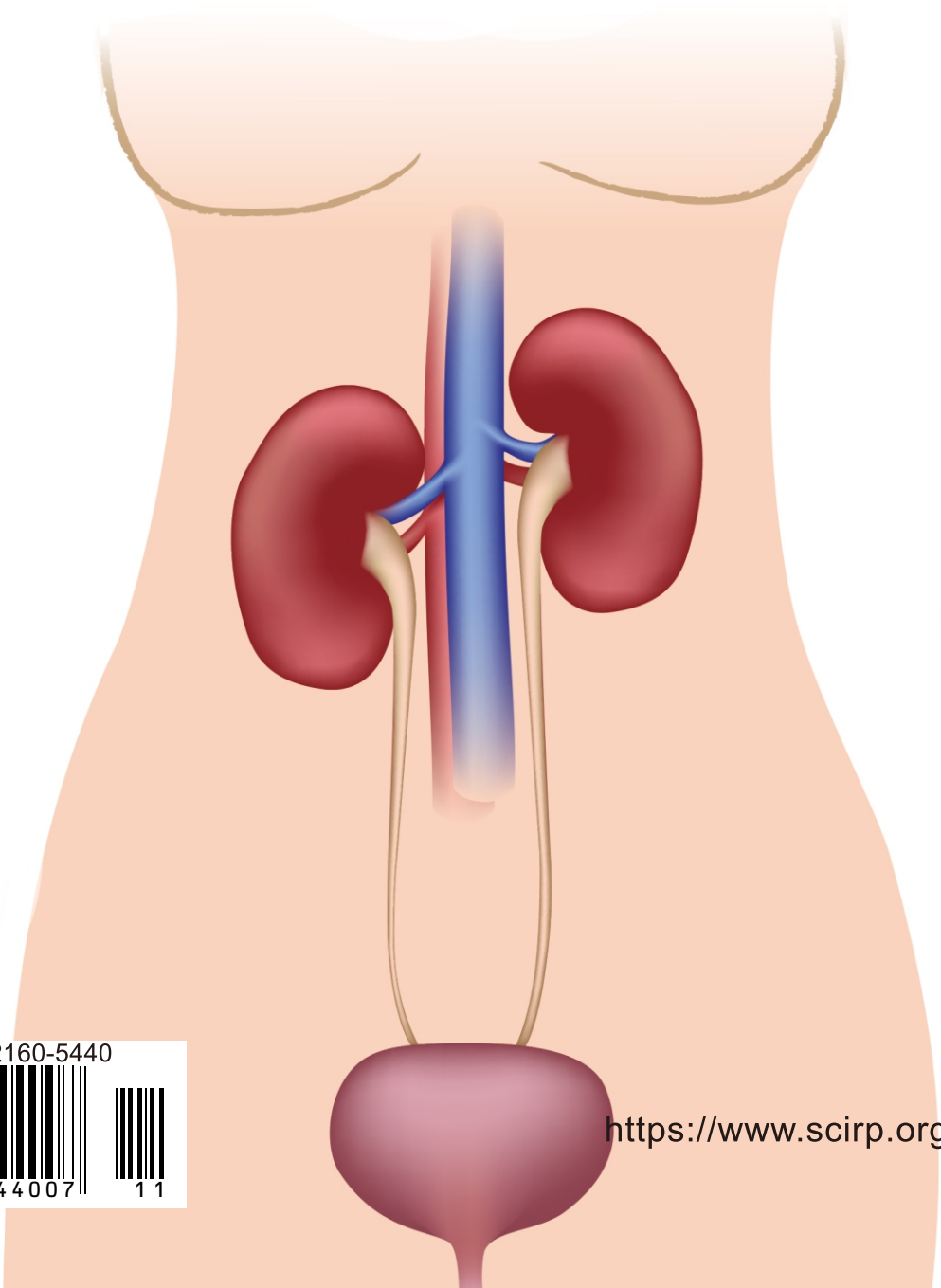


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Effects of Additional Glycine in Outpatients Being Treated for Urine Storage Disorders

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Abstract

Objectives: This study aimed to determine whether additional glycine can improve urine storage symptoms in outpatients. **Methods:** We recruited 50 outpatients (15 females, 35 males) with an Overactive Bladder Symptom Score (OABSS) of 3 or more. Participants being treated for urine storage disorders took additional glycine for 8 weeks at a dose of 3 g twice a day. Outcome measures included blood pressure, the International Prostate Symptom Score (IPSS), OABSS, Nocturia Quality of Life (N-QOL) score, urination frequency, sleep latency, time until the first void at night, bladder pain, improvement in urinary symptoms assessed with the Global Self-Assessment (GSA), and adverse events. **Results:** In the OABSS, the number of nighttime voids, urgency to urinate, urgent incontinence, and total score were improved. Improvements were also found in the IPSS total score for urine storage items, blood pressure, IPSS-QOL, time to first void, bladder pain, and GSA score, but no changes were seen in the frequency of urination at night, sleep latency or N-QOL score. No adverse events were recorded. **Conclusion:** Oral glycine improves objective and self-assessed urine storage symptoms, blood pressure, and bladder pain.

Keywords

Chronic Prostatitis, Glycine, Interstitial Cystitis, Overactive Bladder, Urine Storage Symptoms

1. Introduction

The amino acid glycine is commonly used not only as a sweetener but also as an over-the-counter supplement for improving the quality of sleep, and it has not been found to have any adverse effects [1]. Endogenous glycine acts as the main inhibitor of neurotransmission in the spinal cord [2], and this inhibition plays an essential role in the micturition reflex [2] [3] and sensitivity to pain [4] [5]. Glycine levels decrease after spinal cord injury, and men with benign prostatic hyperplasia also have lower levels than healthy individuals [6]. Studies in rats showed that, as glycine levels decrease, bladder activity increases, bladder contractions are more frequent, and the maximum bladder contraction pressure is higher [3] [7]. Other studies in rats showed that oral glycine (administered as 1% to 3% of the diet) reduces both the frequency of bladder contractions and the maximum contraction pressure [8] [9] [10].

Previously, in a 4-week study, we compared oral glycine (3 g twice a day) with glucose in 20 patients receiving treatment for urine storage symptoms and found greater improvements by additional glycine in urine storage symptoms, cardiovascular function, bladder pain, and sleep quality [11]. Because this study had a small sample size, we subsequently performed an 8-week study of glycine versus glucose in a larger sample. Unfortunately, the drop-out rate was extremely high in the glucose group because of insufficient symptom improvement; however, an encouraging finding was that no patients in the glycine group discontinued the study at least for 4 weeks. Therefore, we aimed to conduct a single-blind, uncontrolled study to evaluate the effects of oral glycine in ameliorating symptoms of urine storage.

2. Materials and Methods

2.1. Study Participants

We recruited 50 males and females outpatients being treated at six urological clinics in Japan (Kitakami Central Hospital, Kobe Medical Center, Yamada Urological Clinic, Kitanodai Clinic, Okinawa Hokubu Hospital, and Okinawa Kyodo Hospital) from April 2013 to April 2016. Patients were eligible to participate if they were aged 20 years and older and had urine storage symptoms that showed no improvement after 8 weeks of standard treatment; a diagnosis of overactive bladder, chronic prostatitis, or bladder pain syndrome/interstitial cystitis; and an Overactive Bladder Symptom Score (OABSS) [12] of 3 or more. Exclusion criteria included urinary tract infection; relevant untreated organic diseases, such as benign prostatic hyperplasia with urine voiding symptoms, prostate cancer, bladder neck obstruction (sclerosis), stricture of the urethra, and bladder tumor or stones; 100 mL or more of residual urine after voiding; and a lack of urgency to urinate. Participants were permitted to continue taking all their regular medications.

The study protocol was approved by the Okinawa Kyodo Hospital Ethics Committee (approval no. 2012-005) for all participating institutions. All patients

provided written informed consent to participate.

2.2. Study Drug

Although the study was uncontrolled, participants were informed that they would be assigned to receive small pouches containing either glucose or glycine. However, all participants actually received glycine (Nippon Garlic Corporation, Takasaki, Japan) at a dose of 3 g twice a day (morning and evening). The dose was chosen as being equivalent to about 1% of the dry weight of an adult man's daily food intake.

2.3. Outcome Measures

The following variables were assessed at baseline and after 4 and 8 weeks of treatment: overall clinical status; blood pressure and pulse rate; number of daytime voids; sleep latency; time until first nighttime void; and number of nighttime voids. At the same visits, patients also completed the following self-assessment tools: International Prostate Symptom Score (IPSS) (**Appendix 1**) [13]; IPSS quality of life (IPSS-QOL); OABSS (**Appendix 2**); nocturia quality of life (N-QOL) (**Appendix 3**) [14]; and visual analogue scale for bladder pain.

Transabdominal ultrasonography was performed at baseline to assess prostate volume and at baseline and the end of the study to assess the volume of residual urine after voiding. After 4 and 8 weeks, patients completed a global self-assessment (GSA) scale to assess changes in symptoms, as follows: 0, excellent improvement; 1, good improvement; 2, fair improvement; 3, no change; 4, worse. Adverse events were recorded at weeks 4 and 8.

2.4. Statistical Analysis

Results are reported as the mean \pm standard deviation. Higher scores corresponded to worse outcomes in all self-assessment tools except the N-QOL, in which a higher score corresponded to a better outcome. Changes over time were analyzed by Student's *t*-test for paired data, and significance was set as a *p* value of less than 0.05.

3. Results

The 50 participants comprised 35 males and 15 females with a mean body mass index of 23.4 ± 3.2 and a mean age of 66 ± 15 years. Diagnoses were as follows: chronic prostatitis with overactive bladder (15 males); mild benign prostatic hyperplasia with overactive bladder (9 males); bladder pain syndrome/interstitial cystitis with overactive bladder (5 males and 12 females); and overactive bladder (6 males and 3 females) (**Table 1**). Concomitant diagnoses were hypertension in 12 patients and type 2 diabetes in 7. The mean prostate size was 21.9 ± 7.8 mL (range, 12.3 - 35.7 mL). Concomitant medication included anti-muscarinic drugs for overactive bladder (*n* = 39) and anti-muscarinic tricyclic antidepressants for bladder pain syndrome/interstitial cystitis (*n* = 11). Nine patients with benign

Table 1. Characteristics of patients.

Sex	Diagnosis	Number of cases
Male	Chronic prostatitis with overactive bladder	15
	Benign prostatic hyperplasia with overactive bladder	9
	Bladder pain syndrome/interstitial cystitis with overactive bladder	5
	Overactive bladder	6
		total 35
Female	Bladder pain syndrome/interstitial cystitis with overactive bladder	12
	Overactive bladder	3
		total 15

prostatic hyperplasia were also receiving an alpha-1 blocker, and fifteen with chronic prostatitis, an anti-inflammatory botanical preparation.

At 4 weeks, we found a decrease in diastolic blood pressure compared with baseline (baseline: 67.2 ± 10.5 mmHg vs 4 week after: 65.1 ± 10.5 mmHg, $p < 0.05$), but no change in systolic blood pressure (124.7 ± 17.3 mmHg vs 123.3 ± 17.3 mmHg, respectively) or pulse rate (75.0 ± 13.2 /min vs 73.3 ± 12.5 /min, respectively) (**Table 2**). The IPSS showed an improvement in total score, urgency to urinate, and total score of items related to urine storage. The OABSS showed improvements in total score, number of nighttime voids, urgency to urinate, and urge incontinence. Regarding quality of life, the IPSS-QOL score improved, as did the total score and total score of items about worries on the N-QOL. The number of day- and nighttime voids, bladder pain, and sleep latency showed no changes, but the time until the first void at night improved.

At 8 weeks, we found a decrease in systolic (baseline: 124.7 ± 17.3 mmHg vs 8 week after: 121.2 ± 15.5 mmHg, $p < 0.05$) and diastolic blood pressure compared with baseline (67.2 ± 10.5 mmHg vs 65.1 ± 10.5 mmHg, respectively, $p < 0.05$) but no change in pulse rate (75.0 ± 13.2 /min vs 73.4 ± 14.2 /min, respectively). The IPSS showed an improvement in total score, frequency of urination, nocturia, and total score of items related to urine storage. In the OABSS, the same improvements from baseline were seen at 4 weeks. IPSS-QOL score was higher than at baseline, but neither the N-QOL total score nor any of the individual items showed an improvement from baseline. Neither the number of day- and nighttime voids nor sleep latency showed an improvement from baseline. The time until the first void at night was still higher than at baseline, and bladder pain improved slightly, but significantly. The volume of residual urine after voiding showed no change from baseline to 8 weeks (27.8 ± 26.6 mL vs 28.6 ± 25.9 mL, respectively).

Mean GSA scores showed a fair improvement at both 4 (2.4 ± 0.8) and 8 weeks (2.2 ± 1.1), and no adverse events were recorded at either visit.

Table 2. Comparison of parameters and self-assessed questionnaires between before and after glycine treatments.

	Before		4 weeks after		8 weeks after	
Number of cases	50		50		40	
Blood pressure (mmHg)						
Systolic	124.7	± 17.3	123.3	± 17.3	121.2	± 15.5*
Diastolic	67.2	± 10.5	65.1	± 10.5*	65.1	± 10.5*
Pulse rate (/min)	75.0	± 13.2	73.3	± 12.5	73.4	± 14.2
IPSS						
Incomplete emptying	1.2	± 1.2	1.0	± 1.1	1.1	± 1.2
Frequency	2.8	± 1.6	2.6	± 1.5	2.3	± 1.6*
Intermittency	1.3	± 1.6	1.2	± 1.4	1.1	± 1.3
Urgency	1.9	± 1.5	1.3	± 1.2**	1.6	± 1.4
Weak stream	2.0	± 1.7	1.9	± 1.7	1.9	± 1.5
Straining	1.0	± 1.4	0.8	± 1.2	0.8	± 1.3
Nocturia	2.1	± 1.2	2.0	± 1.3	1.8	± 1.3*
Voiding Total	4.3	± 3.9	3.9	± 3.5	3.7	± 3.2
Storage Total	6.6	± 3.1	5.8	± 2.8**	5.6	± 3.4**
Total score	12.3	± 6.2	10.8	± 6.2**	10.4	± 6.9*
IPSS-QOL	4.7	± 1.2	4.1	± 1.5**	3.6	± 1.6**
Urinary frequency (times)						
Diurnal	10.5	± 3.4	10.8	± 6.7	10.6	± 7.3
Nocturnal	2.1	± 1.3	1.9	± 1.6	1.7	± 1.7
OABSS						
Diurnal urination	1.2	± 0.9	1.1	± 0.5	1.0	± 0.6
Nocturnal urination	2.0	± 0.8	1.8	± 0.9**	1.5	± 0.9**
Urgency	2.5	± 1.6	2.0	± 1.5**	1.8	± 1.4**
Incontinence	1.3	± 1.6	1.1	± 1.5*	0.9	± 1.3*
Total score	7.0	± 3.6	6.0	± 3.4**	5.3	± 3.4**
N-QOL						
Q1	2.9	± 0.9	3.1	± 0.9*	3.1	± 1.1
Q2	2.9	± 1.0	2.8	± 1.0	2.9	± 1.2
Q3	2.4	± 1.2	2.6	± 1.2	2.5	± 1.2
Q4	2.9	± 1.0	3.0	± 0.9	2.9	± 1.1
Q5	2.7	± 1.2	3.3	± 3.2	2.9	± 1.2
Q6	2.4	± 1.3	2.7	± 1.0	2.7	± 1.1
Q7	2.2	± 1.1	2.3	± 1.2	2.4	± 1.2
Q8	3.6	± 1.0	3.7	± 0.8	3.6	± 0.9
Q9	3.1	± 1.1	3.2	± 0.9	3.2	± 1.1

Continued

Q10	2.4 ± 1.3	2.6 ± 1.2	2.7 ± 1.0
Q11	2.4 ± 1.2	2.5 ± 1.3	2.8 ± 1.3
Q12	2.3 ± 1.2	2.6 ± 1.1	2.6 ± 1.3
Q13	3.9 ± 2.7	3.4 ± 2.7	3.3 ± 3.0
Vitality Total	16.0 ± 5.2	17.2 ± 6.1	16.8 ± 5.9
Worries Total	16.1 ± 5.5	17.3 ± 4.9*	17.4 ± 5.4
Total score	35.9 ± 7.6	37.9 ± 8.1*	37.5 ± 8.3
Sleep latency (min)	24.6 ± 20.6	23.3 ± 19.5	21.2 ± 19.6
First nocturia latency (min)	181.5 ± 93.9	203.9 ± 93.2**	206.5 ± 94.8*
Bladder pain (VAS)	2.3 ± 2.9	1.8 ± 2.5	1.8 ± 2.8*
Global self-assessment		2.4 ± 0.8	2.2 ± 1.1

The larger is the number, the better is the N-QOL, but the worse is the other questionnaires. Mean ± standard deviation. *: $p < 0.05$, **: $p < 0.01$ vs before.

4. Discussion

The current study found that 8 weeks' administration of oral glycine improved urine storage symptoms such as nocturia, urgency to urinate, and urge incontinence; patient quality of life; and bladder pain. These findings are in line with our earlier 4-week study that compared glycine with glucose, although that study also found improvements in sleep [11]. Both studies also found a decrease in blood pressure but no change in pulse rate. Taken together, these findings indicate that oral glycine has positive effects on urine storage symptoms, blood pressure, and bladder pain.

Oral glycine given at a dose of 1% to 3% of food weight was found to increase the time between bladder contractions in healthy rats [8] and in those with pelvic vein congestion [10] and to reduce the strength of bladder contractions in rats with spinal cord injury [8]. Another study in rats found that orally administered glycine increased glycine levels in brain tissue, indicating that glycine can cross the blood-brain barrier [15]. Both our earlier [11] and the present study found that symptoms improved in patients receiving anti-muscarinic drugs for urine storage symptoms. These drugs usually have a peripheral action [16], and our findings indicate that concomitant treatment with centrally acting glycine may result in further improvement of symptoms.

Although both the IPSS and OABSS showed improvements in nighttime urinary parameters in the current study, the number of nighttime voids did not improve significantly. This result is in contrast to our previous study, where the number of nighttime voids decreased significantly after 4 weeks' administration of glycine [11]. The maximum possible score for nighttime voids is 5 on the IPSS and 3 on the OABSS, even if the actual number of voids is higher. Therefore, any reduction in the number of nighttime voids to a number that is still above 5 (IPSS) or 3 (OABSS) will not be recorded, even though the change may be sig-

nificant. The large standard deviation in our data may also explain why our current study found no significant improvement in the number of nighttime voids.

Glycinergic interneurons in the spine may help regulate neurotransmission of pain and reduce neuropathic pain [5] and may also decrease sensitivity to pain [4]. Consequently, glycine probably can also reduce bladder pain, which may explain our respective findings.

Glycine is widely used at a dose of 3 g as an over-the-counter supplement for sleep and has no known side effects [1]. It inhibits orexin neurons, which stimulate active wakefulness, and increases the duration of non-rapid eye movement sleep [17]. In addition, it binds to N-methyl-D-aspartate receptors in the suprachiasmatic nucleus shell, leading to dilation of peripheral blood vessels, which promotes sleep [18]. Our earlier study confirmed the sleep-promoting effects of glycine [11]; however, the current study did not, which may be a chance finding related to the time of glycine administration: Participants were instructed to take the two doses of glycine at different times (morning and evening) each day, but the exact times were not specified. Future studies need to evaluate whether administering glycine at bedtime has positive effects on sleep.

The finding in the present study that systolic and diastolic blood pressure decreased after 4 to 8 weeks' administration of glycine may be related to the peripheral vasodilation caused by binding of glycine to N-methyl-D-aspartate receptors in the suprachiasmatic nucleus shell [18]. Glycine also binds to these receptors in the rostral ventral medulla, an area involved in the maintenance of arterial baroreceptor reflex [19]. Furthermore, a study in rats with diabetes showed that oral glycine leads to an increase in blood nitric oxide levels, resulting in vasodilation [20]. These central and peripheral effects of glycine may act together to reduce blood pressure.

There are limitations of the current study. Although our previous 4-week study comparing oral glycine with glucose as a placebo found greater improvements by additional glycine in urine storage symptoms, cardiovascular function, bladder pain, and sleep quality [11], this study had a small sample size. In the current study, we started an 8-week study of glycine versus glucose in a larger sample. However, the drop-out rate was extremely high in the glucose group. Therefore, it was not possible to compare the effects of glycine and placebo, and we conducted a single-blind, uncontrolled study but not double-blind, controlled study to evaluate the effects of oral glycine.

Nighttime urination has a negative effect on the quality of life, but the frequency of voiding is not the only related issue reported by patients [21] [22]. Other problems include time to first nighttime voiding and bladder pain, both of which improved in the present study, as did the OABSS, which reflects many related symptoms. These positive changes may explain the increase in IPSS-QOL and GSA scores.

5. Conclusion

Glycine appears to improve symptoms of urine storage, blood pressure, and

bladder pain. It does not cause any adverse events or increase the volume of residual urine after voiding. Furthermore, it is inexpensive. Therefore, we suggest that glycine is a safe concomitant treatment for urine storage symptoms and bladder pain and may be particularly useful in patients with hypertension.

Conflicts of Interest

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

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Abbreviations

BPH = benign prostatic hyperplasia
 BPS/IC = bladder pain syndrome/interstitial cystitis
 GSA = global self-assessment
 IPSS = international prostate symptom score
 N-QOL = nocturia quality of life
 OAB = overactive bladder
 OABSS = overactive bladder symptom score
 QOL = quality of life
 SCI = spinal cord injury

Appendix 1. International Prostate Symptom Score (IPSS)

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score	
1. Incomplete Emptying								
How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5		
2. Frequency								
How often have you had to urinate less than every 2 hours?	0	1	2	3	4	5		
3. Intermittency								
How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5		
4. Urgency								
How often have you found it difficult to postpone urination?	0	1	2	3	4	5		
5. Weak Stream								
How often have you had a weak urinary stream?	0	1	2	3	4	5		
6. Straining								
How often have you had to strain to start urination?	0	1	2	3	4	5		
	None	1 Time	2 Times	3 Times	4 Times	5 Times		
7. Nocturia								
How many times did you typically get up at night to urinate?	0	1	2	3	4	5		
Total IPSS Score								
Score:	1 - 7: Mild		8 - 19: Moderate		20 - 35: Severe			

Continued

Quality of Life Due to Urinary Symptoms

If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?

0 1 2 3 4 5 6

Appendix 2. Overactive Bladder Symptom Score (OABSS)

	Score	Frequency
How many times do you typically urinate from waking in the morning until sleeping at night?	0	7 or less
	1	8 - 14
	2	15 or more
How many times do you typically wake up to urinate from sleeping at night until waking in the morning?	0	0
	1	1
	2	2
	3	3 or more
How often do you have a sudden desire to urinate, which is difficult to defer?	0	not at all
	1	less than once a week
	2	once a week or more
	3	about once a day
	4	2 - 4 times a day
	5	5 times a day or more
How often do you leak urine, because you cannot defer the sudden desire to urinate?	0	not at all
	1	less than once a week
	2	once a week or more
	3	about once a day
	4	2 - 4 times a day
	5	5 times a day or more

OABSS (sum of scores) =

Appendix 3. Nocturia Quality of Life Questionnaire (N-QOL)

The following statements are about the impact of “having to get up at night to urinate”. For each item, please mark an (X) in the box next to the response that best describes how you have felt. Please mark only one box for each statement.

OVER THE PAST 2 WEEKS, HAVING TO GET UP AT NIGHT TO URINATE

score	4	3	2	1	0	
1	Has made it difficult for me to concentrate the next day	<input type="checkbox"/> Every day	<input type="checkbox"/> Most days	<input type="checkbox"/> Some days	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never
2	Has made me feel generally low in energy the next day	<input type="checkbox"/> Every day	<input type="checkbox"/> Most days	<input type="checkbox"/> Some days	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never
3	Has required me to nap during the day	<input type="checkbox"/> Every day	<input type="checkbox"/> Most days	<input type="checkbox"/> Some days	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never
4	Has made me less productive the next day	<input type="checkbox"/> Every day	<input type="checkbox"/> Most days	<input type="checkbox"/> Some days	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never
5	Has caused me to participate less in activities I enjoy	<input type="checkbox"/> Extremely	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> A little bit	<input type="checkbox"/> Not at all
6	Has caused me to be careful about when or how much I drink	<input type="checkbox"/> All the time	<input type="checkbox"/> Most of the time	<input type="checkbox"/> Some of the time	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never
7	Has made it difficult for me to get enough sleep at night	<input type="checkbox"/> Every night	<input type="checkbox"/> Most nights	<input type="checkbox"/> Some nights	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never

OVER THE PAST 2 WEEKS, I HAVE BEEN

8	Concerned that I am disturbing others in the house because of having to get up at night to urinate	<input type="checkbox"/> Extremely	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> A little bit	<input type="checkbox"/> Not at all	
9	Preoccupied about having to get up at night to urinate	<input type="checkbox"/> All the time	<input type="checkbox"/> Most of the time	<input type="checkbox"/> Some of the time	<input type="checkbox"/> Rarely	<input type="checkbox"/> Never	
10	Worried that this condition will get worse in the future	<input type="checkbox"/> Extremely	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> A little bit	<input type="checkbox"/> Not at all	
11	Worried that there is no effective treatment for this condition (having to get up at night to urinate)	<input type="checkbox"/> Extremely	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> A little bit	<input type="checkbox"/> Not at all	
12	Overall, how bothersome has having to get up at night to urinate been during the past 2 weeks?	<input type="checkbox"/> Extremely	<input type="checkbox"/> Quite a bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> A little bit	<input type="checkbox"/> Not at all	
13	Overall, I would rate my quality of life to be	Very good 0 1 2 3 4 5 6 7 8 9 10 Very poor					

The Impact of 18F-DCFPyL PSMA PET-CT in the Management of Prostate Cancer Biochemical Recurrence

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Abstract

Purpose: We evaluated the findings from 18F-DCFPyL PSMA PET-CTs performed on patients presenting biochemical recurrence (BCR) of prostate cancer (PCa) and assessed its impact on staging. **Methods and materials:** This was a multicenter retrospective analysis of patients with PCa and BCR who underwent 18F-DCFPyL PSMA PET-CT in 2020. The patients were stratified into two groups: BCR after prostatectomy (PSA \geq 0.2 ng/mL) or BCR after radiotherapy (PSA \geq 2 ng/mL + nadir). We analyzed the lesions according to number and location. The Shapiro-Wilk test was used to estimate the distribution of the variables. We calculated representative statistics for the quantitative variables including the mean, standard deviation, median, and interquartile range. The association between qualitative variables was examined using Chi-squared tests. **Results:** 40 patients with BCR were analyzed; 67.5% presented disease progression, predominantly distant recurrence (42.5%), which was found exclusively in bone; 55% presented \leq 5 lesions and of these, 68.2% only presented 1 lesion. There was a change in staging in 66.7% of the cases; 17.7% received ablative treatment with stereotactic radiotherapy (SABR). **Conclusions:** 18F-DCFPyL PSMA PET-CT represents a new way to manage patients with BCR that, in this study, resulted in a change in staging in 66.7% of cases and early identification of oligometastatic progressions in the subgroup of patients with PSA < 0.5 ng/mL.

Keywords

Prostate Specific Membrane Antigen, Prostate Cancer, PET-CT PSMA 18F-DCFPyL, Biochemical Recurrence

1. Introduction

According to figures from the Spanish National Institute of Statistics (INE), prostate cancer (PCa) is the most prevalent neoplasm and is the third leading cause of mortality (after lung and colorectal cancer) in the male population in Spain [1] [2] [3]. Of the patients with localized or locally advanced PCa treated with radical prostatectomy or radiotherapy, between 27% - 53% will experience a local or distant recurrence in the 10 years following treatment [4] [5]. Biochemical recurrence (BCR) is determined based on the level of prostate-specific antigen (PSA) present in the blood, according to the Phoenix criteria [6]. The challenge so far has been to find an imaging test that complements this analytical parameter which can provide more information about the location of the recurrence, especially when PSA values are low. The sensitivity and specificity of conventional imaging techniques (CITs) in patients with BCR and low PSA levels are limited, especially when PSA < 1 ng/mL [7]. 11C-choline or 18F-choline PET-CT is currently the main test used in prostatectomized patients with PSA levels > 1 ng/mL [8]. Until now, the problem facing physicians has been the underdiagnosis of patients with BCR values < 1 ng/mL by CITs. However, the relative efficiency of 68Ga-PSMA-11 PET-CT for the determination of locoregional and distant recurrences in these patients has been reported [9]. Furthermore, the 18F radiotracer has recently been shown to offer crucial advantages over 68Ga, including [1] greater availability; [2] increased detectability because of its lower photon energy (0.6 MeV for 18F vs. 2.3 MeV for 68Ga) which improves image resolution and photonic richness (96.6% vs. 89.1%, respectively); and [3] its longer half-life (1.83 h vs. 1.13 h, respectively), which allows late studies and facilitates discrimination [10] [11] [12]. This current study aimed to describe the outcomes after performing 18F-DCFPyL PSMA PET-CT in patients with BCR, and to analyze whether the use of this technique resulted in a change in the staging and management of these patients.

2. Materials and Methods

Patient population: This was a descriptive study carried out in 40 patients with PCa and BCR from one of two centers who underwent 18F-DCFPyL PSMA PET-CT. The patients were stratified into the following groups: BCR after radical prostatectomy with PSA \geq 0.2 ng/mL or BCR after external radiotherapy with PSA \geq 2 ng/mL + nadir [13]. Of all these patients, 75% had previously undergone CITs and some of them had not presented conclusive or suspicious signs of malignancy. The median follow-up period of the patients was 12 months.

Image acquisition and analysis: The 18F-DCFPyL radiopharmaceutical was synthesized in a cyclotron, according to good manufacturing practice conditions. The GE Discovery IQ 5r PET-CT equipment (GE Healthcare) underwent routine quality controls by the European Association of Nuclear Medicine Research Ltd., according to the recommendations of the European Association of Nuclear Medicine (EARL), which promotes scientific and inter-center initiatives

[14]. The patients did not require prior fasting or withdrawal or modification of their medications, nor were they administered a diuretic. A peripheral venous line was placed and they were injected with ¹⁸F-DCFPyL at a dose of 333 MBq (9 mCi). The rest period ranged from 80 to 120 minutes. Next, a CT (120 Kv, 25 - 120 mA) was performed to obtain the correction map, and then a whole-body PET acquisition was carried out. The images were corrected for decay, scatter, randomness and coincidences, and photon attenuation and were reconstructed, applying an iterative Bayesian penalty algorithm (Q.Clear) with a β of 350 q, to improve the convergence of the lesion, guaranteeing a sufficient signal-to-noise ratio. The imaging test results were evaluated with the AW 3.2 expansion 3.0 processing server and Volume Viewer software (GE Healthcare) by two senior specialists in nuclear medicine, according to PSMA RADS 1.0 criteria [15] [16], by collecting the peak standardized uptake value (SUV) normalized by lean body mass (SUL) value of each of the lesions [17] [18]. The number of lesions as well as their location were analyzed and coded.

Statistical analysis: As the study sample comprised fewer than 50 patients we used the Shapiro–Wilk test to assess the distribution of the variables; $p \leq 0.05$ for those with a non-normal distribution which were presented as medians and interquartile ranges (P25 - P75); while $p > 0.05$ for those with a normal distribution which were represented as means and standard deviations. The association between qualitative variables was studied using Chi-squared tests, using Fisher exact tests when the frequency was less than 5.

3. Results

Patient characteristics: 40 patients with a median age at diagnosis of 66.5 years (range 48 - 78) were included in this study. The primary tumor was treated by radical prostatectomy in 75% of cases, while the remaining patients received radiotherapy. Of the latter, one patient received a brachytherapy boost after external radiation therapy. The group characteristics are shown in **Table 1**.

Characteristics of the primary tumor: in the overall sample, the median PSA at the time of diagnosis of the primary tumor was 7.08 ng/mL (range 5 - 13.6); 46.2% of the patients were stage II and III, respectively. According to the International Society of Urological Pathology (ISUP) prognostic group classification guidelines, the most frequent classification was ISUP3 (in 30% of the cases). Of the 75% of patients who underwent radical prostatectomy, half had positive margins. In addition, 80% of the patients who received irradiation were also treated with hormonal therapy (for 24 months in 87.5% of the cases).

Evaluation of the recurrence sites and number of lesions: ¹⁸F-DCFPyL PSMA PET-CT provided conclusive evidence of local, lymph node, or distant progression in 27 patients. Lymph node recurrences (26.7%) included both regional (pelvic, hypogastric, obturator, internal or external iliac, and sacral) and extra-pelvic lymphadenopathies. Distant recurrence was observed in 42.5% of these patients, in bone in every case (**Figure 1**). The number of lesions observed

Table 1. Patient characteristics.

Variables	Global <i>n</i> = 40	BCR ¹ after pros- tatectomy <i>n</i> = 30	BCR ¹ after radiotherapy <i>n</i> = 10
Age (years)	66.5 (48 - 78)	65.50 (48 - 72)	71 (58 - 78)
PSA ² at diagnosis (ng/mL)	7.08 (5 - 13.6)	6.89 (4.14 - 45.83)	10.07 (4.62 - 55.65)
Stage			
II	46.2%	55.2%	20%
III	46.2%	34.5%	80%
IVa	7.7%	10.3%	
ISUP³			
1	22.5%	16.7%	40%
2	25%	26.7%	-
3	30%	40%	20%
4	7.5%	6.7%	10%
5	15%	10%	30%
D'Amico risk			
Intermediate risk	17.5%	20%	10%
High risk	82.5%	80%	90%
1st treatment			
Surgery	75%	100%	-
EBRT ⁴	EBRT ⁴ 22.5% EBRT ⁴ + BT ⁵ 2.5%		EBRT ⁴ 90% EBRT ⁴ + BT ⁵ 10%
Hormonal therapy			
Yes	20%	-	80%
No	80%	-	20%
Time HT⁶ (months)			
12 months	-	-	12.5%
24 months	-	-	87.5%
Surgical margins			
Positive	37.5%	15 (50%)	-
Negative	37.5%	15 (50%)	-
BCR ¹ -free interval (months)	20.5 (1 - 162)	17 (1 - 118)	85.5 (12 - 162)
PSA ² doubling time (months)	9.78 (1.31 - 75.45)	7.61 (1.51 - 33.25)	12 (0.9 - 60.85)
Comorbidities			
Diabetes mellitus	17.5%	20%	10%
Arterial hypertension	62.5%	60%	70%
Dyslipidemia	50%	60%	20%
Cardiological	20%	20%	20%

BCR¹ = biochemical recurrence; PSA² = prostate specific antigen; ISUP³ = International Society of Urological Pathology; EBRT⁴ = external beam radiotherapy; BT⁵ = brachytherapy; HT⁶ = hormonal therapy.

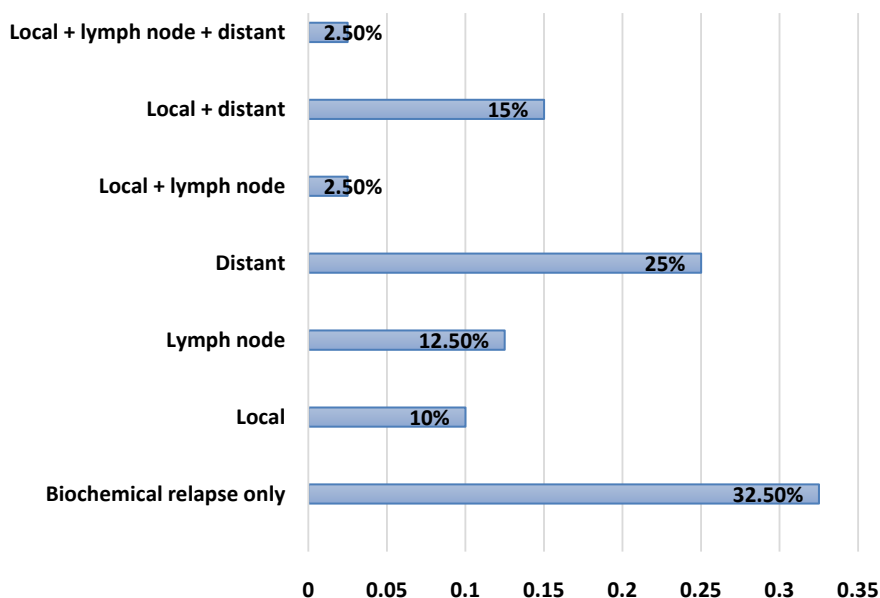


Figure 1. Recurrence site.

upon progression (1, 2, 3, 4, 5, 6 - 10, or >10) were quantified and used to recode the patients into three groups: local, lymph nodes and distant recurrence. Of the patients with local, lymph nodes, or distant relapses, 55% had ≤ 5 lesions (**Figure 2**) and within this group, only 1 lesion was observed in 68.2% of cases. Of note, 66.7% of patients with a lesion belonged to the prostatectomized subgroup. Eight of the patients had PSA levels of 0.2 - 0.5 ng/mL and presented ≤ 5 lesions, with a significance level of $p = 0.001$ (**Figure 3**). Of all the patients, 75% had previously undergone CITs (CT, bone scintigraphy, or MRI) or 18F-choline PET-CT imaging. Although the latter was considered a new generation imaging test, it is indicated in prostatectomized patients with PSA > 1 ng/mL and so we considered it a routine test for this patient profile. After comparing these prior results with those from the 18F-DCFPyL PSMA PET-CT, the latter imaging resulted in a change in staging in 66.7% of cases (**Table 2**), hence indicating that conventional CITs currently lead to underdiagnosis, especially in the surgical subgroup (65% vs. 35%, $p = 0.064$). The detection of distant disease was 65% (vs. 25% regional vs. 10% local), of which 23.1% had metastatic involvement with low PSA levels (<0.5 ng/mL). This modification in the initial staging allowed 9 patients (45%) to be treated with ablative intent using SBRT techniques (**Table 3**). Finally, in the subgroup of patients undergoing radiotherapy in which both CITs and 18F-DCFPyL PSMA PET-CT were performed, the change of staging after PET PSMA was statistically significant ($p = 0.038$; **Table 2**). The use of 18F-DCFPyL PSMA PET-CT as an initial diagnostic test detects disease in 70% of cases, showing a trend between its use and the detection of disease ($p = 0.29$).

4. Discussion

The purpose of this study was to evaluate the impact of 18F-DCFPyL PSMA

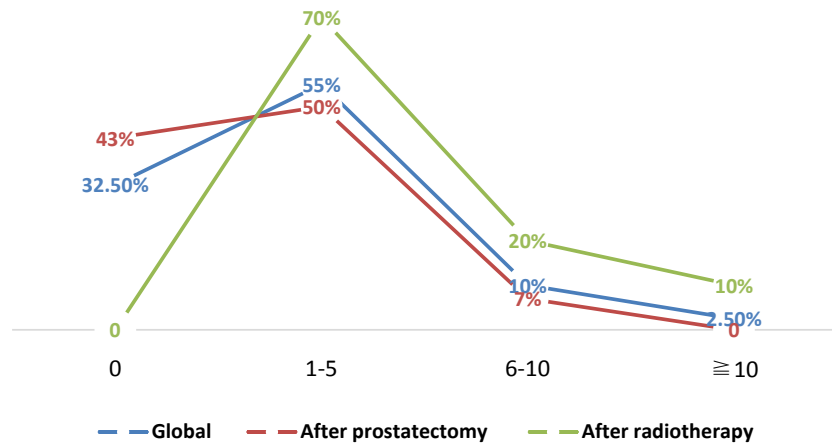


Figure 2. Number of lesions according to the primary treatment ($p = 0.008$).

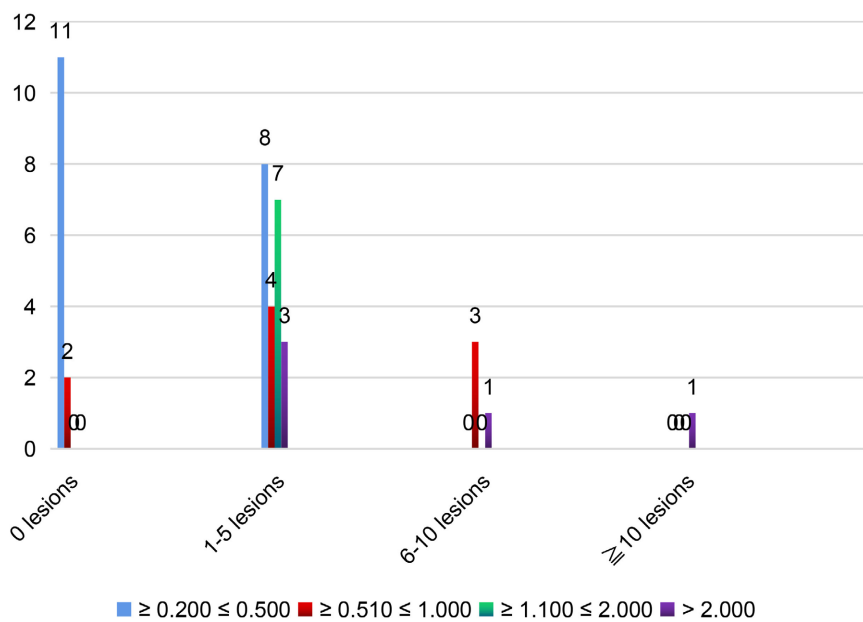


Figure 3. Number of lesions as a function of prostate specific antigen levels (ng/dL) during biochemical recurrence ($p = 0.001$).

Table 2. Staging change based on primary treatment with previous conventional tests ($p = 0.038$).

		1st tumor treatment			
		Prostatectomy	Radiotherapy	Global	
Staging change after 18F-DCFPyL PSMA PET-CT	YES	n	13	7	20
		%	43.30%	23.30%	66.70%
	NO	n	10	0	10
		%	33.30%	0.00%	33.30%
Total		n	23	7	30
		%	76.70%	23.30%	100.00%

n: number of patients, % percentage.

Table 3. Therapeutic attitude in comparable patients who have modified their staging.

	Global <i>n</i> = 20	BCR ¹ after prostatectomy <i>n</i> = 13	BCR ¹ after radiotherapy <i>n</i> = 7
RT ²	5%	7.7%	-
HT ³	30%	15.4%	57.1%
RT + HT	10%	15.4%	-
SBRT ⁴ + HT	25%	23.1%	28.6%
RT + SBRT + HT	20%	30.8%	-
Enzalutamide + HT	10%	7.7%	14.3%

BCR¹ = biochemical relapse; RT² = external radiotherapy; HT³ = hormonal therapy; SBRT⁴ = stereotactic body radiotherapy.

PET-CT on the diagnosis and therapeutic management of patients with PCa BCR after local treatment. Patients with BCR after prostatectomy and with PSA levels > 1 ng/mL usually undergo a 18F-choline PET-CT [5]. Moreover, prostatectomized patients with PSA < 0.5 ng/mL are usually administered salvage radiotherapy, without first performing complementary imaging tests. This indication assumes that most recurrences are local and mainly occur near the anastomosis. In addition, no imaging tests with sufficient sensitivity or specificity to better study these recurrences are currently available [5]. However, despite this salvage treatment, some of these patients subsequently present both regional and distant recurrences, which has led to the need for complementary studies to help determine the location of these recurrences with greater precision and thus, individualize patient treatments.

There is now sufficient bibliographic evidence demonstrating the diagnostic benefit of 68Ga-PSMA-11 PET-CT in patients with PCa BCR, to support its use in the detection of disease in these patients when PSA < 1 ng/mL, thereby making it the imaging technique of choice for this patient subgroup [19] [20]. The 18F radiotracer is even more valued than 68Ga because of its advantageous characteristics over the latter, as discussed above [21] [22]. Both 68Ga and 18F have shown acceptable sensitivity and specificity when it comes to detecting progression, even with low PSA levels [10] [23].

In Spain, 68Ga-PSMA-11 is performed in two situations: after treatment of the primary tumor in patients with BCR and PSA < 2 ng/mL, or in those with any PSA level and a recent (in the last 6 months) 18F-choline PET-CT figure negative for malignancy. Despite the proven benefits of the use of 68Ga-PSMA-11, the 18F-DCFPyL PSMA radiopharmaceutical has not yet been authorized for use in clinical practice. However, while a multicenter phase III European clinical trial (PYTHON) analyzing 18F-DCFPyL PSMA PET-CT in patients with PCa and BCR is underway [24], the Spanish Ministry of Health does allow its compassionate use when requested with a supporting report. The limited experience of Spanish centers in the management and evaluation of images using 18F-DCFPyL

PSMA PET-CT, means that it would be helpful to collect and analyze the data arising from the collective experience of our centers.

Many authors have written about recurrence sites in oligometastatic PCa patients [25] [26], although controversy remains when determining the number of lesions that should classify different patient sub-groups, the best treatment type, and therapy administration sequence. For example, a maximum of 3 or 5 lesions currently defines the intermediate stages of disease, but insufficient biological evidence is available to establish a definitive figure. In this sense, Lievens *et al.* pointed out that no validated biomarkers that differentiate the intermediate stage of oligometastatic disease are currently available. Ideal candidates to identify these patients would be microRNAs, free circulating DNA, or intratumoral heterogeneity, and would not focus exclusively on the number of lesions present [26]. In our work, we classified the number of lymphadenopathies by considering affected lymph nodes as independent lesions and not as a group when they occurred within the same lymph node region. It is possible that although only one affected region may be present in a patient with a PCa recurrence, this region may contain a conglomerate tumor, thereby increasing the overall tumor burden. By stratifying our patients according to individual lesions, we tried to extrapolate the theoretical tumor volume more accurately. Recent clinical trials have demonstrated the clinical benefit of treating patients with this oligometastatic profile in terms of increased BCR-free survival and metastatic progression-free survival [27] [28].

Although the study by Rousseau *et al.* [21] had a larger sample size, the characteristics of the patients they included were like those included in this present study, especially in terms of the lesion distribution in patients with ≤ 5 lesions. In addition, Giesel *et al.* [22] presented similar levels of bone recurrence after ^{18}F -DCFPyL PSMA PET-CT as we report here. When we analyzed our subgroups in greater detail, the patients that had undergone irradiation presented more progressions, which ties in with the fact that the characteristics of these patients (e.g., ISUP 4 - 5, higher mean age) tended to be associated with a poorer prognosis. The patients in our sample were hormone-sensitive, except for one who was castration-resistant. Many studies published in the academic literature have examined these two profiles [21], but in this current work, we wanted to focus on a single, more homogeneous group.

Our objective was to diagnose a subgroup of patients who presented a low disease burden that could be treated with ablative intention rather than exclusively with hormonal therapy. Thus, by using ^{18}F -DCFPyL PSMA we obtained a more precise diagnosis in 66.7% of our cohort, leading to a change in treatment in oligometastatic patients and reaffirming the data already described in the literature [21] [29]. This greater specificity in categorising patients allows us to intensify our therapeutic efforts and thus theoretically prolong progression-free survival and delay the initiation of systemic treatment. We identified a subgroup of patients with PSA < 0.5 ng/mL who presented lymph node or distant progression that would have been understaged and therefore undertreated had we not

performed an 18F-DCFPyL PSMA PET-CT. Indeed, there was a tendency towards significance ($p = 0.29$) among the patients who only underwent 18F-DCFPyL PSMA PET-CT imaging. The TITAN study [30] suggests that this diagnostic test will allow the early detection of patients with hormone-sensitive metastatic PCa, allowing them to start timely treatment with second-generation hormone therapy, thereby directly impacting their overall survival.

Regarding the limitations of our study, first, this was a retrospective, descriptive, observational study with a small sample size. The fact that most, but not all, of the patients we included had previously undergone CITs (75%) reduced the value of our data analysis because there were no results to compare our data to in 25% of the cases. As an initial diagnostic test, 18F-DCFPyL PSMA PET-CT may involve a bias, however, this test may be useful when faced with a clinical picture in which there is BCR in the absence of correlation with conventional CITs along with the clinical deterioration of the patient, which therefore corresponds to a decline in quality of life. Confirmation of the diagnostic benefit of this imaging test in patients with BCR will require the development of randomized studies to compare this procedure with CITs and to quantify the real impact of changing patient staging based on 18F-DCFPyL PSMA PET-CT imaging in terms of BCR-free survival and overall survival. This work, and other similar studies are currently being planned in the hospital centers involved in this work.

5. Conclusion

18F-DCFPyL PSMA PET-CT could lead to a change in the management of patients with BCR. This test promotes the early diagnosis of oligometastatic relapses, especially in patients with PSA levels < 0.5 ng/mL, allowing physicians to make better therapeutic decisions for these patients.

Compliance with Ethical Standards

The research ethics committee approved the study at both hospitals.

Research with Human and/or Animal Participants

The authors declare that no animal research was carried out.

Conflicts of Interest

All the listed authors gave their approval for the submission of the article; none of them have any potential conflicts of interest associated with this research.

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Bilateral Ectopic Kidneys Presenting as Lower Abdominal Pain

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Abstract

Background: Bilateral Ectopic Kidney is uncommon and usually diagnosed during a routine medical checkup. It could be misdiagnosed as an abdominopelvic mass. In-depth knowledge of its presentation will aid in its management. A poor anatomical relation of the kidneys with other abdominopelvic organs could lead to renal complications and surgical errors. This is of gynaecological importance and worthy of discussion for a lady of her reproductive age. **Case presentation:** A 20-year-old nulliparous lady of African descent presented with a long-standing history of dull lower abdominal pain. The pain has been intermittent and occasionally associated with a sensation of movement in the lower abdomen. She has a regular and normal menstrual cycle and has no lower urinary tract symptoms. Physical examination was unremarkable with intact secondary sexual characteristics. The abdomen was soft, non-tender and without any organomegaly. Abdominal ultrasonography, renal pyelogram and urinalysis were carried out after her consent was sought in accordance with the institution's protocol. Urine analysis was normal and culture was negative. However further imaging revealed a bilateral pelvic ectopic kidney. **Conclusion:** Most of the cases reported are usually unilateral ectopic kidneys. It is, therefore, our belief that this information will be useful to medical practitioners such as surgeons, urologists, radiologists and gynaecologists. Such a diagnosis will enable clinicians to follow up with the client and preserve the renal function whiles preventing iatrogenic injuries during surgical procedures.

Keywords

Case Report, Bilateral Ectopic Kidney, Lower Abdominal Pain, Abdominal Ultrasonography

1. Introduction

Embryologically, the kidneys develop in the pelvis and migrate to their normal anatomical position in the upper abdomen. As a result, the kidney is often associated with various anomalies such as shape, position, size and rotation. Anomalies of the kidneys are mostly asymptomatic and the specific clinical findings on the ectopic kidney are often absent. However, clinical recognition is estimated to be only 1 in 10,000 patients generally [1] and even rare in some populations [2]. The case of bilateral ectopic kidneys worldwide is uncommon and is rarely reported.

Ectopic kidney is normally seen as incidental findings during urological physical examination or diagnostic procedures such as Ultrasonography, Computed Tomography (CT) scan, Intravenous Urography (IVU) and Magnetic Resonance Imaging (MRI). Even though ectopic kidney could be located at the thoracic, iliac fossa and lumbar regions [3], it is commonly seen in the pelvic region [4]. Pelvic ectopic kidney sometimes confuses inexperienced sonographers and surgeons and could be mistaken as the pelvic tumour. Ectopic kidney has always been linked with other abnormalities such as agenesis of the contralateral kidney, vascular malformation and genital anomalies [5] [6]. Hydronephrosis, urinary tract infection and renal lithiasis are complications associated with the ectopic kidney [1]. This case report is intended to highlight the rare incidence of bilateral renal ectopia in a patient with recurrent lower abdominal pain and to raise clinician awareness of this condition.

2. Case Presentation

A 20-year-old nulliparous otherwise healthy lady presented with long-standing dull intermittent lower abdominal pain. She has no lower urinary tract symptoms neither was there any association with her menstrual cycle nor her bowel movement. She had no past medical history of significance. With the exception of the mother who was hypertensive well controlled on a single agent, the rest of the family history was unremarkable.

Her vital signs reveal a blood pressure of 100/60mmhg, pulse 68 beats/minute a body mass index of 26.6. Abdomen was soft, non-tender, and without any organomegaly and rest of physical examination was essentially normal. Urine microscopy, culture and sensitivity test; and serum beta human chorionic gonadotropin were all negative. Incidentally, the ultrasound examination revealed bilateral ectopic kidneys with both renal fossae empty. The left kidney was found in the umbilical region adjacent to the umbilicus and the right was located at the right iliac fossa, an indication of bilateral kidney ectopia. The following are the ultrasound scan images compiled (**Figures 1-4**). Both kidneys measured approximately 9×4 cm and there was no hydronephrosis or calculi detected. Ejection of urine from ureters into the urinary bladder was demonstrated during the pelvic ultrasound indicating that at least a unit of the kidneys is functioning. Reproductive organs were present and normal without any abnormality detected. Her serum urea, creatinine and electrolytes levels were within normal limits.

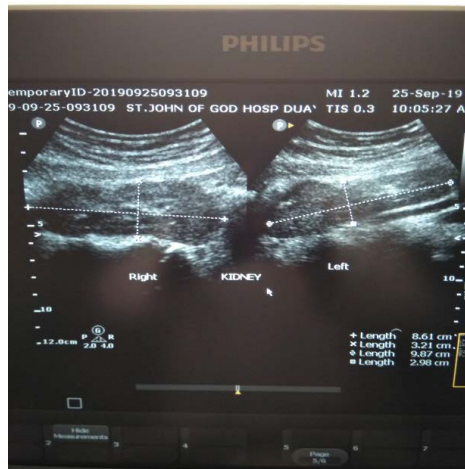


Figure 1. Shows longitudinal view of right and left kidneys located at the right iliac fossa and umbilical region respectively.

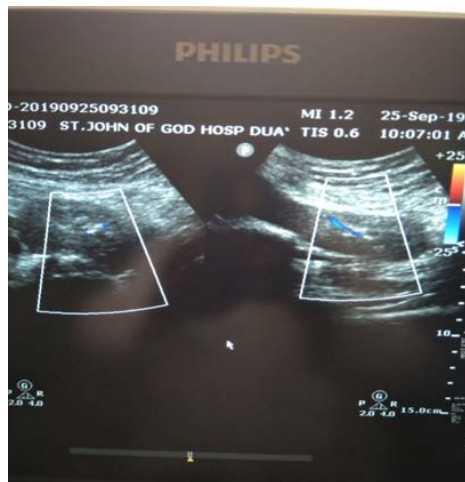


Figure 2. Shows transverse view of right and left kidneys located at the right iliac fossa and umbilical region respectively.

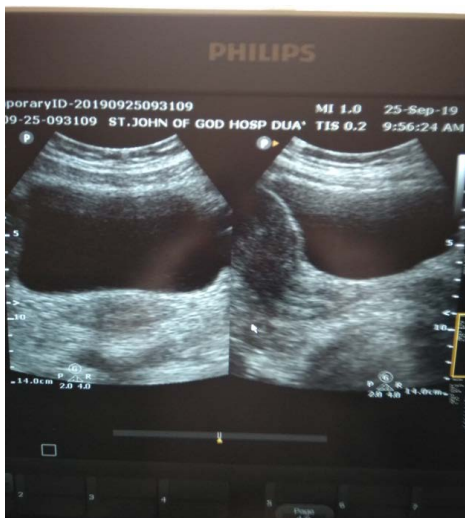


Figure 3. Shows full urinary bladder indicating normal ejection of urine.

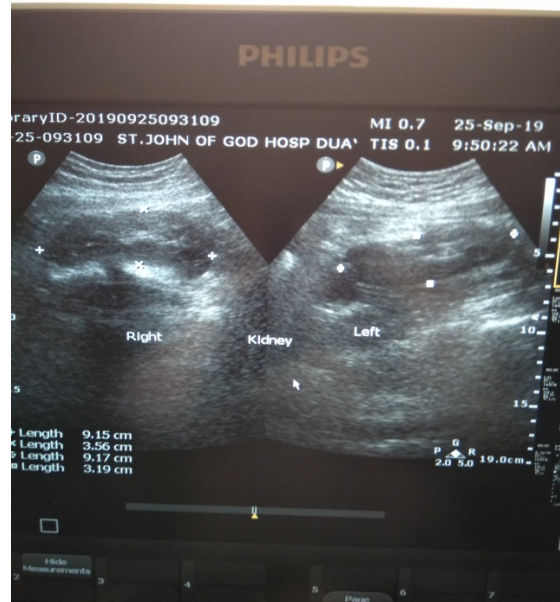


Figure 4. Indicates both ectopic kidneys.

We proceeded to assess individual kidney function by an Intravenous Urography (IVU). Images were obtained from the IVU as shown in **Figures 5-9**. An adequate preparation was made on the client abdomen prior to examination (**Figure 5**). The study showed a prompt nephrogram and excretory phases on the left kidney (**Figure 7** and **Figure 8**) and associated malrotation as evident from the anterior position of the drainage system. However, there was absent nephrogram and excretion of contrast material on the right. The prone view (**Figure 9**) could not demonstrate the right kidney and ureter. These findings were suggestive of a solitary functioning (left) kidney in a bilateral ectopic kidney. The cause of the non-functioning right kidney was not apparent from our studies and due to limitations both financial and logistics in a third world district hospital, a Dimercaptosuccinic acid (DMSA) or other form of radionuclide imaging could not be done. Client did not require any intervention and is currently on six monthly follow up with repeats abdominopelvic ultrasound. Efforts have been made to ensure that she maintains healthy lifestyle in order to preserve function of the solitary kidney and also to avoid nephrotoxic medications. The client has since been enrolled into the urology clinic for this routine follow up and efforts are being made to screen her parents and other siblings for possible renal anomalies. The recurrent abdominal pain is managed with acetaminophen, warm compress at the abdomen and regular exercise regimen.

3. Discussion

The kidneys are paired organs located at the retroperitoneum with the right kidney usually lower than the left for the sake of the bulk of the liver. Each kidney is approximately three vertebrae in length. This can be used to gauge any changes in size when interpreting radiographs. Each kidney moves in a vertical



Figure 5. Indicates control film.



Figure 6. Shows immediate film taken.

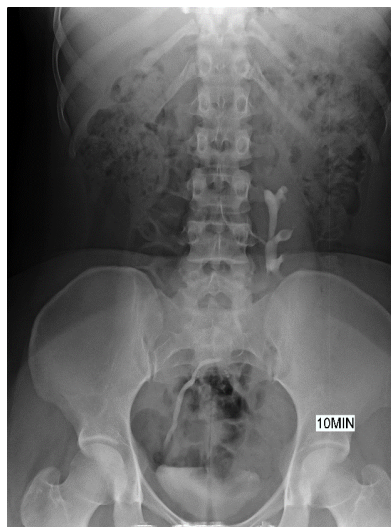


Figure 7. Shows 10 min film with compression.



Figure 8. Shows 20 min film with release.

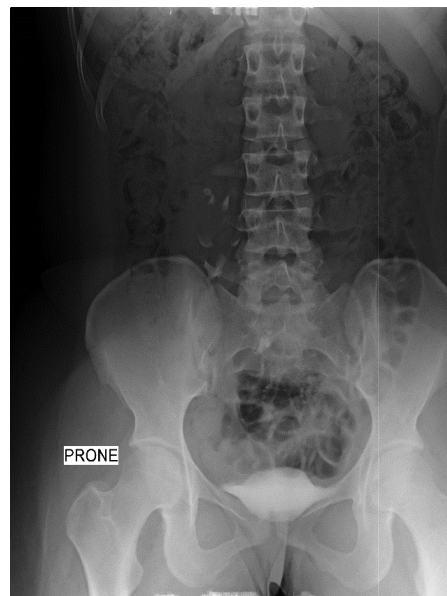


Figure 9. Indicates prone film.

range of 2 cm during the full respiratory excursion of the diaphragm [7]. The Left kidney which is usually located at T11-T12 has the upper pole overlies the eleventh rib was situated anterior at the umbilical region almost sitting on the urinary bladder.

An ectopic kidney is classified as unilateral or bilateral when one or both kidneys are misplaced respectively. It could be classified as thoracic, abdominal, lumbar or pelvic kidney based on its anatomical location. The thoracic cavity and the bilateral ectopic kidney are very uncommon hence are rarely reported [8]. Pelvic ectopic kidney is seen in an estimated 1 of 2100 to 3000 necropsies [9]. Nephroptotic or floating kidneys could be misdiagnosed as ectopic kidneys.

It occurs more often in very thin people whose adipose capsule or renal fascia is deficient and can predispose to hydronephrosis due to kinking of the ureter.

Congenital abnormalities of the kidneys can arise as a result of abnormal development of the ureteral bud and a defect in metanephric tissue during embryogenesis. This can be due to maternally related ailments, genetic anomalies and teratogenicity [5]. Most congenital renal abnormalities are compatible with life and are asymptomatic. However, complications such as hydronephrosis, calculi disease, recurrent pyelonephritis and chronic pain may prompt clinical evaluation of underlying renal abnormality [6] [10].

Most renal anomalies are detected incidentally, usually during evaluation for an abdominopelvic-related complaint [11]. The abnormal relation with other intra-abdominal and pelvic organs may also cause symptoms related to the organ such as urgency due to compression of the urinary bladder and foetal growth restriction from compression of a gravid by an ectopic pelvic kidney. It is also important for surgeons to know of such anatomical anomaly before it is mistaken for abnormal growth or tumour and more importantly prevent iatrogenic injuries to the urinary tract.

In the case under consideration, both kidneys are in ectopic sites, the abdomen and the pelvis with the left abdominal kidney also having malrotation. As under ascent is more common than over-ascent, ectopic kidneys are more commonly found in the pelvis or lower abdomen [7].

Among earlier researchers, few have reported on bilateral ectopic kidneys, their relations with other structures and existence with other morbidities and anomalies. The cases reported vary in representation. In Sudan [12] reported on bilateral pelvic kidneys with upper pole fusion and malrotation on a 36-year-old female Sudanese patient. The patient presented with a long history of recurrent urinary tract infections unresponsive to antibiotics. They observed that a recurrent urinary tract infection without a known cause may be suggestive of renal anomaly and should be investigated expediently. In Nigeria [13] also reported on a 42-year-old male who presented with bilateral, fused pelvic, ectopic, laterally rotated kidneys with acute unilateral flank pain. This was like our case was incidentally discovered with the similar presentation but sex and age difference.

Also, [14] reported on a case with bilateral ectopic kidney and vascular anomaly that is associated with hypertension and renal dysfunction in a 67-year-old woman. A report on ureteropelvic junction obstruction coexisting with renal calculi in children was demonstrated [15]. In another vein, [16] reported on rare comorbidities of crossed fused renal ectopia, Thrombocytopenia and Absent Radius (TAR) syndrome.

In the present case report, the bilateral ectopic kidney is incidentally seen in a young lady in her fertility age. Further diagnostic measures have to be carried out and the needed treatment rendered to avert potential complications.

This case report confirms how subtle renal anatomical abnormality could be present. It is imperative that thorough clinical assessment and basic imaging are carried out even in resource-stricken third-world countries in order to diagnose

such anatomical abnormalities. This will assist in risk stratification of the client and measures can be instituted to better preserve renal function.

Declaration

Ethics Approval and Consent to Participate

Ethical approval is not applicable but the client willingly consented to participate in this case report.

Consent for Publication

The client provided written informed consent for the publication of this report and it is available on request.

Availability of Data and Material

All figures and data used during the current case report are provided in a separate document.

Authors' Contributions

BA and TB: Managed the patient, reported the case, collected background information, and compiled the manuscript for publicity. **EOS:** Provided clinical advice and reviewed the report. All authors have read and approved the manuscript as its true state.

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We appreciate the effort of our client who unreservedly made herself available for this case report

Conflicts of Interest

We declare that we have no conflicts of interest.

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List of Abbreviations

BEK—Bilateral Ectopic kidney

CT—Computed Tomography

IVU—Intravenous Urography

MRI—Magnetic Resonance Imaging

Calcification of the Renal Vein and Inferior Vena Cava on a Renal Tumor: An Exceptional Case

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Abstract

Background: A thrombus of the inferior vena cava and renal vein makes the management of renal cancer more difficult. **Aim:** The aim is to highlight and discuss the management of a case of renal cancer with an unusual thrombus in our context. **Case Presentation:** We report the case of a 49-year-old female with left kidney cancer, complicated by a calcified thrombus of the renal vein and inferior vena cava. A calcification of renal vein and vena cava was discovered during surgery, even though the diagnosis prior to surgery was a renal tumor with partial thrombus of the IVC. We performed a thrombectomy and left nephrectomy. The post-operative course was marked by the death of the patient a month later. **Conclusion:** Renal vein and inferior vena cava (IVC) calcifications are uncommon. Preoperative diagnosis is difficult but guided by medical imaging. Renal cancer is one of the causes. A thrombus or calcification of the vena cava worsens the prognosis of cancer.

Keywords

Renal Cell Carcinoma, Inferior Vena Cava Thrombus, Thrombectomy

1. Introduction

Most renal tumors are cancers. Renal cancer is the third urological cancer after prostate and bladder and represents about 3% of adult cancer. Due to the anatomic position of the kidney, renal cancer has a long latency, and the discovery is done luckily during investigations for another reason. Most of the time it is done at a metastatic stage. During its progression, cancer will cross the kidney capsule,

invade peri renal fat and spread into lymph nodes, renal vein and inferior vena cava (IVC). A thrombus of the IVC during the course of renal cancer is infrequent (2 - 10%). The occurrence of calcification of the inferior vena cava (IVC) with a kidney tumor is more difficult to find [1] [2]. Few cases have been reported in literacy. In Côte d'Ivoire, no case has been previously reported. We are presenting the case of a patient whose IVC calcification was suspected by the computed tomography scan and confirmed during the surgery. The aim of this report was to emphasize the morbidity and mortality and difficult management of such cases in the underequipped area. Informed consent was obtained from the family to report this case.

2. Case Report

The patient was a 49 years old female, known to be hypertensive and was being followed. She came to us with an abdominal mass. The onset of the signs occurred about 4 months ago, with a progressive worsening left lumbar pain. It was described as a permanent constriction, with a paroxysmal episode, without any triggering factor or objective sedation. There was no hematuria or burning of the urine. She consulted a community health centre where the diagnosis of lumbar osteoarthritis was made, with the introduction of analgesic treatment. Given the persistence of the signs, she consulted a private care unit where scanographic and biological explorations were performed. She was then referred to us for care.

She had a major history of undocumented exploratory laparotomy. There was no notion of previous nephropathy or exposure to hydrocarbons. We also noted the absence of personal or familial venous thromboembolic disease. She had 4 children. She was menopausal without any notion of metrorrhagia.

On admission, she was vigilant, with a WHO score of 1. The conjunctiva were stained, there was no edema of the lower limbs. Blood pressure was 140/100 mmHg with a pulse rate of 79/minute. There was a median laparotomy scar. The urogenital examination showed a left lumbar curvature with lumbar contact and kidney swelling. The rest of examination was unremarkable. We concluded that it was a left renal tumor syndrome.

Computed tomography scan coupled with study of the kidney vessels objectified a hypervascular tumor of the lower pole of the left kidney with thrombus of the left renal vein and IVC. The upper pole of the thrombus was calcified and its upper level was located at the junction of the suprahepatic veins, corresponding to a level III of the MAYO classification. In addition, a dilatated left gonadal vein was noted (**Figure 1** and **Figure 2**).

An anticoagulant treatment with low-molecular-weight heparin at a curative dose was instituted preoperatively for 5 days. Our surgical attitude was sequenced as follows. We approached this tumor with a xyphopubic laparotomy. After detachment of the right Toldt fascia (**Figure 3**), the IVC was exposed from the confluence of the iliac veins to the subhepatic portion of the renal vessels.

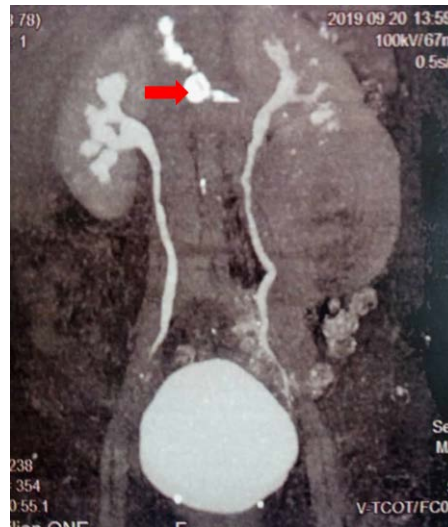


Figure 1. Computed tomography showing calcification in the IVC.



Figure 2. Computed tomography of the renal vessels showing, (a) A hypervascular lower pole tumor of the left kidney; (b) A dilatation of the left gonadal vein.

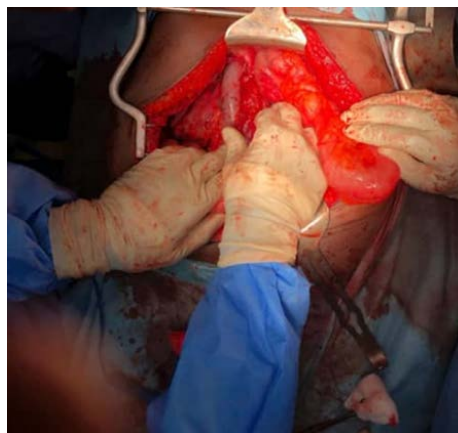


Figure 3. Right total fascia detachment.

Medical loops were placed around the sub-renal and supra-renal portion of the IVC respectively, but also on the right and left renal veins. After clamping the medical loops (subrenal IVC, right renal vein and then suprarenal IVC) we performed a cavotomy with a cold scalpel and extracted the calcification (**Figure 4**). The suture of the IVC was performed with 5-0 non-adsorbable suture. We then did the extended left nephrectomy (**Figure 5**).

3. Discussion

The presence of a renal tumor can usually be correlated with a vena cava thrombus. In our context, CT scan is systematically requested in the assessment of operability of kidney tumors. This is an unprecedented situation as no similar case has been reported in Côte d'Ivoire.

Renal cancer with tumor thrombus is uncommon (2% - 10%). The largest cohort in Europe was reported by Manceau and involved 97 patients. This team has 30 years of experience in surgery in renal cancer with thrombus. Its mortality and morbidity were significant [2]. The first observations of calcification of IVC thrombus were described by Morgagni, on autopsy series, about 1769. These early descriptions were made on abdominal images. The classic appearance is a bullet-shaped calcification [3].



Figure 4. Calcification of the IVC.



Figure 5. Tumor of the inferior pole of the left kidney.

The surgical management of this type of cancer implies removal of the thrombus. It is therefore important to locate the exact level of the top of the thrombus. For this purpose, the Mayo classification is useful to assess the level of the thrombus. According to this classification, there are five levels. Level 0, thrombus extending to the renal vein only; level I, thrombus extending into the IVC to no more than 2 cm above the renal vein; level II, thrombus extending into the IVC to more than 2 cm above the renal vein but not to the hepatic vein; level III, thrombus extending into the IVC to above the hepatic vein but not to the diaphragm; and level IV, thrombus extending into the supradiaphragmatic IVC or right atrium.

In our patient, the IVC thrombus was suspected on the computed tomography scan. The hyperdensity of the upper pole of this thrombus made us doubt the real nature. It was a level III thrombus according to the Mayo classification (**Figure 6**) [4]. The location of the top of the thrombus is so important that it may be necessary to use MRI for that.

There is no general consensus or guidelines for the treatment of this condition. In general, long-term anticoagulation has been recommended for patients with symptoms of pulmonary embolism or systemic embolization [5]. In our case, the anticoagulant treatment was started immediately preoperatively at a curative dose on the instruction of the cardiologist and stopped 48 hours before the surgical procedure.

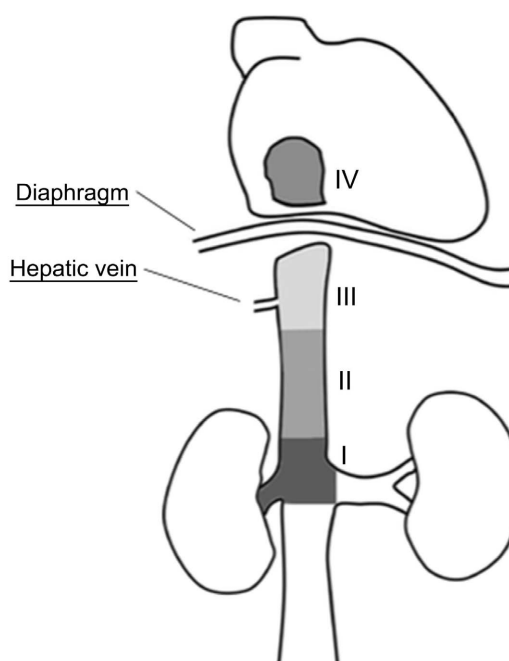


Figure 6. Classification of tumor thrombus level according to the Mayo staging system. Level 0, thrombus extending to the renal vein only; level I, thrombus extending into the IVC to no more than 2 cm above the renal vein; level II, thrombus extending into the IVC to more than 2 cm above the renal vein but not to the hepatic vein; level III, thrombus extending into the IVC to above the hepatic vein but not to the diaphragm; and level IV, thrombus extending into the supradiaphragmatic IVC or right atrium [4].

The tumor can be approached via a different way. It can be a flank, sub-costal or midline incision. We performed an abdominal midline incision for a wide access to the kidney and the IVC. Control of the IVC is the first step in this surgical management to avoid inadvertent migration. We did not have to mobilize the liver. After venous control and cavotomy, thrombectomy with dissecting forceps was easy due to the solid character of the thrombus. It is important to put the clamp on the IVC above the top of the calcification to avoid any wound to the IVC and have effective vascular control. The calcification was addressed electively to reduce blood loss. Opening the IVC just as needed allows a quick suture after removal of the calcification and consequently a quick removal of the vascular clamps.

Aggressive surgical management for this condition is proposed by some authors. It allows a possible cure. This surgery is clearly difficult, and the outcomes can be discouraging regarding the percentage of mortality and morbidity. But, doing nothing will worsen the outcomes. In Hatakeyama's study, the perioperative mortality rate in patients with ICV thrombus was 6.7%. Two patients (6%) developed perioperative complications of Clavien grade \geq III, and there were no deaths within one month of surgery. In patients who received surgical management, the 5-year survival rate was 78% [4]. Median survival time was significantly longer in patients who had surgical management [6] [7] [8]. These different authors demonstrate that this surgery is possible with good results. A more recent study showed a poor prognosis of renal cancer with IVC thrombus. There was a link between surgical complications and hospital stay [2]. It is important to give clear details of the case to the patient and his family. The definitive choice is guided by the patient's choice and the multidisciplinary team's decision. If a surgical option is selected, it has to be well prepared. In that case, neoadjuvant therapy using molecular-targeting agents is useful to improve the results [4].

4. Conclusion

The prognosis of kidney tumor with IVC thrombus is poor and associated calcification remains exceptional. The prognosis is poor, however, some studies have demonstrated an improvement in the prognosis by surgical treatment.

Conflicts of Interest

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

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Clinical Anatomopathological and Therapeutic Aspects of Buschke-Lowenstein Tumor

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Abstract

Introduction: Buschke Lowenstein Tumor (BLT) is a tumor, belonging to the group of verrucous carcinomas. It is endowed with an unpredictable potential of recurrence and degeneration. The aim of the work is to present the anatomical and therapeutic characteristics of BLT at the University Hospital of National Reference of N'Djamena in Chad. **Patients and Method:** Prospective descriptive study of 13 patients with BLT, from May 2009 to April 2019 in the department of urology was included. The patients more than 15, carriers of TBL located at: external genitalia, perineum and anal margin whose clinical, paraclinical assessment allowed the diagnosis of BLT, management and follow-up at the said service. Respect for the patient's identity and consent, the patient's consent is obtained and the anonymity of the photographs is observed. **Result:** A total of 13 patients had BLT, 11 males and 2 females. The average age of the patients was 32.5 years. The lesions were cauliflower-like and located on the vulva (n = 2), the penis, the perineum, the anorectal region in men (n = 11). Serology was positive for: HIV (n = 3), chlamydia (n = 4). The management was surgical by cauterization and excision. Cystoscopy and rectoscope were normal. The cure was obtained in all patients. Two patients had a recurrence at 5 months requiring a second successful cure. **Conclusion:** BLT is a frequent pathology in the urology department of the University Hospital of National Reference of N'Djamena in Chad. The surgical treatment by "cauterization exeresis" gives a better treatment.

Keywords

Condyloma, Degeneration, Cauliflower, Cauterization-Exeresis, N'Djamena,

Chad

1. Introduction

Buschke Lowenstein Tumor (BLT), also known as giant condyloma acuminata, is a rare tumor belonging to the verrucous carcinoma group with unpredictable recurrence and degeneration potential [1] [2] [3]. Infection usually occurs through sexual contact in patients with decreased immunity or increased estrogen receptors. It can also be transmitted through linen and other soiled materials due to the resistance of the virus in environmental conditions. The lesion was first described by Buschke in 1925 [4]. The lesion is mainly located in the external genitalia, the perineum and the anorectal region in the form of a cauliflower-like, sometimes ulcerated or suppurated tumor. The causative agent is papillomavirus of which serotypes 1, 6, 16 and 18 are potentially carcinogenic [5] [6]. Surgical treatment remains effective in spite of the new therapeutic arsenal, notably: CO₂ laser, immunotherapy. We report 13 cases of Buschke Lowenstein Tumor treated surgically in the urology department of the University Hospital of N'Djamena in Chad.

2. Patients and Method

This was a prospective descriptive study from May 2009 to April 2019 in the department of urology on patients with a tumor located in the sphere of external genitalia and anal margin. Patients over 15 years of age with a tumor located in the external genitalia, perineum and anal margin were included. The clinical and paraclinical workup allowed the diagnosis of Buschke Lowenstein Tumor, which was managed and followed up at the department. The variables were of several kinds. Clinical variables included age, sex, marital status, sexual habits, number of partners, location of the lesion, appearance of the lesion, psychological impact, and history. Paraclinical variables included serology (HIV, Chlamydia and syphilis), blood glucose, creatinine, cyto bacteriological examination of urine, cystoscopy and rectoscopy, and histology of the surgical specimen. The therapeutic and evolutionary variables included: surgery by “cauterization of the exeresis”, the use of the urethrovesical probe after the operation (simple or complicated), recurrence, and cure. The consent of the patients was obtained before including them in the study as well as their agreement to use the photographs anonymously and for scientific purposes.

3. Results

At the end of the study, 13 patients had met the eligibility criteria. They were 11 men and 2 women. The average age was 32.53 years with extremes of 60 and 19 years. The lesions were cauliflower-like (n = 8) and papillary with sessile base (n = 5) (Figure 1). The lesions were located on the vulva (n = 2) in women in a fat

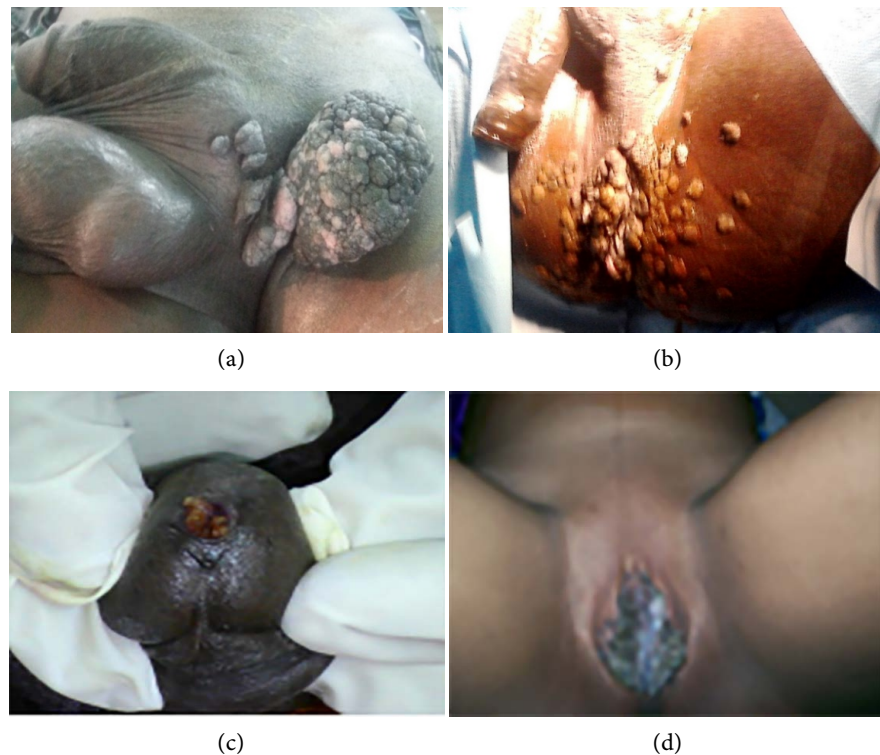


Figure 1. Different clinical aspects of Buschke Lowenstein tumor.

state and in men, on the urethral meatus ($n = 5$), on the external genitalia, perineum and anal margin ($n = 6$). The average duration between the first observation of the lesion by the patient and the first consultation was 2 years and 8 months with extremes of 6 years and 2 months. The consultation was motivated by the notion of pruritus ($n = 13$), pain during sexual intercourse ($n = 7$), urinary burning ($n = 8$), worsening of the lesion ($n = 9$) and fear of a skin “cancer” ($n = 5$). Serology was positive for: HIV ($n = 3$), syphilis ($n = 1$) and chlamydia ($n = 4$). The Cyto-Bacteriological Examination of the Urines had allowed objectifying an *Escherichia Coli* infection in 4 cases. Urethroscopy and rectoscopy, which were performed in all patients, allowed to rule out other localizations of the lesion, notably bladder and rectal. Speculum examination in the 2 women invalidated the presence of visible lesions in the vaginal cavity and the uterine cervix. The treatment was surgical (**Figure 2**) by “cauterization-exeresis” in all patients with a fatty dressing separating the 2 lips of the vulva in the female patients. A ureterovesical catheter was necessary for 7 days in the 5 patients with lesions located in the urethral meatus and in the 2 women with vulvar lesions. The operative parts were sent for histological analysis, the results of which all concluded to be a Buschke Lowenstein tumor (**Figure 3**). The postoperative course was simple. Two cases of recurrence at 5 months were successfully treated.

4. Discussion

For Weaver, Human Papilloma Virus (HPV) infection reaches 80% of the population over 50 years of age, but only 1% of women will develop condylomata. For

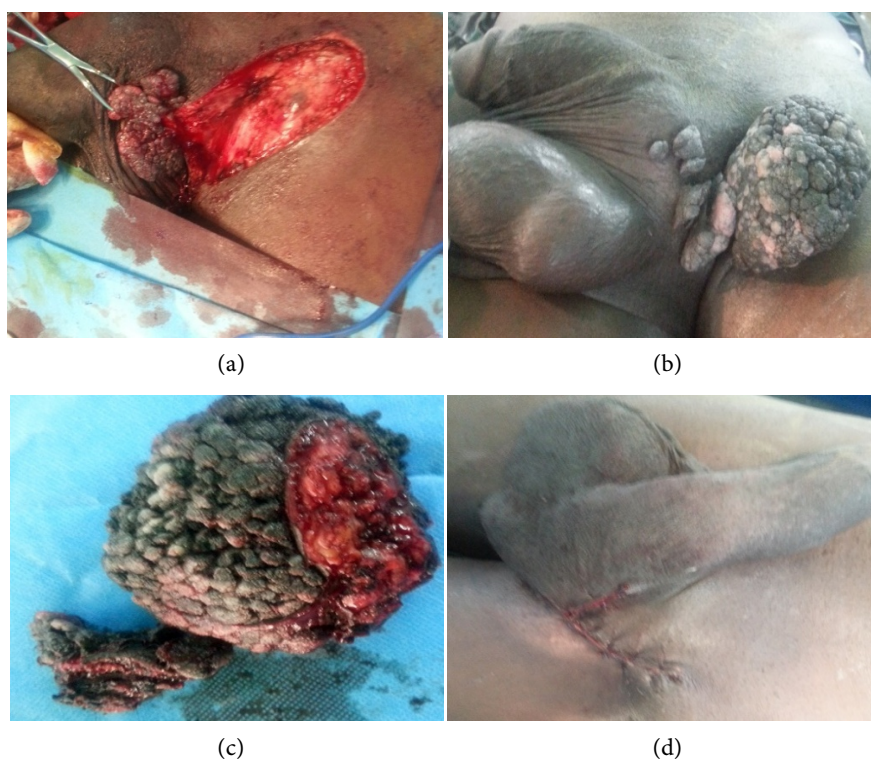


Figure 2. Surgical images.

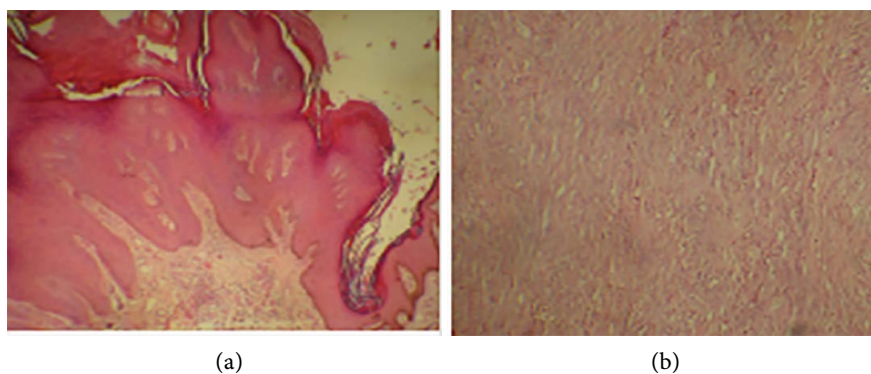


Figure 3. Anatomopathological images.

El Mejjad only 0.1% of infected women will develop Buschke Lowenstein Tumor. On the other hand, 80% of the genitally active adult population has HPV infection, but only 1% will develop the disease [5] [7]. Serotypes 6, 11, 16 and 18 are the most frequent, however, 16 is more oncogenic compared to the others and the uterine cervical mucosa, which is known to be mechanically and immunologically fragile, seems to be the preferred site for cancerous lesions in women. Multiple risk factors and comorbidity have been reported in the literature, including HIV infection, syphilis, chlamydia, pregnancy, promiscuity, and genital candidiasis. Only three risk factors have been identified: pregnancy in two patients, positive HIV status in another, and a stay in a prison environment. According to Zhenhui [8], transmission is mainly by sexual contact [1] [9] [10], but

also by linen, gloves and other soiled materials. Mother-to-child transmission can occur in utero through the placenta or during vaginal delivery, justifying the need to examine at birth any newborn child of a mother with a Buschke Lowenstein Tumor lesion. Caesarean section is no longer appropriate in pregnant women with Buschke Lowenstein Tumor as a protective measure for the newborn.

In both patients, the tumor was located in the vulva, had a soft consistency, a sessile base, and a surface finely bristled with bangs about 3 to 8 mm high and 2 mm in diameter, giving a cauliflower-like appearance. This cauliflower-like appearance, also described by many authors [11] [12], is psychologically traumatic for the two young pregnant women, aged 18 and 27 years respectively, justifying the urgency of they do not even recognize their sex anymore because of the monstrousness of the lesion. They do not even recognize their sex anymore because of the monstrosity of the lesion. Their main objective is to be cured at all costs before delivery so as not to be humiliated by presenting a vulva of such appearance to the midwives during delivery. In 5 male patients, the tumor, obviously inflammatory, was located in the navicular fossa, with irregularly shaped bangs that emanated like a bouquet of flowers at the urethral meatus. It should be noted that this location makes sexual intercourse difficult because of the trauma and urethrorrhagia that it causes, motivating the consultation and the urgency of the management. As for the 6 patients whose cauliflower lesions were located in the external genitalia, the perineum and the anal margin, apart from the monstrosity of the lesion, it was the fear of a cancerous degeneration of the tumour that motivated their consultation. One of these patients was referred from a prison environment where he had been for 2 years. The promiscuity in the prisons of the place undoubtedly explains the contamination and must be considered as an indicator of decreased immunity.

The natural evolution can be towards; a local invasion, a recurrence or a malignant transformation. For El Mejjad this malignant transformation can reach 8.5% to 23.8% in the form of a squamous cell carcinoma. Recurrence, which is always local, single or multiple, poses therapeutic problems, particularly when the excision is limited or incomplete. Only 2 patients presented recurrence at 5 months, justifying a second surgical cure with success. In order to reduce the frequency of recurrence, we decided to perform urethrocystoscopy, rectoscopy and speculum examination to look for other hidden locations that could involve the proximal urethra, bladder, vaginal cavity, cervix and rectum. The absence of localization at these sites explains the good result obtained, in particular the low frequency of recurrence, which was successfully managed at the second surgical cure.

Surgical treatment by “cauterization-exeresis”, which we prefer following the example of other authors [1] [9] [11], is associated with precise procedures, in particular: systematic use of a urethrovesical probe to prevent stenosis of the urethral meatus when the localization is meatic and fatty dressings separating

the edges of the vulva to prevent vulvar synechiae.

Healing is not only physical, but also psychological and even sexual: especially for pregnant patients who are waiting in depression and anxiety for childbirth, for urethral tumor carriers who need to return to normal sexual life and for those who live in fear of cancerous degeneration to be reassured of the benignity of the lesion by the result of the histology

The diagnosis is often based on the clinic for an experienced clinician who easily rules out condyloma planus from secondary syphilis. However, histology is necessary to avoid misdiagnosis of a potential malignant transformation.

5. Conclusion

Giant condyloma acuminata or Buschke Lowenstein tumor remains a frequent pathology in the urology department of the CHU-RN of N'Djamena in Chad. Pregnant women with this tumor suffer from nightmarish psychological trauma. Sexual intercourse becomes traumatic for men with a BLT located in the urethral meatus. The reference treatment is surgical, with the aim of obtaining physical and psychological recovery and the resumption of normal sexual activity.

Conflicts of Interest

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

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Endoscopic Internal Urethrotomy (EIU): Results of a Dynamic Study at the Urology-Andrology Department of the University Hospital Center (UHC) of Conakry

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Abstract

Introduction: Endoscopic internal urethrotomy (EIU) is a technique that consists of an incision of the stenosed urethra under visual control. Its indication is widespread since the first description in 1971 by Sachse. The objective was to analyze the results of EIU in the treatment of urethral stenosis (US) at the Andro-Urology Department of the UHC of Conakry. **Methodology:** It is a prospective descriptive study, lasting 18 months (January 2016-30 June 2017). It involved 102 patients. The variables were: age, etiology of US, type of catheter, duration of catheter wear and recurrences. After a 12-month follow-up, our results were considered good in the absence of recurrences. **Results:** The average age was 54.25 years with the extremes comprising between 16 and 96 years. The main reasons for medical checkup were chronic urine retention at 58.82%. Etiology infection was the most frequent with a ratio of 81.37%, while *Escherichia coli* was found at 51.29%. US was bulbar (71.57%), unique (67.64%) and less than 1 cm (60.78%). Surgical complication occurred with 9 patients (8.82%) with urethrorrhagia and the external genital organs infiltration in 4 cases. Results were good for 77 patients (75.49%). Stenosis post infection, long and multiple stenoses, urethral catheterization with latex catheter and urethral catheterization of more than 4 days were strongly associated with the recurrence occurrence. **Conclusion:** The EIU is a minimally invasive surgical technique that offers good results.

Keywords

Urethral, Stenoses, Endoscopic, Urethrotomy, Conakry

1. Introduction

Endoscopic Urethrotomy (EIU) is an endoscopic surgical technique indicated in the treatment of urethral strictures (US) which consists of the midday incision of the entire thickness of the narrowed urethral wall using a cold blade, under-eye control. This technique was first described by Sachse in 1971 and reported an 80% success rate in 1974 [1]. US is the second cause of hospitalization in our department after prostate tumors and EIU is the first-line indication in its management.

The EIU was introduced into our service in 1987 with the team of Professor Jean DeLeval from the University of Liege in Belgium. The 1st study on the EIU carried out by Guirassy S *et al.* [2] between 1991 and 1997 reported a success rate of 51.80% after a one-year follow-up. Mortality was zero and morbidity was assessed at 9%. After two decades, our goal is to analyze the results and morbidity of this technique in the treatment of urethral strictures at the urology-andrology department of the University Hospital Center (UHC) of Conakry.

2. Patients and Method

This was a prospective study of the descriptive type, lasting 18 months from January 1, 2016 to June 30, 2017. It included 102 patients with urethral stricture who had undergone a EIU, then reviewed at 3, 6 and 12 months. The diagnosis of stenosis was suggested in any context of dysuria, associated with a history of sexually transmitted infections, trauma to the pelvis or urethra by bladder catheterization, and confirmed by retrograde urethrocytography with voiding images. The latter in addition to showing the narrowing, specified the number, location and extent.

EIU was performed on sterile urine through a full thickness incision of the stenosis at 12 o'clock using a cold blade (Wolf) with 0° optic Under visual control. The procedure was performed under locoregional anesthesia

After cystoscopy, upon removal of the urethrotome, an additional incision was sometimes necessary. A silicone or latex urethral catheter was left in place for 3 to 7 days.

The study variables were age, reason for consultation, etiology of US, results of cytobacteriological urine examen (CBUE), Retrograde urethrocytography and + Voiding cystography (RUC + VC), type of urethral catheter, length of time the urethral catheter was worn. postoperative and the occurrence of recurrences.

After a 12-month follow-up, our results were judged:

- ✓ Good: in the absence of recurrence;
- ✓ Bad: in the presence of a recurrence justifying another surgical procedure.

The data were collected from the files of patients operated for urethral stenosis, and from the registers of operative reports, on a pre-established survey sheet. Then, they were introduced and analyzed by Epi info in its version 7. We ensured the anonymity of the patients by encoding the data.

3. Results

Between January 2016 and June 2017, 162 cases of urethral strictures were hospitalized in our department, of which the EIU was the therapeutic indication in 62.96% (n = 102).

The average age was 54.25 years with extremes of 16 and 96 years. The 61 to 80 age groups were the most affected (**Figure 1**).

Patients consulted for chronic urine retention in 58.82% (n = 60), acute urine retention in 31.37% (n = 32), lower urinary tract symptoms (LUTS) in 6.86% (n = 7) and urethral stricture complicated by peri-urethritis in 2.94% (n = 3) (**Table 1**).

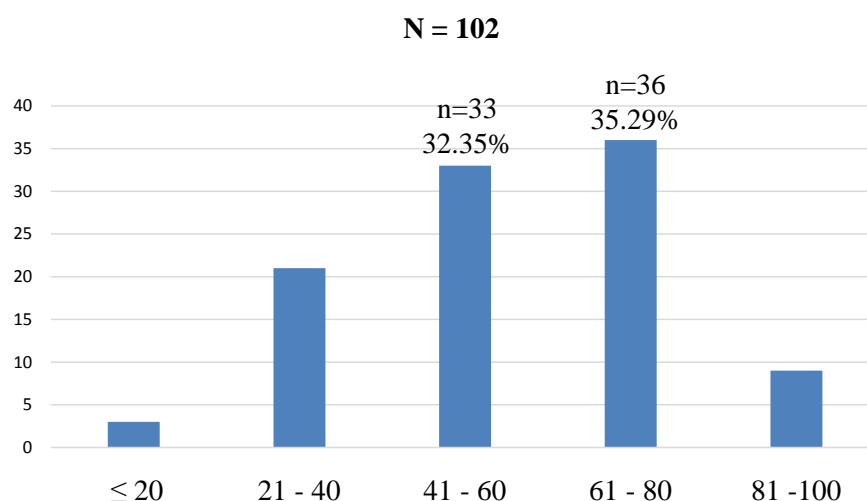


Figure 1. Distribution of patients by age (Average age: 54.25 years, range: 16 and 96 years).

Table 1. Distribution of patients according to clinical data.

clinical data	Effective	%
Reason for consultation		
Chronic retention of bladder urine	60	58.82
Acute retention of bladder urine	32	31.37
Lower urinary tract symptoms	7	6.86
urethral stricture complicated by periurethritis	3	2.94
Etiologies of urethral strictures		
infectious	83	81.37
iatrogenic	14	13.72
traumatic	5	4.90
characteristics of urethral strictures		
bulbar seat	73	71.57
single stenosis	69	67.64
stenosis length ≤ 1 cm	62	60.78

Etiologies of infectious origin were by far the most frequent with 81.37% of cases (n = 83) followed by iatrogenic in 13.72% (n = 14). Traumatic etiologies represented only 4.90% of cases (n = 5) (**Table 1**).

The strictures were complicated by urinal infection in 78 patients (76.47%). The most common germs were *Escherichia coli* in 51.29% (n = 40) followed by *Staphylococcus aureus* in 30.77% (n = 24). *Candida albicans* and *Enterobacter* were isolated in 7.70% (n = 6) and 5.12% (n = 4), respectively. *Streptococcus* and *Klebsiella* were each isolated in 2.56% (n = 2) (**Table 2**).

The US was of bulbar site in 71.57% (n = 73), unique in 67.64% (n = 69) and ≤ 1 cm of extent in 60.78% (n = 62) (**Table 1**).

The duration of postoperative drainage was ≤ 4 days in 82 patients (80.39%) and > 4 days in 20 others (19.61%). The rate of per- and post-operative complications was 8.82% (n = 9) due to urethrorrhagia (n = 5 cases) and infiltration of the external genital organs in 4 cases (**Table 3**).

One month after the catheter was removed, the voiding stream was good in 97.06% (n = 99) and weak with dysuria in 2.94% (n = 3). After 12 months of follow-up, the results of the EIU were good in 75.49% (n = 77) and bad (recurrence) in 24.51% (n = 25) (**Table 3**).

The highest recurrence rate was found with post-infectious urethral strictures in 25.30% (n = 21). Eighty-four percent (84%) of recurrences were of infectious origin and 12% (n = 3) of iatrogenic origin.

The Latex catheter was the postoperative drainage material in 37 patients. It was associated with recurrence in 32.43% (n = 12). The silicone probe was used in 65 patients and the recurrence rate was 20% (n = 13).

The recurrence rate went from 24.68% (19/82) when the lead time was ≤ 4 days to 30% (6/20) when the lead was > 4 days.

Depending on the extent, the recurrence rate increased from 30.64% (19/62) when the extent of US was ≤ 1 cm to 44.44% (4/9) when it was between 1.1 - 2 cm.

Based on the number of urethral strictures, the recurrence rate increased from 18.84% (13/69) when it was single to 30% (12/40) when it was multiple.

Table 2. Distribution of patients according to the germs responsible for urinary complications of strictures.

Germs isolated on cytobacteriological examination of urine	Effective	%
<i>Escherichia coli</i>	40	51.29
<i>Staphylococcus aureus</i>	24	30.77
<i>Candida albicans</i>	6	7.70
<i>Enterobacter</i>	4	5.12
<i>Streptococcus</i>	2	2.56
<i>Klebsiella</i>	2	2.56
Total	78	100

Table 3. Distribution of patients according to therapeutic and follow-up data.

Therapeutic and follow-up data	Effective	%
nature of the probe (N = 102)		
silicone probe	65	63.73
latex probe	37	36.27
Drainage time (N = 102)		
≤4 days	82	80.39
>4 days	20	19.61
Per and post-operative complications (N = 9)		
Urethrorrhagia	5	55.55
infiltration of the external genitalia	4	44.45
Quality of urination one month after catheter removal (N = 102)		
good voiding stream	99	97.06
Dysuria	3	2.94
Treatment results after 12 months (N = 102)		
Good results	77	75.49
Bad results (recurrence)	25	24.51

4. Discussion

EIU was the first-line indication in our department with 62.96% of cases in the treatment of urethral strictures. It represented 74.28% in the study by Zango *et al.* [3] and 58% in that of Ngaroua *et al.* [4]. It was practiced up to 85.60% in the United States in 2006 [1]. The EIU can also be used as a second-line treatment for recurrent urethral stricture after urethroplasty. Sukumar *et al.* [5] in a multi-center study of 130 patients reported an indication of 41% (n = 53) of EIU after urethroplasty. The minimally invasive nature offering the possibility of performing the procedure on an outpatient basis or at the cost of a short hospital stay has made this technique very popular among urologists.

In our study, the most affected age group was 61 - 80 years (35.29%). The average age was 54.25 years with extremes of 16 and 96 years. The 60 - 80 years age group was the most affected in the series by Djé K *et al.* [6]. For Benjelloun *et al.* [7], the average age was 51 years with extremes of 16 and 90 years. She was 69 years old (range: 56 - 77) in a series of 360 patients for Hong [8]. Urethral stricture was more common in the second half of life. This period being that of the after-effects of active and ill-informed youth, but also and above all of the polygamy, particularly in our country.

Among the reasons for consultation in our study, chronic retention of bladder urine took first place with 60 cases (58.82%) followed by acute retention of bladder urine: 32 cases (31.37%). Zango B *et al.* [3] reported 48.57% urinary bladder retention. Dysuria was the main reason for consultation in the series by

Benjelloun [7] and Niang [9] with 82% and 83.6% of cases respectively. Likewise, Hong *et al.* [8] reported 53% of lower urinary tract symptoms with dysuria as the main symptom and 13% of urine retention. This difference could be explained by the late consultation deadline in our regions.

While iatrogenic urethral stenosis is the most common in developed countries [10] [11], in developing countries the infectious etiology remains the main provider of urethral strictures. In our study, urethral strictures were infectious in 81.37% of cases (n = 83). Ndour *et al.* [12] and Zango *et al.* [3] reported 71.04% and 68.6%, respectively, of urethral strictures of infectious etiology. These results could be explained by the multiplicity of partners set up as a way of life, the use of self-medication or traditional therapy at the origin of an apparent cure of urethritis.

Urethral stricture was complicated by urinary tract infection in 78 patients (76.47%). The germs responsible for this infection were dominated by *Escherichia coli* in 51.29% (40 cases) and *Staphylococcus aureus* in 30.77% (24 cases). Benjelloun *et al.* [7] had reported a urinary tract infection in 21 patients (8.61%) and among them, *Escherichia coli* was found in 89.8%. Niang *et al.* [9] found a urinary tract infection with *Escherichia coli* in 25.2% of cases. Stephenson *et al.* [13] reported 10% urinary tract infection.

Bulbar US, ≤ 1 cm in extent, were the most represented with 71.57% (n = 73) and 60.78% (n = 62) respectively in our study. Djé K *et al.* [6] reported 67.90% of bulbar urethral strictures with an extent of less than 3 cm in 89.29%. In the series by Benjelloun *et al.* [7], the urethral stenosis was bulbous in 73.8% and less than 2 cm in extent in 70.5%. These data are consistent with those in the literature which recognize that the bulbar urethra is the site of predilection for urethral stenosis.

Complications from EIU are rare and usually minor. The rate of intraoperative and postoperative complications in our series was 8.82% (n = 9) including 5 cases (4.90%) of urethrorrhagia and 4 cases (3.92%) of external male genital infiltration. Niang *et al.* [9] reported 13% morbidity, such as aspiration (n = 1), urethrorrhagia (n = 4) and extravasation of irrigating fluid in the external genitalia (n = 3). Morbidity was 5% in the series by Benjelloun *et al.* [7]. Zheng *et al.* [14], comparing classic EU (cold slide) to that using Laser from a review of the literature on 7 articles with 453 patients concluded that the efficacy was similar in regarding the rate of recidivism in the short and long term. However, the laser group had a lower risk of bleeding and a lower reoperation rate, but a longer operation time. Mortality after EIU is zero in the literature [3] [6] [7]

After a one-year follow-up, our results were considered good in 75.49% (n = 77) and poor in 24.51% (n = 25). Guirassy S *et al.* [2] in the same department reported 51.80% good results after a follow-up of one. This difference could be explained by the selection of patients and the experience gained over these 2 decades. Our results were similar to those of Benjelloun *et al.* [7] who reported 75.4% good results. A success rate of 77% after 369 UIE in 225 patients has been reported by Holm-Nielsen *et al.* [15]. A success rate of 42% after EU on recur-

rent urethral strictures after urethroplasty has been reported by Sukumar *et al.* [5]. In this last study, this rate was higher than that of a urethral dilation, better after a replacement urethroplasty compared to an anastomotic urethroplasty [5]. All these results corroborate and make the EIU a low morbid technique that offers good results.

The analysis of the recurrences according to the etiologies, the type of the urethral catheter, the duration of catheter wearing, the extent of the urethral strictures and the number of this made it possible to retain the following: recurrences were more observed in infectious strictures. Eighty-four percent (84%) of these recurrences were of infectious origin and 12% (n = 3) of iatrogenic origin. The post-infectious sclero-inflammatory etiology was found in 70% of treatment failure cases in the series by Niang *et al.* [9]. For other authors, risk factors for failure of EU were the penile site of urethral stricture (as opposed to bulbar stenosis), extensive lesions (>1 cm or >2 cm) and etiology traumatic [16] [17] [18].

- the latex probe was the most associated with recurrence (32.43%). Recurrence went from 20% when the urethral catheter was made of silicone to 32.43% when the latter was made of latex. The reaction of the latex on the mucosa predisposes to recurrence [3]. In the series by Ze Ondo *et al.* [19], 86% of their patients had worn a latex catheter.
- the longer the length of time the catheter was worn, the higher the recurrence rate. This rate had gone from 24.68% for a probe port of fewer than 4 days to 30% if the latter was greater than 4 days. In the past, some authors kept the urethral catheter for 2 to 3 weeks [3] [6] to hope for a remodeling of the urethra around the catheter. This attitude does not give more good results than if the catheter were withdrawn between 3 and 5 days [7] [9]. In his series, AK Patrice and al. left the urethral probe in place for an average of 14 days motivated by urethrotomy made difficult on the one hand by the significant fibrosis, and on the other hand by the existence of false routes observed in the extensive stenosis [20]. Prolonged wearing of a urethral catheter would instead expose to a new infection of the urethra and genital tract in addition to its inconvenience. We believe that if the patient did not have a cystostomy and the EIU was easy, the catheter could be removed between the 3rd and 4th day. On the other hand, the presence of a cystostomy or a laborious EIU would require keeping the urethral catheter for 5 to 7 days. Stephenson *et al.* [13] in a multicenter randomized study reported that the EIU was performed on an outpatient basis and the patient was readmitted on the 2nd or 3rd day for catheter ablation.
- the longer and more multiple the stenosis was, the more it was associated with high rates of recurrence with 44.44% and 30% respectively. In the series by Djé K *et al.* [6], among the recurrences, 1 in 2 involved strictures extending over 3 cm. In that of Niang *et al.* [9], multiple strictures had only 3.27% good results.

The relatively small size of our sample remains the main limitation of our

study. Despite this limitation, our conclusions are generally quite close to the data in the literature on the subject.

5. Conclusions

UIE is a first-line endoscopic surgical technique for the treatment of urethral strictures. It offers little morbidity, short hospital stays and good results.

Long and multiple infectious strictures as well as the length of time the urethral catheter was worn were strongly associated with the occurrence of recurrences.

Ethics Committee

The research protocol for this work was initially approved by the urology department before being validated by the Ethics and Research Committee of the Faculty of Medicine of Gamal Abdel Nasser University in Conakry.

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Conflicts of Interest

The authors declare that they have no conflict of interest regarding this work.

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Clinical Characteristics and Difficulties in the Management of Cancer of the Penis

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Abstract

Introduction: Penile cancer is a rare primary malignancy that occurs in patients in their 60s and 70s. The aim of the study was to describe the anatomical aspects of penile cancer and to report the difficulties of its management. **Materials and Methods:** This was a retrospective descriptive study of patients with penile tumors from January 2007 to December 2019. Patients of sexual age with an ulcerated lesion of the penis, who came to our department and whose clinical and paraclinical workup led to the diagnosis of penile cancer, were included. The variables studied were clinical, paraclinical and therapeutic. **Results:** In 12 years, we diagnosed and managed 8 patients with penile cancer, an incidence of 0.7 per year. The reason for consultation was the chronic ulcerating wound of the penis with a “cauliflower” aspect. The first medical consultation was late (n = 8) after a long latency period lost to traditional healers. The lesion was located in the glans penis (n = 6) and/or in the corpus cavernosum (n = 2). Histological analysis of the cores concluded to a squamous cell carcinoma. Patients were classified as T2N+M+ (n = 3) and T2N0M0 (n = 5). One patient had accepted partial amputation of the penis. **Conclusion:** Penile cancer is a rare tumor. Partial amputation of the penis is the only alternative in our practice context, an alternative often refuted.

Keywords

Glans Penis, Ulcerating Penis, Squamous Cell Carcinoma, Metastasis, Brachytherapy

1. Introduction

Penile cancer is a rare malignant tumor that represents 0.5% of all male cancers in general [1] [2] [3]. It is the 4th most common urological cancer in men after prostate, bladder and kidney cancer. It is even rarer in populations that practice circumcision during childhood for ritual, religious or hygienic reasons. The diagnosis of certainty is anatomopathological. Squamous cell carcinoma is the histological type found in 95% of cases. In Europe, patients consulted early for minimal lesions benefit from conservative treatment, in particular Curie therapy and CO₂ laser [3] [4]. On the other hand, in under-medicalized countries, patients consult late at the stage where the lesions are “florid, ulcerating or suppurating”, requiring radical treatment that is often refuted by the patients [2] [5]. The authors report the clinical and anatomopathological aspects and the difficulties of management.

2. Materials and Methods

This was a retrospective descriptive study of patients with a penile tumor during a 12-year period from January 2007 to December 2019 in the urology department of the University Hospital of National Reference (CHURN) in N’Djamena, Chad. Patients of sexual age with an ulcerated lesion of the penis, who came to the department for clinical and paraclinical evaluation and were diagnosed with penile cancer were included. The variables studied were of several kinds. The clinical variables included: the age of the patient, the appearance and location of the lesion, the age of the lesion and the general condition of the patient at the first consultation, the reason for the consultation, the notion of circumcision during childhood, the notion of previous treatment with “traditional practitioners and charlatans”. Paraclinical variables: serologies (HIV, Chlamydia, syphilis), ECBU, the result of the analysis of the penile biopsy specimen, ultrasound of the urinary and abdominal tract, thoraco-abdominopelvic CT. Therapeutic variables: acceptance of partial amputation of the penis, adjuvant treatments (medical evacuation for chemotherapy or radiotherapy), duration of hospitalization, outpatient follow-up results.

Data were collected from the following registers: consultation, hospitalization, operative reports, and outpatient follow-up. The study was approved by the scientific ethics committee, the management of the RN University Hospital and the head of the urology department. The use of the photos was done in the respect of the patient’s identity and consent. Data entry and analysis were done using Microsoft Office 2007 software, in particular Excel, Word and SPSS 18.0.

3. Results

In 10 years, we diagnosed and treated 8 cases of cancer of the penis. The average age of the patients was 60 years with extremes of 46 and 80 years. The reason for consultation was the presence of a suppurating ulcerated penile wound. The average age of the penile wound at the first medical consultation was 18.8 months

with extremes of 4 months and 30 months. General condition was impaired on admission (n = 4). The patients were cattle breeders (n = 5), farmers (n = 2) and employees/civil servants (n = 1). Patients were circumcised (n = 6), uncircumcised (n = 2) and polygamous (n = 8). The lesion involved the body of the penis (n = 6), the glans (n = 2), the body of the penis and the glans (n = 1) (**Figures 1(A)-(D)**). The serologies were positive for: HIV (n = 1), chlamydia (n = 3) and syphilis (n = 0). The histological analysis of the penile biopsy specimen concluded to a squamous cell carcinoma in all patients (**Figure 2**). Complementary examinations, in particular ultrasound and thoraco-abdominopelvic CT, revealed lesions that allowed the patients to be classified as T2N+M+ (n = 3) and T2N0M0 (n = 5). One patient had given consent for amputation of the penis (**Figure 3**).

4. Discussion

Penile cancer is rare cancer as evidenced by the scarcity of publications generally involving very few cases [6] [7] [8] [9]. In 12 years of study, we have diagnosed 8 documented cases of penile cancer in the Urology Department of the University Hospital of National Reference of N'Djamena in Chad. During this same period, we hospitalized 3255 patients, all urological pathologies included. Penile cancer is a cancer of men over 60 years of age in Europe where cancer registries are the best kept [10] [11]. In Senegal, penile cancer represents 0.97% of adult male cancers and 0.35% of all cancers [5]. In a large American series of 1605 cases

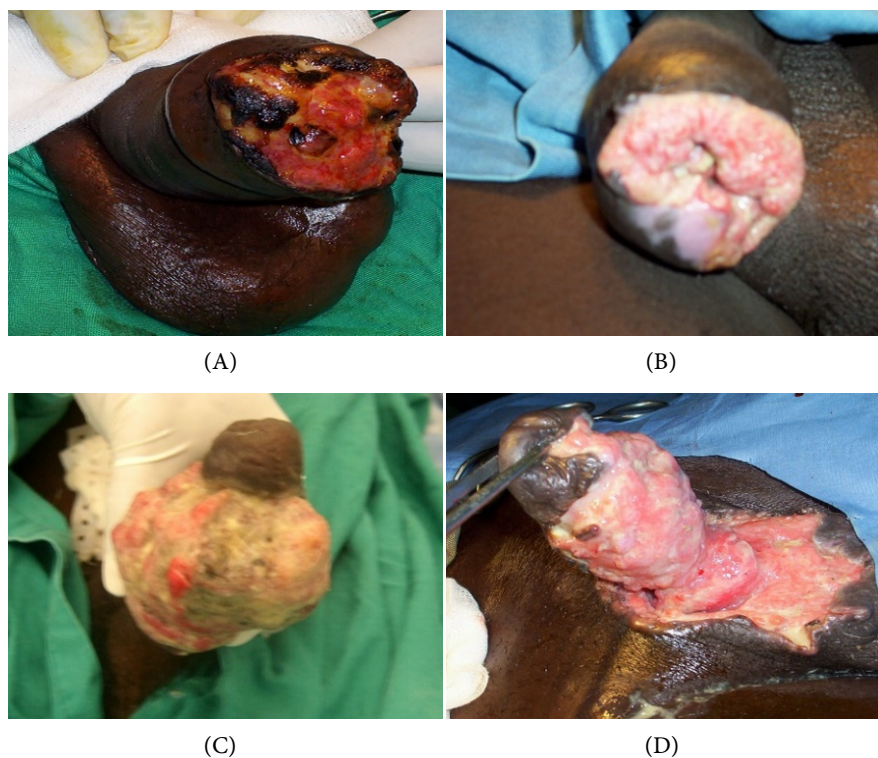
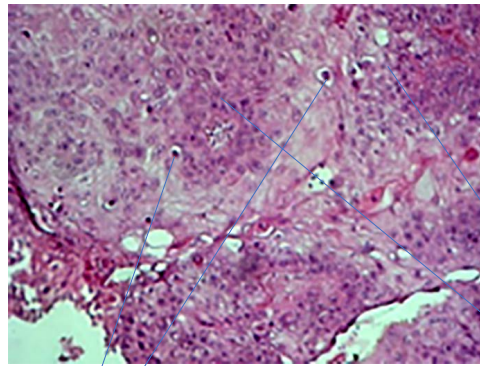


Figure 1. Different sites of penile cancer. (A) glandular; (B) preputial and glandular; (C) body of the penis; (D) glans and body of the penis.



Koilocytes = cells with a clear perinuclear halo characteristic of an HPV lesion

Figure 2. Histological image of a verrucous squamous cell carcinoma of the penis. Proliferation of frankly malignant cells arranged in lobules and showing a clear squamous differentiation.



Figure 3. Surgical image of a partial penile amputation. Regularization of the proximal stump after amputation.

of penile cancer, 9.9% of patients were African-American [2] [12]. The study found that all patients were polygamous. It should be noted that polygamy is well tolerated in Chad and should be considered as a favourable factor since it is synonymous with multiparity, which is a source of sexually transmitted infection. Although the average age at diagnosis is 60 years in our series, cancer of the penis seems to affect young people in Chad, as shown by the presence of two patients aged 54 and 46 years. The delay in the first consultation is notorious; the undeniable and visible witness of this delay is the monstrosity of the lesions observed. Indeed, there is a very long latency time between the patient's observation of the appearance of the first lesions of the penis and the first medical consultation. This precious time that could have been used in the hope of curing the disease is wasted in consulting "charlatans and other marabouts" in the first instance. These patients often go to the medical consultation under pressure from their parents who are bothered by the nauseating odor emanating from the tumor. This leads African authors to say that the diagnosis is often made at an ad-

vanced stage of the disease, in connection with modesty, taboos and religious beliefs [5] [9]. This suggests that prevention necessarily involves education and communication to change behavior. The lesions observed are voluminous, budding, ulcerated, suppurated and in some cases infested with maggots. These lesions can be mistaken for Donovanosis, which is a bacterial infection caused by *Klebsiella granulomatis*, mainly genital and essentially sexually transmitted, predominant in tropical areas among livestock farmers. Giemsa and Whartin-Starry stains show Donovan bodies in the cytoplasm of macrophages, in the form of small rods swollen at each end. The lesions observed in our series are located on the glans penis where the distal part of the body of the penis and the glans penis in our series. According to the literature, malignant tumors of the penis are preferentially located on the glans [3]. Malignant tumors of the penis are often diagnosed in Europe at an early stage where the lesion is minimal and could be treated with brachytherapy or a minimalist surgical procedure with an acceptable carcinological safety margin. It is not easy to report with precision in our context that the tumor originated in the glans penis or in the body of the penis, as the tumor is so large and old at the first medical consultation that the patient may be confused. The glandular location of the lesion and the notion of the absence of circumcision often reported by the authors certainly suggest an insufficiency of local hygiene or a local infectious factor. Nowadays, circumcision is recognized as a protective factor against penile cancer provided that it is performed during childhood [8]. Circumcision is a common practice in Chad, either for religious reasons in the Muslim faiths or for hygienic, aesthetic, or even ritual reasons for Christians and animists. By removing the skin of the foreskin, circumcision leaves the glans exposed, facilitates its cleansing, and thus favors the keratinization of the glans, making it less vulnerable to papillomavirus and Acquired Immune Deficiency Syndrome (AIDS). The protective role of circumcision is evoked and retained in view of the low prevalence of penile cancer in populations that practice it and the increase in prevalence in those that do not practice it. However, a man with a flexible foreskin, allowing easy removal of the glans and correct genital hygiene, is as well preserved as a circumcised man [5]. This last hypothesis may explain the low number of cases in Europe, where circumcision is not systematic. The only histological type encountered in our series is squamous cell carcinoma, which according to the literature represents 95% [9] [11]. Apart from one case of bulky inguinal adenopathy, one case of adenopathy detected by ultrasound and one case of hepatic metastasis, it is clear that the extension work-up was normal despite the monstrous nature of the lesions observed on the penis. This rarity of metastasis suggests that a local curative procedure can be performed, provided that the patients consult at an early stage and accept a partial penile amputation respecting the required carcinological margin. It should be emphasized that the development of cancer of the penis is slow. Invasion is local, distant metastases are rare. This slow development explains in part the delay in the first consultation. Despite the Florida appearance of the lesions observed in our patients, the extension workup at the time of diagnosis is

Table 1. Distribution of patients according to refusal of penile amputation.

Authors	Country	Year of publication	Number of patients	Average age	Carcinoma Squamous cell	Refusal of amputation
Bah [13]	Guinea Conakry	2007	2	39	2	0
Kara [3]	France	2007	6	65.6	5	0
Odzébé [14]	Congo Brazza	2010	1	42	1	1
Nouri [11]	Morocco	2012	6	60.5	6	1
Sow [9]	Senegal	2012	8	51.5	8	7
Kambou [2]	Burkina Faso	2015	3	73.3	2	2
Mansouri [1]	Tunisia	2018	11	64	9	4
Gueye [5]	Senegal	1992	11	55	11	8
Our study	Chad	2021	8	60	8	7

poor. Three patients are classified as T2N+M+, the other 5 as T2N0M0. The treatment of penile cancer aims to reconcile two imperatives: destruction or removal of the tumor with a sufficient safety margin and cosmetic and functional preservation. The means used can be surgical (partial or total amputation of the penis or even emasculation) or physical (laser, radiotherapy or brachytherapy) [3] [4]. Surgical treatment, which is very mutilating, is poorly accepted by the population for psychological reasons [2] [5]. In the absence of radiotherapy in our practice context, partial amputation of the penis or, in the worst cases, emasculation remains the only alternatives in our practice context, refused by 7 of the 8 patients. This refusal of amputation is also reported by other authors as shown in **Table 1**. It should be noted that in Africa in general and in Chad in particular, penile amputation is not accepted by patients for whom the penis is the visible expression of masculinity. Therefore, they would rather die than have their penis amputated, as **Table 1** clearly shows.

There is only one palliative procedure left to perform, namely urinary diversion cystostomy for reasons of dysuria due to the invasion of the urethra and cleanliness in order to avoid soiling or even permanently irritating a lesion that is already over-infected and foul-smelling.

5. Conclusion

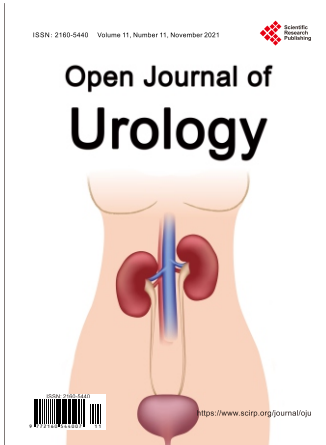
Penile cancer is rare cancer in men aged 50 years and older. Its diagnosis is late in our practice context where patients consult late at the stage of “florid” lesion from which emanates a nauseating odor. Squamous cell carcinoma is the only histological type encountered. The only possible surgical treatment is amputation of the penis, which is generally rejected by the patients.

Conflicts of Interest

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

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