abidjan (Ivory Coast) over the period from 1 December 2007 to 31 December 2017. The study parameters were epidemiological, etiological, characteristics of the narrowing and the outcome of the treatment according to the predictive elements. **Results:** 233 patients were treated with endoscopic internal urethrotomy (EIU). All patients were male. The mean age of the patients was 49 years with extremes from 17 to 84 years. Dysuria (55.79%) was the most frequent reason for consultation: the etiologies were infectious (51.50%), traumatic (32.18%), and iatrogenic (13.73%) and not found (2.57%). Retrograde urethrocystography with fictional films performed in all patients showed the following characteristics: the stricture was bulbar (81.04%), unique (55.79%) and short in 68.6%. There was a 39.91% good outcome after the first EUS. The average follow-up was 3 years. Mortality was nil and morbidity was assessed at 4.72%. The result was better when the procedure concerned a short (≤3 cm), single stenosis on the posterior urethra. The average duration of the postoperative urinary catheter

was 14 days on average. The poor results (60.08%) were observed in cases of long stenosis, located on the anterior urethra or concerning elderly patients. 69.28% were cured after a second urethrotomy; the remaining cases were managed by urethroplasty or urethral dilatation. **Conclusion:** IEU is a simple, reproducible and attractive procedure with an overall success rate of 81.54% in 3 years. Its indication must be made in the case of short stenosis, single posterior and in the young subject.

Keywords

Stenosis, Urethra, Endoscopic Internal Urethrotomy

1. Introduction

Urethral stricture or urethral stenosis is a narrowing of the urethral lumen usually resulting from ischaemic spongiofibrosis. In Africa, in general, and in Ivory Coast in particular, it represents a late complication of sexually transmitted infections and trauma [1]. Its diagnosis is evoked in front of urinary disorders of the lower apparatus, infectious or traumatic antecedents and confirmed by retrograde urethrocystography with fictional pictures. Management is difficult and a real challenge in Urology. The various techniques of open repair are known to urologists as well as the related postoperative problems which are related to the importance of the lesions often extended and to the sepsis in connection with our working conditions with its procession of complications [1]. The endoscopic internal urethrotomy is a simple method, of fast realization, devoid of major morbidity and requiring only a short hospitalization. The aim of our work is the retrospective evaluation of the results of the treatment of urethral strictures by endoscopic internal urethrotomy in a series of 233 cases.

2. Patients and Methods

This is a retrospective and descriptive study conducted from December 1, 2007 to December 31, 2017 in a private facility in Abidjan (Ivory Coast); 233 male patients were treated by endoscopic internal urethrotomy. The diagnosis of urethral stricture was made on the basis of a history of sexually transmitted infection, trauma to the pelvis or urethra after bladder catheterization, clinical evidence and diagnostic confirmation by retrograde urethrocystography with voiding films showing the location, number and length of the stricture as well as its impact on the upstream pocket. All urethrotomy was performed after a standard prior operative workup and after ensuring the sterility of the urine from the urine cytobacteriological examination. All urethrotomy was performed using a cold blade urethrotomy (STORZ) with 0˚ optics. The procedure was performed under loco-regional anaesthesia. Sectioning of the stricture was performed under visual control at 12 o'clock from front to back until the peri-urethral tissue was visible. It extended in the digital plane to the healthy mucosa. The irrigation flu-

id used was saline (9% saline). A CH20 urethral catheter was used to drain the urine postoperatively for 14 days. After removal of the catheter, the postoperative follow-up was 3 years for each patient. It includes:

- Clinical: fictional comfort;
- Radiological: retrograde urethrocystography;

The parameters studied were epidemiological, etiological and the result of the treatment according to predictive criteria.

Outcome evaluation criteria:

- Good outcome;
- Patient has comfortable voiding;
- Patient has no voiding problems;
- Normal retrograde urethrocystography;
- No post-void residual.

Poor result (two criteria present):

- Patient has uncomfortable voiding;
- Presence of voiding disturbance;
- retrograde urethrocystography: urethral stricture;
- Presence of post-void residual.

The predictive criteria for the outcome of the urethrotomy were:

- Age;
- Characteristics of the stricture (location, length, number).

The data were collected from the patients' files, a survey form and the register of surgical reports of patients operated on for urethral stricture. All data were entered into the WORLD software and processed with Epi info 2.10.

We have protected the confidentiality of the information collected during the survey. Thus, an anonymity number was assigned to each survey form with prior authorization obtained from the administrative and health authorities.

3. Results

3.1. Clinical Data

1) Circumstances of discovery

Dysuria is the most frequent circumstance of discovery with 55.79% (Table 1, n = 130).

2) Etiology

Infectious causes are frequent with 51.50% (n = 120, Table 2).

3.2. Radiographic Data Retrograde Urethrocystography

1) Site

The bulbar urethra is the predominant site with 81.54% (n = 190, Table 3).

2) Number of narrowings

Single narrowing represents 56% (n = 125, Table 4).

3) Extent of narrowing

Short narrowing represents 68.6% (n = 160, Table 5).

Table 1. Distribution of patients according to discovery circumstance.

Circumstance of discovery	Number	Percentage
Dysuria	130	55.79
Acute or chronic retention of urine	70	30.04
Urinary urgency associated with urinary frequency or burning	13	5.57
Recurrent epididymitis	12	5.15
Urethral fistula	8	3.43
TOTAL	233	100

Table 2. Distribution of patients according to the aetiology of narrowing.

Etiology	Number	Percentage
Infectious	120	51.50
Traumatic	75	32.18
Iatrogenic	32	13.73
Not found	06	2.57
TOTAL	233	100

Table 3. Distribution of patients by site.

Parameter	Numbers	Percentage
Bulbar urethra	190	81.54
Penile	33	14.16
Bulbo-membranous	10	4.29
TOTAL	223	100

Table 4. Distribution according to the number of strictures.

Number	Number	Percentage
Single	130	55.79
Multiple		
≤3	70	30.04
≥3	33	14.16
TOTAL	233	100

Table 5. Distribution of patients according to the extent of the stricture.

Extent	Number	Percentage
Short ≤ 3 cm	160	68.6
Long > 3 cm	72	30.9
Unspecified	1	0.42
TOTAL	233	100

The cytobacteriological examination of the urine showed a urinary infection in 92 patients (39.48%); the most frequent germ was Escherichia coli in 72 patients (78.26%). The patients were treated with antibiotics adapted to the preoperative antibiogram. The CH20 urethral catheter was left in place for an average of 14 days, with extremes of 3 to 21 days depending on the extent of the stenosis, in cases of difficult endoscopic internal urethrotomy and significant urethral fibrosis.

The average duration of the procedure was 15 minutes with extremes of 5 to 45 minutes.

The average hospital stay was 3 days with extremes of 1 to 6 days.

The operative morbidity was 4.72% (n = 11) represented by:

- Six (6) false routes benefited from a second endoscopic internal urethrotomy (EIU) with favorable outcome one week after the first urethrotomy. Two (2) scrotal fluid extravasations were resolved by suspension of the bursa. One urinary tract infection and one orchid epididymitis treated with antibiotic therapy adapted to the antibiogram. One patient presented with transient sexual impotence which resolved spontaneously with time. Infectious complications and false routes all occurred in patients with an extensive stricture.
- Operative mortality was zero.

4. Overall Results

- 93 patients (39.91%) had a good outcome immediately after removal of the urinary catheter. This result remained the same throughout the study period. 140 patients (60.08%) had a poor outcome after the first endoscopic internal urethrotomy with recurrence occurring on average 18 months with extremes from 1 to 36 months. Of these patients, 97 (69.28%) were definitively treated after a second EIO. The remaining 43 patients were never cured by UIE even after a third urethrotomy attempt.

A TOTAL of 190 patients out of 233 (81.54%) were cured after one (n = 93) or two (n = 97) endoscopic internal urethrotomy. The 43 patients not cured by EUS were treated by urethral dilation (n = 32; 13.73%) or urethroplasty (n = 11; 4.72%).

- Two-year (36 months) outcomes by predictors.

We found 86.84 good results for posterior urethral strictures (165 patients) versus 13.15% for penile strictures (25 patients); for short strictures less than or equal to 3 cm (156 patients), the results were good in 82.1% versus 17.85% for long strictures greater than or equal to 3 cm (34 patients) Beyond three areas of narrowing, the rate of poor results was 100%.

We found 79.4% good results (n = 151) in the group of patients under 45 years of age (n = 189) against 20.52% (39 patients) in the group of patients over 55 years of age (n = 44). 77.33% (n = 58) of good results were found for narrowing of traumatic origin, 56.2% (n = 18) for iatrogenic causes and finally 45.83% for infectious causes.

5. Discussion

Urethral stricture is a not uncommon pathology in urology and can occur at any age. In our study, the mean age of the patients was 49 years (17 - 84 years); in a similar study in Cameroon, 49 patients were recorded and the mean age was 47.6 [2]; in Togo, the mean age of the patients was 44.4 years [3]; in North Africa (Morocco), 244 patients had a mean age of 51 years [4]. The results show that urethral stricture is pathology of the adolescent and young adult. Indeed, sexual freedom, extended to the plurality of partners on the one hand, and on the other hand, sexually transmitted diseases that affect mainly adolescents and young adults who constitute the sexually active population could explain these results. Our study recorded only men. Urethral stricture is a rare condition in females and the literature reports only one case in a series of 112 patients in Kenya [5].

Dysuria is the major finding of urethral stricture in our study with 55.79%. This finding is similar to that of other authors on the African continent, Ngaroua in Cameroon 70.17% [6], Hounnasso in Togo 48.1% [3], and Benjelloun in Morocco 82% [4]. Dysuria is explained by the fact that urethral stricture is a reduction in the lumen of the urethra resulting in an obstacle to the flow of urine out of the bladder. They can be infectious, traumatic and iatrogenic [1] [2] [3] [4]. In our study, the main etiologies were infectious and traumatic. Indeed, we recorded 51.50% of infectious aetiologies. This predominance of infectious causes is also found in the studies of several African authors [1] [2] [3] [4]. This result could be explained by the low socio-economic level, poor hygiene conditions and risky behavior and the plurality of sexual partners favoring sexually transmitted infections. Traumatic aetiology came second to infectious causes with 32.18%. The narrowing of the urethra as a result of trauma accounts for road accidents and late consultations. The iatrogenic causes are due in our practice to iterative catheterization and/or prolonged wearing of urinary catheters after adenomectomy complicated by vesico-cutaneous fistulas. However, in developed countries, iatrogenic causes are most often due to endoscopic maneuver [7] [8] [9]. In our study, analysis of the characteristics of urethral strictures revealed the following: the strictures were essentially bulbar (81.54%), single (55.79%) and short (68.6%), as in the series by Benjelloun et al in Morocco [4], Hounnasso in Togo [3], Moby in Cameroon [2] and Ndour in Senegal [10]. On the other hand, Zongo et al in Burkina Faso reported a predominance of long and multiple strictures, respectively 69% and 75% [11]. In our series of 233 patients with urethral strictures with a 3-year follow-up, we report an overall cure rate of 81.54% of cases. Our results are comparable to those reported in the series of Ngaroua which is 87.73% of cure rate while Ahmed [12] reports only 58.1% of cure rate. The bulbar site could be explained by the configuration of the bulb whose cul-de-sac constitutes a reservoir where germs swarm due to urinary stasis. For Culty [13], endoscopic internal urethrotomy is more often unsuccessful in post-traumatic stenosis than in post-infectious stenosis [13]; for André, the results are less good in sclero-inflammatory stenosis [12], whereas for post-traumatic stenosis the re-

sults are better [8]. For Ahmed, the best results are obtained when it is a stenosis of the proximal urethra [12]. In our series, we recorded 60.08% of recurrences. They appear late, on average 18 months after the first EUS. A second urethrotomy was proposed in these cases with 69.28% success rate, but a poor outcome after a second urethrotomy was never improved by an additional urethrotomy. The results of our study analyzed at 24 months, show that good results are obtained in young subjects with short, single and posterior strictures. In contrast, poor results were observed in patients with extensive and multiple strictures. In our series, the urethral tube was left in place for an average of 14 days, whereas Benjelloun in Morocco left the catheter in place for two days. The duration of 14 days in our series could be explained by the often difficult urethrotomy due to the important fibrosis of the stricture on the one hand and on the other hand the false routes in case of extensive stenosis. However, prolonged catheterization has not been shown to improve the outcome of urethrotomy [1] [4]. The morbidity of endoscopic internal urethrotomy is minimal and is known from the literature [14] [15] [16]. In our series, the morbidity was 4.72%. The literature reports a morbidity rate of between 4% and 9.5% [1] [4] [9] [17]. This low morbidity found in our study confirms the thesis according to which endoscopic internal urethrotomy is devoid of major morbidity claimed by several authors with regard to open surgery [1] [4] [7] [8] [12].

6. Conclusion

Endoscopic internal urethrotomy is a simple procedure, easy to perform, repetitive and attractive in view of the overall success rate which is 81.54% at 3 years in our study. It should be offered as a first-line procedure to patients with any short, single and proximal stenosis in young subjects. Open surgery should be indicated in case of failure after two attempts of endoscopic internal urethrotomy. This study has limitations that must be taken into account when interpreting the results. As this is the retrospective nature with significant loss of information.

Contributions of the authors

AVION Kouassi Patrice, AKASSIMADOU N'diamoi, OUATTARA Fatoumata, AGUIA Brice, ZOUAN Fredy, ALLOKA Venance, CAMARA Sadia, BONY Gnissan: Performing statistical analysis and proofreading the article. KRAMO Nykan, ANZOUA Kacou, DJE Koffi: Documentary research and formatting of the work.

Ethical Considerations

We have protected the confidentiality of the information collected during the survey. Thus, an anonymity number was assigned to each survey form with prior authorization obtained from the administrative and health authorities.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Fournier's Gangrene: Experience with Two Severe Cases

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Abstract

Fournier's Gangrene is a formidable rare disease characterized by high mortality rates despite optimal medical and surgical management. It is an acute surgical emergency and requires a high degree of suspicion. The mainstay of treatment is swift open drainage and early aggressive surgical debridement of all necrotic tissue, followed by targeted antibiotic therapy. The authors report on two patients who were admitted to the surgical ward. Both presented with initial perianal sepsis complicated by painful swollen scrotum with rapid progression of gangrene of the scrotal skin and subcutaneous tissue, extensive cellulitis of the perineum, and in one patient crepitation of the anterior abdominal wall. A diagnosis of Fournier's Gangrene was made and they were both managed by prompt resuscitation, broad-spectrum antibiotics, extensive debridement of all necrotic tissue in theatre, daily wound dressing, and repeated neurectomy on the ward. One of the patients had a colostomy done and the other a cystostomy to divert feces and relieve chronic urinary retention respectively. These patients were successfully treated despite the severity of their conditions which was complicated by severe sepsis in the face of limited diagnostic capabilities and resources, using a multidisciplinary approach and basic clinical monitoring as a guide.

Keywords

Fournier's Gangrene, Surgical Debridement, Necrotic Tissue, Sepsis, Antibiotic Therapy

1. Introduction

In 1883, the French venereologist Jean Alfred Fournier described a series in which

5 previously healthy young men suffered from rapidly progressive gangrene of the penis and scrotum without apparent cause. This condition is now known as Fournier's gangrene (FG) [1].

Fournier's gangrene (FG) is a rare, synergistic, fulminant form of necrotizing fasciitis involving the genital, perineal, and perianal regions [2], with gangrene of the overlying skin.

The incidence of the disease is higher in males with Sorensen *et al.*, reporting an overall incidence rate of 1.6 cases per 100,000 males/year [3]. Eke [2] found a mean incidence of 97 cases per year in a review of 1726 cases in a 10-year retrospective study.

Fournier's gangrene is characterized by high mortality rates, the reported mortality rate for FG widely varies from 20% - 40% to as high as 75% - 88% [1] [3] [4]. The predisposing factors believed to contribute to the development of the disease are diabetes mellitus, alcoholism, malignancies, immunosuppression, liver, and renal disease [5].

It is an acute surgical and urological emergency. The keystones of management are hemodynamic stabilization, effective antibiotic treatment, and urgent aggressive surgical debridement [5].

We present two cases of Fournier's gangrene following perianal sepsis which was successfully treated in our department despite the severity of the patient's condition in the face of limited diagnostic and monitoring capabilities.

2. Case 1

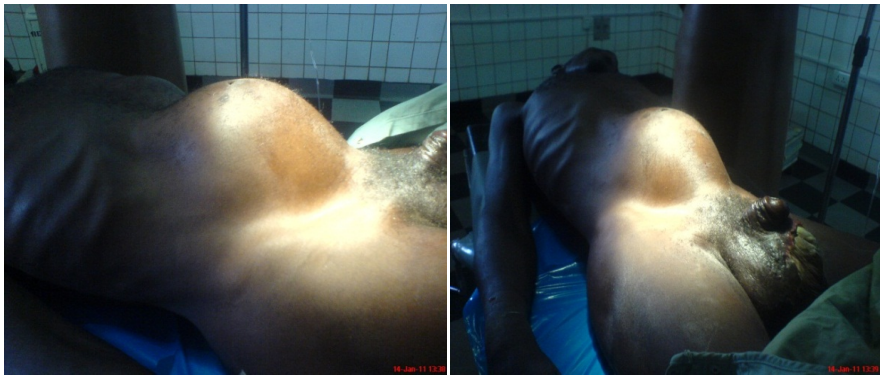
A 45-year-old male who had undergone a below-knee amputation of the left leg on account of a chronic ascending ulcer (No histology diagnosis available) about 4 years ago, was admitted by the urology team with severe painful swollen scrotum of 3 days duration and infected perianal ulcers of about 2 weeks associated with high-grade fever and offensive discharge. He also had a painless inability to pass urine of 2 days duration. On examination; the Patient looked moderately wasted, was pale and febrile 39.0˚C, hypotensive (80/50mmHg) tachycardic (104 bpm regular and bounding), and Respiratory rate was 24 cpm.

He had a grossly distended bladder, 5 cm above the umbilicus. Infected perianal ulcers were identified, the scrotum was grossly swollen with gangrene of the anterior part of the skin and cellulitis of the perineum (**Figure 1(A)** and **Figure 1(B)**).

Hemoglobin was 8.6 g/dL, white blood cells (WBC) 18,000 u/L, Platelets 382, Sickling was Negative, Fasting blood sugar (FBS) was 6.4 mmol/L and the retroviral screen was negative.

A diagnosis of Septic Shock secondary to Fournier's Gangrene and perianal sepsis was made as well as Chronic Urinary Retention.

The patient underwent aggressive fluid resuscitation and hemodynamic support, Intravenous third-generation cephalosporin and metronidazole were commenced immediately and the patient was prepared for emergency suprapubic



(A) (B)

(C)

Figure 1. The picture shows Case 1—Chronic retention of urine with gross distension of bladder and gangrene of scrotal skin (A and B). The last picture (C) was taken after 6 weeks post-surgery showing a residual small ulcer which was closed in theatre.

cystostomy and debridement under Local anesthesia and conscious sedation respectively.

Intraoperatively, 2.4 litres of dark urine were drained from the bladder gradually, scrotal skin had a gangrenous patch anteriorly of about +6 cm, and about 0.4 L of purulent discharge was drained from the scrotum up to the inguinal area. Testis and Spermatic cords were intact and healthy.

Postoperatively the patient was put on intravenous Ampicillin (500 mg qid), Metronidazole (400 mg tid), and Gentamycin (80 mg only in the evenings to reduce nephrotoxicity) for 72 hours with instructions for 6 hourly daily dressing. He underwent series of subsequent wound debridement on the ward under analgesia and the moist dressing was with normal saline-soaked gauze. Wound swab for culture yielded *Staphylococcus*, micro-aerophilic hemolytic *Streptococcus*, *E. Coli*, and *Cl. Welchii*, and sensitivity results (Augmentin, Ceftriaxone, Meropenem and Gentamicin) guided the antibiotic therapy. Patient received intravenous doses of Augmentin (1 gm bd) and Ceftriaxone (1 gm daily).

Intravenous antibiotics were converted to oral after post-op day 7, spiking of temperature resolved by post of day 5. Glucose remained normal and healthy

granulation tissue was observed after about 4 weeks of the wound dressing. Recovery from then onwards was progressive and uneventful.

He was discharged on the 50th post-op day and reviewed in the outpatient department (OPD) a week later, scrotal wound was almost closed leaving a small patch that has been repaired in theatre, he can now void urine through his urethra and cystostomy has been closed (**Figure 1(C)**).

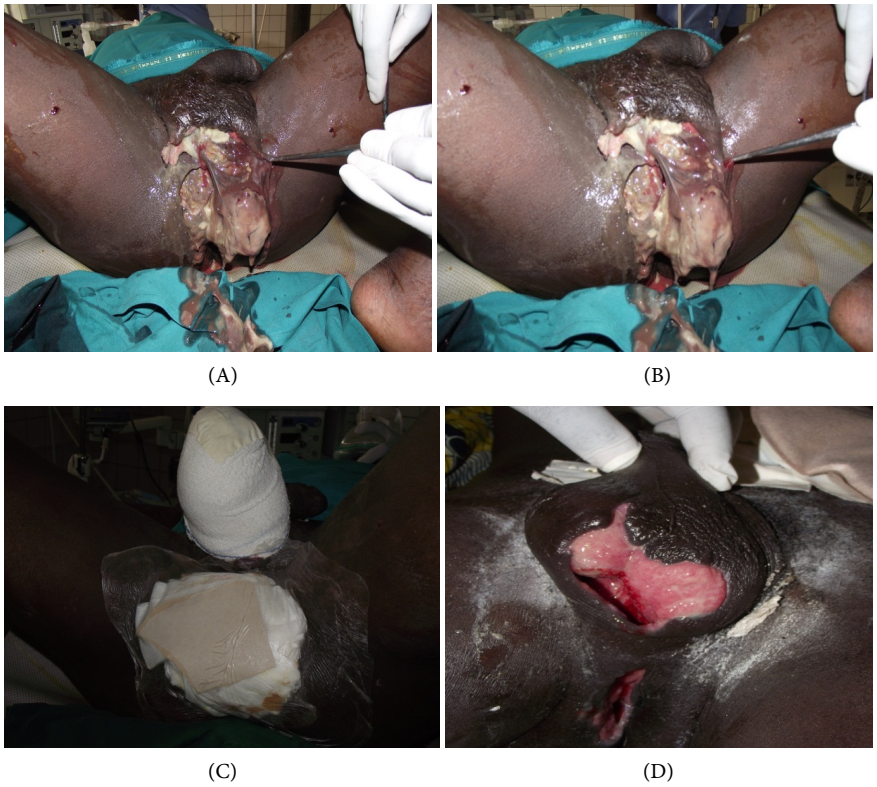
3. Case 2

A 35-year-old man with a one-year history of 3rd-degree hemorrhoids presented to the OPD with a 4-day history of perianal pain. The pain was throbbing in nature and associated with painful defecation. An impression of thrombosed hemorrhoids was made and the patient was sent to the medical ward. Severe tenderness of the perianal area with non-cooperation to examination was documented. His blood pressure (BP) was 110/80mmHg, pulse 68 beats per minute, Respiration rate 16 cycles per minute, and temperature 37.0˚C.

Two days on admission, the swelling had progressed to involve the whole scrotum associated with severe pain, difficulty in micturition, and fever. Pulse was now 100 bpm, Respiratory rate was 22 cpm, and the temperature was 38.8˚C and BP 90/60. There was crepitus over the right iliac fossa and right lumber areas of the anterior abdominal wall associated with severe tenderness. A urologist consult was sought and a diagnosis of Severe Sepsis secondary to an Ischiorectal abscess affecting the scrotum due possibly to a gas-forming bacteria was made. The patient was transferred to the surgical ward and prepared for emergency incision and drainage. Hemoglobin was 14.5 g/dL, fasting blood sugar was 6.8 mmol/L, Intravenous Ciprofloxacin 200 mg bd and Metronidazole 400 mg tid commenced as well as fluid administration. Over the next few hours, the ischiorectal abscess ruptured with the overlying skin gangrenous and exposing the anorectum circumferentially, anal hygiene was grossly inconveniencing and the scrotal skin was rapidly becoming gangrenous. The general surgeons were involved in the plan for fecal diversion (**Figure 2(A)** and **Figure 2(B)**).

The working diagnosis was now ischiorectal abscess complicated by Fournier's Gangrene. In theatre, under general anesthesia, a double-barrel sigmoid colostomy was accomplished, and extensive necrosectomy of the scrotal skin and perineum was done evacuating the area into open drainage. The testis and spermatic cords were debrided and remained intact. Copious amounts of pus were expressed from the right lumber and right iliac fossa area via the groin. About 500 ml of pus drained in total. The cavity was irrigated with copious amounts of Normal saline and Povidone Iodine and dressed in gauze and absorbent material. The sample was taken for culture yielded *Staphylococcus*, micro-aerophilic hemolytic *Streptococcus*, *E. Coli*, *Cl. Welchii*, and Bacteroides.

Postoperatively, 6 hourly dressing was instituted with normal saline-soaked gauze under sedation and analgesia, colostomy functioned normally, Intravenous ciprofloxacin 200 mg bd, clindamycin 300 tid, and metronidazole 400 mg tid



(A) (B)

(C) (D)

Figure 2. Pictures of Case 2—Findings before surgery showing the extent of disease (A, B and C) and 3 weeks after surgery revealing significant wound healing (D).

continued for 8 days. The patient continued to spike high temperatures associated with rigors daily for 7 days with attenuation of intensity. The broad-spectrum antibiotic response was monitored by the patient's vital signs; pulse, respiratory rate, temperature pattern blood pressure, and wound progress.

A high protein diet was encouraged, as well as ambulation. Healthy granulation tissue was observed after about 2weeks of daily dressing, blood glucose remained normal, and the patient gradually gained weight. Hemoglobin rose to 12.0 g/dL, retroviral screen-negative. He was able to void urine through the external meatus.

Has had scrotoplasty done and the perineal ulcer healed (**Figure 2(C)**). Return of colostomy was carried out after 5 weeks (**Figure 2(D)**).

4. Discussion

Fournier's gangrene (FG) is the result of a highly lethal and rapidly progressive necrotizing infection of the perineal and genital fascia, with gangrene of the overlying skin [6].

The syndrome of FG is an uncommon but quite serious problem. This entity affects both men and women and at a wide age range, from neonates to the very elderly [5].

The male-to-female ratio is approximately 10:1. The lower incidence in females may be caused by better drainage of the perineal region through vaginal

secretions. Most reported cases occur in patients aged 30 - 60 years. A literature review found only 56 pediatric cases, with 66% of those in infants younger than 3 months [1]. Our patients were 45 years and 35 years old, which is following the reported age incidence.

The disease was originally described as idiopathic, of sudden onset, and occurred in previously healthy patients [7]. In contrast to the original description, doctors today know that the disease is not limited to young or male patients, and a causative etiology is usually identified [1].

As seen now, in the majority of cases, there is an underlying problem [7] such as, genitourinary infections, Anorectal sepsis, and traumatic infections which are the most common causes of Fournier's gangrene [6].

With regards to the genitourinary tract, urethral strictures and transurethral instrumentation are the most frequent aetiologies; other causes include surgery of the penis and scrotum, transrectal prostate biopsy, urethral calculi, bladder cancer infiltrating the urethra, and phlebitis of dorsal penis vein [5]. Anorectal sources of infection include ischiorectal, perianal, and intersphincteric abscesses, especially those inadequately treated [8]. Diverticular perforation, carcinoma of the sigmoid colon and rectum, perforated acute appendicitis, internal hemorrhoids ligated with rubber bands, and anal dilatation, have also been reported in the etiology of FG [5].

In women, septic abortions, vulvar or Bartholin gland abscesses, hysterectomy, and episiotomy are documented sources.

In men, anal intercourse may increase the risk of perineal infection, either from blunt trauma to the area or by the spread of rectally carried microbes.

In children, circumcision, strangulated inguinal hernia, omphalitis, insect bites, trauma, urethral instrumentation, perirectal abscesses, systemic infections, and burns have led to the disease [1].

Inability to practice adequate perineal hygiene or the presence of chronically indwelling catheters, such as in paraplegic patients, poses an increased risk [1].

In our report, perianal Sepsis was found to be the initiating cause of the Fournier's gangrene in both patients.

It is a polymicrobial infection caused by the synergistic, opportunistic infection of both aerobic and anaerobic organisms including; *Staphylococcus*, micro-aerophilic hemolytic *Streptococcus*, *E. Coli*, *Fusobacterium*, *Cl. welchii*, and Bacteroides from the patient [7]. The infection arises from bacteria inoculation in the perineal area. This procedure can be facilitated by any condition that results in impairment in the immune system [5]. Wound cultures from patients with Fournier gangrene reveal an average of 4 isolates per case [1].

The bacteria involved act synergistically, via collagenases, hyaluronidases, and other enzymes to invade and destroy fascial planes. Ultimately, an obliterative endarteritis develops, and the ensuing cutaneous and subcutaneous vascular necrosis leads to localized ischemia and further bacterial proliferation. Rates of fascial destruction as high as 2 - 3 cm/h have been described [1].

The cutaneous manifestations of Fournier's gangrene are mere "the tip of the iceberg" because the infection spreads aggressively along recognized fascial planes [6].

The most common clinical features are perianal pain and swelling if the anorectal area is the portal of entry, whereas urinary retention, testicular, or scrotal pain is present if the infection launches from the genitourinary tract [8]. Other systemic manifestations such as fever, tachycardia, hypotension, electrolyte imbalances, and hyperglycemia may also be present [5].

In our case, both patients were admitted with severe perianal pain, had scrotal swelling and pain. One of them had anterior abdominal wall crepitus which was indicative of *Clostridium* species involvement. Both had a fever, tachycardia, and low blood pressure indicative of severe sepsis and were resuscitated with fluid therapy.

Various studies serve as diagnostic adjuncts; however, a definitive diagnosis is made during the initial surgical wound exploration [9].

Once a diagnosis of FG has been established, the central principles of management are aggressive hemodynamic stabilization, parenteral broad-spectrum antibiotics which will be either changed or continued according to the culture findings and nutritional support. However, the most important aspect of treatment to ensure a successful outcome is urgent and extensive surgical debridement [2]. All frankly necrotic tissue and those with doubtful viability should be carefully debrided and excised. Multiple surgical procedures may be necessary to bring the infection under control. High mortality rates may stem from multiple comorbidities but unequivocally are due to delayed diagnosis and surgical treatment. In the majority of instances, the testes, glans penis, bladder, and rectum are spared destruction because of their separate blood supplies [5] [6] [9].

Targeted antibiotic therapy is commenced based on culture results. In our case, we continued with broad-spectrum antibiotics based on culture and sensitivity results and using clinical examinations such as temperature pattern, pulse, respiration, and general well-being of the patient as a guide.

In some studies, patients underwent orchiectomy when severe infection in the peritesticular tissues was observed intraoperatively [5]. Both patients in this report had their testes and spermatic cords intact and not completely exposed.

Diversion of the fecal and urinary streams may not always be necessary but should always be considered on a case-by-case basis [6].

We involved the general surgeons who performed a diverting colostomy in one of our patients since the gangrene extended to the perianal area and anal sphincter was involved as such fecal contamination was expected. The other patient had a suprapubic cystostomy on account of the failure of catheterization with chronic urinary retention.

Patients' metabolic status and the extent of disease at presentation is an important factor in the prognosis of Fournier's gangrene [10].

Attempts to predict mortality in patients with Fournier's gangrene include the use of the Fournier gangrene severity index (FGSIS), and patient vital signs, and

laboratory tests to calculate a score that could be used to monitor therapy and predict mortality [11]. FGSIS involves a determination of some laboratory parameters such as creatinine, bicarbonate, sodium, potassium, total protein, albumin, leukocyte count, hematocrit, lactate dehydrogenase, and alkaline phosphatase most of which could not be determined in our facility but did not serve as a hindrance to the treatment and survival of our patients.

The value of hyperbaric oxygenation in Fournier's gangrene remains unproven, but there are theoretical reasons why it may be beneficial, at least in some cases [6]. The mortality in Fournier's Gangrene is highest in patients presenting with sepsis, diabetes mellitus, and late admissions to the hospital [12]. Severe sepsis was a complication of both patients in this report.

Hospitalization for this disease is extremely long with a reported average of six weeks [13]. Our patients survived and were discharged 50 days and 47 days after admission to the hospital, despite the severity of their condition.

5. Conclusions

Fournier's gangrene is an uncommon but severe necrotizing infection of the external genitalia and perineum which can spread to involve the superficial fascia of the lower abdominal wall with rapid progression of gangrene and deterioration of the patient. Early recognition with aggressive surgical debridement, resuscitation, broad-spectrum antibiotics, and nutritional support remains the cornerstones of therapy.

Patients often may require care from a combined effort of urological and general surgeons; hence we suggest a multidisciplinary approach to improve patient outcomes not only in inpatient survival but also in the quality of life.

Clinical parameters should serve as a guide to the response of broad-spectrum antibiotics when there is limited capability to identify specific organisms implicated and their sensitivity pattern. Inability to carry out culture and sensitivity studies of the wound discharge should not impede good clinical management based on time-tested principles such as the use of broad-spectrum antibiotics, surgical debridement, and supportive care.

Repeated surgical debridement on the ward under analgesia and sedation may be required for complete eradication of infection.

Statement of Informed Consent

Verbal informed consent was obtained from the patients for the information and images used in this publication.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of the paper.

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Positive Surgical Margins (PSM) after Open Retropubic Radical Prostatectomy: Evaluation of Patient Survival

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Abstract

Background: Many patients who have had radical prostatectomy for prostate cancer may present with microscopic extraprostatic extension of the disease. Positive surgical margins are a common pathological finding in this subgroup of patients. To report the epidemiological, clinical and therapeutic aspects of PSM after radical prostatectomy (RP) and to evaluate the follow-up of patients. **Patients and methods:** A single-center retrospective descriptive study of patients who underwent radical prostatectomy between June 1, 2004 and December 31, 2019 was conducted. Patients who had radical prostatectomy with PSM on pathology report were included. The parameters studied were age, initial prostate specific antigen (PSA), Gleason and International Society of Uropathology (ISUP) scores, cTNM and pTNM stages, operative technique, PSA levels after surgery, adjuvant treatment and patient survival. **Results:** Eighty-six (86) radical prostatectomies were performed. PSM was found in 23 patients (26.7%). The mean age of the patients was 63.7 ± 6.1 years. The mean preoperative total PSA was 31.5 ng/mL (6.31 - 146 ng/mL). Prostate biopsy showed only prostatic adenocarcinoma. Thoracic-abdominopelvic CT was performed in all patients. Prostate cancers were found at the localized stage in 12 patients and locally advanced in 11 patients. A classification adjustment was obtained after pathological examination of the surgical specimen. The ISUP score 3 and 1 on the surgical specimen were in the majority with 9 and 7 patients respectively. After the recurrence, all patients who consented received hormone therapy, which was either medical with Goserelin and Triptorelin (7 patients) or surgical with testicular pulpectomy (1 patient). PSA was undetectable (<0.1 mg/mL) in 4 patients. The mean overall survival

(OS) time was 28.1 months. Biological recurrence-free survival in the series was 25.7 months. **Conclusion:** RP with PSM is a fairly common condition that varies from less than 10% to more than 40% depending on the stage of the disease and the operators, and for which the main mean of treatment in our practice setting is hormone therapy.

Keywords

Prostate Cancer, Surgical Margins, Survival

1. Introduction

Prostate cancer is leading cancer in older men and the second leading cause of death (after lung cancer). It is the fourth leading cause of death due to cancer in the general population [1]. In Africa, prostate cancer is diagnosed primarily at locally advanced or metastatic stage [2]. In Senegal, most prostate cancers are diagnosed in locally advanced or metastatic stage [3]. Radical prostatectomy (RP) is a surgical treatment of prostate cancer in which the prostate and seminal vesicles are removed [4]. The oncological principles of cancer surgery advocate the complete removal of cancer with negative surgical margins. In localized prostate cancer, the management of the positive surgical margin (PSM) after radical prostatectomy remains controversial [5] [6]. Positive margins after total prostatectomy are a common pathological situation (10% - 40%) in the daily practice of urologists dealing with prostate cancer. The presence of positive margins correlates with the presence of residual tumor in about 50% of cases [7]. A positive surgical margin (PSM) is defined as the presence of cancerous tissue in contact with the inked borders of the prostatectomy specimen [8]. In our regions, there is no study interested in PSM. The aim of this study was to report the epidemiological, clinical and therapeutic aspects of PSM after radical prostatectomy and to evaluate the follow-up of patients.

2. Patients and Methods

This was a single-center retrospective descriptive study of patients who underwent radical prostatectomy (RP) between 1 June 2004 and 31 December 2019 in Urology-Andrology department of Aristide Le Dantec Hospital in Dakar, Senegal. We collected data from the medical records and registers of patients. All patients who had (RP) with invaded surgical margins on pathology report were included. A positive surgical margin (PSM) was defined as the presence of cancerous tissue in contact with the inked borders of the prostatectomy specimen. Patients who had RP with margins status not specified on the pathology report, patients who had invaded margins and were lost to follow-up, and patients with unexploitable records were not included. The parameters studied were age, initial PSA, Gleason and ISUP scores, cTNM and pTNM stages, operative technique, PSA levels after prostatectomy, adjuvant therapy and patient survival.

Excel 2013 software was used for statistical analysis and survival was calculated according to Kaplan Meier.

3. Results

During the study period 86 radical prostatectomies were performed. PSM was found in 23 patients (26.7%). The mean age of the patients was 63.7 ± 6.1 years (54 - 74 years). The mean preoperative total PSA level was 31.5 (6.31 - 146 ng/mL). The prostate biopsy showed only prostatic adenocarcinoma. The ISUP 1 group was predominant in our series with 15 patients. Magnetic Resonance Imaging (MRI), Thoracic-abdominal-pelvic Computer Tomography (CT) and scintigraphy was performed to assess the extension of the disease. The prostate cancers were found at the localized stage in 12 patients and locally advanced in 11 patients. A classification adjustment was obtained after pathological examination of the surgical specimen. T-stage was underestimated in 12 patients. All patients who had cancers classified as intermediate risk of recurrence according to D'Amico's classification were finally at high risk of recurrence (Table 1).

Table 1. Classification of cancers (TNM and ISUP).

Age	PSA Initial (ng/mL)	CTNM	ISUP Pré opératoire	Classification de D'Amico	PTNM	ISUP post opératoire
65	80	T3aN0 M0	G5 (5 + 4)	haut risque	T3bN0 M0	G3 (4 + 3)
58	14.97	T3a N0 M0	G5 (4 + 5)	Haut risque	T3aN0 M0	G5 (5 + 4)
67	146	T3b N0 M0	G4 (4 + 4)	Haut risque	T3bN0 M0	G4 (4 + 4)
70	52	T3a N0 M0	G4 (4 + 4)	Haut risque	T3aN0 M0	G4 (4 + 4)
64	25	T3b N0 M0	G3 (4 + 3)	haut risque	T3bN0 M0	G4 (4 + 4)
67	98.6	T3b N0 M0	G3 (4 + 3)	Haut risque	T3bN0 M0	G3 (4 + 3)
73	16.6	T3a N0 M0	G3 (4 + 3)	Haut risque	T3aN0 M0	G3 (4 + 3)
63	11.24	T3a N0 M0	G3 (4 + 3)	Haut risque	T3aN0 M0	G3 (4 + 3)
63	42	T2c N0 M0	G1 (3 + 3)	Haut risque	T3a N0 M0	G3 (4 + 4)
68	40	T2b N0 M0	G1 (3 + 3)	Haut risque	T3b N0 M0	G3 (4 + 3)
59	20.8	T2b N0 M0	G1 (3 + 3)	Haut risque	T3b N0 M0	G3 (4 + 3)
55	15	T2b N0 M0	G1 (3 + 3)	Risque intermédiaire	T3b N0 M0	G3 (4 + 3)
57	12.23	T3a N0 M0	G1 (3 + 3)	Haut risque	T3a N0 M0	G3 (4 + 3)
62	24.93	T2b N0 M0	G1 (3 + 3)	Haut risque	T2c N0 M0	G2 (3 + 4)
54	17.33	T1c N0 M0	G1 (3 + 3)	Risque intermédiaire	T3b N0 M0	G2 (3 + 4)
74	13.34	T3b N0 M0	G1 (3 + 3)	Haut risque	T3b N0 M0	G2 (3 + 4)
70	36	T2b N0 M0	G1 (3 + 3)	Haut risque	T3a N0 M0	G1 (3 + 3)
71	14.4	T1C N0 M0	G1 (3 + 3)	Risque intermédiaire	T3a N0 M0	G1 (3 + 3)
57	12.5	T2b N0 M0	G1 (3 + 3)	Risque intermédiaire	T2c N0 M0	G1 (3 + 3)
55	9	T2c N0 M0	G1 (3 + 3)	Haut risque	T3a N0 M0	G1 (3 + 3)
66	8	T2c N0 M0	G1 (3 + 3)	haut risque	T3a N0 M0	G1 (3 + 3)
58	8.5	T3a N0 M0	G1 (3 + 3)	Haut risque	T3a N0 M0	G1 (3 + 3)
69	6.31	T2c N0 M0	G1 (3 + 3)	Haut risque	T3b N0 M0	G1 (3 + 3)

Treatment was open radical retropubic prostatectomy. After RP, the PSA level was undetectable (<0.1 ng/mL) in 4 patients over 4 - 6 weeks. After recurrence all patients who were consenting had hormone therapy. Hormone therapy was medical with Goserelin and Triptorelin (7 patients) or surgical with bilateral testicular pulpectomy (1 patient). A response to hormone therapy was obtained in 05 patients and in 08 patients we noted progression.

The mean overall survival (OS) of the patients in the series was 28.1 ± 34 months. The overall survival of the series at 12 months; 24 months and 36 months was 69%; 65% and 30% respectively (**Figure 1**). The mean biological recurrence-free survival in the series was 25.7 ± 23 months. Biological recurrence-free survival at 12 months; 24 months and 36 months was 80%; 66%; 60% and 20% respectively (**Figure 2**).

4. Discussion

Positive surgical margins in men undergoing radical prostatectomy for prostate cancer are a common situation. According to Wright [9] PSM were reported in 21.2% of cases and were more common in pT3a than pT2 tumors and higher-grade tumors. We found a rate of 26.7% PSM. Data from the literature reported rates ranging from 16% to 47% [10] for series contemporary with ours.

In our context, the incidence of PCM may be related to the difficulty of radical prostatectomy in high-risk cancers but also to the locally advanced stage of the cancer in 91.3% of our patients (n = 21). Depending on the stage, there is an increase in PSM rate. For stages T1a, from 0% to 21%, for stages T1b from 30% to 35% [11] For T2 stages, the figures range from 9% for T2a, 24% for T2b and 40% for T2c in Rosen's series [12]. In the Mayo Clinic series [13], there were 30 and

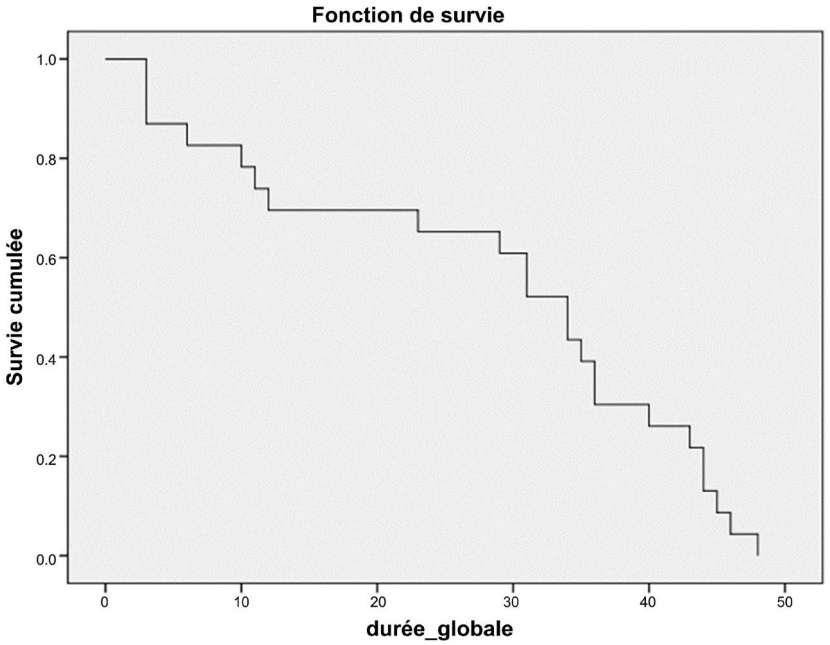

Figure 1. Overall survival curve (months).

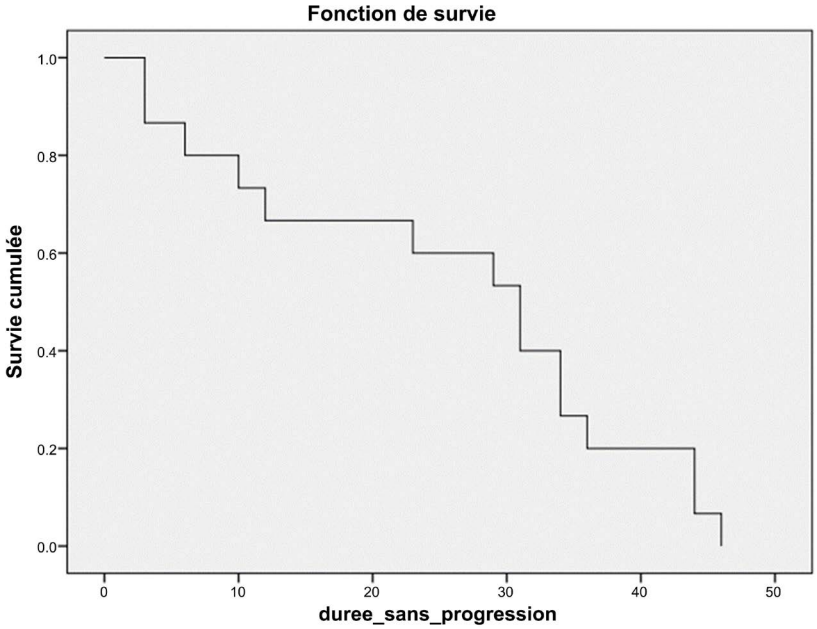

Figure 2. Biological recurrence-free survival curve (months).

60% margins for T1 and T2. Moreover, a statistically significant interaction was found between surgical margin status and Gleason score 7 to 10 ($P < 0.008$) and lymph node invasion ($P < 0.001$).

The mean pre-therapeutic PSA level was 31.5 ng/mL. The relationship between pre-treatment PSA and positive surgical margins is known. Indeed, Gomez and Shelfo have reported a correlation between PSA and PSM levels [14] [15].

Retropubic radical prostatectomy was performed in all our patients. Bladder neck preservation was not specified in the surgical report. According to Arroua [16] bladder neck preservation does not increase the risk of a PSM. In fact, more than 70% of their patients had early postoperative continence without increasing the number of positive surgical margins.

There is no consensus regarding the optimal management of PSM after total prostatectomy. Treatment options include surveillance, adjuvant radiotherapy and/or hormone therapy or salvage management at biological recurrence [17].

Immediate external irradiation after radical prostatectomy improves biochemical progression-free survival and local control in patients with positive surgical margins [6].

After recurrence all patients who were consenting received hormone therapy because hormone therapy was the main option to be offered to patients. We noted a response to hormone therapy in 5 patients and progression in 8 patients.

In our study then margins location were not specified. The effect on biochemical recurrence was influenced by the site of the surgical margin, with a posterolateral location having the most significant effect on prognosis [18]. Aydin *et al.* [19] have shown that the presence of surgical margins at the cervix increases the risk of biologic recurrence more than for any other location.

According to Wright [10] PSM in men undergoing radical prostatectomy for prostate cancer are associated with an increased risk of biochemical recurrence.

The 7-year disease specific survival rates for those at highest risk for prostate cancer specific mortality (higher grade pT3a) were 97.6% for cases with negative surgical margins and 92.4% for those with positive surgical margins.

Overall survival and biological recurrence-free survival in our patients were low compared to data in the literature. This can be explained by the high rate of high risk of recurrence and locally advanced tumor in our series.

The limitation of this study is that it is a small series, we did not explore the factors that affect the prevalence of the PSM such as the surgical approach, the experience of the surgeon, and the tumor status and their localization in the prostate specimen are not specified.

5. Conclusion

Positive margins after total prostatectomy are a relatively common pathological situation in our daily practice of urologists dealing with prostate cancer. The status of the surgical margins as well as their situation in the event of positivity must be specified in the histology reports. Their presence should lead to a search for a biological recurrence in order to offer patients adequate treatment. Standard hormone therapy and radiotherapy are the therapeutic means available in our regions and they offer less survival to patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Next Generation Sequencing for Microbial Analysis to Select Prophylactic Antibiotic Selection before Urologic Stone Surgery: A Culture Change

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Abstract

Background: This paper aims to determine if the combination of polymerase chain reaction (PCR) and next-generation sequencing (NGS) could identify bacteria in culture-negative urine that would alter prophylaxis management. **Methods:** We sent approximately 5 - 10 mL of a preoperative urine sample to MicrogenDx for PCR/NGS analysis performed after surgery (blind to the surgeon). The physician prescribed standard of care antibiotic prophylaxis. Cases modeling the hospital course of 3 random patients were reviewed by eight urologists after surgery to determine if NGS results would change their prophylaxis regimen. An infectious disease pharmacist reviewed the cases and provided the "ideal" regimen. **Results:** Urine cultures identified bacteria in 11% (2/18) of cases. Culture speciation results were consistent with NGS results. NGS detected a dominant bacteria in 56% (10/18) of negative cultures and targetable bacteria in all samples. There was a 15% (3/20) infection rate. In both cases, NGS results suggest inadequate prophylaxis. In response to the case scenarios, 100%, 88%, and 88% of the urologists reported they would change prophylaxis with NGS results. During a case scenario, physicians would tend to overprescribe antibiotics given PCR/NGS data for prophylaxis selection. **Conclusion:** NGS identifies a targetable bacterium in up to 80% of negative urine cultures before urologic stone surgery. Responses to case scenarios indicate that physicians would change management based on NGS results. Inter-professional (urologic and pharmacy) antibiotic selection with PCR/16S DNA testing may be helpful to improve antibiotic stewardship.

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Keywords

Health-Care Associated Infection, Urinary Tract Infection, Infection Prevention, Surgical Site Infection

1. Introduction

Ureteroscopy for urinary tract urolithiasis is a standard procedure with an estimated 9200 cases in the US per year [1]. Despite antibiotic prophylaxis, the incidence of significant infections after flexible ureteroscopic (URS) lithotripsy is on the rise [2]. To prevent infections, the standard of care is to obtain a negative urine culture before surgery. However, with the next-generation sequencing, we are now able to understand that the urine is not sterile and that pathogenic bacteria may be still present, undetected by urine culture.

One of the challenges when choosing a prophylactic agent is that preoperative urine cultures often show no growth for patients who later develop SIRS [3] [4] [5]. Singh *et al.* found no significant association between pelvic urine cultures or stone cultures and the occurrence of SIRS [6]. We hypothesize the stone or previously placed stent may allow bacteria to form biofilms containing a small number of essential bacteria not detected by standard cultures.

Next-generation sequencing (NGS) poses an alternative to the traditional culture model by using high-throughput sequencing of rapid PCR for resistance genes combined with 16S rRNA (a type of NGS) to detect specific bacterial strains and has been used for the detection of urinary tract infections [7]. With its improved sensitivity, NGS (PCR/16s rRNA) with resistance genes could be used to guide antibiotic therapy. In this study, we pilot this novel approach quantitatively to evaluate the NGS platform's ability to identify bacteria in culture-negative urine that would alter the choice of antibiotic prophylaxis for patients undergoing urologic stone procedures. We also evaluate this approach qualitatively to determine its usefulness to urologic surgeons to inform clinical trial design.

2. Materials and Methods

2.1. Population

After IRB approval (HSC20050234H), subjects were recruited from urology clinics at their preoperative appointment before their planned ureteroscopy (URS) surgery for urinary stone. We did not exclude patients with ureteral stents, including all patients undergoing percutaneous nephrolithotomy (PCNL) or URS within the next two weeks. We informed patients that the results were purely for research purposes, and no analysis performed until after surgery. We also described we would not provide additional information to their physician that could alter antibiotics.

2.2. Next-Generation Sequencing

We collected whole urine (approximately 30 - 50 mL) utilizing special vaccutanors supplied by MicrogenDx. We sent around 5 - 10 mL of urine taken for culture to MicroGen Diagnostics, a CAP-accredited and CLIA licensed clinical diagnostic lab, for analysis. MicrogenDx performed rapid PCR for common resistance genes in 21 subjects before URS. Each initial target bacterial or fungi DNA, whose concentration was measured to obtain an initial concentration (ng/uL), was diluted to obtain a six to eight-fold serial dilution series and run on the quantitative PCR (qPCR) panel assay on the Roche LightCycler 480 II instrument. We sequenced the V1-V2 hypervariable bacterial regions with 16S RNA using Ion Torrent (Ion Torrent PGM). Physicians did not obtain results before surgery. The physician proceeded with surgical management and standard of care antibacterial prophylaxis.

2.3. Data Collection

We recorded data from physician notes and medical record review regarding the details of patient history, urologic stone procedure, postoperative course, and infection outcomes. We recorded all speciation results from the standard of care urine cultures. We then compared these results to speciation results in the PCR/NGS (16s rRNA).

2.4. Case Study Creation

We perform a qualitative review in the form of case scenarios to determine if NGS would indeed alter antibiotic prophylaxis. Choosing from the cases enrolled, we randomly selected three cases to be reviewed by eight board-certified Urologists. One infectious disease pharmacists also reviewed the case reports and recommended the "ideal" antibiotic regimen for each case. The cases are highlighted in **Supplemental Figures S1-S3** representing each case scenario to include:

Case 1: Standard culture No Growth, PCR/16s showed primary bacteria with *Enterococcus* (82%) and secondary Staphylococcus (17%) with resistance genes for macrolide and aminoglycoside.

Case 2: Standard culture showed no growth; PCR/16s showed primary bacteria of *Enterococcus* (99%) with no resistance genes.

Case 3: Standard culture showed "normal flora," PCR/16s showed *Citrobacter* (79%), and *E. coli* (12%) with resistance genes of methicillin, beta-lactam, quinolone, and macrolide.

The questions included:

1) Based on PCR/16s results, would you change your antibiotic?

2) Choose from your usual antibiotic choice, what antibiotic would you choose?

3) Exit survey questions:

a) Would this test improve my confidence to prevent infection?

b) Would I use this test again?

c) Would I recommend this test to other urologists?

d) How important do you think this test would be in urologic practice?

e) I have concerns about using this technology for antibiotic prophylaxis selection?

3. Results

3.1. Patient Characteristics

Participants had a median age of 59 (interquartile range: 37 - 70), were predominantly white (80%), and non-Hispanic (60%). They had a median BMI of 30.8 (interquartile range: 24.8 - 34.1). Most patients (14, 70%) were not diabetic. Most patients (12, 60%) did not have any allergies to antibiotics. 5 (25%) patients had indwelling stents when urine was collected, and 5 (25%) patients had percutaneous nephrostomy tubes (Table 1).

3.2. Surgical Methods

A variety of urologic stone procedures were represented in this cohort, with cases of PCNL and URS, laser lithotripsy, and basket retrieval, with and without

Table 1. Patient characteristics.

Characteristics n, (%)	**Total patients** (n = 20)
Gender	
Men	11 (55%)
Women	9 (45%)
Age years, (IQR)	59 (37 - 70)
Race	
White	16 (80%)
Unknown	3 (15%)
Black	1 (5%)
Ethnicity	
Non-Hispanic	12 (60%)
Hispanic	6 (30%)
Unknown	2 (10%)
Body Mass Index (IQR)	30.8 (24.8 - 34.1)
Diabetes status	
Non-Diabetic	14 (70%)
Diabetic	6 (30%)
History of UTIs	
No	13 (65%)
Yes	7 (35%)
Stent in place on presentation	
No	15 (75%)
Yes	5 (25%)
Catheter in place on presentation	
No	15 (75%)
Yes	5 (25%)

Abbreviations: IQR: interquartile range; URS: ureteroscopy.

nephrostomy tube/ureteral stent placement. There was 1 case of a TURP in addition to URS, and 1 case of an added endopyelotomy (Table 2).

3.3. Bacterial Identification and Antibiotic Resistance

Of the 20 cases, only 2 SOC cultures had speciation results and 16s rRNA analysis identified the exact bacteria colonized on both accounts (Figure 1). One patient had grown two bacterial species on culture, and NGS identified both species. In the 10 cases where SOC cultures resulted in no growth, NGS was able to identify targetable bacteria. In only 2 of those 10 cases with no growth, the dominant species detected by NGS (*Citrobacter* and *Lactobacillus*) was unlikely to cause postoperative infections. The other dominant species identified in these cases were *E. coli* and *S. epidermidis*, respectively. In nearly 80% of negative cultures, NGS provided dominant speciation data to consider when choosing antimicrobial prophylaxis before urologic stone procedures (Figure 2).

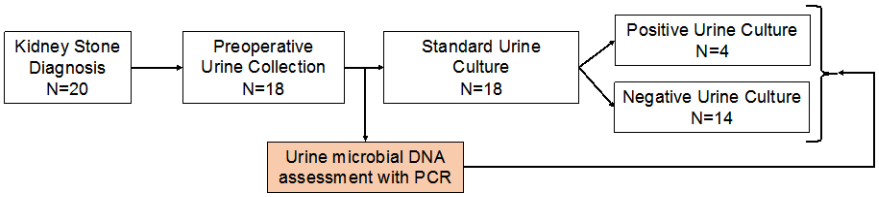
3.4. Cases of Infection

Of the 18 patients who underwent their procedure, 2 cases (11%) developed infections postoperatively. In the first infection case, the patient did not supply a urine culture before URS. The surgeon chose cefazolin for antibiotic prophylaxis. NGS detected a high bacterial load (>107): 53% Morganella morganii and 45% *E. coli*. NGS was also able to identify resistance genes against beta-lactams and fluoroquinolones. Based on this data, we would recommend trimethoprim-sulfamethoxazole or a 3rd generation cephalosporin rather than a 1st generation cephalosporin. In the second case of infection, three or more organisms present, each higher than 10,000 cu/mL, per SOC UC results. The surgeon chose cefazolin and piperacillin/tazobactam for prophylaxis. NGS detected *Citrobacter* (64%), Veillonella atypica (27%), and resistance genes to methicillin, beta-lactams, macrolides, and aminoglycosides. NGS also detected *Candida albicans* in its fungal

Table 2. Surgical methods.

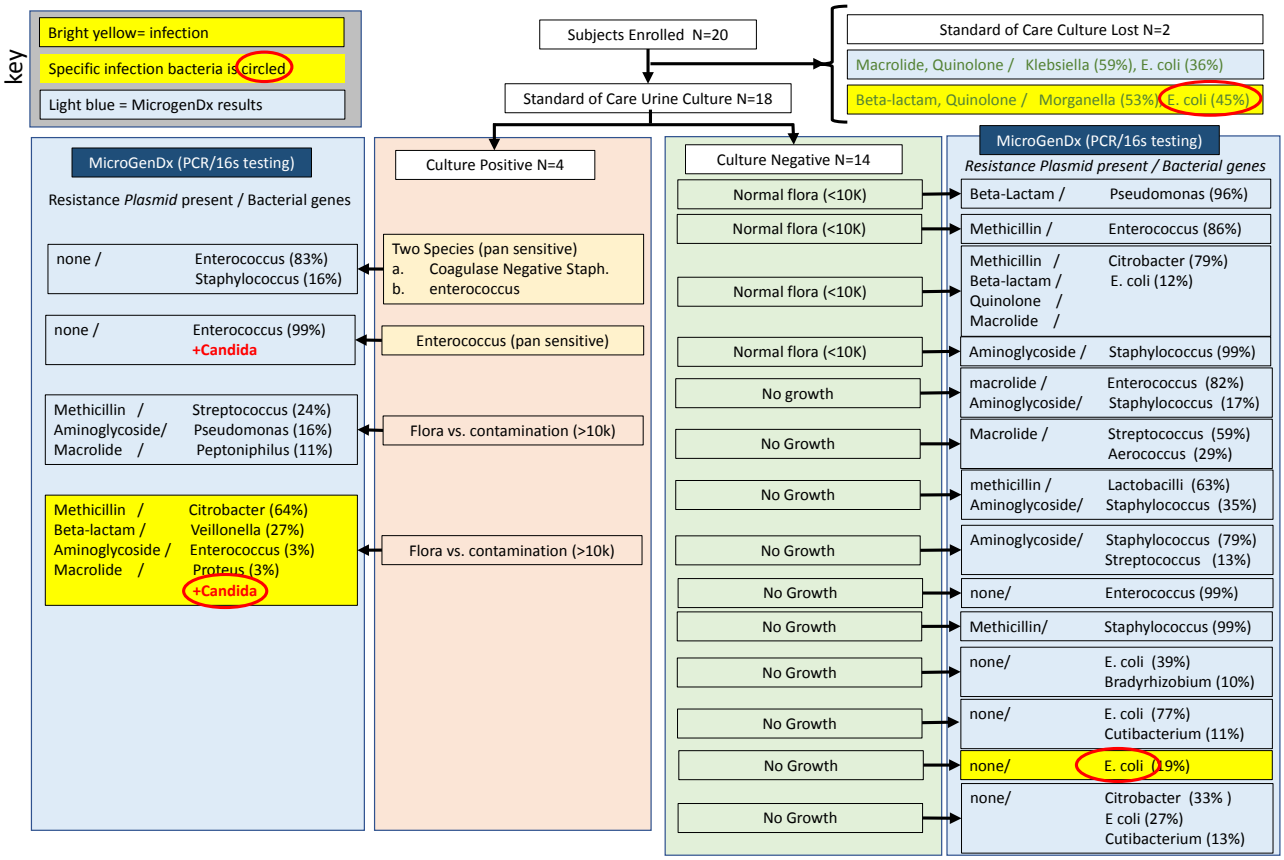
Surgical procedure	Total Patients (n = 20)
U PCNL with nephrostomy placement	3 (15%)
B PCNL with nephrostomy placement	1 (5%)
U PCNL	1 (5%)
U URS, LL with stent placement	5 (25%)
B URS, LL with stent placement	4 (20%)
B URS, LL with stent placement	1 (5%)
B URS, LL and unilateral Basket retrieval, bilat stent placement	1 (5%)
U URS, Basket retrieval, TURP	1 (5%)
U URS, endopyelotomy with stent placement	1 (5%)
Surgery cancelled	2 (10%)

Abbreviations: B: bilateral, U: unilateral, LL: laser lithotripsy, URS: ureteroscopy, TURP: transurethral resection of prostate.



We display our enrollment of 20 subjects through the study. The urine was split between culture and next-generation sequencing with PCR of plasmid genes. We then compared the results of the PCR to the culture specimen as ground truth.

Figure 1. Consort diagram.



We display a diagram of urine culture and corresponding PCR results from subjects On the left are the positive urine cultures noting alignment between genetic and phenotypic results. Of note, Candida is not routinely cultured before urologic stone procedures. On the right are all of the negative urine culture results and their associated NGS/PCR results. Bright yellow represents those that had postoperative clinical infection with a red circle to indicate the causative organism. The orange squares were those subjects selected for the case reports in the supplemental figures.

Figure 2. Results diagram.

screen as a standard part of the test. The patient developed funguria postoperatively with *Candida albicans*, indicating that NGS may be specific enough to recommend antifungal prophylaxis appropriately. These findings would be helpful in PCNL patient's that have had multiple antibiotics with high level of suspicion for candida

3.5. Case Scenario Data

Eight urologists responded to the three case scenarios, and in each of the 3 cases, 100%, 88%, and 88% of the physicians would have changed their prophylaxis

management given NGS results (**Supplemental Figures S1-S3**). The ideal antibiotic of choice based on the ID Pharmacist recommendations was oral Bactrim for all cases, and only 50%, 0%, and 0% selected this option. In contrast, 38%, 25%, and 63% chose to escalate the antibiotic to vancomycin, Zosyn, or Amikacin in conjunction with a second antibiotic. Overall, on exit survey, urologists reported that it is moderately important (n = 2, 25%), important (n = 4, 50%), or very important (n = 2, 25%) to test this technology in this context, while 38% have concerns about using this technology for antibiotic prophylaxis related primarily to implementation.

4. Discussion

We report several findings from our pilot study that include: NGS may provide actionable information above standard urine culture, urologists find the information useful, and concern for antibiotic escalation may benefit from interprofessional collaboration with pharmacists to select preoperative antibiotics in the context of PCR/NGS testing. Testing NGS is a practical extension to standard urinary culture in that the specimen can be split and sent for culture and NGS. Results of NGS are available in 48 hours to allow for time for preoperative antibiotic selection well before surgery.

In our first question, we address the usefulness of a PCR/NGS based urine profile before URS in this pilot study. We found that NGS detects targetable bacteria and fungi in culture-negative urine and propose utilizing this data in a prospective trial to use NGS to determine preoperative antibiotic prophylaxis. NGS may be more effective and specific than those predicated upon SOC preoperative urine cultures mostly negative before surgery. For example, we identified several culture-negative patients with dominant bacterial types that may influence a physician to prescribe a 1st generation cephalosporin compared to a gram-negative dominant group that may need a fluoroquinolone or 3rd generation cephalosporin. Importantly, urologists do not typically send a urine specimen specifically for fungi (*candida* sp.). The PCR/NGS test readily makes this information available, and in one patient that was positive did have sepsis caused by Candida, which was later cultured from the patient's blood. Many studies have reported the low sensitivity of preoperative urine cultures for predicting infectious complications of urologic stone procedures [3] [4] [5] [8]. Eswara *et al.* (2013) compared sensitivities among preoperative and perioperative pelvic urine and stone cultures for pathogen detection, reporting that of the patients who develop urosepsis, 0% had positive midstream preoperative urine cultures, while 73% had positive stone cultures. [9] However, they report a 64% concordance rate in urosepsis patients between stone cultures and readmission cultures, indicating that stone cultures did not always appropriately guide antibiotic selection in up to 36% of cases. Moreover, an antibiotic selection from stone culture rarely is provided in a timely fashion to alter postoperative antibiotics, and many of our patients go home the same day of the procedure. Our study, while small,

found that NGS was able to detect pathogens and provide alternate antimicrobial prophylaxis, especially in those who did have an infection.

Our findings are consistent with those of Long *et al.* (2016) and Grumaz *et al.* (2016), who reported that NGS is more sensitive than blood cultures for detecting pathogens in ICU patients Notably, their studies observe the clinical utility of NGS to guide therapy in a high-risk population of ICU patients [10] [11]. Many studies have reported the increased sensitivity of NGS when compared to cultures, but further research is needed to establish cases where the improved sensitivity delivers cost-effective, clinically applicable data. The results of this study suggest that NGS may improve the standard of care in patients undergoing invasive urologic stone procedures.

Infectious complications are the most common cause of death following urologic stone procedures and present a sizeable economic drain on the American healthcare system [1] [12]. Other studies have found that up to 17% of urosepsis cases follow urologic interventions [13] [14] [15] [16] [17]. Koras *et al.* (2014) observed signs of SIRS in up to 27% of patients who underwent PCNL, 7.6% of which were diagnosed with sepsis [13]. Given the mortality rates and economic costs of urosepsis, SOC practices must be optimized to reduce the risk of infectious complications following urologic procedures.

Our qualitative questions address the usefulness of PCR/NGS testing to urologists before URS. We identified that 88% - 100% of urologists reported that they would have changed their prophylactic regimen based on NGS results in the post case survey. However, during the cases, most urologists did not choose the ideal regimen recommended by infectious disease pharmacists and in many escalated antibiotic use to either more antibiotics or broader spectrum. The findings of this study suggest that interdisciplinary collaboration between physicians and pharmacists may prevent excessive use of aggressive therapy when utilizing highly sensitive pathogen detection modalities, such as NGS.

We have several limitations to our study. The sample size limits the power of this study; however, this is a pilot study to inform a larger clinical trial and is informative for planning. We decided to publish these results due to the novelty of the research and its potential to change the preoperative antibiotic selection for a large number of patients. The increased sensitivity of NGS compared to SOC urine cultures reported herein was observed in a cohort of 20 patients. However, 88% - 100% of urologists surveyed stated that NGS with PCR for resistance genes would change their management in the 3 case scenarios we prepared, suggesting that physicians would use NGS in cases where it detected bacteria not found on preoperative cultures. More extensive studies are required to conclude that NGS can detect targetable microbes in culture-negative urine. Another limitation of this study is the lack of direct comparisons to perioperative cultures. However, as these perioperative cultures cannot guide antimicrobial prophylaxis, a direct comparison between preoperative studies was used. Lastly, this was a repository study using data from chart review. We did not call patients to follow

up to confirm the postoperative course. We did not perform a full cost analysis and the current cost of the specific PCR method in this study through MicroGenDx is $199.00 US. Urine testing is variable depending on if an analysis was sent first and if the culture is positive then species detection and resistance profiling is performed (average $30 - $80).

5. Conclusion

Infectious complications are the most common cause of death following urologic stone procedures. This study found that NGS can identify a targetable bacterium in up to 80% of negative urine cultures before urologic stone surgery. Responses to case scenarios indicate that physicians would change management based on NGS results. Using this data we have initiated a clinical trial using NGS to augment antibiotic section in urine culture negative patients prior to ureteroscopy for stone surgery (NCT04404855).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplemental Figures

Case Scenario 1

A man in his late 50's presents with nephrolithiasis and blood in the urine. He is allergic to penicllins. The patient is planned to undergo bilateral ureteroscopy. SOC urine culture result showed no growth.

What would you select as your antibiotic for surgery prophylaxis? _____

Based on Microgen results:

1. Would you change your antibiotic? _____
2. What would you select? _____

MicroGen DX
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Case Scenario 1

Next Generation Sequencing Results

MicroGen Diagnostics' comprehensive testing (patent pending) is a relative quantitative universal test for bacteria/fungi. DNA sequencing methods are used to identify the microorganisms' genetic signatures and the estimated percentage of organisms present in the specimen. Virtually all bacteria/fungi are screened for and the most predominant populations are reported.

Rapid Screening (PCR Results)	Amount per mL
Bacterial Load (Medium)	10^5-10^7
Enterococcus faecalis	2.57×10^5
Klebsiella pneumoniae	Not Detected
Streptococcus agalactiae	Not Detected
Pseudomonas aeruginosa	Not Detected
Staphylococcus aureus	Not Detected
Proteus mirabilis	Not Detected
Escherichia coli	Not Detected
Mobiluncus curtisii	Not Detected
Mobiluncus mulieris	Not Detected
Gardnerella vaginalis	Not Detected
Ureaplasma urealyticum	Not Detected
Ureaplasma parvum	Not Detected
Staphylococcus saprophyticus	Not Detected
Prevotella bivia	Not Detected
Mycoplasma hominis	Not Detected
Lactobacillus gasseri	Not Detected
Lactobacillus crispatus/acidophilus	Not Detected
Resistance Genes Detected	
Macrolide	
Aminoglycoside	
Resistance Genes Not Detected	
Vancomycin	
Methicillin	
Beta-lactam	
Carbapenem	
Tetracycline	
Quinolone	

Comprehensive Identification (Sequencing Results)	
Detected Bacteria:	
Enterococcus faecalis	82%
Staphylococcus epidermidis	11%
Staphylococcus lugdunensis	6%
NO FUNGAL SPECIES DETECTED	

Complete Antibiotic Analysis [Next Page(s)]

ANTIBIOTIC DISCLAIMER: Southwest Regional PCR assumes no liability to patients with respect to the actions of physicians, health care facilities and other users, and is not responsible for any injury, death or damage resulting from the use, misuse or interpretation of information obtained through this antibiotic report. Therapeutic options listed by the program are based upon national antibiotic susceptibility data and antibiograms. Therapy should not be undertaken without a thorough assessment of the indications, contraindications and side effects of any prospective drug or intervention. Furthermore, the database is curated and derived from incidence and prevalence statistics whose accuracy will vary widely for individual diseases and regions of the country. Changes in endemicity, incidence, and drugs of choice may occur. The list of drugs, infectious diseases and even country names will vary with time. Although we endeavor to include such new information on a timely basis, a delay cannot be avoided. For more information please contact us at 855-208-0019

Case Scenario 1

Class	Generic	Topical	PO	IV	Gram / Resp	82 Enterococcus faecalis + FAn	11 Staphylococcus epidermidis + FAn	6 Staphylococcus lugdunensis + FAn	Enterococcus faecalis + FAn
Aminoglycoside	amikacin*	√		√		√			√
Extended spectrum penicillin/beta-lactamase inhibitor	amoxicillin/clavulanate (Augmentin)		√			√	√		√
fluoroquinolone	levofloxacin		√	√		√	√		√
	ciprofloxacin (Cipro)	√	√	√			√		
	moxifloxacin		√	√				√	
Glycopeptide	vancomycin	√		√		√	√	√	√
	nitrofurantoin		√			√		√	√
	tmp/smx (Bactrim)	√	√	√		√	√	√	√
Oxazolidine	linezolid	√	√	√		√	√	√	√
penicillins	penicillin v		√			√			√
anti-psuedomonal penicillins	piperacillin/tazobactam	√		√			√		
Carbapenem	doripenem			√			√		
Cephalosporin 1st generation	cephalexin (Keflex)		√				√		
	cefazolin			√				√	
RNA sythetase Inhibitor	Mupirocin (bactroban)	√					√	√	

Gram Stain
+: Positive, -: Negative, I:Indeterminate, N: not applicable U: Unknown
Respiration
Ae: Aerobic, An: Anaerobic, FAn: Facultative anaerobic, Unk: Unknown
* Resistance genes found. Consultation with a pharmacist on an appropriate course of treatment with recommendations made at the discretion of the physician based on known interaction and concentrations is recommended.

Supplemental Figure S1. Case scenario 1 with microgen.

Case Scenario 2

A man in his mid 30's presents with nephrolithiasis and a right ureteral calculus. He has no known allergies to antibiotics. The patient is planned to undergo bilateral ureteroscopy. SOC urine culture result showed no growth.

What would you select as your antibiotic for surgery prophylaxis? _____

Based on Microgen results:

1. Would you change your antibiotic? _____
2. What would you select? _____

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Case Scenario 2

Next Generation Sequencing Results

MicroGen Diagnostics' comprehensive testing (patent pending) is a relative quantitative universal test for bacteria/fungi. DNA sequencing methods are used to identify the microorganisms' genetic signatures and the estimated percentage of organisms present in the specimen. Virtually all bacteria/fungi are screened for and the most predominant populations are reported.

Rapid Screening (PCR Results)	Amount per mL
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Enterococcus faecalis	3.04×10^5
Klebsiella pneumoniae	Not Detected
Streptococcus agalactiae	Not Detected
Pseudomonas aeruginosa	Not Detected
Staphylococcus aureus	Not Detected
Proteus mirabilis	Not Detected
Escherichia coli	Not Detected
Mobiluncus curtisii	Not Detected
Mobiluncus mulieris	Not Detected
Gardnerella vaginalis	Not Detected
Ureaplasma urealyticum	Not Detected
Ureaplasma parvum	Not Detected
Staphylococcus saprophyticus	Not Detected
Prevotella bivia	Not Detected
Mycoplasma hominis	Not Detected
Lactobacillus gasseri	Not Detected
Lactobacillus crispatus/acidophilus	Not Detected
Resistance Genes Detected	
None	
Resistance Genes Not Detected	
Vancomycin	
Methicillin	
Beta-lactam	
Carbapenem	
Macrolide	
Aminoglycoside	
Tetracycline	
Quinolone	

Comprehensive Identification (Sequencing Results)	
Detected Bacteria:	
Enterococcus faecalis	99%
NO FUNGAL SPECIES DETECTED	

Complete Antibiotic Analysis [Next Page(s)]

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Case scenario 2

Class	Generic	Topical	PO	IV	Gram Resp	Enterococcus faecalis + FAn	Enterococcus faecalis + FAn
Aminoglycoside	amikacin	√		√		√	√
Extended spectrum penicillin/beta-lactamase inhibitor	amoxicillin/clavulanate (Augmentin)		√			√	√
fluoroquinolone	levofloxacin		√	√		√	√
Glycopeptide	vancomycin	√		√		√	√
	nitrofurantoin		√			√	√
	tmp/smx (Bactrim)	√	√	√		√	√
Oxazolidine	linezolid	√	√	√		√	√
penicillins	penicillin v		√			√	√

Gram Stain
+: Positive, -: Negative, I:Indeterminate, N: not applicable U: Unknown
Respiration
Ae: Aerobic, An: Anaerobic, FAn: Facultative anaerobic, Unk: Unknown
* Resistance genes found. Consultation with a pharmacist on an appropriate course of treatment with recommendations made at the discretion of the physician based on known interaction and concentrations is recommended.

Supplemental Figure S2. Case scenario 2 with microgen.

Case Scenario 3

A woman in her early 60's presents with a right ureteral stone and nephrolithiasis. She has no known allergies to antibiotics. Approximately 2 months prior, she developed a fever and chills and was diagnosed with a UTI. She was treated with antibiotics and her symptoms improved. The patient is now planned to undergo bilateral ureteroscopy. SOC urine culture result showed 'Multiple organisms present, each less than 10,000 CFU/mL. These organisms, commonly found on external and internal genitalia, are considered to be colonizers. No further testing performed.'

What would you select as your antibiotic for surgery prophylaxis? _____

Based on Microgen results:

1. Would you change your antibiotic? _____
2. What would you select? _____

MicroGen DX
Superior Diagnostics. Targeted Treatments. Better Outcomes.
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Case Scenario 3

Next Generation Sequencing Results

MicroGen Diagnostics' comprehensive testing (patent pending) is a relative quantitative universal test for bacteria/fungi. DNA sequencing methods are used to identify the microorganisms' genetic signatures and the estimated percentage of organisms present in the specimen. Virtually all bacteria/fungi are screened for and the most predominant populations are reported.

Rapid Screening (PCR Results)	Amount per mL
Bacterial Load (High)	$> 10^7$
Escherichia coli	8.25×10^5
Enterococcus faecalis	1.49×10^5
Klebsiella pneumoniae	3.19×10^4
Streptococcus agalactiae	Not Detected
Pseudomonas aeruginosa	Not Detected
Staphylococcus aureus	Not Detected
Proteus mirabilis	Not Detected
Mobiluncus curtisii	Not Detected
Mobiluncus mulieris	Not Detected
Gardnerella vaginalis	Not Detected
Ureaplasma urealyticum	Not Detected
Ureaplasma parvum	Not Detected
Staphylococcus saprophyticus	Not Detected
Prevotella bivia	Not Detected
Mycoplasma hominis	Not Detected
Lactobacillus gasseri	Not Detected
Lactobacillus crispatus/acidophilus	Not Detected
Resistance Genes Detected	
Methicillin	
Beta-lactam	
Macrolide	
Quinolone	
Resistance Genes Not Detected	
Vancomycin	
Carbapenem	
Aminoglycoside	
Tetracycline	

Comprehensive Identification (Sequencing Results)	
Detected Bacteria:	
Citrobacter freundii	79%
Escherichia coli	12%
Streptococcus anginosus	6%
NO FUNGAL SPECIES DETECTED	

Complete Antibiotic Analysis [Next Page(s)]

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Case scenario 3

Class	Generic	Topical	PO	IV	Gram	Citrobacter freundii	Escherichia coli	Klebsiella pneumoniae	Escherichia coli	Streptococcus anginosus	Enterococcus faecalis
					Gram	-	-	-	-	+	+
					Resp	FAn	FAn	FAn	FAn	FAn	FAn
Aminoglycoside	amikacin	√		√		√	√		√		√
	gentamicin	√		√				√			
Cephalosporin 3rd/4th generation	ceftriaxone*			√		√					
	cefepime*			√		√					
fluoroquinolone	ciprofloxacin (Cipro)*	√	√	√		√	√	√	√		
	levofloxacin*		√	√			√		√	√	√
Glycopeptide	nitrofurantoin		√			√	√		√		√
	tmp/smx (Bactrim)	√	√	√			√	√	√		√
	vancomycin	√		√						√	√
Polymyxin antibiotic	colistimethate (colistin)	√		√		√	√		√		
Carbapenem	doripenem			√			√		√		
	ertapenem			√						√	
Cephalosporin 1st generation	cephalexin (Keflex)*		√				√		√		
Cephalosporin 2nd generation	cefuroxime*			√			√		√		
	cefprozil*		√					√			
Extended spectrum penicillin/beta-lactamase inhibitor	amoxicillin/clavulanate (Augmentin)*		√				√		√		√
Tetracycline	doxycycline	√	√	√			√		√		
	tetracycline		√					√			
anti-psuedomonal penicillins	piperacillin/tazobactam*	√		√				√			
Oxazolidine	linezolid	√	√	√						√	√
penicillins	penicillin g			√						√	
	penicillin v		√								√

Gram Stain
+: Positive, -: Negative, I:Indeterminate, N: not applicable U: Unknown
Respiration
Ae: Aerobic, An: Anaerobic, FAn: Facultative anaerobic, Unk: Unknown
* Resistance genes found. Consultation with a pharmacist on an appropriate course of treatment with recommendations made at the discretion of the physician based on known interaction and concentrations is recommended.

Supplemental Figure S3. Case scenario 3 with microgen.

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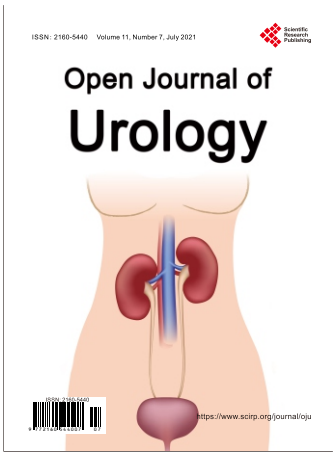

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