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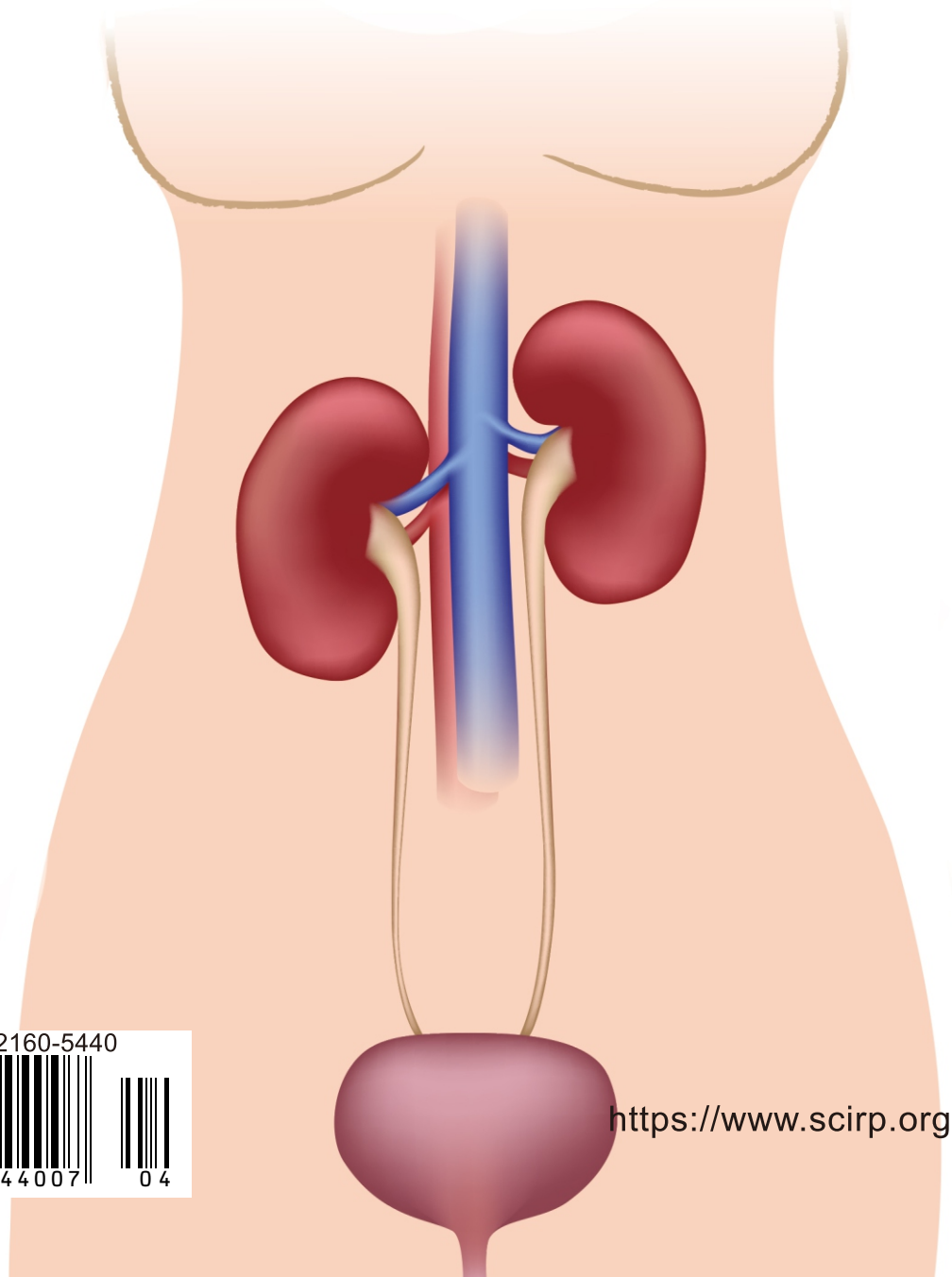

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Short-Term Haematogical Effects of Androgen Deprivation and Radiotherapy in Prostate Cancer Patients

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Abstract

Androgen deprivation therapy (ADT) is known to cause a decline in hemoglobin (Hgb), but the effect on other blood parameters is less well studied. In the lab, androgen manipulation has an effect on leukocyte counts. We evaluated the effects of androgen ablation alone on Hgb, white blood cell (WBC), granulocyte, and lymphocyte counts in 99 prostate cancer patients. In addition, since radiation therapy decreases those counts, we evaluated whether the addition of ADT makes it worse, comparing 162 patients receiving both radiation and ADT to 149 patients with radiation alone. ADT alone did significantly (but minimally) cause a drop in the Hgb (~0.5 g/dl), the WBC ($-0.39 \times 10^3/\mu l$) and granulocyte ($-0.32 \times 10^3/\mu l$), but not the lymphocyte counts. The combination of ADT with radiation did cause a greater decline in the Hgb levels at the end of treatment, but at follow up there was no difference. There was no additional effect on WBC, granulocytes or lymphocyte counts. Our results confirm clinically that ADT alone has minimal effect on WBC and its components and that there is no synergistic detriment of androgen ablation on the effects of radiation therapy on those cells.

Keywords

ADT Effects, White Blood Counts, Lymphocytes, Granulocytes

1. Introduction

Androgen deprivation therapy (ADT) has been shown to cause a decline in hemoglobin, leading to anemia in some patients [1] [2]. The exact mechanism remains uncertain [3]. The effect on other blood parameters such as white blood cell (WBC) counts is less well studied. Laboratory data show [4] that there are androgen receptors on leukocytes, raising the possibility of positive or negative

effects. Mice lacking androgen receptors have been shown to have neutropenia with risk of infection [5]. It has also been shown that androgens can affect lymphocyte counts [6], although in humans there has minimal documented effect. Despite its wide spread use, there is minimal clinical data on the effect of androgen deprivation on overall leukocyte (white blood cell), granulocyte (neutrophil) or lymphocyte counts. The question remains relevant with the current interest in enhancing the immunotherapy approaches to cancer treatment. With the widespread use of androgen ablation in prostate cancer, it raises the question as to the effects of androgen ablation on leukocyte counts and whether such treatment enhances the suppressive effects of radiation therapy on those parameters.

2. Material and Methods

The transition to intensity modulated radiation therapy (IMRT) has changed the radiation dose distribution throughout normal tissue. While allowing a more focal delivery of the higher doses of radiation, the tradeoff is to deliver smaller doses to a larger volume. The larger radiation fields expose more normal tissue to radiation. Given the unknown consequence of this and in consideration of the known effect of radiation on blood components, we started routinely collecting complete blood counts (CBC) on our prostate cancer patients who were receiving lymphatic (pelvic) radiation therapy. With institutional review board approval, we performed this retrospective review of prospectively collected (2014-2019) data. Complete blood counts were collected pretreatment and during the last week of treatment. Given the observation that there was an obvious decline in leukocytes (white blood counts, WBC) early on, we collected blood at the 3-month follow up visit to document recovery. Some of these patients had been started on neoadjuvant androgen ablation. This universally consisted of leuprolide injections; a few patients also received an antiandrogen short term. For those that were started on ADT in the radiation oncology clinic, a complete blood count was usually collected before starting. Our analysis is on the effect of androgen ablation alone on leukocyte (specifically granulocyte and lymphocyte) counts and whether androgen ablation enhanced the detrimental effects of radiation on those same counts.

Lymphatic radiation therapy consisted of 54 Gy delivered to the internal, external and common iliac lymphatics via linac based IMRT treatment. For post prostatectomy patients, the prostate fossa received a total of 70 Gy and for intact prostate, 78 Gy. Patient characteristics are shown in **Table 1**. The entire cohort was 311 patients. Ten did not go on to radiation after receiving ADT and are included in the pretreatment ADT analysis only. Three hundred one patients received radiation therapy. They were almost evenly divided between those that were (n = 162) and were not (n = 149) on short-term androgen ablation.

Worth noting is that in the literature outcomes are reported for either granulocytes or neutrophils. To be specific, granulocyte counts include neutrophils, basophils and eosinophils, with neutrophils being the predominant component

Table 1. Patient characteristics.

N = 311	
Age	Mean 69.7 yrs
mean	69.7 yrs
range	49.1 - 89.1 yrs.
ADT	
yes	162
no	149
pelvis treatment	
yes	250
no	51
Total dose	
78 Gy*	192
70 Gy	109

ADT = androgen deprivation therapy. *includes: 4 with 70 Gy/28 fractions, 22 brachytherapy boost, 1 stereotactic body radiation therapy boost. 10 patients started ADT and did not receive radiation therapy.

(>95%). Our lab reports the total granulocyte count. Also worth noting is that androgen deprivation therapy is facilitated via luteinizing hormone releasing hormone (LHRH) agonists (leuprolide) (or rarely a LHRH antagonist) alone. Sometimes treatment will include an antiandrogen which is then called total or combined androgen blockade (TAB, CAB).

3. Statistics

Sample characteristics were described using descriptive statistics. Frequencies and percentages were used to describe categorical variables. Means and standard deviations (or medians and ranges where appropriate) were used to describe continuous variables. A one-sample t-test (or Wilcoxon rank-sum test) was used to test for changes before and after androgen ablation. A two-sample t-test (or Wilcoxon rank-sum test when appropriate) was used to test for differences between patients who received neoadjuvant androgen ablation and those who did not. Statistical significance was set at $p < 0.05$.

4. Results

One hundred sixty-two patients received pre radiation therapy ADT. Sixty-three started ADT without a baseline CBC and 99 patients had a pre-ADT CBC. The median time on androgen ablation between measurements was 3 months (83 days). Results are shown in Table 2. Hemoglobin, WBC and granulocyte counts declined significantly, although the actual changes were small. Lymphocytes did not decline significantly. The mean HGB declined from 14.09 g/dL to 13.51 g/dL ($p \leq 0.0001$), mean WBC from $7.45 \times 10^3/\mu l$ to $7.06 \times 10^3/\mu l$ ($p = 0.0222$), mean

Table 2. Effect of androgen deprivation therapy alone on parameters.

	N	Mean baseline	change		P-value
			mean	median	
Hgb	97	14.09 g/dL	−0.58	−0.50	<0.0001
WBC	99	7.45 × 10^3/μl	−0.39	−0.30	0.0222
granulocytes	94	4.53 × 10^3/μl	−0.32	−0.32	0.0144
lymphocytes	94	1.98 × 10^3/μl	−0.03	−0.01	0.8363

Hgb = hemoglobin WBC = white blood cells.

granulocytes from 4.53 × 10^3/μl to 4.21 × 10^3/μl (p = 0.0144) and lymphocytes from a mean of 1.98 × 10^3/μl to 1.95 × 10^3/μl (p = 0.8363).

Next, we evaluated whether with radiation, the addition of ADT had a greater effect on the blood parameters. Overall, most patients (83%) received lymphatic (pelvis) radiation followed by a prostate fossa (n = 109) or prostate (n = 192) boost. For the primary prostate patients, most patients (86%) received a total external beam dose of 78 Gy and all the post radical prostatectomy patients received 70 Gy. To control for confounding variables, we first evaluated whether the surgical status, the total dose or whether they had pelvic radiation influenced outcomes. We found that pretreatment, the post-surgery patients have a lower baseline Hgb, total WBC and granulocyte count than the non-surgery patients, but the decline with treatment was no different. Pretreatment, the mean lymphocyte counts were similar, but the postoperative patients had a greater decline (from mean of 2.00 to 0.63 × 10^3/μl) than the non-surgery patients (mean 1.99 to 0.78 × 10^3/μl) (p = 0.0008). By three months after treatment, there was no difference in lymphocyte counts (p = 0.0642). Also, the total dose to the prostate/prostate fossa made no significant difference on any parameter. It was not unanticipated that the larger (pelvic) fields could influence the counts, but to confirm, we evaluated that specifically (**Supplemental Table A1**). The larger fields had a more profound effect on WBC, granulocyte and lymphocyte counts. We found that for the overall evaluation it did not change the outcomes due to the small number that did not receive pelvis radiation. For full transparency, we report the results for both the total and then for those only with pelvic radiation (**Table 3**, **Table 4**, respectively).

For the entire cohort, 162 patients received ADT and 149 did not. ADT did not affect the WBC decline (p = 0.4583), granulocyte decline (p = 0.3885), or lymphocyte decline (p = 0.7755) at the end of radiation treatment (**Table 3**). There was a greater decline in hemoglobin if on ADT (p = 0.0038).

At three months after treatment, compared to baseline there was no difference in hemoglobin (p = 0.3470), WBC count (p = 0.7517), granulocyte count (p = 0.7964) or lymphocyte count (p = 0.4226) between those on ADT and those not. The hemoglobin had recovered proportionally to the greater decline with treatment. There were subtle differences in the numbers, but the results were the same when evaluated by only patients that received pelvic radiation (**Table 4**).

Table 3. All patients (with and without pelvis radiation).

HGB (g/dL)	N	Baseline (mean)	end	change	P-value	3 months	Change from baseline	P-value
No ADT	143	14.32	13.48	−0.84	0.0038	13.57	−0.81	0.3470
ADT	151	13.57	12.46	−1.14		12.87	−0.68	
WBC ($\times 10^3/\mu l$)								
No ADT	143	6.93	4.97	−1.95	0.4583	5.30	−1.65	0.7517
ADT	151	6.90	4.75	−2.09		5.15	−1.68	
Granulocyte ($\times 10^3/\mu l$)								
No ADT	141	3.97	3.36	−0.58	0.3885	3.44	−0.55	0.7964
ADT	150	4.11	3.30	−0.77		3.44	−0.65	
Lymphocytes ($\times 10^3/\mu l$)								
No ADT	141	2.06	0.80	−1.29	0.7755	1.07	−1.00	0.4226
ADT	150	1.93	0.65	−1.28		0.94	−0.98	

Table 4. Only patients with pelvis radiation.

HGB (g/dL)	N	Baseline (mean)	end	change	P-value	3 mos	Change from baseline	P-value
No ADT	106	14.40	13.44	−0.95	0.0412	13.59	−0.81	0.1782
ADT	144	13.63	12.46	−1.18		12.91	−0.72	
WBC ($\times 10^3/\mu l$)								
No ADT	106	6.81	4.64	−2.16	0.9541	5.09	−1.72	0.7160
ADT	144	6.70	4.71	−2.16		5.11	−1.59	
Granulocyte ($\times 10^3/\mu l$)								
No ADT	106	3.89	3.20	−0.67	0.6077	3.38	−0.51	0.7294
ADT	144	4.11	3.28	−0.81		3.42	−0.69	
Lymphocytes ($\times 10^3/\mu l$)								
No ADT	106	2.01	0.66	−1.38	0.3609	0.93	−1.08	0.1313
ADT	144	1.92	0.63	−1.30		0.92	−1.29	

5. Discussion

It is documented that androgen ablation consistently causes a drop in hemoglobin [1] [2]. We confirmed that short-term androgen ablation in our patients causes a modest (~0.5 g/dL), but still significant ($p \leq 0.0001$) drop in hemoglobin. Not well studied previously is the effect on granulocytes and lymphocytes. The finding of androgen receptors on leukocytes [4] raises the possibility that there will also be an effect on those components.

Our results show that short-term androgen ablation has a mild, but still significant negative effect on granulocytes and the total white blood count with no effect on lymphocytes. There is limited data in the literature. One study [7], showed no effect on total leukocyte counts, while another [3] showed a 9% decrease. There were no specifics as to granulocyte or lymphocyte counts in these

studies, although in clinical studies [8] with the administration of testosterone, there was an increase in neutrophils. Chuang [5] reported a decrease in neutrophils in castrated mice, but non-significant decrease in neutrophils in 33 men after castration. In a similar small study (n = 16) [9] a significant increase in lymphocytes (including T cells and NK cells) occurred with TAB. The latter study is supported by mice data [10] [11] [12] [13] where it has been shown that there is a correlation with suppression of androgens and increased lymphocyte production. This is different from what we saw (no change) and was confirmed in a clinical series like ours [14]. In that study, nineteen patients received neoadjuvant total androgen blockade (an LHRH agonist and anti-androgen) and then pelvis radiation with a prostate radiation boost. From androgen ablation alone, the mean WBC count dropped from 6.37 to 6.19 × 10^3/μl (−0.18 × 10^3/μl), granulocytes from 4.34 to 4.10 × 10^3/μl (−0.24 × 10^3/μl), and lymphocytes (obtained by adding the subgroups) stayed the same from 1.64 vs. 1.66 × 10^3/μl (+0.02 × 10^3/μl) (p values not given). We saw changes of −0.39 × 10^3/μl, −0.32 × 10^3/μl, −0.03 × 10^3/μl, respectively.

Regarding the addition of androgen ablation to radiation therapy, it is thought to have a synergistic effect with radiation in the treatment and killing of prostate cancer. This raises the possibility of a synergistic effect that might be detrimental to blood components beyond that of radiation alone. We found no such effect on hemoglobin levels, granulocyte, lymphocyte or total white blood cell count. In addition, while recovery is incomplete at 3 months, there appeared to be no negative effect on recovery (**Table 3** and **Table 4**).

The additive effects of ADT and radiation on Hgb levels has been infrequently reported. In a study [15] of 141 patients, 2 months of total androgen blockade (LHRH agonists and antiandrogen) resulted in a median drop of 1.6 g/dL and after radiation, the total decline was 2.8 g/dl. We saw a smaller (−1.17 g/dL) decrease. The difference may be due to the use of total androgen blockade in that study versus the LHRH antagonist alone that we used.

We could find only one study similar to ours that evaluated the effect of adding androgen ablation to radiation [14]. For radiation without ADT, mean change in WBC count was 6.29 to 4.67 × 10^3/μl (−1.62 × 10^3/μl) vs 6.16 to 4.84 × 10^3/μl (−1.32 × 10^3/μl) for radiation plus ADT (non-significant); for granulocytes 4.26 to 3.74 × 10^3/μl (−0.52 × 10^3/μl) vs 4.1 to 3.81 × 10^3/μl (−0.29 × 10^3/μl), respectively (non-significant); and for lymphocytes 1.62 to 0.54 × 10^3/μl (−1.08 × 10^3/μl) vs 1.68 to 0.68 × 10^3/μl (−1.0 × 10^3/μl), respectively (p-value not given for total lymphocytes). They reported that the T lymphocyte subgroup was more resistant than NK cells or B lymphocytes with addition of ADT. Overall, they confirmed that androgen ablation did not significantly affect the impact of radiation on blood parameters.

6. Conclusion

In conclusion, as in most series, we found that even short-term androgen abla-

tion by itself causes a drop in hemoglobin. We also found that it caused a small, but still significant decline in WBC and granulocyte, but not lymphocyte counts When added to radiation therapy, ADT caused a greater decline in hemoglobin, but it recovered more quickly, so there was no difference at 3-month follow up. The combination of radiation with ADT did not cause a greater decline in WBC, granulocytes or lymphocyte counts compared to radiation therapy alone. Our findings would indicate that the addition of ADT should not have any effect on immune function beyond that of radiation therapy alone.

Conflicts of Interest

The authors declare no conflict of interest.

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Supplementary

Supplemental Table A1. Effect of treatment volume (prostate/prostate fossa only versus whole pelvis) and androgen deprivation therapy (ADT).

HGB (g/dl)	Pelvis treated	n	Baseline (mean)	end	change	P-value	3 months	Change from baseline	P-value
No ADT	yes	106	14.40	13.44	−0.95	0.0097	13.59	−0.86	0.6453
	no	43	14.13	13.58	−0.54		13.54	−0.70	
ADT	yes	144	13.63	12.46	−1.18	0.0003	12.91	−0.69	0.5062
	no	8	12.76	12.36	−0.40		12.21	−0.55	
WBC ($\times 10^3$/mcl)									
No ADT	yes	106	6.81	4.64	−2.16	0.0040	5.09	−1.70	0.2380
	no	43	7.26	5.81	−1.38		5.80	−1.51	
ADT	yes	144	6.87	4.71	−2.16	0.0580	5.11	−1.73	0.0472
	no	8	6.69	5.60	−1.09		5.81	−0.88	
Neutrophils ($\times 10^3$/mcl)									
No ADT	yes	106	3.89	3.20	−0.67	0.1145	3.38	−0.50	0.5473
	no	43	4.19	3.79	−0.34		3.59	−0.70	
ADT	yes	144	4.11	3.28	−0.81	0.0451	3.42	−0.66	0.0526
	no	8	3.86	3.72	−0.14		3.76	−0.09	
Lymphocytes ($\times 10^3$/mcl)									
No ADT	yes	106	2.01	0.66	−1.38	0.0102	0.93	−1.08	0.0092
	no	43	2.19	1.15	−1.04		1.42	−0.78	
ADT	yes	144	1.92	0.63	−1.30	0.0244	0.92	−1.00	0.0456
	no	8	1.91	0.99	−0.92		1.17	−0.74	

The radiation volumes clearly have a marked effect on the decline in lymphocytes, somewhat less so for neutrophils. The lack of significant difference in the ADT subgroup likely reflects the small number of whole pelvis patients. Due to the significant difference that the volume makes on the blood counts and the imbalance between the ADT and no ADT groups in the percent of patients receiving whole pelvis radiation, further evaluation was limited to the large radiation field patients.

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Clinical Study on Evaluation of Autonomic Nervous Dysfunction Based on Imaging Urodynamic Examination with Slow Filling and Synchronous Blood Pressure Monitoring in the Patients with Cervicothoracic Spinal Cord Injury

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Abstract

Objective: Explore the rule of autonomic nervous dysfunction in the patients with urination disorder after high level spinal cord injury, and seek a safe, objective and accurate method to evaluate autonomic nervous function. **Patients and Method:** 48 patients with dysuria after cervicothoracic SCI were selected. Before, during and after imaging urodynamic examination with slow filling in supine position, blood pressure and ECG were monitored simultaneously. The symptoms of sweating, shivering, headache, flushing and chills were observed and recorded. The study of the relationship among the changes of blood pressure, heart rate and urodynamic indexes and the above symptoms was analyzed. **Results:** They were divided into three groups: group A (no obvious abnormality), group B (hyperactivity) and group C (hypoactivity) according to their BP, HR and existing the symptoms or not. **Conclusion:** The incidence of autonomic dysfunction in the high level SCI patients with dysuria was very high (79.17%), most of them were hyperactivity, and a few were low function. The changes of SBP and DBP in the hypoactivity group all appeared an increasing and then declining trend, while the change of HR in the low function one was lower than normal and decreased continuously. The main inducements of AD are neurogenic detrusor overactivity, detrusor sphincter dyssynergia, elevated abdominal pressure and abnormal bladder sensitivity. The asymptomatic patients had a higher occurrence rate (43.75%). Only by imaging urodynamic examination with slow filling and synchronous blood pressure monitoring, can autonomic nervous function of

the patients be evaluated safely, objectively, early and accurately.

Keywords

High Level Spinal Cord Injury, Autonomic Nervous Function, Imaging Urodynamic Examination, Slow Filling, Synchronous Blood Pressure Monitoring

1. Introduction

The Patients with dysuria of high level spinal cord injury (SCI) above T6 often have autonomic nervous dysfunction, such as sudden significant increasement of blood pressure, tachycardia, or transient hypotension, bradycardia, and or accompanied by sweating, shivering, headache, blushing, chills, hyperspasmia of muscles below the injury level and other symptoms [1] [2]. Severe cases have the risk of cerebral hemorrhage [3], retinal hemorrhage [4], or seizures, and even cardiac arrest [5], which is one of the most serious complications after SCI. It may even aggravate the neurological symptoms of the patients [6] and affect the rehabilitation process. How can the blood pressure and heart rate change dynamically when autonomic nerve dysfunction occurs in such patients? What is the relationship between it and bladder filling (intestinal irritation)? What are the corresponding mechanisms and main incentives? How to evaluate autonomic nervous function safely and scientifically? The above issues urgently need to be studied and discussed. Therefore, it is very important to clarify the change rule of autonomic nerve dysfunction in the patients with dysuria after high level SCI, to explore its causes, to quantify autonomic nerve function of the patients scientifically, to find a safe, objective, early and accurate method to evaluate autonomic nerve function of them in clinic.

2. Patients and Method

From July 2017 to July 2020, 48 in patients with dysuria after cervicothoracic SCI in our hospital were selected.

The inclusion criteria: 1) 18 ≤ age ≤ 60 years old; 2) Dysuria caused by ASIA classification (A-D grade) of cervical and thoracic spinal cord injury; 3) Course of disease ≥ 1 month; 4) No urinary calculi; 5) No urinary tract tumor; 6) No obvious stress urinary incontinence; 7) No history of urinary tract, bladder and prostate surgery; 8) No serious urinary tract infection and there is a stable condition within a week; 9) Signed the informed consent.

The exclusion criteria: 1) Age < 18 or age > 60 years old; 2) Dysuria caused by injury of lumbar spinal cord and below level; 3) Urination disorder caused by cuaniocerebral diseases; 4) Course of disease < 1 month; 5) Have urinary calculi; 6) Have urinary tract tumor; 7) Have obvious stress urinary incontinence; 8) Have history of urinary tract, bladder and prostate surgery; 9) The symptomatic urinary tract infection occurred within the past week; 10) Those who have been

unstable condition within a week; 11) People who are allergic to iohexol; 12) People with allergies; 13) People who refuse to participate in the study.

The research method: Firstly, the patients were given adequate bowel preparation: They were given cleaning enema once at the night before the examination and once at four hours before the examination on the same day. The enema solution was a mixture of 100 ml normal saline and 40 ml glycerin. Then after their skin preparation in the perineum area, all patients underwent imaging urodynamic examination with slow filling in zero degree supine position. 10% iohexol sodium chloride solution was continuously pumped into the bladder manometer tube. The bladder filling rate was 8 - 10 ml/min. Before, during and after examination, blood pressure and ECG were monitored. Among them, the blood pressure and heart rate during examination are the corresponding values of the leakage point of the patients, or the immediate values when the patients had related discomfort symptoms, or the values at the time of stopping bladder filling. Observed and recorded whether the patients had sweating, shivering, headache, blushing, chills and other symptoms.

Inspection instrument: a set of German Siemens imaging urodynamic examination equipment, a wireless Bluetooth urodynamic instrument from Canada Labry, an ECG monitor of China Shenzhen Jinlu UT4000B.

Statistical methods: SPSS 21.0 software was used for data analysis. The measurement data were represented by mean ± SD, and the count data were indicated by two or three categories. T-test was used for the measurement data, $P < 0.05$ was statistically significant.

3. Results

The patients were divided into three groups according to their BP, HR and existing the symptoms of autonomic nervous dysfunction or not: group A (no obvious abnormality of autonomic nervous function): before, during and after examination, their BP and HR were normal, without accompanying symptoms; group B (hyperactivity of it): both their SBP and DBP rised more than 20% during examination than before, and at least they were accompanied with one of the five symptoms; and group C (hypoactivity of it): they had lower HR (BP) than normal, and or they were accompanied with one of the five symptoms. The values of BP and HR of the patients were shown in **Table 1**. For the sociodemographic and clinical characteristics, see **Table 2**. The data of age, disease course, bladder safety capacity and bladder compliance was listed in **Table 3**. T-test of age, disease course, bladder safe volume and compliance was used to compare between three groups in **Table 4**. T-test of BP, HR was used to contrast between three groups in **Table 5**. The incidence of three groups' patients was evinced in **Table 6**. The results of urodynamic examination were manifested in **Table 7**. The results of a typical case' blood pressure synchronous monitoring were demonstrated in **Table 8**. Group B' SBP trend of change was appeared in **Figure 1**; Group B' DBP trend of change was indicated in **Figure 2**. Group C' HR trend

Table 1. Values of BP and HR of the patients (mean ± SD).

	SBP (mmHg)			DBP (mmHg)			HR (Times/min)		
	SBP1	SBP2	SBP3	DBP1	DBP2	DBP3	HR1	HR2	HR3
A	112.25 ± 4.86	113.00 ± 11.81	116.38 ± 8.99	69.63 ± 5.34	71.25 ± 10.55	74.75 ± 6.67	66.00 ± 3.82	64.75 ± 4.37	66.38 ± 4.69
B	117.13 ± 16.78	144.57 ± 29.67	134.10 ± 18.68	76.40 ± 14.85	92.80 ± 22.50	86.27 ± 14.36	66.03 ± 14.90	66.30 ± 18.70	66.27 ± 12.51
C	103.38 ± 9.59	120.63 ± 5.66	110.13 ± 11.91	60.50 ± 7.87	74.63 ± 6.89	70.75 ± 10.86	59.63 ± 8.85	58.00 ± 8.78	56.50 ± 7.23

Table 2. Sociodemographic and clinical characteristics of the patients.

Group		A	B	C
Gender	M	5	23	7
	F	3	7	1
Hypertension history	No	8	26	8
	Yes	0	3	0
Hypotension history intermittently	No	8	29	7
	Yes	0	1	1
Plane of SCI (%)	Cervical segment	5 (62.50%)	28 (93.33%)	7 (87.50%)
	Upper thoracic segment (≤T6)	3 (37.50%)	1 (3.33%)	0 (0.00%)
	Lower thoracic segment (>T6)	0 (0.00%)	1 (3.33%)	1 (12.50%)
ASIA grades of SCI (%)	Complete	3 (37.50%)	13 (43.33%)	1 (12.50%)
	Incomplete	5 (62.50%)	17 (56.67%)	7 (87.50%)
Concomitant symptoms (%)	No	8 (100%)	15 (50.00%)	3 (37.50%)
	Yes	0 (0.00%)	15 (50.00%)	5 (62.50%)
Hydronephrosis (%)	No	7 (87.50%)	28 (93.33%)	7 (87.50%)
	Yes	1 (12.50%)	2 (6.67%)	1 (12.50%)

Table 3. Patients' age, disease course, bladder safety capacity and bladder compliance (mean ± SD).

Group	A	B	C
Age (years)	42.25 ± 7.92	37.07 ± 10.73	40.13 ± 14.84
Disease course (months)	12.50 ± 13.30	26.03 ± 13.91	31.75 ± 36.10
Bladder safety capacity (ml)	134.13 ± 178.90	211.17 ± 137.83	200.63 ± 116.89
Bladder compliance (ml/cmH_2O)	19.66 ± 48.65	18.52 ± 26.57	27.51 ± 45.22

Table 4. Inter-group comparison of the patients' age, disease course, bladder safe volume and bladder compliance (t-test).

p	Age	Disease course	Bladder safety capacity	Bladder compliance
A-B	0.212*	0.355*	0.195*	0.929*
A-C	0.726*	0.179*	0.394*	0.743*
B-C	0.513*	0.716*	0.844*	0.472*

*: $p > 0.05$.

Table 5. Inter-group comparison of the patients' BP and HR (t-test).

p	SBP (mmHg)		DBP (mmHg)		HR (Times/min)	
A-B	SBP1	0.425*	DBP1	0.217*	HR1	0.995*
	SBP2	0.006***	DBP2	0.013**	HR2	0.819*
	SBP3	0.014**	DBP3	0.035**	HR3	0.981*
A-C	SBP1	0.035**	DBP1	0.017**	HR1	0.082*
	SBP2	0.122*	DBP2	0.461*	HR2	0.072*
	SBP3	0.256*	DBP3	0.390*	HR3	0.006***
B-C	SBP1	0.034**	DBP1	0.006***	HR1	0.226*
	SBP2	0.031**	DBP2	0.032**	HR2	0.234*
	SBP3	0.002***	DBP3	0.007***	HR3	0.043**

*: $p > 0.05$; **: $p < 0.05$; ***: $p < 0.01$.

Table 6. Incidence of three groups' patients.

Group	A	B	C
Number	8	30	8
Percentage (%)	16.67	62.50	16.67
Total (B + C)		79.17	

Table 7. Results of the patients' urodynamic examination.

Group		A	B	C
Detrusor type (%)	Overactivity	5 (62.50%)	23 (76.67%)	7 (87.50%)
	Bladder atony	3 (37.50%)	7 (23.33%)	1 (12.50%)
Bladder compliance (%)	Decreasement	7 (87.50%)	23 (76.67%)	5 (62.50%)
	Increasement	1 (12.50%)	5 (16.67%)	1 (12.50%)
External urethral sphincter-detrusor (%)	Normal	0 (0.00%)	2 (6.67%)	2 (25.00%)
	Incoordination	6 (75.00%)	22 (73.33%)	5 (62.50%)
	Achalasia	2 (25.00%)	8 (26.67%)	3 (37.50%)
Bladder sensation (%)	Sensitive	4 (50.00%)	17 (56.67%)	5 (62.50%)
	lost	4 (50.00%)	9 (30.00%)	2 (25.00%)
	Declining	0 (0.00%)	4 (13.33%)	1 (12.50%)
Higher abdominal pressure (%)	No	6 (75.0%)	14 (46.67%)	1 (12.50%)
	Yes	2 (25.00%)	16 (53.33%)	7 (87.50%)

Table 8. Results of a typical case' blood pressure synchronous monitoring.

	SBP (mmHg)	DBP (mmHg)	HR (Times/min)
Start filling	113	70	77
Stop filling	137	87	65
End examination	130	82	66

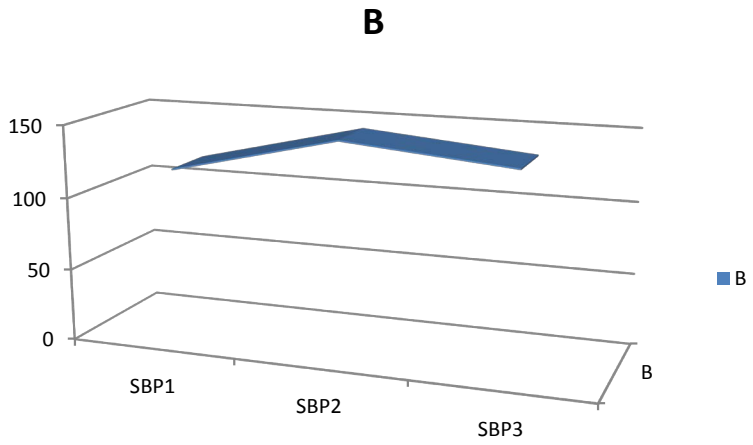

Figure 1. Trend chart of SBP in group B.

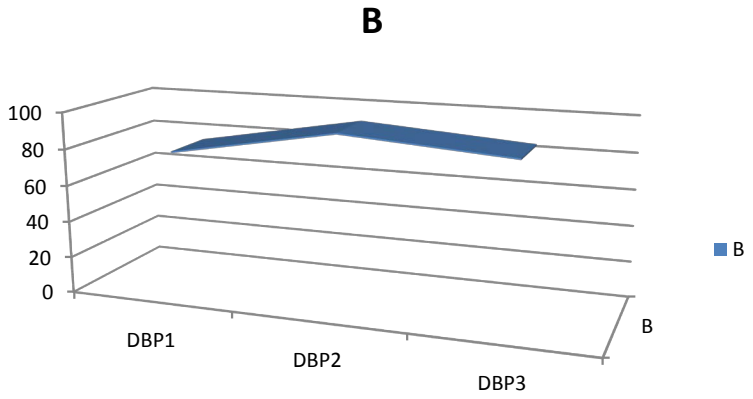

Figure 2. Trend chart of DBP in group B.

of change was revealed in **Figure 3**. The urodynamic graph of a typical case was disclosed in **Figure 4**.

Table 4 exposed that there was no significant difference in age, disease course, bladder safety capacity and compliance between three groups (T-test) ($P > 0.05$). However, from **Table 5**, compared of BP and HR between three groups (T-test), it can be seen that SBP2 of group A-B had extremely prominent discrepancy ($P < 0.01$); SBP3, DBP2 and DBP3 of it had marked distinction ($P < 0.05$). HR3 of group A-C was greatly remarkable different ($P < 0.01$), SBP1 and DBP1 of it had obvious dissimilarity ($P < 0.05$). The diversity between group B-C was more evident. **Figure 1**, **Figure 2** and **Table 1** revealed that the changes of SBP and DBP of group B were increased earlier and then decreased. **Figure 3** and **Table 1** exhibited that the changes of HR of group C was lower than normal and declined continuously. **Figure 4** suggested that the abdominal pressure was significantly higher than the bladder pressure, from the whole course of inspection. **Table 6** displayed the incidence of autonomic dysfunction of the patients with dysuria after high level SCI was very high (about 79.17%, adding B and C), most of them were hyperactivity (62.50%), and a few were hypoactivity (16.67%). **Table 7** manifested: The incidence of NDO [7], low compliant bladder (62.50% - 87.50%),

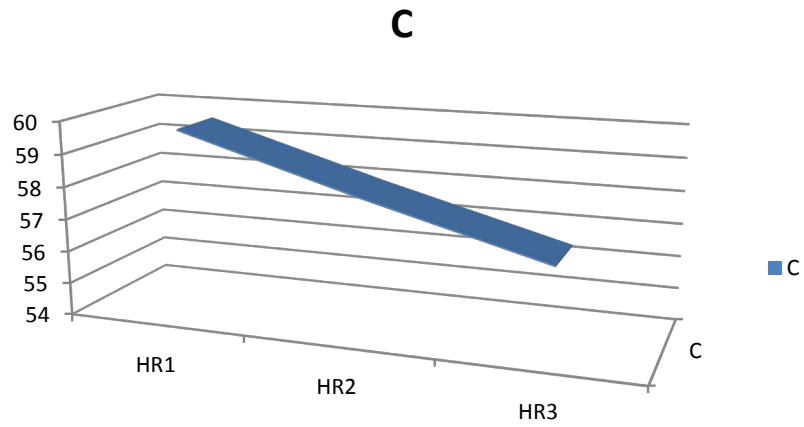

Figure 3. Trend chart of HR in group C.

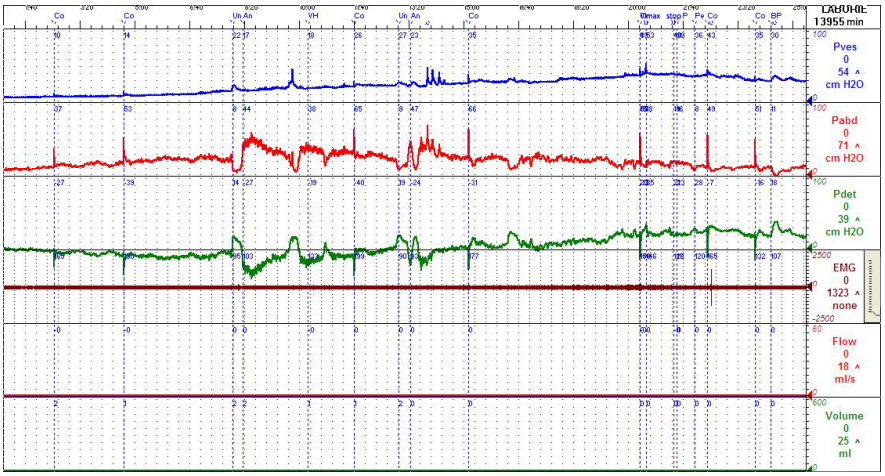

Figure 4. Urodynamic graph of a typical case.

NDSD [8] of group B and C was very high, that of high abdominal pressure of group B, C (53.33%, 87.50%) was evidently more quantity than that of group A (25.00%), the ratio of bladder disappearance of group B, C (30.00%, 25.00%) was fewer than that of group A (50.00%). From **Table 8**, compared with the baseline, it can be demonstrated that the values of SBP and DBP of a typical case at he time of stopping filling increased more than 20 mmHg. From **Table 2**, we found out that the incidence of symptoms without autonomic nervous dysfunction of group B and C was not low (50.00%, 37.50%), and the average incidence was 43.75%.

4. Discussion

Paraplegic patients with high level SCI may have abnormal autonomic reflex or autonomic dysreflexia (AD), especially in the patients with T6 or higher plane, the incidence is nearly 1/2 - 3/4, the latest research shows that: as high as 93% [9], the patients with cervical SCI are more common. Its severity is mainly related to the sudden and distinct increase of BP: such as conscious change, visual impairment, seizures, intracranial hemorrhage, and even death. Headache, facial

flushing, chest tightness, palpitation, sweating and other symptoms are often used as a warning sign of elevated BP. Nevertheless, sometimes patients have elevated BP without any symptoms, which is called "asymptomatic AD" [10]. In this case, patients and doctors may have missed the best time to manage the potential powerful afferent stimuli, which may lead to severe sequelae. In fact, this "silent killer" is more harmful to patients. The Patients with high level SCI can also present hypotension, orthostatic hypotension (OH) [11] [12], reflex bradycardia and cardiac arrest. Available data indicate that the incidence of bradycardia and cardiac arrest of SCI patients can be as high as 30%, and the average HR is 54 times/min, including some patients with severe bradycardia less than 50 times/min [13]. Therefore, we should pay enough attention to the occurrence of serious cardiovascular complications, such as bradycardia and cardiac arrest, especially in the patients with high level paraplegia. At present, circulatory disturbance has become the second leading cause of death in the patients with chronic SCI. Therefore, it is necessary and urgent to study the autonomic dysfunction in the patients with SCI.

The study demonstrated that the incidence of autonomic dysfunction in the high level SCI patients with dysuria was very high (almost 80.00%), most of them were hyperactivity (62.50%), and a few were low function (16.67%). Among them, the increasement of SBP and DBP in the hyperfunction group was greater than 20% of the baseline value when there was no attack, and they all showed a rise firstly and then a fall; the decline of HR (BP) in the hypoactivity one was lower than normal and decreased continuously, before, during and after examination, and or two groups of patients were accompanied with one of the five symptoms: sweating, shivering, headache, facial congestion, chills [14].

Indeed, In addition to bladder overinflation caused by NDO and NDSD is the main causes of AD, the results in **Table 7** suggest that the increase of abdominal pressure is also the main cause of AD. Previous studies have shown that the most common cause of AD is bladder dilation, accounting for 75% - 85%; the second common cause is intestinal irritation, such as fecal impaction, accounting for 20% [15] [16]. Most patients with dysuria of SCI are accompanied by neurogenic intestinal dysfunction. Therefore, with the increament of abdominal pressure caused by bladder filling and intestinal irritation, the conduction through visceral sensory nerve: pelvic nerve and pudendal nerve to the sacral spinal cord can also cause the above AD performance [17]. In this study, the patients of group B and C had more transient paroxysmal increasement of abdominal pressure than ones of group A, and or they were accompanied by transient enhancement of the myoelectric amplitude of the external urethral sphincter. Most of patients' abdominal pressure fluctuated within 10 - 30 cm H_2O for a short period of time, even as high as about 70 cm H_2O, as shown in the urodynamic map of a typical case of SCI (T3 AIS grade B). Although good bowel preparations (cleaning enema twice) had been done before the examination, the patient' bladder was filled slowly in the supine position, and detrusor was recorded uninhibitory contraction during the urine storage period, the maximum detrusor pressure is 35 cm

H_2O, without significant increase, the peak value of abdominal pressure was 71 cm H_2O. Simultaneous cystography showed that when the bladder was filled to 100 ml, it presented the X-ray appearance of neurogenic bladder protruded to the right. The results of synchronous blood pressure monitoring in **Table 8** indicated that the values of SBP and DBP at the time of stopping filling raised by more than 20 mmHg compared to the values at the beginning of filling, even though the patient had no symptoms of AD. Imaging urodynamic diagnosis: bladder sensation disappeared; detrusor was overactivity in the storage period, detrusor contraction was weakness in the voiding period; bladder compliance decreased; bladder safety capacity, urinary bladder capacity was about 356 ml; partial incordination was existed between external urethral sphincter and detrusor; rectal pressure increased significantly; there was no vesicoureteral reflux; autonomic hyperfunction. In **Table 7**, the incidence of high abdominal pressure of group B and C was noticeably higher than that of group A, illustrating that elevated abdominal pressure was actually very common in AD patients.

The results in **Table 7** also imply that the patients with abnormal bladder sensitivity are more likely to induce AD. Under normal circumstances, bladder filling or intestinal stimulation can cause sympathetic nerve excitation, increase blood pressure, stimulate aorta and carotid baroreceptor to regulate and normalize blood pressure; however, the patients with SCI can not reduce blood pressure through visceral vasodilation, the brainstem also can not transmit inhibitory impulses to the sympathetic nerves, If they were accompanied by hypersensitivity of the bladder below the injury level, AD is more likely to occur, and the sympathetic nerve mechanism is dominant, Elevated blood pressure is a clinical manifestation [18]; After the aortic and carotid baroreceptors are stimulated, the impulse is uploaded to the cardiovascular motor center of the brain stem, which can also cause parasympathetic dominance at the level above the injury, excitation of the vagus nerve, thus slowing down the heart rate, but the blood pressure is not necessarily lower, the situation of decline in heart rate is rare [19]. In **Table 1** and **Table 6** of this study, the results of group B and C are consistent with this.

It can be seen from **Table 2** that the average incidence of asymptomatic AD is higher (43.75%), which indicates that asymptomatic AD has great potential harm to the patients with chronic SCI [20]. Therefore, by accurately and objectively evaluating whether the autonomic nervous function of the patients is abnormal, early detection and identification of such asymptomatic patients, timely, scientific and standardized management of bladder and intestinal tract, and comprehensive treatment can effectively, maximally avoid acute attack of AD or deterioration of symptoms in the patients with SCI, reduce or ward off the occurrence of clinical malignant emergencies.

For the SCI patients with urination disorder, the autonomic nerve function is mostly hyperactive and blood pressure tends to rise. Therefore, during the whole process of image urodynamic examination, it is necessary to pay attention to the speed of bladder perfusion should be slow rather than fast, that is, slow filling,

also known as physiological filling refers to the speed of bladder filling is less than 10 ml/min [21], and synchronized blood pressure monitoring is performed to observe and record the patients' blood pressure and heart rate dynamic changes, before, during and after the examination, as well as whether there are five main symptoms of sweating, chills, headache, flushing and chills. Only in this way can the autonomic nervous function of patients be evaluated safely, objectively, early and accurately.

5. Conclusion

The incidence of autonomic dysfunction in the high level SCI patients with dysuria was very high (nearly 80.00%), most of them were hyperactivity, and a few were low function. The changes of SBP and DBP in the hypoactivity group all appeared an increasing and then declining trend, while the change of HR in the low function one was lower than normal and decreased continuously. The main inducements of AD are neurogenic detrusor overactivity, detrusor sphincter dyssynergia, elevated abdominal pressure and abnormal bladder sensitivity. The asymptomatic patients had a higher occurrence rate (43.75%). Only by imaging urodynamic examination with slow filling and synchronous blood pressure monitoring, can autonomic nervous function of the patients be evaluated safely, objectively, early and accurately.

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Conflicts of Interest

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

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Serum Total Testosterone Levels Pre- and Post-Subinguinal Microsurgical Varicocelectomy in Men with Clinical Varicoceles

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Abstract

Background: Varicocele is abnormal dilation and tortousity of the scrotal venous pampiniform plexus that drain blood from each testicle. Recently, it has been linked to low serum total testosterone (TT) levels by affecting the optimal functioning of the leydig cell via increasing the scrotal temperature. Varicocele repair has been found post-operatively to increase the serum levels of TT. This study looks at the pre and post-subinguinal microsurgical varicocelectomy serum TT levels in male patients with clinical varicocele. **Methods:** The study involved 88 male patients with clinical varicoceles who met the inclusion criteria. These patients after good history taking and physical examination had their serum TT levels measured pre varicocelectomy and 6 months post-subinguinal microsurgical varicocelectomy. The varicoceles were diagnosed by physical examination and use of scrotal color Doppler ultrasonography (US). **Results:** The number of patients with varicocele were 88 males. The mean age of the patients was 33.43 ± 7.82 years. There was isolated left varicocele in 57 (64.8%) patients and bilateral varicocele in 27 (30.7%) patients. Pre varicocelectomy, 61 (69.3%) patients had serum TT of between 100 - 290 nanogram/deciliter (ng/dl) and a mean value of 241 ± 0.91 ng/dl. Post varicocelectomy 56 (63.6%) patients had serum TT in the range of 300 - 490 ng/dl with a mean of 482 ± 2.87 ng/dl, showing a robust significant increase in the serum TT post-operatively ($P < 0.001$). **Conclusion:** There was statistically significant improvement in the serum TT levels with 55 (79%) patients exhibiting normalization of serum TT levels after subinguinal microsurgical varicocelectomy.

Keywords

Clinical Varicocele, Serum Total Testosterone, Doppler Color Ultrasonography, Varicocele Grade, Subinguinal Microsurgical Varicocelectomy

1. Introduction

Varicocele is abnormal dilatation and tortousity of the scrotal venous pampiniform plexus that drain blood from each testicle [1] [2] [3] [4]. It is the most commonly identifiable correctable cause of male infertility [5]. Incidence of varicocele in healthy men is found to be 4.4% to 22.6% with an average of 15% [1] [4] [6] [7]. The prevalence in adolescent population and childhood mirrors that of the adult population and is 15.7% [7]. Varicocele affects 21% - 39% of subfertile men [8]. It is found in 35% - 50% of men presenting with primary infertility and 69% - 81% of men presenting with secondary infertility [3] [4] [5] [6]. The left spermatic vein drains into the left renal vein in a perpendicular fashion. This drainage fashion coupled with the fact that the left spermatic vein traverses 8 cm - 10 cm longer with a greater increase in hydrostatic pressure accounts for a preponderance of varicocele on the left side by about 80% - 90% [1] [4] [6] [9] [10]. Where there is a left sided varicocele, there is a 30% - 50% probability it is a bilateral condition [1] [4] [10] [11]. Furthermore, an isolated right sided varicocele may be a pointer to associated situs inversus or retroperitoneal tumors necessitating further investigations [11]. For the diagnosis of clinical varicoceles, physical examination remains the gold standard [11] [12]. Varicoceles are graded according to the scale developed by Dubin and Amelar in 1970 [4] [11] [13].

Grade 1: Varicocele detectable by palpation only during the valsalva maneuver.

Grade 2: Varicocele detectable by simple palpation.

Grade 3: Varicocele visible on inspection and palpation.

A widely accepted US diagnosis of varicocele is the existence of veins larger than 2 millimeters (mm) in diameter [11]. The pathogenic mechanisms of varicoceles which include oxidative stress, heat stress, toxin accumulation can affect adversely the function of the leydig cells of the testis responsible for 95% testosterone production in adult men [6] [14]. This study looks at serum TT in patients with clinical varicocele and also serum TT 6 months post-subinguinal microsurgical varicocelectomy with a view to finding out if there is improvement in the serum TT.

2. Material and Method

This is a prospective study involving male patients seen at the urology clinic of a Federal teaching hospital in southeast Nigeria between January 2016 and December 2018. Approval for the study was obtained from the ethical committee of the hospital and informed written consent from the individual patients.

2.1. Exclusion Criteria

1) Those with un-descended testis.
2) Patients with diabetes mellitus.
3) Those on treatment for any form of Hypogonadism.

4) Those with intra-abdominal mass.

5) History of previous scrotal surgery/varicocelectomy.

A minimal sample size of 102 was calculated for the study. These 102 patients were seen at the urology clinic. 14 of them had one of the exclusion criteria. Eighty eight patients with inclusion criteria were recruited into the study.

The age, marital status, occupation and drug history of the individual patients were obtained and recorded in a proforma. Presenting complaints were documented. A physical examination was conducted on the patient. The varicocele was palpated both in the erect and supine positions. The varicoceles were confirmed using color flow Doppler US of the scrotum and the dimensions in millimeter (mm) recorded. Blood samples of the patients were taken between 8 am and 10 am for serum levels of Follicular stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (TT) and Prolactin (PRL) at recruitment time. The laboratory estimation of serum TT was by an Elisa Kit (AccuBind® Microwell ELISA Kit, Monobind Inc., Lake Forest, CA, USA) [2]. For the infertile men who had been on a stable sexual relationship for at least 12 months in addition had semen analysis. All the patients had a subinguinal microsurgical varicocelectomy and bilateral in those with bilateral varicoceles by the author. At 6 months post varicocele repair, blood samples were taken for TT, FSH, LH and PRL.

2.2. Subinguinal Microsurgical Varicocelectomy

Under spinal anesthesia an oblique 3 centimetres (cm) incision (**Figure 1**) is made across the external ring and extended through Camper's and Scarpa's fascias. Retracting both sides of the incision using Langenberg retractors, the spermatic cord is grasped using Babcock forceps (**Figure 2**) delivered and placed over a sterile guaze. The microscope is brought into the operating field and the cord examined under 10 - 15 power magnification. I incise the external and internal spermatic fascias and examine the cord contents. The external spermatic fascia and associated structures (external spermatic vessels, vas deference and its vessels, cremasteric muscle and its vessels) are separated and secured. The internal spermatic fascia and contents are examined (**Figure 3**). Using subtle pulsation and 20 MHz microvascular Doppler probe, the internal spermatic arteries are identified and preserved. The lymphatic vessels are preserved. I ligate the internal spermatic veins with silk 3/0 and divide.

Contents of the external spermatic fascia are dissected. The vas deference and its artery are preserved, cremasteric artery and other arteries are preserved. The external spermatic veins are ligated with 3/0 silk and divided. Remaining contents of the cord (vas deference and artery, cremasteric muscle and artery, internal spermatic/testicular arteries, lyhmphatic channels) are returned into the wound with a gentle pull on the ipsilateral hemiscrotum. Both Camper's and Scarpa's fascias are closed with 3/0 vicryl suture. The skin is closed with a running subcuticular 3/0 vicryl suture and the wound dressed with a sterile gauze.

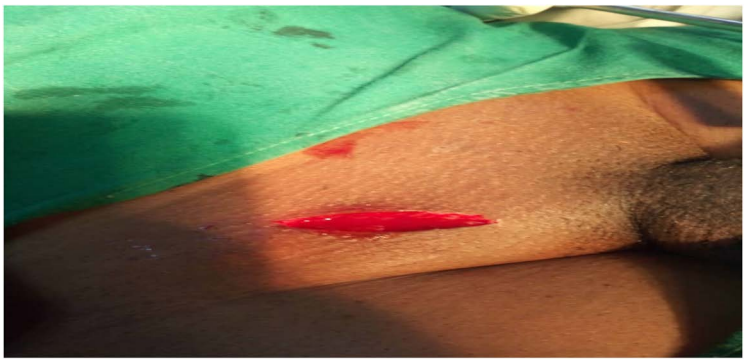

Figure 1. Skin incision.

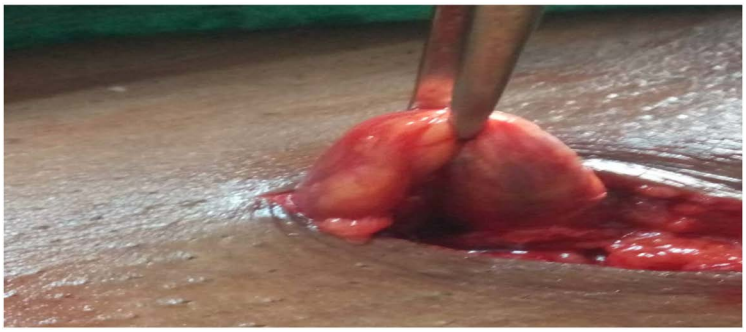

Figure 2. Spermatic cord grasped with babcock forceps.

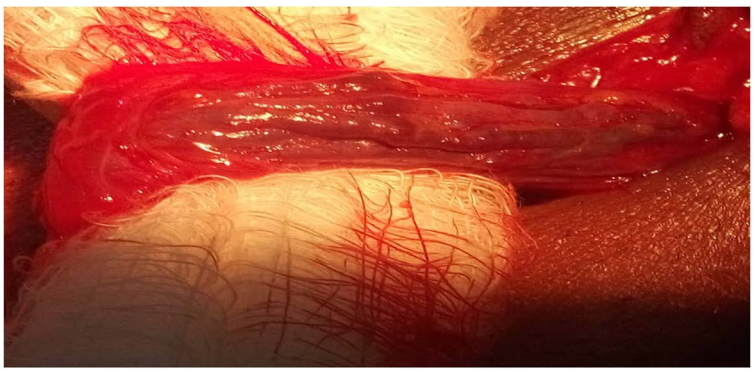

Figure 3. Internal spermatic fascia and contents.

2.3. Statistical Analysis

The data were analyzed using both descriptive and inferential statistics. The descriptive statistics, frequency, percent, mean and standard deviation were used to summarize the data. The inferential statistics, Mann-Whitney test was used to ascertain the effect of varicocelectomy on TT values at 5% level of significance. Kruskal-Wallis and ANOVA were used to compare different increases in TT in the varicocele grades and ages respectively. The unit of testosterone in this study is ng/dl. Significant effect hence existed if P-value was less than 0.05 ($P < 0.05$) otherwise no significance. These statistics were done with the aid of the statistical package for social sciences (SPSS v25 and Microsoft. The normal range of serum total testosterone level in the hospital of study is 300 - 1000 ng/dl.

3. Results

A total of 88 men who met the inclusion criteria were enrolled into the study. The age range was 19 - 58 years with a mean and standard deviation of 33.43 ± 7.82 years. Most of the patients 60.2% were in the fourth decade of life and 52 (59.1%) patients were married (Table 1). Presenting symptoms included, erectile dysfunction (ED) in 59 (67%) patients, scrotal swelling in 48 (54.5%) patients (Figure 4). 16 patients had scrotal pain pre varicocelectomy. Out of these in 15 (93.8%) patients the pain resolved at 3 months post varicocelectomy. The remaining one patient was found to have a transverse left lying testis and intermittent torsion. He had orchiopexy and the pain stopped. Scrotal swelling resolved in all the 48 patients at 3 months post varicocelectomy. Out of the 59 (67%) patients that had erectile dysfunction, 44 (75.58%) patients had improvement in sexual function at 10 months post varicocelectomy. There was improvement in International index of erectile function (IIEF-5) scores from 16.2 ± 3.6 to 20 ± 1.8 $P < 0.001$.

There was isolated left varicocele in 57 (64.8%) patients (Table 1) and (Figure 5). Grade 1 varicocele was present in 19 (17.2%) patients, 39 (35.5%) patients

Table 1. Age of patients in years.

	Frequency	Percent	M ± SD
Age			33.43 ± 7.82
- 10 - 20	5	5.7	
- 21 - 30	20	22.7	
- 31- 40	53	60.2	
- 41 - 50	8	9.1	
- 51 - 60	2	2.3	
Marital status			
- Single	36	40.9	
- Married	52	59.1	
Clinical Characteristics of the Patients		n = 88	
		Frequency	Percent (%)
Symptoms			
- Scrotal Swelling		48	54.5
- Scrotal Pain		16	18
- Poor penile erection		59	67.0
- Infertility		52	59.1
Location of Varicocele			
- Bilateral		27	30.7
- Right		4	4.5
- Left		57	64.8

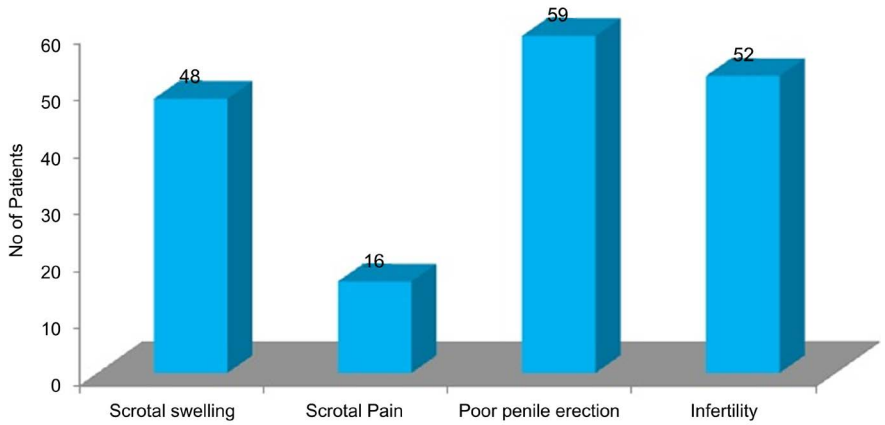

Figure 4. Symptoms experienced by the patients.

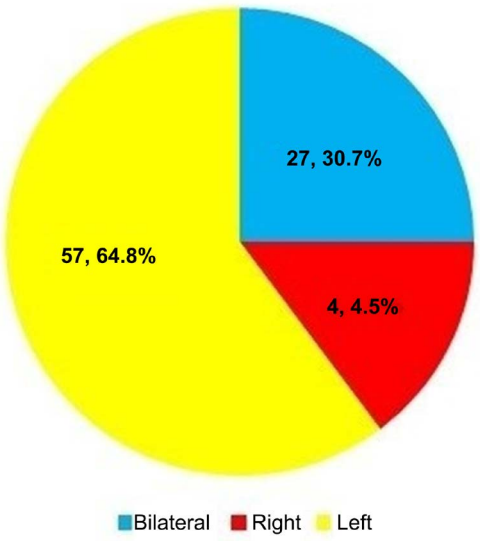

Figure 5. Location of varicocele.

had grade 2 varicocele while grade 3 varicocele was present in 52 (47.3%) patients. Sixty five (59.1%) varicoceles measured between 4.1 - 6.0 mm in diameter. The overall range was between 2.5 - 6.5 mm with mean and standard deviation of 4.2 ± 0.78 mm (Table 2).

Pre-varicocelectomy, 61 (69.3%) patients had testosterone values of between 100 - 291 ng/dl. The range was between 80 - 490 ng/dl with a mean of 241 ± 0.91 ng/dl. Post-varicocelectomy, 56 (63.6%) patients had serum TT values of 300 - 490 ng/dl. The range was 90 - 1500 ng/dl with mean of 482 ± 2.87 ng/dl. The mean serum TT levels increased from 241 ± 0.91 ng/dl to post varicocele repair of 482 ± 2.87 ng/dl ($P < 0.001$). The effect of varicocelectomy on serum TT levels was statistically significant (Table 3 and Table 4) and (Figure 6).

Fifty five (79%) out of 70 patients that had <300 ng/dl testosterone pre varicocelectomy normalized post varicocelectomy. There was mean increase of 260 ng/dl to 395 ng/dl $P < 0.0001$. The percentage increase for individual patients ranged from 52.2%, 69.7%, 78.8% to 110%. The mean difference in the increase

Table 2. Classification and dimension of varicoceles (n = 110).

	No. of Varicoceles	Percent (%)	Range	M ± SD
Classification of Varicoceles				
- 1	19	17.2		
- 2	39	35.5		
- 3	52	47.3		
Dimensions of Varicoceles (mm)			2.5-6.5	4.2 ± 0.78
- 2.5 - 3.0	19	17.3		
- 3.1 - 4.0	23	20.9		
- 4.1 - 5.0	43	39.1		
- 5.1 - 6.0	22	20.0		
- 6.1 - 7.0	3	2.7		

Table 3. Testosterone values pre- and post-varicocelectomy (n = 88).

Testosterone value (ng/dl)	Frequency	Percent
Pre		
- <100	9	10.2
- 100 - 299	61	69.3
- 300 - 499	18	20.5
- 500 - 1000	0	0.0
- >1000	0	0.0
Post		
- <100	2	2.3
- 100 - 299	11	12.5
- 300 - 499	56	63.6
- 500 - 1000	17	19.3
- >1000	2	2.3

Table 4. Effect of varicocelectomy on testosterone.

	Testosterone Value (ng/dl)				Mann-Whitney	p-value
	Range	M ± SD	95% C.I	Mean Rank		
Varicocelectomy					320.0	<0.001
- Pre	80 - 490	2.41 ± 0.91	1.19 - 1.58	48.14		
- Post	90 - 1500	4.82 ± 2.87	5.93 - 7.15	128.86		

in levels of TT after varicocelectomy for grades I, II and III varicoceles were 201 ± 0.08, 205 ± 0.04, 202 ± 0.06 ng/dl respectively. Using Kruskal-Wallis to compare these mean respective increases of TT for grades I, II, and III gave the p-value of 0.951, there is no statistical difference in the increasing levels of TT in

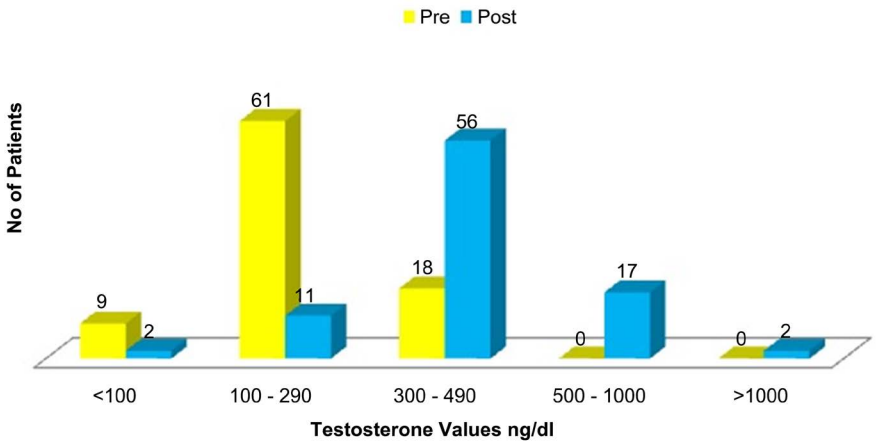

Figure 6. Testosterone values in ng/dl pre- and post-varicocelectomy.

grades I, II and III varicoceles. TT improvement post varicocelectomy is independent of varicocele grade in this study (See Table 5(a)).

Furthermore, analysis into the impact of age on total testosterone improvement post varicocelectomy shows that mean increase in TT for age groupings, less than 30 years, 31 - 40 years and above 40 years were 190 ± 0.33, 169 ± 0.22 and 153 ± 0.28 ng/dl respectively. Using ANOVA to compare these respective mean increases gave a p-value of 0.238. This implies there is no statistical difference between the TT mean increments in the three age groupings. Hence age did not have any impact on TT improvement after varicocelectomy in this study. There is post varicocelectomy improvement in TT at all ages (See Table 5(b)).

4. Discussion

It has been shown that men with clinical varicoceles have lower testosterone levels irrespective of age, with emerging evidence of beneficial effect of varicocelectomy on increases of serum TT regardless of patient's age or laterality of varicocele [15] [16]. The average age of patients in this series was 33.43 ± 7.82 years. In a similar but retrospective study by Tanrikut *et al.* in 2007, the average age of patients was 36 ± 8 years [17]. The incidence of scrotal pain in this study was 18%. In other studies, 10% of varicoceles will present with scrotal pain [3] [4]. The higher prevalence in this study could be due to late presentation with worsening pathophysiology. Left sided varicocele was noted in 95.5% of the patients in this series. A prevalence of 85% - 90% was reported by Leslie *et al.* [1] and by Gat *et al.* [18]. Furthermore bilateral varicocele was found in 30.7% of the patients and this was by physical palpation and color Doppler US of the scrotum. Alsaikhan *et al.* noted that 50% of men had bilateral varicocele [19]. Gat *et al.* using venography in his series found bilateral varicocele in 80.8% of his patients [18].

In this series the pre-varicocelectomy mean TT was 241 ± 0.91 ng/dl. Several mechanisms have been proposed to explain the deleterious effect of varicocele on leydig cell function. These include scrotal hyperthermia, reflux of adrenal and

Table 5. (a) Comparing mean total testosterone levels pre- and post-varicocelectomy based on varicocele grading; (b) Comparing mean total testosterone levels pre- and post-varicocelectomy based on age.

(a)

	Grade	Pre-Repair	Post-Repair	Z	P-value
TT ng/dl	1	297 ± 0.01	498 ± 0.09	−2.810	0.005
	2	234 ± 0.24	439 ± 0.28	−2.805	0.005
	3	210 ± 0.05	412 ± 0.11	−2.812	0.005

(b)

	Age	Pre-Repair	Post-Repair	Z	P-value
TT ng/dl	<30 yrs	298 ± 0.15	488 ± 0.48	−2.524	0.012
	31 - 40 yrs	278 ± 0.47	447 ± 0.69	−2.51	0.012
	>40 yrs	282 ± 0.42	435 ± 0.70	−2.521	0.012

renal metabolites and increased hydrostatic pressure in the internal spermatic vein [14] [19] [20]. Furthermore there is increased exposure of the testis to gonadotoxins from suboptimal drainage due to venous dilatation [21], varicocele induced increase in reactive oxygen species production and testicular hypoperfusion [6] [14] [19] [20]. Leydig cells are the principal androgen producing cells producing up to 95% of TT in men [6] [14]. Patients with clinical varicocele have leydig cell atrophy, leydig cell structural changes and marked decrease in quantity of testosterone positive leydig cells [20]. Testosterone production in leydig cell is a 5-stage enzymatic process that leads to conversion of 17-hydroxyprogesterone to testosterone by the enzyme 17 alpha-hydroxyprogesterone aldolase. The most accepted hypothesis that explains the effect of varicocele on leydig cell function hinges on changes on the testicular thermal environment. The testicular veins leaving the testis form a communicating meshwork of veins that produce a counter—current heat exchange mechanism to cool the arterial blood flowing into the testis [22]. This cooling mechanism is lost in patients with clinical varicocele causing elevated scrotal temperatures by 2.6˚C due to regurgitation of warm abdominal blood through incompetent valves [23] [24] [25]. Thus the scrotal hyperthermia affects adversely this enzyme that produces testosterone [6] [14] [19] [20]. As noted in this study, 69.3% of the patients had serum TT of between 100 - 299 ng/dl pre varicocelectomy. Other studies have shown that varicocele adversely affects leydig cell function leading to low serum TT [26] [27] [28]. Furthermore varicocele increases apoptosis in leydig cells and suppresses the expression of the StAR protein [27]. Six months post varicocelectomy, 63.6% of the patients had serum TT levels of between 300 - 490 ng/dl. The mean serum TT rose to 482 ± 2.87 ng/dl ($P < 0.001$). Subinguinal microsurgical varicocelectomy robustly and significantly raised the serum TT of patients in this series. Other researchers have produced similar results in their respective studies [2] [22] [29] [30] [31] [32]. Furthermore 60% - 80% of men with low serum testosterone will exhibit normalization of testosterone levels after varicocele repair [33]. In this series, 55 (79%) patients exhibited normalization of testosterone le-

vels after repair.

Sathya Srini *et al.* studied 200 infertile men with varicocele who had serum TT of 280 ng/dl. One hundred men underwent surgical repair and had increase in TT from 177.2 ± 18.44 to 301 ± 43 ng/dl ($P < 0.001$) at six months post-operatively [30].

Zohdy *et al.* carried out microsurgical varicocelectomy in 103 men with clinical varicocele and the TT levels increased significantly from 379.1 ± 205.8 to 450.1 ± 170.2 ng/dl ($P < 0.0001$) at 6 months post-operatively [31].

Hsiao *et al.* retrospectively reviewed 78 men. They had subinguinal microsurgical varicocelectomy. At 7 months post-operatively, there was a statistically significant increase in TT from 308.4 ± 7.1 ng/dl to 417.5 ± 14.8 ng/dl ($P < 0.0001$) [32].

Nineteen (17.2%) out of the 110 varicoceles were grade 1 varicoceles and were part of the bilateral varicoceles. These 19 varicoceles were repaired subinguinally. A left varicocele produces blood column of 40 centimeters (cm), and this high hydrostatic pressure is exerted on the pampiniform plexus [34]. When this high venous pressure exceeds the arteriolar pressure in the testicular microcirculatory system, the hypoxic effect occurs bilaterally [34]. It must be stated that both palpable and non-palpable veins have the same adverse effects on the testis and so varicocelectomy on the left ignoring bypasses is not adequate to correct the problem [34]. Thus bilateral varicocele repair was done in these patients to reverse bilateral testicular dysfunction and improve testosterone production.

In stratifying the TT improvement after subinguinal varicocelectomy based on varicocele grade, it was found that varicocele grade had no impact on Serum TT improvement after varicocele repair. Other studies have noted similar findings [32] [33]. Furthermore, stratification of the patients into various age groupings showed that testosterone improvement occurred across all age groupings. Age did not impact the TT improvement after varicocele repair as TT improvement was noted in older age groups in another study [35].

The limitations of the study are low awareness of varicocele within the population of study and thus decrease flow of patients with clinical varicoceles to the urology clinic. Lack of previous research work on the topic from this part of the world thus paucity of local data to work with. Hormonal assays are expensive and posed economic stress on the researcher.

5. Conclusion

The results from this study support the observation that subinguinal microsurgical varicocelectomy robustly increases the serum levels of TT. This will reverse the adverse effects of low testosterone in patients.

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lection.

Permission

The ethical committee of the hospital gave permission for this study to be carried out.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Evolution of Androgenic Deprivation in Treatment of Prostate Cancer in Kinshasa

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Abstract

Context and Objective: Prostate cancer (PCa) is hormone-dependent cancer. In our area, most patients often arrive at the locally advanced stage or the metastatic stage. This justifies the choice of androgen deprivation as the mode of treatment. The objective of this study was to describe the socio-demographic characteristics of patients with PCa. Identifying the period during which the disease remains susceptible to androgen deprivation. Assessing the patient's prognosis in terms of survival. **Methods:** This is a retrospective observational study of the course of patients managed for PCa. It involved 51 cases and was conducted at the Pointe à Pitre clinic (CPAP) in Matete Township during a period of 4 years (from March 2014 to June 2018). **Results:** The mean age of patients was 69.4 ± 9.7 years (40 - 92 years); 39.2% of patients with PCa were aged between 70 - 79 years; 45.1% had consulted for dysuria and 25.5% were hypertensive. All had performed the prostate biopsy, 47.1% were diagnosed at the metastatic stage, with PSA ≥ 100 ng/ml, Gleason scores 8 - 10, and clinical-stage TNM 3 - 4. About 51% were subjected to androcure, 23.5% had been surgically cased and 3.9% had undergone radical prostatectomy. 41.1% had resisted castration within a median of 1.4 years of response to treatment. The median survival was 30 months, with a mean survival of 26.6 months. **Conclusion:** Prostate cancer involved most of the patients in the age bracket of 70 to 79 years. The diagnosis was performed lately with a high resistance rate of castration and median survival of 30 months.

Keywords

Deprivation, Prostate Cancer (PCa), Pointe à Pitre Clinic (CPAP)

1. Introduction

Prostate cancer (PCa) is the most common cancer in men in America (Afro-Americans and Afro-Caribbean) and Europe [1] [2] [3]. Patients with localized or sometimes locally advanced forms benefit from radical prostatectomy or radiotherapy. On the other hand, in patients with aggressive or metastasized forms; the treatment options may be radiotherapy but more commonly androgen deprivation [4]. To reduce the plasma level of testosterone and its derivative, dihydrotestosterone (DHT), androgen deprivation; apart from surgical castration still used by Anglo-Saxons, other practitioners prefer hormone therapy [5]. This hormone therapy has evolved with the emergence of LH-RH analogs, then treatment with non-steroidal anti-androgens, and finally, more recently, LH-RH antagonists, and Gn-RH agonists [6]. Depending on the patient's response, this hormone therapy goes from the first to the third line [7] [8]. Over 90% of patients treated respond to androgen deprivation. Unfortunately, transiently, its duration varies from a few months to a few years. The median being 12 to 18 months, then relapse is observed in 100% of cases. After the escape from this first line of hormone therapy, responses to alternative hormonal manipulations are rare, the tumor is resistant to castration [7] [8]. Once the hormone-independence stage has been reached, the tumor is resistant to castration. Median overall survival is 34 months [6]. Castration-resistant PC (CRPC) is an advanced form characterized by disease progression after surgical or pharmaceutical castration (androgen deprivation). The process by which prostate cancer cells become resistant to castration is not clear, but androgenic privations have been shown to offer a selective advantage to androgen-independent cells, which eventually grow and repopulate the tumor [9]. Compared with castration sensitive PCa, the prognosis of patients with CRPC is poor and survival is reduced. Until very recently, treatment options were mainly limited to symptomatic relief of bone metastases, which are more common in CRPC than in the castration-sensitive form [9] [10] [11] [12]. To provide a clear picture of the burden of CRPC, one must consider the prevalence of the disease, the relative time of onset versus diagnosis, patient characteristics including demographics, comorbidity, the onset of disease, metastatic form, and probable survival. There is, however, insufficiency of epidemiological evidence specifically characterizing CRPC outside of the settings of controlled trials in which patients may not represent the general population and normal disease progression. This can lead to its sub-optimal management; for example, the identification of patients with CRPC who are at risk of developing metastases is currently hampered by a poor understanding of its real epidemiology. Identifying people with CRPC may seem straightforward after androgen deprivation (drug or surgical). The characterization of the disease in epidemiological terms, eg incidence, prevalence, and survival, is however less clear. This can be attributed at least in part to the difficulty of defining, and therefore of studying, the patient population. The varying terminology—CRPC, HRPC (Hormone-refractory PCa), AIPC (Androgen-independent PCa), ERPC (Endocrine-resistant PCa)—reflects subtle differences in dentition that may hamper

research comparison. Practitioners can also use a variety of diagnostic methods: prostate-specific antigen (PSA) assays, the development of metastases, or other factors to determine if a patient is defined as CRPC. The recently published European Association of Urology (EAU) guidelines aim to standardize the diagnosis of CRPC and include a list of five defining factors of CRPC [4].

These are as follows:

- Serum testosterone level.
- Three consecutive increases in Prostate Specific Antigen (PSA) 2 weeks apart resulting in two increases of 50% over the nadir.
- Anti-androgen stops for at least 4 weeks.
- Progression of PSA despite secondary hormonal manipulations.
- Progression of bone or soft tissue damage.

CRPC is a heterogeneous disease, and despite the availability of such guides for diagnosing CRPC, in practice, this can vary. Also, besides, the routes of treatment and clinical practice, particularly the stage of the disease at the onset of androgen deprivation therapy, vary widely between geographic locations and even the individual's clinic. Therefore, establishing common epidemiological estimates for the CRPC population becomes very complex and may become less relevant for individual scenarios [13].

In our environment, most affected patients consult at the advanced stage of the disease; thus, justifying androgen deprivation as a mode of treatment.

This study aimed to improve the clarity of the epidemiological evidence around CRPC, by identifying, assessing, and describing the most relevant elements that characterize the affected patient population using observational data.

Our objective was to assess the responses to hormonal deprivation, patient survival and to identify the different predictors of mortality.

2. Methods

Nature, Period, Framework and parameters of interest.

This is a retrospective observational epidemiological study that focused on the evolution of the 51 patients followed for PCa at the Pointe à Pitre Clinic during the period from March 2014 to June 2018. Pointe-à-Pitre Clinic is a non-profit organization, non-denominational and nonpolitical called "PROSTATE CANCER VIGILANCE AFRIQUE CENTRALE", PCVAC in acronym was created in Kinshasa, capital of the DRC on April 27, 2016. The head office of the association is in Kinshasa, within the Clinic cited above in the city of Kinshasa province in Matete Township, Kinzazi district, n˚ 11D in Matete Health District. During the entire study period, 1364 patients were received at the CPAP and we identified 165 cases of prostate cancer (12%) and among them, only 51 cases were retained to constitute our sample of coverage. Among the 165 patients, many were excluded because their follow-up was incomplete (PSA and Testerone). Our parameters of interest were age, profession, marital status, place of residence, complaints, cTNM, PSA, testosterone biopsy, prostate ultrasound, MRI results, Scintigraphy, radiography (pelvis and column), histological result, Gleason score,

stage of progression, treatment, patient survival, a predictor of mortality. The androgen deprivation method has been either surgical (bilateral orchidectomy) or chemical (hormone therapy). We used for hormonotherapy, Cyproterone acetate (50 - 100 mg), Gosereline (10.8 mg) Bicalutamide (50 mg), and Docetaxel for the chemotherapy. Some patients who have undergone radical prostatectomy have received complete hormone therapy or orchidectomy for PCa recurrence.

2.1. Inclusion Criteria

We considered patients' files with a PCa which was treated and operated during the period of our study.

2.2. Non Inclusion Criteria

Incomplete or absent files on during data collecting have not been taken into account.

2.3. Collection of Data

We collected data by completing an ad hoc form related to the documentary review focused on the medical records and registers of patients.

3. Statistical Analyses

The data were computerized using Excel 2010 software and were analyzed using SPSS version 17 software. Tables or graphs were used, as appropriate, for the presentation of the results. The continuous quantitative variables with Gaussian distribution were presented as mean ± standard deviation; those with non-normal distribution in the form of the median (extremes). Qualitative variables were described as relative frequency (%). Comparison of proportions, medians, and means was performed using Chi-square, Mann Whitney Wilcoxon, and Student's t-tests, respectively. Independent determinants of resistance to surgical castration and PSA ≥ 100 ng/ml were identified using logistic regression. Kaplan Meier's method estimated the probability curve of resistance to surgical castration. It also described survival between the date of diagnosis of CaP and death (complete data) and the end of the study (censored data). The Log-rank test was used to compare survival curves. Cox's regression looked for independent predictors of mortality.

A p-value < 0.05 was considered the threshold of statistical significance.

Ethical Considerations

During the collection and analysis of our data, confidentiality was strictly enforced.

4. Results

4.1 General Characteristics of the Study Population

About 51 patients, the average age was 69.4 ± 9.7 years, with extremes of 40 to 92

years. The age range of 70 to 79 years was the most common (39.2%). Obstructive signs and irritative signs were respectively 72.5% and 33.3%. Dysuria was the obstructive symptom that most prompted patients to consult (45.1%) followed by nycturia (23.5%) like irritative symptoms. Hypertension was the most common comorbidity (25.5%). It appears that; 47.1% of PCa were diagnosed at the metastasis stage, followed by cancers at high risk of progression (25.5%). Only 7.8% of cancers were at low risk. The metastases were from localizations variables; bone (50%), multiples (20%), ganglion (16.7%) and testicles (12.5%). The year 2014 saw more consultations (37.2) and the highest mortality rate was observed during the year 2017 (50%). The overall mortality rate was 19.6% and overall survival was 80.4% (Table 1).

Table 1. General characteristics of the population of the study.

Variables	PSA (ng/ml) Average (extreme)	Sample (n = 51)	Pourcentage (%)	Death n (%)
Age (year) Average		**69.4 ± 9.7 (40 - 92)**		
<60 years		7	13.7	-
60 - 69 years		17	33.3	-
70 - 79 years		20	39.2	-
≥80 years		7	13.7	-
Symptoms				
Obstructive signs		37	72.5	-
Irritative signs		17	33.3	-
Haematuria		4	7.8	-
Medical history				
Arterial hypertension		13	25.5	-
Diabetes		6	11.8	-
PSA	51, 5 (34.3- ≥100, 0)	51	100	-
Stage of diagnosis				
Metastatic cancer		24	47.1	-
High-risk cancer		13	25.5	-
Medium risk cancer		10	19.6	-
Low-risk cancer		4	7.8	-
Metastasis locations		n (24)	47.1	-
Bones		12	50.0	-
Nods		4	16.7	-
Testis		3	12.5	-
Multiples		5	20.8	-
Annual frequency and death				**10 (19.6)***
2014		19	37.2	1 (5.2)
2015		6	11.7	2 (33.3)
2016		14	27.4	1 (7.1)
2017		12	23.5	6 (50)
General survival in 4 years		41	80.4	-

*Global mortality in 4 years.

4.2. Treatment and Evolution

The treatment varied depending on the case (Hormone therapy, Surgery, chemotherapy):

- Ciproterone Acetate (Androcure) 50.9%;
- The Goserelin-Bicalutamide combination in 45.0%;
- Surgical castration in 23.5%;
- Surgical castration was associated with TURP in 11.8% of cases;
- Radical prostatectomy in 3.9%.

From an evolutionary point of view; the rate of castration resistance was 43.1% within a median of 1.4 (1 - 3) years of response to treatment (Table 2).

4.3. Evaluation of Castration Resistance

Castration resistance was observed from the 5th month of treatment, especially for carrier patients with metastases.

4.4. Resistance to Castration According to Gleason Score

Patients with a Gleason score between 8 and 10 had a higher frequency of resistance compared to those with a Gleason score between 6 and 7; log-rank test ($p = 0.018$) (Figure 1).

4.5. Risk of Resistance According to the D'AMICO Classification

According to D'AMICO's classification, the risk of castration resistance was variable:

- Twice for the intermediate-risk PC [OR 2.02 95% CI (1.45 - 3.90); P = 0.021];
- Three for high-risk PC [OR 2.95 95% CI (1.36 - 4.69); P = 0.041];
- And 6 times for metastatic CaP [OR 5.88 95% CI (1.62 - 7.99); P = 0.019] (Table 3).

Table 2. Distribution of patients according to treatment mode.

Variables	Sample (n = 51)	Pourcentage (%)
Traitement		
Hormonotherapy	49	95.9
Ciprotérone acetate	26	50.9
Goselerine/Bicalutamide	23	45.0
Goselrine/Bicalutamide Chemotherapy	2	3.3
Surgery	28	54.9
Surgical Castration	12	23.5
TURP alone	8	15.7
TURP + surgical castration	6	11.8
Radical Prostatectomy	2	3.9
Evolution		
Castration resistance	22	43.1

Table 3. Distribution of resistance according to the D'AMICO classification.

Classification of D'Amico	Resistance to castration		p	OR (IC95%)
	No	Yes		
Low risk cancer	2 (6.9)	2 (9.1)	0.818	1
Intermediate risk cancer	7 (24.1)	3 (13.6)	0.021	2.02 (1.45 - 3.90)
High risk cancer	8 (27.6)	5 (22.7)	0.041	2.95 (1.36 - 4.69)
Metastatic cancer	12 (41.4)	12 (54.5)	0.019	5.88 (1.62 - 7.99)

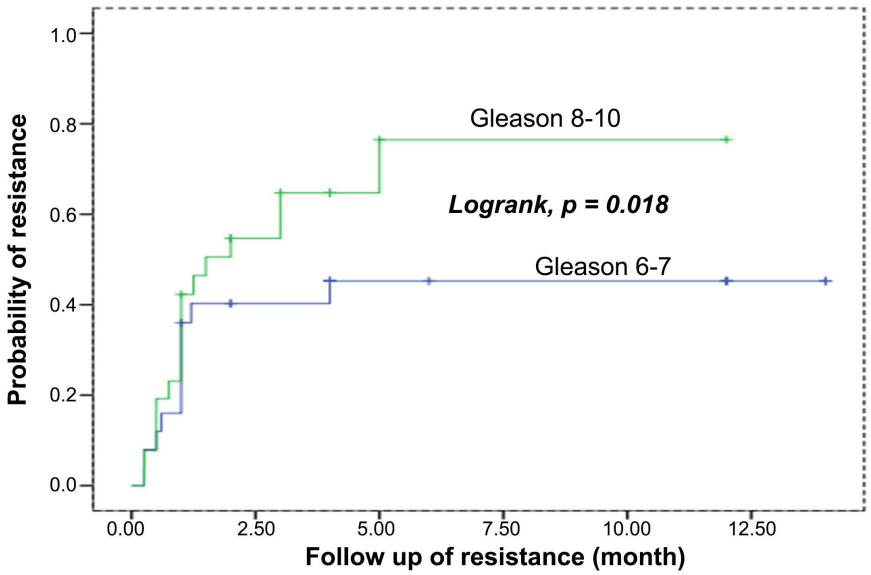

Figure 1. Gleason score and castration resistance.

4.6. Resistance to Castration According to Clinical Signs

Dysuria came first in 39.1%, followed by pollakiuria in 30.4%, nocturia in 26.1%, and bone pain in 21.1% of cases (Table 4).

4.7. Assessment of Prostate Specific Antigen Rate and Testosterone (ng/ml)

During treatment, the PSA level tended to decrease for all patients. Its increase has been observed in some patients from the 4th dosage. The mean PSA was 51.5 (0.3 - 2528.7) ng/ml for un median of 7.75 ng/ml. However, the testosterone level which reached the castration rate still tended to cancel out. Its average was 2.8 ng/ml (0.5 - 8.15).

4.8. Prostate Specifin Antigen Evaluation According to Age, cTNM, and Gleason Score

The PSA level was not statistically significant (p 0.779) compared to the ages of the patients. The increase in PSA level was influenced by clinical stage cT3 - cT4 [OR 15.0 95% CI (2.02 - 17.11); p = 0.006], with a statistically significant difference in cT1 - cT2 (p 0.006) and score Gleason [OR 6.07 95% CI (1.49 - 24.76)] without any statistically significant difference in score 6 - 7 (p = 0.011) (Table 5).

Table 4. Distribution of clinical signs in patients resistant to castration.

Paramètres	Sample (n = 23)	Pourcentage (%)
Dysuria	9	39.1
Pollakiuria	7	30.4
Nycturia	6	26.1
Bone pain	5	21.7
Urinary incontinence	4	17.4
Mictalgia	3	13.0
Drop by drop urination	3	13.0
LLE	2	8.7

Table 5. Distribution of Prostate Specific Antigen levels by age, cTNM, and Gleason score.

Variables	PSA (ng/ml)			p	OR (IC95%)
	All	<100	≥100		
Age				0.779	
<60 years	7 (13.7)	3 (11.5)	4 (16.0)		1
60 - 69 years	17 (33.3)	8 (30.8)	9 (36.0)		0.86 (0.13 - 5.82)
70 - 79 years	20 (39.2)	13 (50.0)	7 (28.0)		0.54 (0.09 - 3.41)
≥80 years	7 (13.7)	2 (7.7)	5 (20.0)		1.50 (0.14 - 16.54)
cTNM				0.006	
cT1 - cT2	14 (76.9)	7 (53.8)	7 (58.3)		1
cT3 - cT4	11 (23.1)	6 (46.2)	9 (41.7)		15.0 (2.02 - 17.11)
Gleason				0.011	
6 - 7	25 (49.0)	13 (50.0)	12 (48.8)		1
8 - 10	26 (51.0)	13 (50.0)	13 (52.2)		6.07 (1.49 - 24.76)

4.9. Assessment of Patients' Survival

The probability of patient survival was 92.2% at 10 months, 84.3% at 15 months, 82.4% at 20 months, and 80.4% at 48 months, respectively. The median patient survival was 30 (24 - 30) months and the mean survival was 26.6 months.

4.10. Assessment of Patients' Survival versus Castration Resistance

Patients resistant to castration had significantly reduced survival compared to those who did not (p = 0.029) (**Figure 2**).

4.11. Assessment of Survival about Prostate Specific Antigen Level

The survival of patients with a PSA level ≥ of 100 ng/ml (p = 0.006) was significantly lower compared to the others (**Figure 3**).

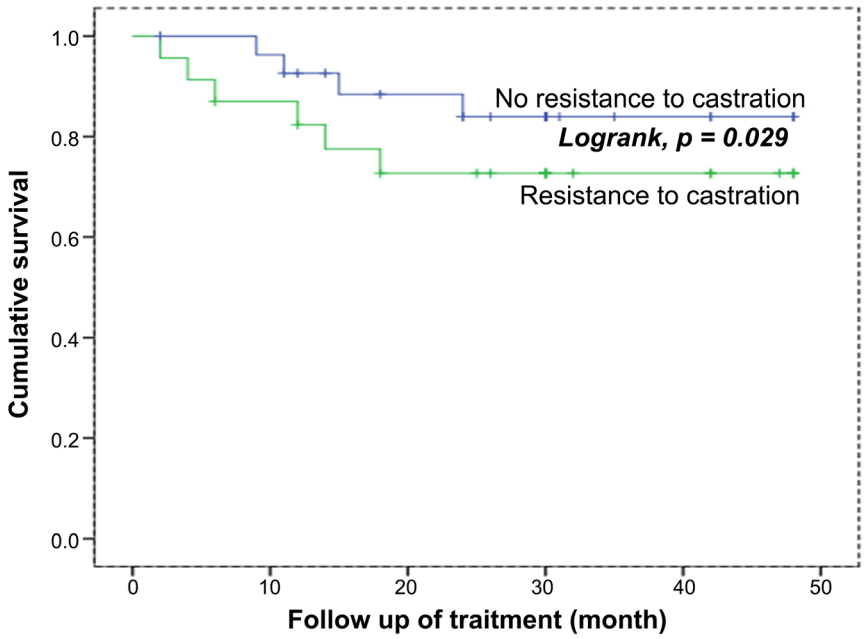

Figure 2. Patients' survival versus castration resistance.

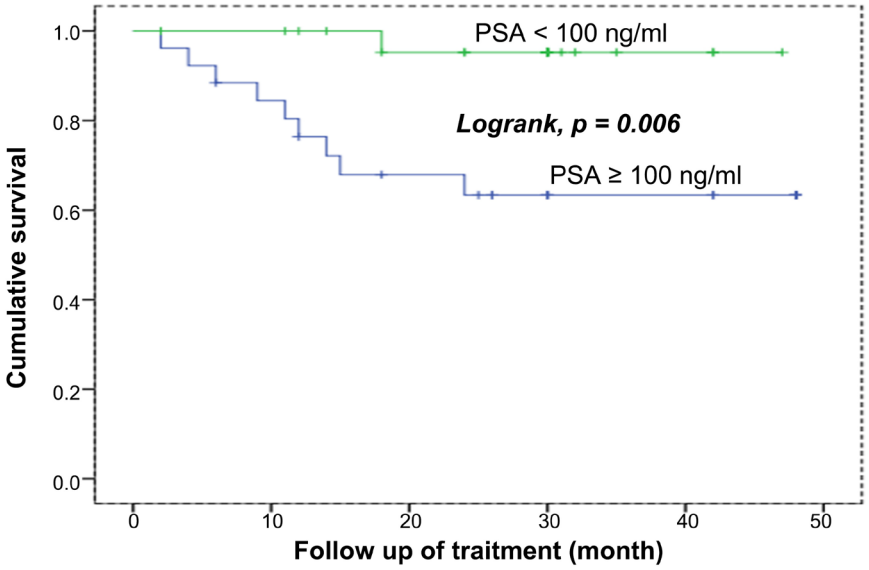

Figure 3. Survival curve as a function of the prostate specific antigen level.

4.12. Assessment of Survival about Gleason Score

The survival of patients with a Gleason score of 8 - 10 (p 0.004) was significantly lower than those with a score of 6 - 7 (**Figure 4**).

4.13. Predictors of Mortality

In univariate analysis; PSA levels ≥ 100 ng/ml [HR 10.20 95% CI (1.29 - 13.56); p = 0.001], Gleason score 8 - 10 [HR 10.97 98% CI (1.39 - 16.68); p = 0.035] castration resistance [HR 3.98 95% CI (1.56 - 7.04); p = 0.017] and metastases [HR 2.67 95% CI (1.69 - 10.35), p = 0.007] were predictors of mortality, without any

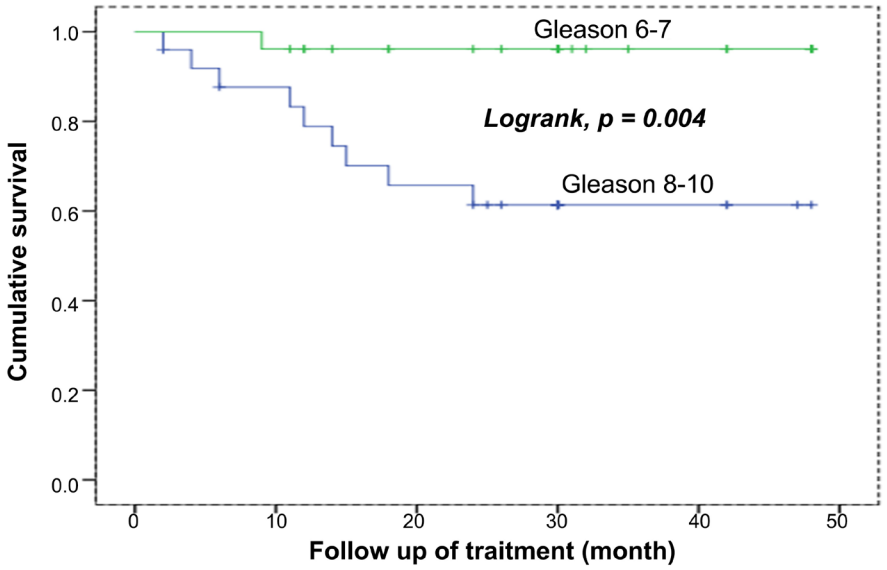

Figure 4. Survival about Gleason score.

significant difference within each group (**Table 6**). In multivariate analysis, the Gleason score 8 - 10 [HRa 10.15 95% CI (2.18 - 12.23); p = 0.035] and the PSA ≥ 100 [HRa 8.49 95% CI (2.15 - 10.56); p = 0.001] were more evident as predictors of mortality (**Table 6**).

5. Discussion

The current study is one of the few to have explored the course of androgen deprivation in 51 patients treated for PCa Apart from the response to this hormonal deprivation, the objective was to evaluate the survival of the patients and to look for the different predictors of mortality. In **Table 1**, it was from the fourth decade that PCa was diagnosed in our patients with an average age of 69.4 years (40 - 92 years). Many studies report either an average around the sixth decade [3] [14] [15] [16] [17] or around the seventh decade [18]-[24] with extremes that do not show significant differences. Only one reports an average of 59.13 years [25] (**Table 7**).

Hypertension was the most common comorbidity in 25.5% of cases. Studies have explored the association of PCa with hypertension as comorbidity and report different results. Some report hypertension as the only comorbidity; 33.3% [17] and 35.4% [26] cases. Others show an increased risk of PC [27], death [28], and an increased prevalence of PCa in hypertensive Africans [29]. Most of the patients were carriers of PCa diagnosed at the stage of metastasis followed by cases at high risk of progression and intermediate risk. Those of low risk have been rare. The same results are described in the literature, with the predominance of metastatic cancers for some authors [15] [21] [24] [29] [30]. Others report more on low-risk and intermediate-risk cancers [31] [32] [33]. Indifferent types of studies. Bone metastases predominated, followed by multiple locations and lymph nodes. PCa is first recognized as osteophytes cancer before any other

Table 6. Distribution of patients according to the predictors of mortality.

Variables	Univaried Analysis		Multivaried Analysis	
	p	HR (IC95%)	p	HRa (IC95%)
PSA (ng/ml)				
<100		1		1
≥100	0.028	10.20 (1.29 - 13.56)	0.001	8.49 (2.15 - 10.56)
Gleason				
6 - 7		1		1
8 - 10	0.023	10.97 (1.39 - 16.68)	0.035	10.15 (2.18 - 12.23)
Metastatic cancer				
No		1		1
Yes	0.015	2.67 (1.69 - 10.35)	0.007	4.77 (1.89 - 6.32)
Castration resistance				
Yes		1		1
No	0.029	3.98 (1.56 - 7.04)	0.017	3.15 (1.25 - 5.36)
cTNM				
cT1 - 2		1		1
cT3 - 4	0.035	2.16 (1.44 - 6.74)	0.736	1.35 (0.24 - 7.71)

Table 7. Char of mean age according to authors.

Authors	Country	Mean Age	Year
Carl K. *et al.* [14]	Colombia	66.0 (49 - 70)	2007
Laurent Brureau *et al.* [3]	Antilles	68.0 (46 - 95)	2009
Laurent Brureau *et al.* [15]	Guadeloupe	66.4 (46 - 95)	2016
B. Sine *et al.* [16]	Sénégal	68.5 (53 - 82)	2016
Dieudonné Moningo *et al.* [17]	DRC	68.9 (43 - 88)	2018
Hwang *et al.* [18]	USA	73.0-	2004
Smith MR *et al.* [19]	NR	75.0 (60 - 80)	2005
Henry Botto *et al.* [20]	France	70.6 ± 8.8 and 72.2 ± 7.1	2007
Daniel *et al.* [21]	USA	70.0 (67 - 81)	2016
Mohamed Ait Chtouk [22]	Morocco	75.0 (51 - 99)	2016
Rozet *et al.* [23]	France	70.0-	2016
Maha Hussain *et al.* [24]	UK	74.0 (50 - 95)	2018
Ngandu TJ *et al.* [25]	Mbujimayi (DRC)	59.1 (57 - 60)	2015
Our study	DRC	69.4 (40 - 90) (**Table 1**)	2020

NR: No reported.

localization [21] [34] [35] [36] [37] [38]. We used clinical signs, PSA and testosterone level, cTNM stage, Gleason score, and medical imaging to assess castration resistance in our patients. Everything was summed up in D'Amico's classification. Numerous studies have explored similar parameters in various ways to assess castration resistance in PCa [39] [40] [41]. Most patients had benefited from castration (hormonal or surgical), radical prostatectomy was very rare (3.9%) (**Table 2**). These results are almost like those found in the literature [20]

[42] [43] [44]. The castration-resistant cancer rate (CRPC) was 43.1% within a median of 1.4 (1 - 3 years) year (17 months) of response to treatment (**Figure 1**). Our results are different from those of other authors [11] [34] [45] [46] [47] [48]. Other studies [49] report that 10% to 20% of PCa evolve into CRPC approximately 5 years after the start of treatment (**Table 8**).

Gleason score 8 - 10 (log-rank; p = 0.018) (**Figure 1**), High-risk Cap [OR 2.95 95% CI (1.36 - 4.69)] (**Table 3**), metastatic [OR 5.88 95% CI (1.62 - 7.99)] (**Table 3**), and dysuria (**Table 4**) were providers of CPRC. These same results are reported by many researchers [11] [21] [34] [44] [49] [50] [51] [52]. The increase in PSA level was influenced by clinical stage cT3 - cT4 [OR 15.0 95% CI (2.02 - 17.11); p = 0.001], and Gleason score 8 - 10 [OR 6.07 95% CI (1.49 - 24.76); p = 0.035] (**Table 5**). These same results are repeated in many studies [53]-[58]. In terms of percentage, patient survival was 94.7%, 88.0%, 89.7%, and 80.4% at 1 year, 2 years, 3 years, and 4 years, respectively. Three groups of auteurs report report different survival percentages. The first indicates a survival at 1 year, 2 years, 3 years, and 4 years between 80% to 90% [16] [21], the second suggests a 5-year survival of 30% for CRPCs [55]. In the end, the Henry Botto team evokes a survival of 21.1%% at 8 years [20].

In terms of months or years, the median patient survival was 30 [24]-[30] months and the mean survival was 26.6 months. Most studies already published report a median survival that varies between 14 to months, with certain differences depending on the stage, grade, and comorbidity [16] [18] [19] [20] [24] [34] [53] [59] [60]. Patients resistant to castration (LogRank, p = 0.029) (**Figure 2**), those with a PSA level ≥ 100 ng/ml (LogRank, p 0.006) (**Figure 3**) or a Gleason score 8 - 10 (LogRank, p 0.004) (**Figure 4**) had significantly reduced survival compared to the others. Other researchers come to the same conclusion [11] [21] [38] [61]. Searching for predictors of mortality; in univariate analysis; PSA levels ≥ 100 ng/ml [HR 10.20 95% CI (1.29 - 13.56); p = 0.001], Gleason score 8 - 10 [HR 10.97 98% CI (1.39 - 16.68); 0.035] resistance to castration [HR 3.98 95% CI (1.56 - 7.04); p = 0.017] and metastases [HR 2.67 95% CI (1.69 - 10.35); p = 0.007] were predictors of mortality, without any significant difference within each group. In multivariate analysis, the Gleason score 8 - 10 [HRa 10.15 95% CI (2.18 - 12.23); p = 0.035] and the PSA level ≥ 100 [HRa 8.49 95% CI (2.15 - 10.56) p = 0.001] (**Table 6**), were more prominent as predictors of mortality.

Table 8. Chart of castration resistance according to the authors (34).

Reference (Autor)	Type (Study)	Country (Year)	Age (Patients)	Period (Study)	Prevalence (CRPC)
Alemayehu [45]	Retrospective	USA (2001-2007)	≥40 ans	>6 years	17.8%
Morgan [46]	Retrospective	UK (1998-2008)	≥40 ans	>10 years	11.2%
Berruti [47]	Prospective	Italy (1996-2003)	47 - 87 years	55 months	53%
Bianco [49]	Retrospective	USA (1990-1999)	-	1 - 145 months (Médiane 55 months)	19%
Our study	Retrospective	DRC (2014-2016)	40 - 92 years	4 years	43.1%

The same observation is made by many authors namely; the mortality is all the higher for high-grade, metastatic PCa, RCPC and a very high PSA rate [21] [36] [51] [61] [62] [63].

6. Conclusion

Prostate cancer is a public health challenge in our area. The average age of the patients was 69.4 years (40 - 92 years). Dysuria was the main symptom of medical consultation. Hypertension was the main comorbidity among our patients. Most of our patients have been diagnosed at metastasis stage or a high-risk stage of progression. Castration resistance was observed from the 5th month of treatment, especially for patients with metastases. The median patient survival was 30 months and the average survival was 26.6 months with a difference depending on the stage, grade, and comorbidity. The overall mortality rate was 19.6%. The patients with castration resistance had significantly reduced survival.

Limitations of the Study

This publication is considered as a pilot study which will be validated by others. The interpretation of the results should consider the limitations. The lack of randomization of the subjects studied and the limited to one center introduced a selection bias and does not allow the generalization of our results. The retrospective nature of our cohort constitutes a significant loss of some useful information. The low socio-economic level of the patients made it impossible to carry out several paraclinical examinations which have a definite influence on the survival of patients. Finally, the relatively small size of the sample could not give enough power to statistical tests to detect possible associations between the variables of interest. To get around these methodological pitfalls, a multicenter randomized longitudinal cohort study is expected.

Authors' Contribution

Dieudonné Molamba Moningo: Research design and supervision.
Junior Konga Liloku: Data collection and writing.
Richard Koseka Demongawi: French English translator.
Nkodila Aliocha: Statistical analysis.
Other authors: Corrections, remarks, and suggestions.

Conflicts of Interest

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

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Appendix

DATA COLLECTION SHEETS

Subject: "EVOLUTION OF ANDROGENIC DEPRIVATION IN TREATMENT OF PROSTATE CANCER IN KINSHASA"

Date of collection at the Pointe à Pitre/Matete Clinic ……

March 2014 to June 2018.

I. IDENTITY

Coded	……
Place and date of birth	……
Weight (kg)	……..... kg
Height (cm)	……..... cm
Marital status	Married: ☐
	Divorced: ☐
	Single: ☐
	Widower:
Age (year)	……. years
Address	C: ……...
	Q: …….....
	Av: …….....
Profession	.....
Province of origin	.....
Phone number	.....

II. MEDICAL HISTORY

1) Personal

- Smoker	Yes ☐ No ☐
- Former smoker	Yes ☐ No ☐
- How many stems/day	.....
- Allergy to a drug	Yes ☐ No ☐
- (which)?	.....
- Hypertensive	Yes ☐ No ☐
- Diabetic	Yes No
- Fracture, in the absence of major trauma	
(If yes, which fracture site)	.....
- Hyperuricemia	Yes ☐ No ☐
- Alcohol	Yes ☐ No ☐

2) Family history

- Prostate cancer	Yes ☐ No ☐
- Breast cancer	Yes ☐ No ☐

III. CLINICAL FINDING

Dominant symptom	.....
Functional signs: 1. pain:	
- Pain in RT	Yes ☐ No ☐
- Bone pain	Yes ☐ No ☐

2) Urinary disorder:

- dysuria Yes ☐ No ☐
- incontinence Yes ☐ No ☐
- mictalgia Yes ☐ No ☐
- pollakiuria Yes ☐ No ☐
- nocturia Yes ☐ No ☐
- resumes post-voiding Yes ☐ No ☐

3) Rectal touch:

- nodule Yes ☐ No ☐
- invasion Yes ☐ No ☐
- lumbar contact Yes ☐ No ☐
- Lower limb edema Yes ☐ No ☐

IV. PARACLINIC

Imaging:

- endorectal ultrasound Yes ☐ No ☐
- MRI Yes ☐ No ☐
- Abdomino-pelvic scanner Yes ☐ No ☐
- bone scan Yes ☐ No ☐

Prostate biopsy:

- Performed Yes ☐ No ☐
- Positive result Yes ☐ No ☐

Method of realization:

- echoguided Yes ☐ No ☐
- transrectal Yes ☐ No ☐

Initial stage

- localized cancer Yes ☐ No ☐
- locoregional cancer Yes ☐ No ☐
- metastatic cancer Yes ☐ No ☐

Clinical classification/Imaging, cTNM cT.....N.....M.....

Gleason score .....

Testosteroneemia (ng/ml) (1.....), (2.....), (3.....), (4.....)

PSA (ng/ml) (1.....), (2.....), (3.....), (4.....)

D'AMICO classe: Low risk (1), Intermediate risk, (2) High risk (3), Metastatic (4)

V. TREATMENT

1) Hormone therapy used R/.....

R/.....

R/.....

Start of treatment (month/year) .....

Duration .....

2) Anti-androgen therapy? Yes ☐ No ☐

Which? R/.....

R/.....

R/.....

3) Surgical castrations .....

.....

Others R/.....

Complications:

- Early .....

.....

-late .....

.....

Evolution of castration .....

.....

.....

Evolutions of testosterone .....

.....

.....

Time to onset of castration resistance after treatment is indicated

.....

.....

Death Yes ☐ No ☐

Death with cancer Yes ☐ No ☐

Age: .....

Time after treatment.....

Other causes .....

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PET/CT with ^{18}F-PSMA in Patients with Prostate Cancer, Review of the Initial Experience

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Abstract

METHOD: We carry out an observational study where reviewed the PET/CT studies with PSMA marked with Fluor-18 (^{18}F) carried out from February 2019 to September 2020. We analyzed the average value of hepatic uptake SUV lean average (SUVlave), acquisition time, age, reason from the study, focal, multifocal and diffuse prostate uptake, analysis of the location of metastases, level of prostate specific antigen (PSA), we describe uptakes of non-prostate origin and focal uptakes in ribs without anatomical representation. **RESULTS:** The average hepatic SUVlave was 9.7, the acquisition times were variable (52 - 183 minutes) without alterations in the white-background relationship, the most frequent indication for the study was staging, the uptake in ribs without anatomical representation were considered benign with certain characteristics, PET/CT has the ability to detect neoplastic activity with low PSA levels in lymph nodes < 5 mm and bone metastatic status. **CONCLUSION:** PET/CT with ^{18}F-PSMA has advantages over bone scan and computed tomography of the abdomen and pelvis for the staging of prostate cancer.

Keywords

^{18}F-PSMA, Prostate Cancer, Non-Prostatic Uptakes

1. Introduction

Prostate cancer is a malignant neoplasm that occurs in older men [1]. In Mexico, it ranks second in causes of death from cancer, after lung [2].

Risk factors include age, since most of the prostate cancer diagnosis appears in men over 64 years of age, first-degree family history, black African-American

race, and a high-fat diet [3].

The diagnosis is determined by the prostate specific antigen (PSA), the Gleason score and the extent of the tumor. Various imaging methods are used for initial staging. Magnetic resonance imaging (MRI) shows promising results in locating the tumor and improves the precision of ultrasound-guided biopsy [4], however, despite the fact that European guidelines recommend the use of magnetic resonance imaging in the event that the tumor does not affect other organs, the images suffer from a certain limitation, especially in the central and transition areas [5] [6].

1.1. Prostate Specific Membrane Antigen (PSMA)

Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein type II, encoded in the follolate hydrosylase 1 gene, also known as the transmembrane glutamate II gene [7]. It is expressed in surface cells of normal prostate tissue and overexpressed in prostate cancer. Its expression increases in high-grade metastatic prostate cancer, in dedifferentiated and resistant to castration [8]. In 2012, Afshar-Oromieh and collaborators at the University Hospital of Heidelberg in Germany, expose for the first time PET/CT images with PSMA, labeled with Galio-68 (^{68}Ga-PSMA) [9].

The physiological biodistribution of ^{68}Ga-PSMA occurs in the lacrimal, salivary glands, small intestine, liver, spleen and in the proximal tubule of the kidney; there is also a significant accumulation of the radiotracer in the ureters and in the bladder due to renal excretion [10] However, among the disadvantages of ^{68}Ga-PSMA is its intense accumulation in the bladder, which can make it difficult to see in the prostate. These results led to the search for other radioisotopes to mark PSMA, finding in ^{18}F-PSMA a lower renal excretion and a longer half-life (^{68}Ga: 68 min vs ^{18}F: 110 min), which allows better availability, and finally, the energy of ^{18}F (0.65 MeV) is lower compared to that of ^{68}Ga (1.90 MeV), which improves spatial resolution [11] (**Figure 1**).

1.2. Initial Staging in High-Risk Patients

Initial staging in high-risk patients due to the fact that in patients with intermediate or high risk prostate cancer, the metastatic nodes may be smaller than 8 mm, the imaging methods (MRI and CT) continue to be of low sensitivity, since they only evaluate size [12]. Primary staging with PET/CT with PSMA has shown greater sensitivity and specificity for extension to metastatic nodes [13] [14], improving the detection of metastatic disease with low levels of PSA (<0.2 ng/mg) and can detect nodes between 3 at 10 mm, these would go unnoticed by CT [12].

TNM Classification [15]

Primary tumor:

- Tx: The presence of the primary tumor cannot be assessed.
- T0: There is no evidence of a primary tumor.

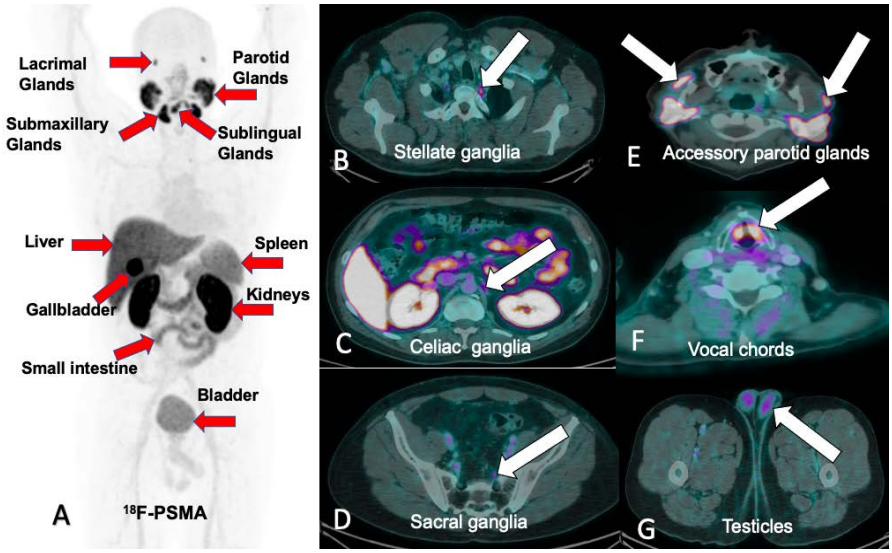

Figure 1. General description of the physiological uptakes with ^{18}F-PSMA. (A) MIP in anterior showing physiological uptake in the lacrimal, parotid, submaxillary and sublingual glands, liver, gallbladder, spleen, small intestine and bladder (red arrows). PET/CT fusion in axial section with physiological uptakes in (B) stellate ganglia (C) celiac ganglia (D) presacral ganglia (E) bilateral accessory parotid glands (F) vocal cords and (G) testes.

- T1: Clinically inapparent tumor (not palpable or visible by imaging techniques).
- T2: Tumor confined to the prostate.
- T3: Tumor that extends beyond the prostatic capsule.
- T4: The tumor invades adjacent organs other than the seminal vesicles.

Lymph node Involvement:

- Nx: Lymph node involvement cannot be assessed.
- N0: Absence of lymph node involvement
- N1: Regional node metastases.

Distant metastasis:

- Mx: The existence of distant metastases cannot be assessed.
- M0: Absence of distant metastasis.
- M1: Distant metastasis (**Figure 2**).

Bone metastases are among the main causes of pain and death in patients with prostate cancer, the degree of bone involvement is essential to define the best treatment strategy [16]. Prostate adenocarcinoma most commonly spreads to well-vascularized bone structures, such as the spine, ribs, skull, and proximal ends of long bones [17].

PET/CT with PSMA shows potential for the detection of bone metastases in patients with prostate cancer, positron emission tomography has shown superiority over bone scintigraphy to determine a generalized condition [18] (**Figure 3**).

1.3. Non-Prostatic Pathologies with PSMA Uptake

The expression of PSMA is found in both malignant and benign non-prostatic

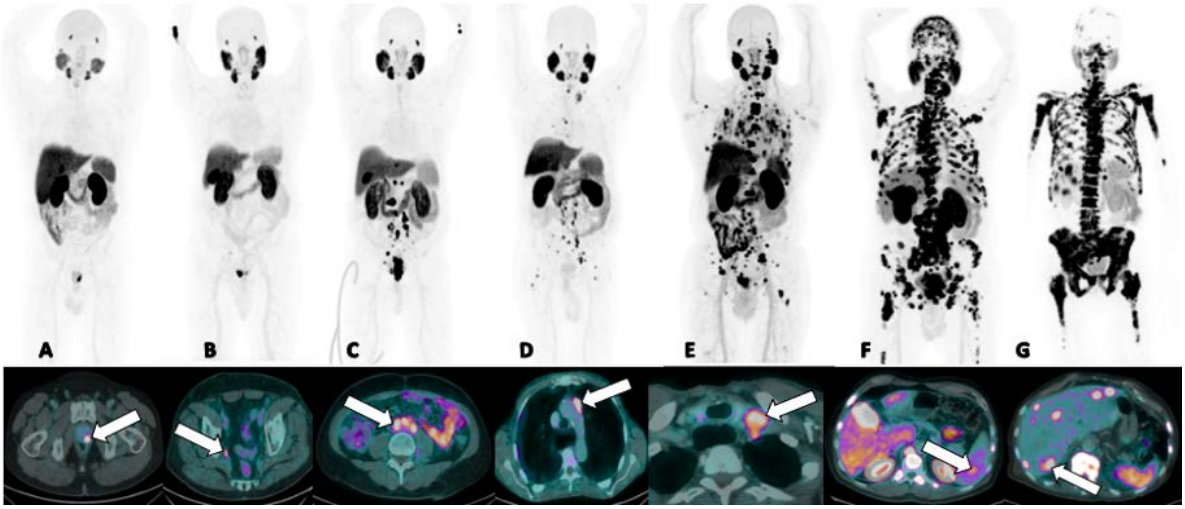

Figure 2. PET images with ^{18}F-PSMA in anterior MIP and fusion in axial section with uptake in (A) focal in prostate (B) prostate with right iliac ganglion (C) prostate with pelvic and retroperitoneal lymphadenopathy (D) multiple bilateral inguinal, pelvic, retroperitoneal, mediastinal and cervical lymphadenopathy (E) prostate, pelvic, retroperitoneal, mediastinal, cervical, axillary lymph nodes, pulmonary nodules, and multiple bone metastases in the axial and appendicular skeleton (F) prostate, pelvic, retroperitoneal, cervical, axillary, pulmonary nodules, multiple bone metastases in axial and appendicular skeleton in the spleen. Is to notice the absence in the uptake of the right submaxillary glandular. (G) prostate, pelvic and retroperitoneal lymphadenopathy, extensive bone metastases in the axial and appendicular skeleton (super scan) and liver metastasis.

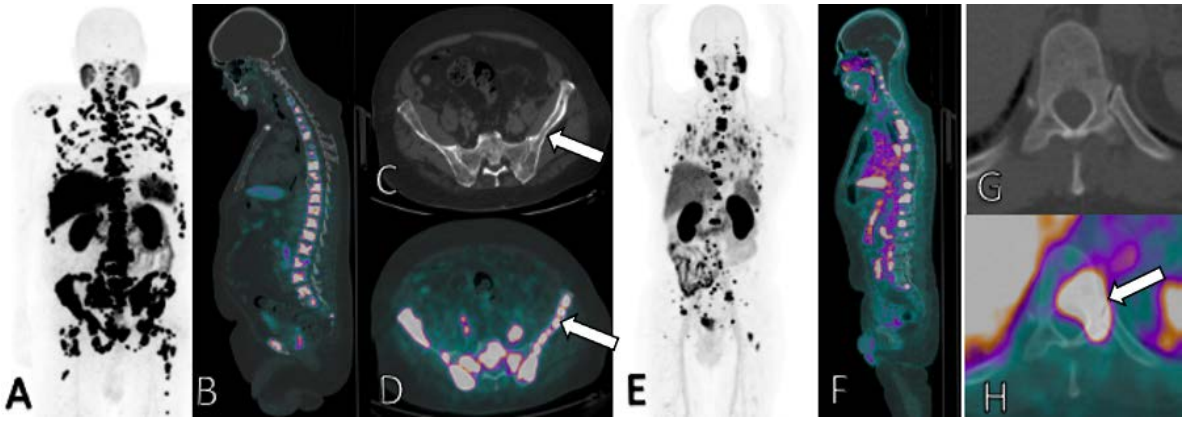

Figure 3. male patient with a 2-month history of lumbar pain and PSA of 233 ng/dl (A) MIP in anterior projection with uptake in the prostate and extensive lymph node and bone tumor burden. (B) PET/CT fusion in a sagittal section where we observe the spine with multiple lesions with intense radiopharmaceutical uptake. (C) and (D) CT and fusion in an axial section at the pelvis level with lytic lesions in both iliac and sacral intense uptake bones (white arrows). A 70-year-old male patient who attended staging for prostate cancer, at the time of the study had PSA of 110 ng/mg; (E) MIP in anterior projection with multiple lesions with intense uptake of diffuse distribution in the axial and appendicular skeleton. (F) PET/CT fusion with bone window in sagittal section; the spine is seen with multiple focal ^{18}F-PSMA uptakes. (G) CT and (H) fusion with PET shows intense radiopharmaceutical uptake involving body, peduncle, and left facet without anatomical representation (white arrow).

pathologies, this situation determines difficulties in interpretation [19] to differentiate prostate cancer metastases from other primary malignant neoplasms [20]. This is because PSMA is expressed in the endothelial cells of the neovasculatures of solid tumors, but not in the endothelial cells of normal vessels [21].

2. Objective General

- Review of the initial experience in the use of PET/CT with ^{18}F-PSMA.
- Average value of hepatic uptake SUV Lean average (SUVlave).
- Age.
- Analysis of the location of metastases.
- Describe and divide the uptakes of non-prostatic tumors and the focal uptakes in the rib without anatomical representation with ^{18}F-PSMA.
- Determine the relationship between the level of prostate specific antigen (PSA) and positive uptakes for prostate cancer, by PET/CT with ^{18}F-PSMA.
- Reason for the study.
- Focal, multifocal or diffuse prostate.
- APE level.

2.1. Justification

In February 2019, we started the use of PET/CT with ^{18}F-PSMA, this work will allow us to show our initial experience with this radiopharmaceutical, observe the spread of prostate cancer, and document uptakes of non-prostatic origin.

2.2. Methodology

A retrospective analysis was performed, in which patients undergoing PET/CT with ^{18}F-PSMA from February 2019 to September 2020 were studied at the CT Scanner San Ángel, Mexico City.

Inclusion criteria: patients with PET/CT study with ^{18}F-PSMA and complete file.

Exclusion criteria: patients with an incomplete file.

A total of 393 studies were conducted, 21 patients were excluded due to incomplete records. In total, 372 studies in 252 patients were analyzed.

The patients signed informed consent to carry out the study.

Definition of variables and measurement scales (Table 1).

3. Results

In the age analysis, we observed that the average was 70.2 years, median 70 and a mode of 73 years. The youngest patient was 42 years old and the oldest patient was 93 (Table 2).

Table 1. Definition of variables and measurement scales.

VARIABLE	CONCEPTUAL DEFINITION	OPERATIONAL DEFINITION	TYPE OF VARIABLE
Average liver uptake value (SUV Lean average).	Used to compare the standardized value of uptake with lesions.	It is obtained by placing an VOI in the right lobe of the liver, this used as a reference value.	Quantitative
Age Independent of the presentation of prostate cancer.	Age Years completed at the time of diagnosis.	It is obtained by ordering the patients by age group.	Quantitative
Reason for the indication of the study.	Valid Reason for Using the ^{18}F-PSMA Diagnostic Test	It is obtained from patient records.	Quantitative

Continued

Focal, multifocal, or diffuse prostatic uptake.	Location of the primary tumor (right or left lobe or both)	Based on the record obtained from the nuclear medicine report.	Quantitative
PET/CT studies, positive, negative.	Case numbers.	Based on the records obtained in the database.	Quantitative
APE level.	A protein produced by the cells of the prostate glands, its concentration in the blood is measured.	The results were obtained from the files.	Quantitative
Analysis based on the location of metastases.	Spread of prostate cancer to lymph nodes and organs.	Based on the PET/CT results, the anatomical location of the metastases was determined.	Quantitative
Non-prostatic tumor uptakes.	Standardized value of uptake in lesions of non-prostate origin with 18F-PSMA	Based on the record obtained from the nuclear medicine report	Qualitative
Focal uptakes in rib.	Standardized uptake value in ribs without anatomical representation.	Based on uptake rib focal only and determined predicter factors.	Qualitative

Table 2. Demographic data of the patients studied with ^{18}F-PSMA.

Ages grouped by ranges	Number of studies
42 to 51	12
52 to 61	71
62 to 73	134
74 to 82	117
83 to 93	38
Total	372

Mean age = 70 age. Standard deviation = 57.47.

3.1. Average Liver Uptake Value (SUV Lean Average)

In all the studies, we measured the SUVlave at the level of the right liver lobe, finding that the highest value was 21.0, the lowest was 1.1, the average was 9.7, the mode was 10.5 and the median was 9.7.

We also analyzed the post-injection acquisition time of each of the studies performed, the maximum time was 183 minutes, the minimum time was 54 minutes, an average of 86.5 minutes, a median of 83 and a mode of 63 minutes.

3.1.1. Analysis Based on the Primary Uptake of the Prostate and Location of Metastases

The results of the PET/CT with ^{18}F-PSMA were the following: 281 were positive, 87 negative and 4 doubtful.

The prostate uptakes and the distribution of metastases were analyzed, the results were as follows.

Lesion exclusively in the prostate and surgical bed: 81 studies (28.8%) divided into unifocal (30), multifocal (31) and diffuse (20) lesions. Surgical bed with 18 (6.4%).

The highest SUVlmax was 41.1 and the lowest SUVlmax was 2.7 in injuries exclusively to the prostate.

In the surgical bed, the highest SUVlmax was 40.1 and the lowest was 2.7.

Exclusively lymph nodes: 13 (4.6%) studies, in which we found the following:

- 9 Studies with local nodes.
- 1 Study with local + retroperitoneal ganglia.
- 1 Study with local + retroperitoneal + mediastinal nodes.
- 1 Study with local + retroperitoneal + mediastinal + left cervical lymph nodes.
- 1 Study with retroperitoneal + mediastinal lymph nodes.

Exclusively bone metastases: 9 studies (3.2%):

- 1 Study with a single osteoblastic lesion.
- 5 Studies with multiple osteoblastic lesions.
- Studies with multiple lesions without anatomical representation.

Prostate + lymph nodes: 54 (19.2%) studies:

Unifocal: 21 studies:

- 14 Local node studies.
- 5 Local node studies + retroperitoneal.
- 1 Study with retroperitoneal ganglia.
- 1 Study with mediastinal lymph nodes.

Multifocal: 15 studies:

- 7 Local node studies.
- 5 Studies with local + retroperitoneal nodes.
- 2 Studies with local + mediastinal nodes.
- 1 Study with mediastinal lymph nodes.

Diffuse: 18 Studies:

- 10 Local node studies.
- 3 Studies with local + retroperitoneal lymph nodes.
- 1 Study with bilateral retroperitoneal + mediastinal + axillary nodes.
- 2 Studies with retroperitoneal nodes.
- 1 Study with local + retroperitoneal + bilateral cervical nodes.
- 1 Study with local + retroperitoneal + mediastinal + left cervical nodes.

Prostate + bone metastasis: 10 studies (3.55%).

Unifocal: 5 studies:

- 3 Studies with multiple osteoblastic lesions.
- 1 Study with a single metastatic lesion without anatomical representation.
- 1 Study with single osteoblastic lesion.

Multifocal: 4 studies:

- 2 Studies with multiple osteoblastic lesions.
- 1 Study with a single lesion without anatomical representation.
- 1 Study with a single osteolytic lesion.

Diffuse: 1 Study with multiple bone lesion without anatomical representation.

Prostate + lymph nodes + bone metastases: 53 (18.86%) studies.

Unifocal: 17 studies:

- 4 Studies with local lymph nodes + single osteoblastic lesion.

- 3 Studies with local ganglia + multiple osteoblastic lesions.
- 6 Studies with local + retroperitoneal ganglia + multiple osteoblastic lesions.
- 1 Study with local + retroperitoneal ganglia + multiple osteoblastic lesions.
- 1 Study with local lymph nodes + single bone lesion without anatomical representation.
- 1 Study with local + retroperitoneal + mediastinal nodes + single osteoblastic lesion.
- 1 Study with local lymph nodes + left cervical + multiple osteoblastic lesions.

Multifocal: 17 studies:

- 6 With local ganglia + multiple osteoblastic lesions.
- 2 With local lymph nodes + single blastic lesion.
- 1 With local lymph + retroperitoneal + left cervical ganglia + multiple osteoblastic lesions.
- 1 With local lymph + retroperitoneal ganglia + multiple lytic bone lesions.
- 1 With local ganglia + multiple bone lesions without anatomical representation.
- 1 With local nodes + single lytic bone lesion.
- 1 With local retroperitoneal ganglia + single osteoblastic lesion.
- 2 With local nodes + retroperitoneal ganglia + single osteoblastic lesion.
- 1 With local + retroperitoneal ganglia + multiple osteoblastic lesions.
- 1 With local retroperitoneal ganglia + mediastinal + left cervical ganglia and multiple osteoblastic lesions.

Diffuse: 18 studies:

- 2 Studies with local retroperitoneal lymph nodes + single osteoblastic lesion.
- 2 Studies with local ganglia + single lesion without anatomic representation.
- 4 Studies with local lymph node studies + multiple osteoblastic lesions.
- 1 Study with local + retroperitoneal ganglia + single osteoblastic lesion.
- 1 Study with local ganglia + retroperitoneal + mediastinal + multiple osteoblastic nodes.
- 1 Study with local ganglia + retroperitoneal + mediastinal ganglia + multiple osteoblastic and lithic lesions.
- 1 Study with local ganglia + retroperitoneal + multiple bone lesions without anatomical representation.
- 2 Studies with local retroperitoneal nodes + multiple osteoblastic lesions.
- 1 Study with mediastinal lymph nodes + multiple osteoblastic lesions.
- 2 Studies with local lymph nodes + multiple bone lesions without anatomical representation.
- 1 Study with local ganglia + multiple osteolytic lesions.
- 1 Study with local retroperitoneal ganglia + left cervical + multiple bone lesions without anatomical representation.

Ganglion + bone metastasis: 19 studies:

- 1 Study with local lymph nodes + pulmonary hilum + multiple osteolytic lesions.

- 2 Studies with mediastinal lymph nodes + multiple osteoblastic lesions.
- 1 Study with local lymph nodes + multiple osteoblastic lesions.
- 1 Study with local + retroperitoneal + left cervical ganglia + multiple osteolytic lesions without anatomical representation.
- 1 Study with local + retroperitoneal + mediastinal nodes + left pulmonary hilum, left cervical + multiple osteoblastic lesions.
- 2 Studies with local lymph nodes + single osteolytic lesion.
- 1 Study with local + retroperitoneal ganglia + multiple osteoblastic lesions.
- 1 Study with retroperitoneal + mediastinal lymph nodes + multiple osteoblastic and lytic lesions.
- 1 Study with retroperitoneal + mediastinal ganglia + multiple osteoblastic lesions.
- 2 Studies with retroperitoneal lymph nodes + multiple osteoblastic lesions.
- 1 Study with local + retroperitoneal + mediastinal ganglia + multiple osteoblastic and lytic lesions.
- 1 Study with local ganglia + multiple osteoblastic lesions.
- 1 Study with local lymph nodes + retroperitoneal + mediastinal + bilateral cervical nodes + multiple osteoblastic lesions.
- 1 Study with retroperitoneal ganglia + left cervical + multiple osteolytic lesions.
- 1 Study with retroperitoneal ganglia + mediastinal + multiple osteoblastic lesions.
- 1 Study of mediastinal lymph nodes + multiple osteoblastic lesions.

Surgical bed + lymph node: 10 studies (3.55%):

- 8 Local node studies.
- 1 Studies with local + retroperitoneal lymph nodes.
- 1 Study with local + retroperitoneal + left cervical lymph nodes.

Surgical bed + Bone metastases: 5 (1.77%): With multiple osteoblastic lesions.

Surgical bed + lymph nodes + bone metastases: 9 studies (3.2%):

- 1 Study with local + retroperitoneal lymph nodes + single lesion without anatomical representation.
- 1 Study with local + retroperitoneal ganglia and multiple bone lesions without anatomical representation.
- 1 Study with left retroperitoneal + mediastinal + cervical ganglia and single osteoblastic lesions.
- 1 Study with local ganglia + multiple osteoblastic lesions.
- 2 Studies with local + retroperitoneal ganglia + multiple osteoblastic lesions.
- 1 Study with local lymph nodes + single osteoblastic lesion.
- 1 Study with local ganglia + cervical + multiple bone lesions without anatomical representation.
- 1 Study with local retroperitoneal ganglia + multiple osteoblastic and lytic bone lesions (Figure 2).

3.1.2. Particular Discoveries

37 (13.16%) had positive nodes smaller than 5 mm.

27 (9.60%) studies with lymphadenopathy in 38 supradiaphragmatic regions: 12 left cervical nodes, 1 bilateral cervical, 21 mediastinal lymph nodes, 3 in pulmonary hilum and 1 bilateral axillary.

We detected 16 (5.69%) studies with unusual metastases: 7 pulmonary, 3 hepatics, 3 in the penis, 1 splenic, 1 muscular and 1 in the mesorectum (**Figure 4**).

3.1.3. ^{18}F-PSMA PET/CT Results Based on PSA Numbers

Of the 393 studies carried out, we have PSA levels in 181 (45.93%). The minimum PSA value was 0.001 and the highest value was 1789 ng/ml (**Table 3**).

3.1.4. Distribution for Reasons of Request

The reasons for the studies were varied, with staging (144), re-staging (104), assessment of response to treatment (53), surveillance (53) and recurrence (18).

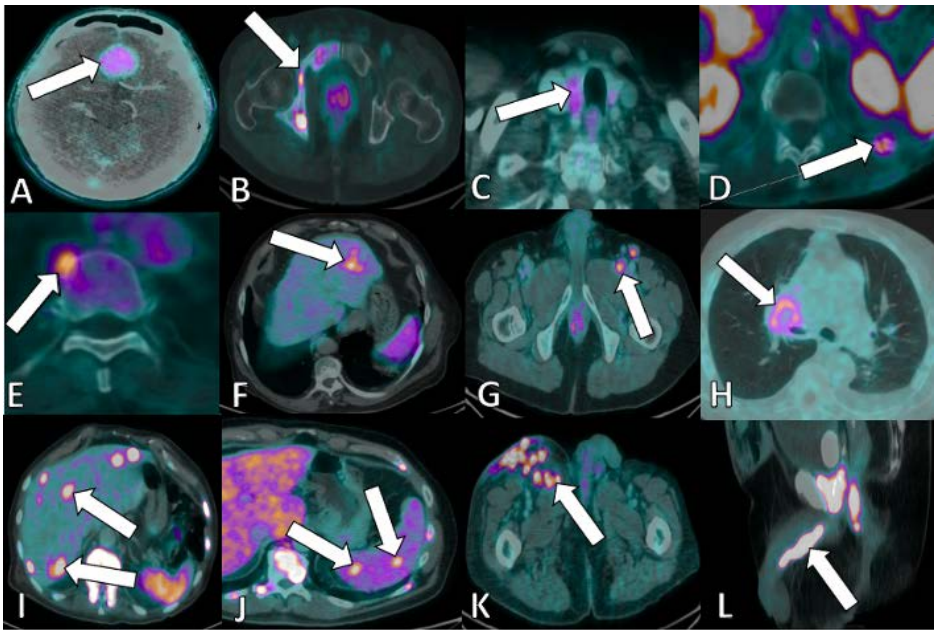

Figure 4. Fusion of PET/CT with ^{18}F-PSMA axial section with examples of uptake of non-prostatic origin and non-usual metastases (A) Skull with extra-axial lesion dependent on the cerebral falx with ^{18}F-PSMA uptake, compatible with meningioma (white arrow). (B) increased density in bone structures of the right hemipelvis associated with heterogeneous uptake (white arrow) in a patient with Paget's disease. (C) Right thyroid lobe with solid nodules with uptake (we have a histological report showing hyperplastic nodules). (D) posterior costal arch fracture with focal radiopharmaceutical uptake. (E) lumbar vertebral body with anterior marginal osteophyte with radiopharmaceutical uptake. (F) lesion in the left liver lobe with uptake of the radiopharmaceutical that suggests malignant etiology (hepatocarcinoma) as the first possibility. (G) known patient with Hodgkin lymphoma shows left inguinal lymphadenopathy with ^{18}F-PSMA uptake. (H) lesion in the right pulmonary hilum with heterogeneous uptake compatible with a second primary neoplasm. Uncommon metastases, (I) hypodense liver lesions with intense uptake (J) spleen with focal uptakes (K) right pelvic limb with implants intense uptake located in the anterior compartment (L) sagittal section with intense linear uptake in the cavernous bodies of the penis.

3.1.5. Non-Prostatic ^{18}F-PSMA Uptake

95 studies (25.5%) with uptake of non-prostatic origin with ^{18}F-PSMA, which we divided into three groups, benign 59 (63%), malignant 9 (9%) and nonspecific 27 (28%) (Table 4, Figure 4).

3.1.6. Focal Uptakes in Ribs without Anatomical Representation

9.6% of the studies (36) presented focal uptakes of the radiopharmaceutical in ribs but without anatomical representation, we have classified them as nonspecific. In the SUVlmax analysis, the highest was 8.2 and the lowest was 1.8 (average of 4.0 and mode of 2.6) (Figure 5).

Table 3. PET/CT results based on PSA level.

PSA ng/ml	PET+	PET−	PET UNCERTAIN
0.001 to 0.01		6	
>0.01 to ≤0.07	2	11	1
≥0.1 to ≤0.5	10	11	
>0.5 to ≤1	6	1	
>1 to ≤5	32	1	1
>5 to ≤10	37	1	2
>10 to ≤15	17	1	
>15 to ≤20	7		
>20	34		
Total	145	32	4

Table 4. In the following table we divide the pathologies of non-prostatic origin with uptake.

Benign	Number of studies	Malignant	Number of studies	Unspecific	Number of studies
Osteodegenerative	19	Urothelial origin	3	Diffuse thyroid uptake	11
Pulmonary nodules	3	Hepatocarcinoma	1	Linear in lung	1
Pulmonary infiltrates	4	Lymphoma	1	Thickening of the rectum	1
Lung consolidation	1	Pancreatic neoplasia	2	Bladder wall	1
Hemangiomas	4	Lung primary	1	Nonspecific osseous	6
Inflammatory esophagus	5	Liposarcoma in pancreas	1	Rib with lytic area	1
Enchondroma	1			Iliac nodes	1
Epididymis	1			Penis	2
Fractures	3			Inguinal ring	1
Atrial lipoma	1			Intestinal polyp	1

Continued

Meningioma	1	Inguinal canal cyst	1
Paget's disease	2		
Fibrocicatricial changes in the lung	2		
Thymoma	1		
Muscular	1		
Adrenal adenoma	1		
Thyroid nodule	1		
Bladder wall	1		
Pleura	1		
Bladder wall	1		
Lymph nodes (axillary, mediastinal and cervical)	5		

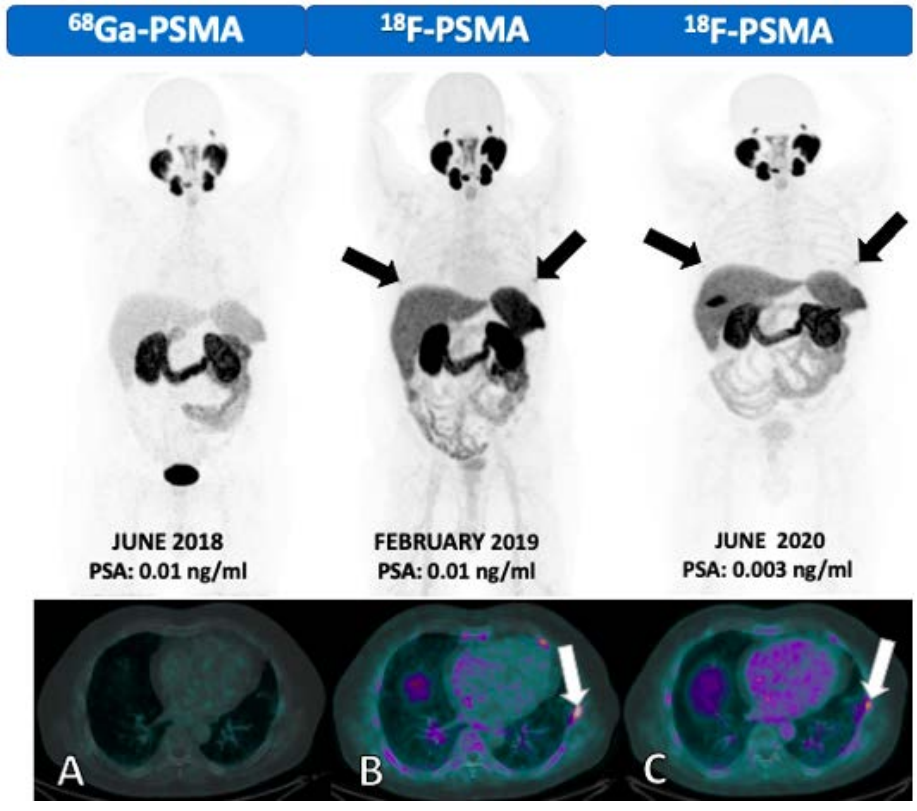

Figure 5. Follow-up of a patient with a history of prostate cancer (A) MIP in anterior and PET/CT in axial fusion with ^{68}Ga-PSMA performed in June 2018 without evidence of abnormal uptakes (B) Follow-up carried out in February 2019 with ^{18}F-PSMA where minimal focal uptake is observed in the sixth bilateral costal arch with SUVlmax of 3.5, the PSA at the time of the study was 0.01 ng/ml. (C) PET/CT with ^{18}F-PSMA performed in June 2020, the focal uptakes in the costal arches continue with minimal uptake and without significant changes in size, the PSA at the moment of the study was 0.003 ng/ml.

4. Discussion

Prostate cancer is the second malignant tumor and the second most frequent cause of death in men, PET/CT with ^{18}F-PSMA has proven to be a fundamental non-invasive technique in the initial staging in high-risk patients, important in the planning of the surgical approach, functional in the planning of radiotherapy, location of the tumor in biochemical recurrence, useful as a guide for biopsy in patients with high suspicion of cancer with negative previous biopsy results, and to assess the response to treatment.

The objective of this study is to evaluate the results obtained in the scans carried out with PET/CT with ^{18}F-PSMA during the period: February 2019 to September 2020.

We measured the SUVlave (SUVLean average) in the liver of each one, the highest value found was 21 and the lowest was 1.1, this last value corresponds to a patient with extensive tumor burden (superscan), we found a mode of 10.5 and an average of 9.7. The liver belongs to the physiological uptake of ^{18}F-PSMA, when placing this reference ROI in the liver, verify that the gallbladder is not included.

The acquisition time of most studies (mode) was 63 minutes. 183 minutes the longest and the shortest at 54 minutes. Although the acquisition times were variable, the analyzes have an appropriate quality, with no alterations in the white background relationship.

The average age was 70.2 years, with a mode of 73 years, 124 patients are in the range of 62 to 73 years, our youngest patient with 42 years and our oldest patient 93 years. Our result agrees with the referenced literature, where age is recognized as a risk factor, since most of the prostate cancer diagnosis appears in men older than 64 years.

In the positive PET/CT, the most frequent involvement was observed in lesion exclusively in the prostate with 29.7% (82) with a predominance of multifocal lesions; second, involvement of the prostate + lymph nodes + bone lesions with 21.2% (58) studies.

Surgical bed + bone metastases and surgical bed + lymph nodes were the least frequent with 8 and 10 studies respectively.

37 studies (13.4%) presented nodes smaller than 5 mm with radiopharmaceutical uptake.

As unusual findings, we found 7 pulmonary metastases, 3 liver, 3 in the penis, 1 splenic, 1 of axillary lymphadenopathy, 8 cervical on the left side and 1 bilateral, 1 nodular lesion in the mesorectum and 1 study in a muscle implant.

Despite the high incidence of prostate cancer, there are few reports of metastatic involvement of the cervical nodes, the predilection for the left side is due to the fact that tumor cells can lodge in the nodes by retrograde spread, due to the proximity of the duct thoracic with left subclavian vein [22].

Hepatic metastases are considered the third site of extra nodal metastases in prostate cancer, after bone and lung; occur in disease refractory to hormonal treatment and in late stages, PSMA uptake in liver metastases may be due to the

diversity of prostate cancer phenotypes, predominantly neuroendocrine transdifferentiation [23]. The spleen and muscle are the least common extra nodal metastasis sites [24].

Most of the reasons for the request were staging with 144 studies.

Of the PET/CT performed we have the PSA value in 179. 18 positive studies with PSA < 1.0, of which the minimum value with positive PET/CT was 0.01 ng/ml.

We documented 89 studies with ^{18}F-PSMA uptake of non-prostatic origin with a predominance in lesions of benign etiology, being the osteodegenerative changes the ones that occurred more frequently, the highest SUVlmax value was 8.5 and the lowest 2.6. Regarding uptakes of non-prostate malignant origin, we present 9 documented studies that present a second primary tumor. In the literature, the association of these uptakes with endothelial neovasculature is well known, showing that PSMA is not exclusive to prostate tissue, this must be taken with relevance, since they can simulate prostate cancer metastasis.

36 studies presented focal uptakes in rib(s) without anatomical representation. In our initial experience, we considered these uptakes as nonspecific, however there was no significant change in size and SUVlmax at follow-up. There is little literature that mentions the nature of these solitary uptake in ribs, however we identified that most of them are of benign origin; taking into account the low uptake of the radiopharmaceutical, the correlation with any signs of trauma and PSA levels [25].

5. Conclusions

- The acquisition times were varied, from 54 to 183 minutes, all studies have adequate quality for interpretation without alterations in the white-background relationship.
- The average hepatic SUVlave is 9.7.
- Staging occupied the highest percentage of PET/CT indication.
- We detected both unifocal and multifocal uptakes in the prostate with PET/CT with ^{18}F-PSMA.
- There are uptakes in both benign and malignant lesions due to its expression in the endothelial cells of the neovasculature, that can cause false positives, it is advisable for the doctor who examines the study to have this knowledge in order to obtain an accurate interpretation. There is little literature on solitary uptakes in ribs without anatomical representation with ^{68}Ga-PSMA. To our best knowledge, this is the first study with ^{18}F-PSMA to evaluate and describe uptakes at the rib level. Our results indicate that these findings are considered benign, when PSA levels and the rest of the study are negative.
- Although there is literature that mentions that liver metastases are not so uncommon (25%, 8%) [24] [26], in the 281 positive studies, 2 patients (3 studies) had hyper-uptake liver metastases (0.71%). Among the findings of one of these two patients, we found PSA of 169 ng/mg, histological report of invasive prostatic adenocarcinoma and extensive tumor burden (superscan),

the patient died 7 months after the first PET/CT, for which reason we agree with the literature that mentions a mortality of 6 to 14 months with this type of lesion [26]. Liver metastases are frequently associated with neuroendocrine transdifferentiation, which is why PET/CT with ^{18}F-FDG is useful in metastatic disease with mutation.

- PET/CT with PSMA has the ability to determine bone metastatic status, there are even hyper-uptake bone metastases that we can detect without anatomical representation. We found 11 studies (3.91%) with hyper-uptake lytic lesions, as well as 12 (4.27%) studies with hyper-uptake bone metastases without anatomical representation. In interesting cases, we have the follow-up of patients in evaluation of response to treatment who show partial response to ^{18}F-PSMA uptake, but with a considerable increase in the number of osteoblastic lesions. This analysis reveals that there may be a disagreement between the functional (PERSIST) and the anatomical (RESIST) assessment; considering that the molecular precedes the morphological (**Figure 6**).
- We have 179 studies correlated with PSA. 10.05% (18 studies) were positive with PSA < 1.0, this demonstrates the ability of ^{18}F-PSMA to detect neoplastic activity with low PSA levels.
- We detected 20 studies (7.2%) with supradiaphragmatic lymphadenopathy, which are not so frequent, however, it should be taken into consideration that they may be present in advanced cases of the disease. Supradiaphragmatic extension occurs by hematogenous spread through the vertebral venous system or Batson's plexus.
- Conventional studies (MRI, ultrasound and CT) have limitations to detect metastatic nodes smaller than 10 mm in the initial staging of patients with high-risk prostate cancer. ^{18}F-PSMA PET/CT has the potential to detect ma-

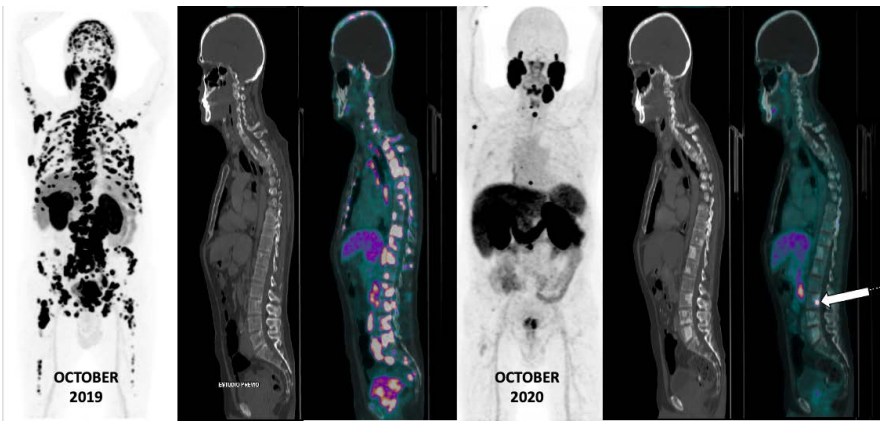

Figure 6. 67-year-old male patient with prostate cancer. MIP in the anterior projection of PET/CT with ^{18}F-PSMA performed in October 2019 (PSA 1789 ng/mg) manifest extensive lymph node tumor burden and predominance in bone; window CT for bone and fusion in the sagittal section with multiple uptakes with poor anatomical representation in the spine. In the PET/CT to assess response to treatment one year later, there is a significant decrease in hyper-uptake bone metastases, however the number of osteoblastic lesions (inactive metastases) increased.

lignant infiltration in nodes smaller than 5 mm, which can be considered normal on anatomical studies

- Considering the previous points, PET/CT with ^{18}F-PSMA has advantages over bone scintigraphy and computed tomography of the abdomen and pelvis for the staging of prostate cancer.

Conflicts of Interest

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

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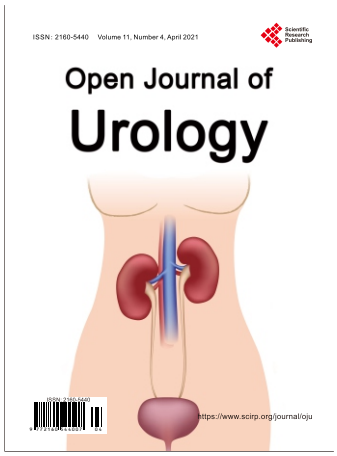

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