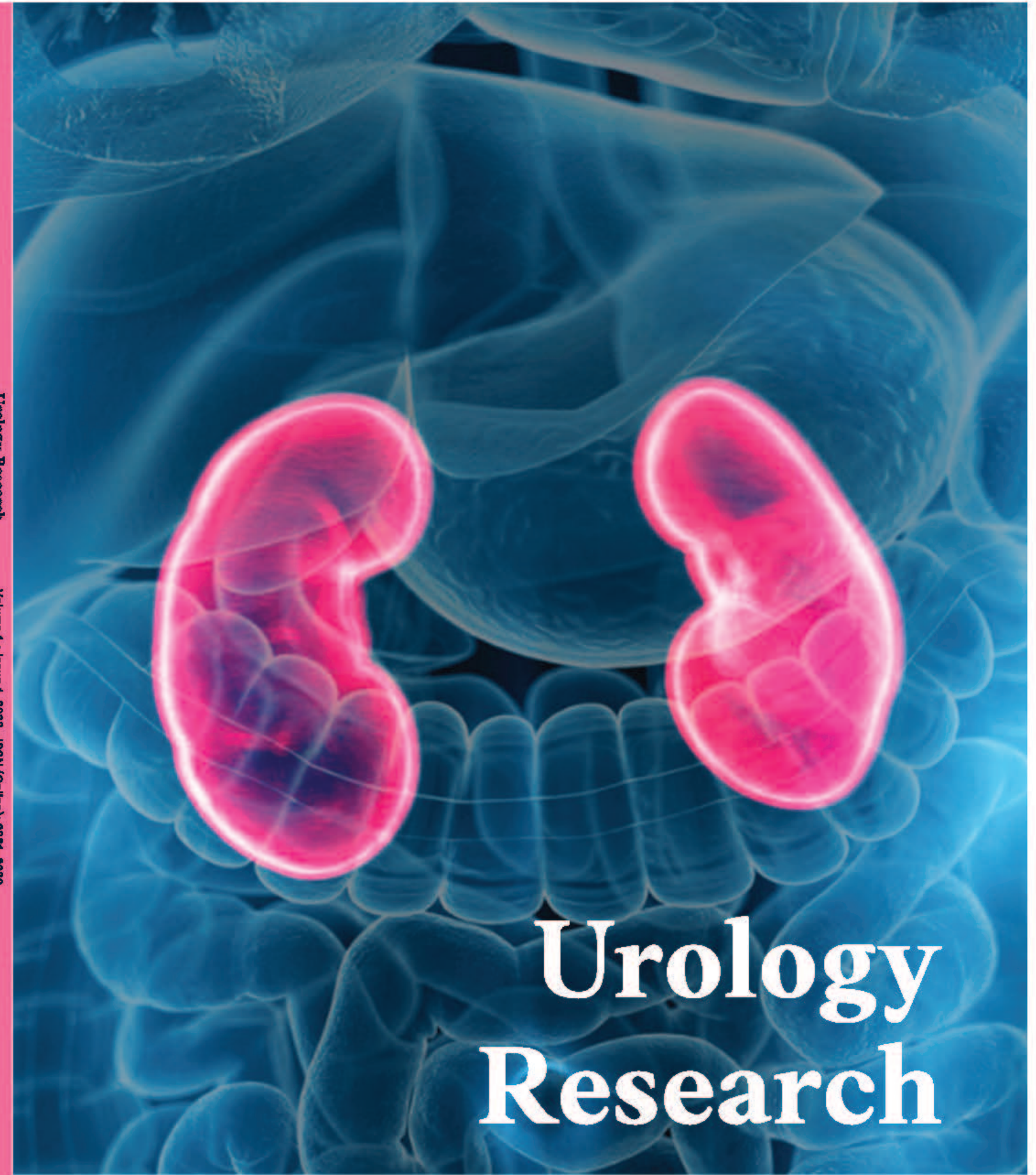




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Is Laparoscopic Oncological Surgery After an Open Surgery Possible?

Vladimir Erik Vargas-Rocha^{1*}, Patricia Segales-Rojas², Brian E Vargas Rocha³

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Abstract: This paper presents a case of a 55-year-old male patient with pain in the right lumbar region and hematuria. An abdominopelvic computed tomography was performed, and a tumor was discovered in the right renal pelvis. An open right radical nephrectomy was performed. She returned again with hematuria, thus cystoscopy, ureteroscopy, and selective cytology were performed, and local recurrence in the right ureter was documented. A radical right radical ureterectomy with laparoscopic bladder encirclement and extended lymphadenectomy was performed, with a histopathological report of right ureter with low-grade urothelial carcinoma. The patient showed satisfactory progress and was monitored. With this article, we stress that with adequate training, experience, and practice in laparoscopic surgery, excellent oncological and aesthetic results can be obtained, which is comparable to open surgery, but with the benefit of rapid recovery and less pain and bleeding. Therefore, we believe that with practice, laparoscopic oncological surgery after an open surgery is perfectly feasible.

Keywords: Urology; Medical oncology; Laparoscopy

Online publication: June 14, 2023

1. Introduction

In the last decade, laparoscopic surgery has caused a revolution in urological surgery, and the beginning of surgery using the laparoscopic approach is attributed to Cortesi ^[1] in 1979. For several years, this type of approach was not yet the first option until the first nephrectomy was performed by Clayman in 1991 ^[2], which is when it began to be accepted and popularized. However, it progressed slowly during the first few years due to technical and material limitations. Staging lymphadenectomy for the treatment of prostate cancer was among the first laparoscopic techniques. This surgery was described by Schuessler, which showed the viability of pelvic lymph node dissection with less bleeding and with greater ease, making it the ideal technique. This was when the majority of urology services began to promote and encourage laparoscopic methods ^[3].

The horizons of laparoscopic surgery have expanded in the urological field over the last few decades. In some urological procedures, laparoscopy has proven to be superior to open surgeries, and it has found an important place in the management of neoplasms of the genitourinary tract. While it was originally described for the treatment of renal cancer, it has become an important method for the treatment of adrenal, upper tract, bladder, prostate, and testicular neoplasms. Laparoscopic surgery combines the oncological principles of an open surgery while being minimally invasive ^[4].

Urothelial tumors of the urinary tract involving the renal pelvis or ureter are relatively rare and account for 5-7% of all renal tumors and about 5% of all urothelial tumors [5]. It has been found that 25–75% of patients with upper urothelial tumors will eventually develop bladder cancer [6]. Tumors are most commonly located in the lower third of the ureter: proximal, 3%; middle, 24%; distal, 73% [7-10]. These tumors rarely develop before the age of 40 and have a peak incidence at the age of 65, and they are twice as common in men [11-12].

Smoking is the most important factor related to these tumors and it is associated with an increased risk of approximately 3 times higher than the general population. Other factors are excessive consumption of analgesics such as aspirin, phenacetin, and salicylates with or without caffeine, and codeine, as well as the use of cyclophosphamide [13-14]. There is also a significantly increased risk of upper urinary tract tumors in workers of the chemical, petroleum and plastics industries [15].

When there is a suspicion of a urothelial tumors in the urinary tract, it is necessary to carry out cabinet studies that allows the evaluation of not only the urinary tract, but also the rest of the anatomy, in search of metastases or other associated lesions. CT urogram with excretory phase offers a sensitivity of approximately 67–100% and a specificity of 93–99%. Another study such as magnetic resonance imaging is approximately 75% sensitive towards tumors < 2 cm. Another tool that is available is ureteroscopy with or without biopsy, which is 95% effective in detecting flat and small tumors [16].

For the treatment of urothelial tumors of the upper urinary tract, whether an open or laparoscopic approach is used, complete distal ureterectomy with bladder segmentation is recommended because of the higher survival and cure rate. The general principles include complete intact resection of the ureter with controlled occlusion of the ureteral orifice. The entire distal ureter is removed, including the intramural portion and the ureteral orifice [17-18]. It is important to note that the management of the distal ureter remains a dilemma, as no technique has been proven to be superior towards others [19].

In cases where a segment of ureter is left, the risk of local tumor recurrence in the residual ureter is 73%. Therefore, in these cases, surgery should be completed with resection of the residual ureter segment and its intramural portion and ureteral orifice in the bladder, in order to achieve adequate oncological control [20].

2. Presentation of the case

We present the case of a 55-year-old male patient with a history of systemic arterial hypertension and type 2 diabetes mellitus diagnosed 4 years ago, and was under medical treatment, with adequate control. 18 months before presenting to the hospital, he began to suffer from mild pain in the right dorsolumbar region, colicky, radiating to the left hemi-intestine, with intensity 8/10, accompanied by total macroscopic hematuria with intermittent elimination of filiform clots. The patient had received multiple treatments with analgesics and antibiotics for probable urinary tract infections, colitis and gastritis, and all were unsuccessful, with partial improvement of the symptoms. 18 months after the onset of the symptoms, a simple and contrasted abdominal-pelvic tomography was performed, documenting tumor lesions in the right renal pelvis, causing moderate right hydronephrosis. Paraclinical examinations were performed, and all parameters were found to be normal. An open radical right nephrectomy was performed, with a histopathological report of high-grade papillary urothelial carcinoma in the renal pelvis, without muscle involvement, with a negative ureter section border. The patient did not come back for follow-up.

One year after radical kidney surgery, he came to our service with a new event of total macroscopic hematuria, with persistent clots, leading to anemic syndrome, so the Urology Department performed an emergency cystoscopy and ureteroscopy. The right ureteroscopy revealed multiple tumor fronds along the entire course of the remaining right ureter, with active bleeding and severe inflammation (**Figure 1**), with no evidence of tumor activity in the bladder. Urinary cytology reports suggest of malignancy on the right

side and negative on the left side, so a laparoscopic radical right ureterectomy was performed, with laparoscopic bladder encirclement and right pelvic lymphadenectomy, pre-caval, paracaval, and intercavaortic (**Figure 2**).

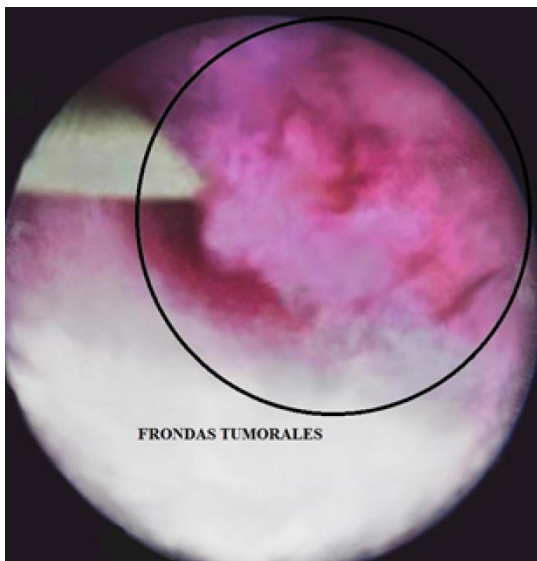


Figure 1. Right ureteroscopy: Hydrophilic guidewire (white) on the left, and on the right, multiple friable, actively bleeding, papillary-looking tumor fronds



Figure 2 Extended lymphadenectomy shows dissected vena cava and aorta

The procedure was performed in the left Israel Bergman position at 45°, an 18 Fr Foley catheter and three trocars were placed: one 10 mm paraumbilical trocar and two more 5 mm ones at the mid-clavicular line (**Figure 3**).



Figure 3. Patient position, 45° lateral decubitus, with the arms extended with fixation and support on the pelvis and thorax

Adhesions from previous surgery were released, and the ureter was identified and dissected from its

previous surgical ligature, following its trajectory up to the ureterovesical junction. After filling the bladder, a direct cut of the bladder is made with bipolar energy, with a margin of 5 mm around the meatus, and then bladder closure is performed with a continuous stitch with Vicryl 2-0 in two planes, to close the wound (**Figure 4**).

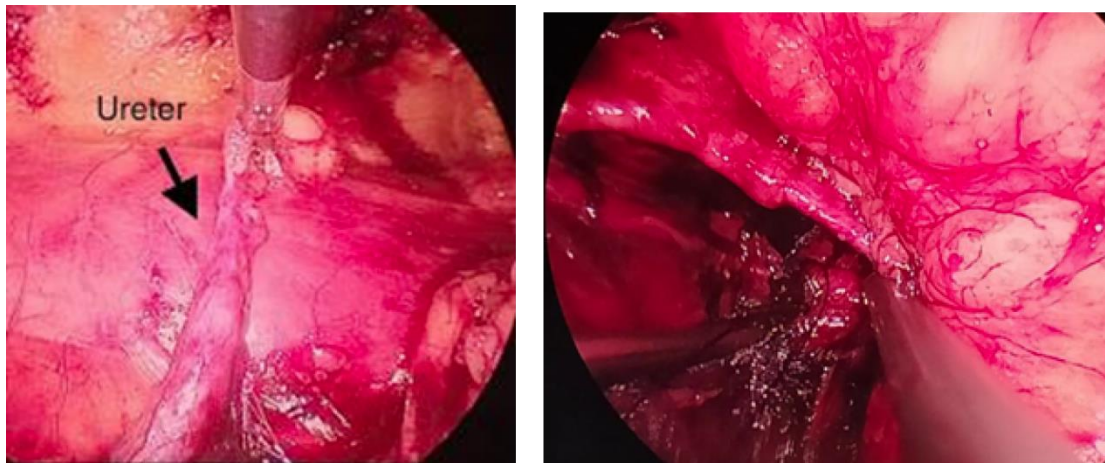


Figure 4. Ureter dissection (left), bladder closure with 2-0 Vicryl (right)

The ureter and impeller were extracted through a 10 mm port. The surgery was completed in 90 minutes, and no leakage and a satisfactory hemostasis was reported (**Figure 5**). The bleeding was approximately 50 mL. The patient progressed well and was discharged the following day, with catheterization for 10 days, with subsequent uncomplicated removal.

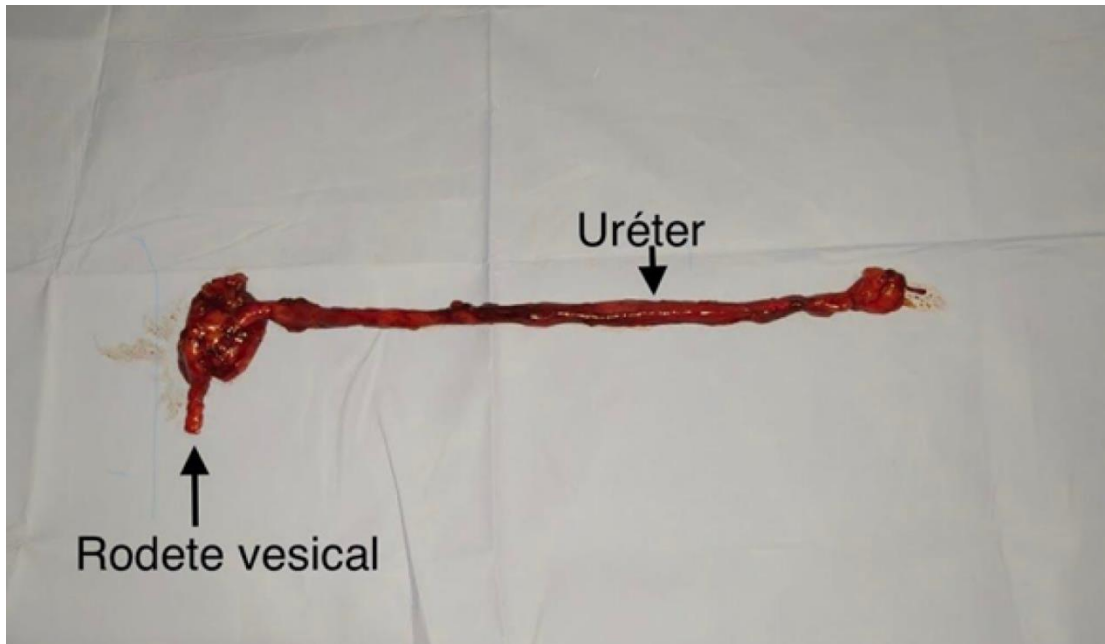


Figure 5. Surgical specimen, showing the entire ureter, with the bladder segment, intact and with a complete specimen

Results of histopathological reports: right ureter with low-grade papillary urothelial carcinoma, without invasion of the muscularis, mild chronic non-specific inflammation, negative for malignancy, with negative surgical margin. Lymphadenectomy was negative for malignancy.

At the six-month follow-up after surgery, the patient was found to have no evidence of recurrence or

tumor activity through cystoscopy and urinary cytology.

3. Discussion

The most frequent symptoms of upper urothelial tumors are hematuria, either macroscopic or microscopic, and lumbar pain, both of which occur in 56–98% and 10–40% respectively [20].

These two signs were present in this case study, the first one manifested weekly as thready hematuria, leading to an anemic symptom, accompanied by the second most frequent clinical sign – lower back pain. It has been reported that the sensitivity for detecting malignant disease of the upper tract through these methods are close to 100%, with a specificity of 60% and a negative predictive value of 100%. Hydronephrosis, also present in the patient, is linked to invasion in 80% of ureteral tumors.

Initially, an open radical right nephrectomy was performed, while the most appropriate approach in this case would have been a radical nephroureterectomy; however, a laparoscopic radical right ureterectomy was performed, with bladder encirclement and extended lymphadenectomy. The incomplete removal of the entire distal ureter and ureteral orifice is associated with a high rate of tumor recurrence. In fact, radical nephroureterectomy is recommended because it provides an optimal chance of survival in various cases. Several studies have shown lower morbidity rates with the laparoscopic approach compared to the open technique for renal pelvis and proximal or intermediate ureteral tumors.

The aim of this article is to show that the treatment of urological tumors can be approached laparoscopically, even if the initial approach was an open surgery. Therefore, an open surgery should not be a contraindication to offer laparoscopic treatment, considering that it is recommended in many papers. Laparoscopic treatment is safer, with adequate oncological control, minimal bleeding, quick recovery, and excellent aesthetic results. Therefore, this approach can be recommended for the treatment of urological pathologies even for those who underwent open surgery.

4. Conclusion

With this article, we wish to emphasize that with adequate training, experience and practice in laparoscopic surgery, excellent oncological and aesthetic results can be obtained, similar to that of an open surgery, except that the patients can recover faster with less pain and bleeding. Therefore, we believe that with practice and patience, laparoscopic oncological surgery after open surgery is absolutely feasible.

We show in this article that the laparoscopic approach after an open surgery for the treatment of oncological pathologies is totally safe and reproducible. It is a less invasive approach, and it allows adequate oncological control, and it is safer for the patient, which is why we recommend keeping this option in mind even with the history of an open surgery.

Disclosure statement

The authors declare no conflict of interest.

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Study of Tethered Spinal Cord Syndrome Diagnosis Following a Close Examination of Daytime Urinary Incontinence

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Abstract: *Background:* Tethered spinal cord syndrome refers to neurological disorders caused by the lower end of the spinal cord becoming entrapped in the caudal tissue. Dysuria is one of the most common symptoms and often appears at an early stage. In this study, we investigated cases of children with tethered spinal cord syndrome who were presented to the urology department with daytime urinary incontinence. *Subjects and methods:* Eighteen children with tethered spinal cord syndrome were diagnosed between March 2011 and October 2017 after a visit to the urology department with daytime urinary incontinence as the main complaint. The reasons for the diagnosis of tethered spinal cord syndrome and the changes in clinical symptoms before and after laminectomy were investigated. *Results:* Nine boys and nine girls were selected as the study subject. The mean age at the first examination was 6.3 years (range 4–9 years). All patients underwent urodynamics and voiding cystourethrogram (VCUG) for refractory daytime urinary incontinence. Spinal MRI was performed in all patients to investigate abnormal findings on VCUG and urodynamics. Only four patients had indications of tethered spinal cord syndrome on MRI. Eight patients had lipoma of the filum terminale, four patients had potential tethered spinal cord syndrome, four patients had low-lying conus, one patient with conus lipoma, and one patient had intrasacral meningeal cyst. The mean follow-up after laminectomy was 66.3 (22–116) months, 11 patients were asymptomatic, 4 patients had residual nocturia only, and 3 patients were managed with intermittent voiding. *Conclusion:* It is necessary to treat patients with daytime urinary incontinence is one of the symptoms of the tethered spinal cord syndrome. Bladder function assessed by urodynamics may provide a diagnostic sign for spinal cord compression.

Keywords: Diurnal urinary incontinence; Spinal cord compression; Urodynamics

Online publication: June 14, 2023

1. Introduction

The most common clinical manifestation of spina bifida is tethered spinal cord syndrome. Tethered spinal cord syndrome is a condition in which the lower end of the spinal cord is fixed (entrapped) in caudal tissues (dura mater, subcutaneous tissue, etc.) due to neural tube dysplasia during the embryonic period. Continued caudal traction of the spinal cord results in increased lower limb skeletal muscle tendon reflexes and autonomic disorders. Dysuria, in particular, is considered to be one of the earliest manifestations of tethered spinal cord syndrome ^[1]. In the present study, we investigated a case of a child presenting with daytime

urinary incontinence and nocturia, which led to the diagnosis of tethered spinal cord syndrome.

2. Methodology

We retrospectively studied 18 children who presented to our urology department between March 2011 and October 2017 with daytime urinary incontinence and were diagnosed with tethered spinal cord syndrome upon examination. Cases in which tethered spinal cord syndrome had already been detected by MRI or other means prior to the visit to the urology department were excluded. The age, gender, voiding cystourethrogram (VCUG), reason for spinal MRI, diagnosis of spinal MRI, urodynamics before and after surgery, postoperative voiding symptoms, and urinary tract management of the patients were investigated. Besides, the patients' background, reasons for spinal MRI, and spinal MRI diagnosis were assessed descriptively terms of percentage: maximum bladder capacity at VCUG, maximum bladder capacity/expected bladder capacity ^[2], bladder deformity ^[3] or vesicoureteral reflux (VUR), urodynamic parameters (presence or absence of detrusor overactivity [DO], bladder compliance) before and after untethering were compared using the Mann-Whitney U test or Fisher's exact test. This study was reviewed and approved by the Research Review Committee within the Ethics Committee of the Tokyo Metropolitan Children's General Medical Centre (Ethics Committee No. 2019b-105).

3. Results

Nine boys and girls were selected as test subjects in this study. The mean age at the first examination was 6.3 years (range 4–9 years). The patients' background is shown in **Table 1**. All patients were referred from other hospitals for a thorough examination of daytime urinary incontinence or refractory urinary incontinence, and 13 (72%) had concomitant nocturia. All patients underwent bladder function tests, VCUG, and urodynamics at an average of 5.8 months after the initial examination for refractory urinary incontinence.

The mean maximum bladder capacity on VCUG was 133 ± 69 mL, and the mean maximum bladder capacity/expected bladder capacity was $60 \pm 29\%$. It was found that 4 patients had grade 1 bladder deformity, 2 patients with grade 2, and 1 patient with grade 3 bladder deformity according to the Ogawa classification ^[3], and VUR was observed in 2 patients. Urodynamics showed DO in 12 patients (67%), with a mean compliance of 15.0 ± 15.4 mL/H₂O.

Table 1. Patient background

	All cases (<i>n</i> = 18)	Boys (<i>n</i> = 9)	Girls (<i>n</i> = 9)	<i>P</i>
Age at first consultation (years)	6.3 ± 1.6	6.4 ± 1.7	6.2 ± 1.4	0.97
Nocturia <i>n</i> (%)	13 (72)	6 (67)	7 (78)	0.88
Constipation, <i>n</i> (%)	4 (21)	3 (33)	1 (11)	0.30
Sacral dimple, <i>n</i> (%)	5 (26)	2 (22)	3 (33)	0.85
VCUG				
Maximum bladder capacity* ¹ (mL)	133 ± 69	107 ± 40	159 ± 81	0.33
Maximum bladder capacity/EBC* ² (%)	60 ± 29	49 ± 17	71 ± 35	0.62
Bladder deformity, <i>n</i> (%)	12 (67)	6 (67)	6 (67)	1.0
VUR, <i>n</i> (%)	2 (11)	1 (11)	1 (11)	1.0

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	All cases (n = 18)	Boys (n = 9)	Girls (n = 9)	P
<i>Urodynamics</i>				
DO+, n (%)	12 (67)	8 (89)	4 (44)	0.13
Bladder compliance, mL/cmH ₂ O	14.9 ± 15.8	17.4 ± 20.9	12.3 ± 7.0	0.66
Age at the time of surgery (years)	7.3 ± 1.6	7.0 ± 1.8	7.6 ± 1.3	0.34
Period between surgery and initial consultation (months)	16.7 ± 10.7	13.0 ± 11.0	20.4 ± 8.9	0.22
Period between final observation from initial consultation (month)	66.3 ± 23.8	67.7 ± 27.7	65.0 ± 19.0	0.92

Abbreviations: VCUG, voiding cystourethrogram; EBC, expected bladder capacity; VUR, vesicoureteral reflux; DO, detrusor overactivity. *¹VCUG, *²(Age +1) × 30 mL.

All patients underwent spinal MRI; one patient had a sacral dimple, which was performed at the same time as the bladder function test. The other 17 patients (95%) were screened for spinal cord disease and tethered spinal cord syndrome based on the results of urodynamics or cystography (**Table 2**). Eight patients (44%) had filum terminale lipomas, four (22%) had low-lying spinal conus, one (6%) had a conus lipoma, and one (6%) had an intrasacral meningeal cyst. Spinal MRI showed tethering of the spinal cord or abnormal spinal conus position in only 4 patients (22%); 14 patients (78%) had no anatomical tethering of spinal cord but were diagnosed with symptomatic tethered spinal cord syndrome based on urinary incontinence symptoms and urodynamic results that indicated the need for a surgery. Four patients (22%) were diagnosed with occult tethered cord syndrome (OTCS) without any abnormal findings on imaging, such as filum terminale lesions or abnormal spinal conus position. In comparison between OTCS and non-OTCS cases, all patients in the OTCS group had DO and significantly lower bladder compliance (**Table 4**).

Table 2. Reasons for spinal MRI

	n (%)
DO or low compliance	16 (89)
Bladder deformity	1 (6)
Sacral dimple	1 (6)

Abbreviation: DO, detrusor overactivity.

Table 3. Diagnosis on spinal MRI scan

	n (%)	Tethering, n
Ulnar lipomatosis	8 (44)	0
Potential occult tethered cord syndrome (OTCS)	4 (22)	0
Low spinal cord conus	4 (22)	3
Conus lipoma	1 (6)	1
Intrasacral meningocele cyst	1 (6)	0

Abbreviation: OTCS, occult tethered cord syndrome.

Table 4. Comparison of potential OTCS with other cases

	OTCS (<i>n</i> =4)	Other than OTCS (<i>n</i> = 14)	<i>P</i>
Age at first consultation (years)	6.3 ± 1.5	6.3 ± 1.6	1.00
VCUG			
Maximum bladder capacity* ¹ (mL)	109 ± 45	140 ± 70	0.49
Maximum bladder capacity/EBC* ² (%)	54 ± 23	62 ± 31	0.49
Bladder deformation, <i>n</i> (%)	4 (100)	8 (57)	0.25
VUR, <i>n</i> (%)	1 (25)	1 (7)	0.41
Urodynamics DO+, <i>n</i> (%)	4 (100)	8 (57)	0.16
Bladder compliance (mL/cmH ₂ O)	7.6 ± 2.7	16.2 ± 17.7	*0.038
Age at laminectomy (years)	6.5 ± 1.7	7.5 ± 1.6	0.36

Abbreviation: OTCS, occult tethered cord syndrome; VCUG, voiding cystourethrogram; EBC, expected bladder capacity; VUR, vesicoureteral reflux; DO, detrusor overactivity. **P* < 0.05

All patients underwent laminectomy, and their bladder capacity increased from 148 ± 93 mL to 182 ± 97 mL after surgery, but there was no statistically significant difference. Bladder deformity improved in six patients, VUR disappeared in one patient, and DO disappeared in seven patients (**Table 5**). Bladder compliance improved markedly from 15.0 ± 15.4 to 26.5 ± 36.3 cmH₂O (*P* < 0.0001). Daytime urinary incontinence resolved in all patients: four were treated with anticholinergics for frequent urination and oliguria, four remained nocturia only and were treated with desmopressin or anticholinergics, and three were on intermittent voiding control and anticholinergics.

Table 5. Changes in bladder capacity and urodynamics before and after laminectomy

	Before surgery	After surgery	<i>P</i>
Maximum bladder capacity* ¹ (mL)	133 ± 69	167 ± 76	*0.021
Maximum bladder capacity/EBC* ² (%)	60 ± 29	64 ± 27	0.090
Bladder deformation or VUR, <i>n</i> (%)	14 (78)	7 (39)	*0.049
DO+, <i>n</i> (%)	12 (67)	5 (28)	*0.049
Bladder compliance (mL/cmH ₂ O)	14.9 ± 15.8	26.5 ± 36.3	* < 0.0001

Abbreviation: EBC, expected bladder capacity; VUR, vesicoureteral reflux; DO, detrusor overactivity. **P* < 0.05, *¹ VCUG, *² (Age + 1) × 30mL.

4. Discussion.

The standard treatment for daytime urinary incontinence in children is generally conservative treatment emphasizing on urotherapy, followed by pharmacological treatment with anticholinergic drugs [4]. In refractory cases, screening for bladder dysfunction by urodynamics and VCUG is recommended [4]. There are a number of brain and spinal cord disorders that can cause a suspected neurogenic bladder, the most common of which is spina bifida in children [5]. In general, the earlier the surgery for spina bifida is performed, the better the long-term functional prognosis, including urinary function [6-9]. In this study, children diagnosed with tethered spinal cord syndrome following a close examination for daytime urinary incontinence were included. All patients underwent laminectomy, and as a result, postoperatively daytime urinary incontinence disappeared, and urodynamic parameters improved.

Invasive tests such as urodynamics are not recommended in the early stages of the treatment of daytime urinary incontinence and nocturia^[4,10]. However, in our study, all patients were children under 10 years of age, and none of them were presented with symptoms due to puberty-related changes in body size, and all presented with persistent daytime urinary incontinence since childhood. Secondary nocturia is defined as the reappearance of nocturia after more than 6 months of absence^[12], and it is considered necessary to consider underlying neurogenic bladder disorders such as tethered spinal cord syndrome for secondary nocturia^[10]. All patients with nocturia in the present study (13 patients: 68%) had primary nocturia and none had secondary nocturia.

In our hospital, children presenting for refractory urinary incontinence are often assessed for bladder function using urodynamics or other methods if consent is obtained. Screening for bladder dysfunction using urodynamics^[13] and early diagnosis and intervention of tethered spinal cord syndrome have been reported to be effective in the prognosis of future voiding function^[14-16]. At our hospital, 369 patients underwent urodynamic and VCUG screening for daytime urinary incontinence and nocturia in the same period, and spinal MRI was performed in 129 patients. Approximately 5% of children presented to our hospital with daytime urinary incontinence had tethered spinal cord syndrome. It is difficult to determine the exact frequency of spinal cord entrapment syndrome in children with daytime urinary incontinence because our clinic is often referred to by other hospitals as a refractory case. However, the possibility of tethered spinal cord syndrome being present in children with daytime urinary incontinence as the main complaint should be taken into account during treatment, and bladder function assessment should be actively considered, at least when the patient is considered refractory^[4].

In this study, only 4 (21%) children had tethered spinal cord syndrome findings on MRI, and all 4 had a shallow ulcer in the sacral region. Tamura *et al.* reported that 5.8% of children with sacral dimple had tethered spinal cord syndrome^[17]. Although there are differing opinions as to whether all cases of sacral dimple should be investigated by MRI or other methods, it should be noted there is a certain possibility of tethered spinal cord syndrome^[18]. Tamura *et al.* reported that 7.8% of their patients were diagnosed with tethered spinal cord based on abnormal findings in urodynamics, although anatomical indications was not observed^[18]. In the present study, 14 patients (78%) had no anatomical spinal cord involvement, and four of them did not even have spinal cord lesions such as a filum terminale lipomas, leading to a diagnosis of OTCS^[19-21]. The four OTCS patients also had no skin abnormalities, including sacral dimple. Although there is controversy regarding surgical intervention and timing of surgery in the absence of anatomical spinal cord involvement on imaging studies, children with clinical symptoms of neurogenic bladder, with or without anatomical spinal cord involvement, are indicated for laminectomy as symptomatic patients^[22-23]. It is important to recognize that some children with daytime urinary incontinence or nocturia may be candidates for spinal deactivation and an accurate assessment of bladder function should be performed using urodynamics.

In our hospital, the main focus is on children with spina bifida who often require voiding care, including the patients in this study, and conferences are held in the departments of urology, gastroenterology and neurosurgery. In some cases, the patient has bladder dysfunction on examination but no abnormal findings on MRI, and Hinman syndrome^[24] is suspected based on the history and examination, but after a conference. In these cases, laminectomy is not performed. The patients who underwent laminectomy as OTCS often had DO and findings of low bladder compliance. As shown in **Table 5**, abnormal findings in urodynamics that could not be explained in OTCS cases played a role in determining the need for surgery. The patient's bladder was not found to have a low bladder compliance. However, if neurogenic bladder is strongly suspected based on urodynamic results, the possibility of OTCS should be considered, and the indication for laminectomy should be discussed with the neurosurgeon. There is no difference in surgical findings between OTCS and non-OTCS cases; pathological investigation of terminal

thread lesions in OTCS may lead to a better understanding of the pathogenesis of OTCS and warranting more studies in the future.

5. Conclusion

In this study, we report on a child diagnosed with tethered spinal cord syndrome are complaints of daytime urinary incontinence was reported. It is necessary to treat cases in which daytime urinary incontinence is one of the symptoms of tethered spinal cord syndrome. A detailed bladder function assessment should be performed in cases of refractory daytime urinary incontinence, and screening for tethered spinal cord syndrome should be considered.

Disclosure statement

The authors declare no conflict of interest.

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Giant Cell Osteoclast-Like Bladder Carcinoma: A Case Report

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Abstract: *Introduction:* Osteoclast-like giant cell bladder carcinomas are an extremely unusual and aggressive histological subtype of urothelial carcinomas. Only 30 cases have been reported globally. *Clinical case:* A 79-year-old male patient was presented to our Urology Department due to macroscopic hematuria that persisted for six months. As part of his diagnostic protocol, a CT scan of the abdomen and pelvis with elimination phase was performed, finding a filling defect of 12 mm at the level of the posterior wall of the bladder. A cystoscopy was subsequently performed, confirming the presence of a 1.5 cm bladder tumor, which was resected in its entirety. Pathology analysis with hematoxylin and eosin stain revealed a composition of mononuclear cells and osteoclast-like giant cells. Immunohistochemistry was positive for epithelial markers cytokeratins AE1/AE3, EMA, P53, and CD68. *Conclusion:* Osteoclast-like giant cell bladder carcinomas are extremely unusual and aggressive. The only diagnostic method is through immunohistochemistry, confirming the presence of epithelial markers for urothelium in the neoplastic cells. Radical surgical treatment is recommended and there has been no proven effective adjuvant treatment to date. The patients' median survival is 15 months.

Keywords: Bladder; Urinary neoplasms; Urogenital; Hematuria; Urology

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1. Introduction

We present a case of a 79-year-old male patient diagnosed with osteoclast-like giant cell carcinoma of the bladder, an extremely unusual and aggressive histological subtype of the urothelial carcinomas. There are only 30 cases reported worldwide, so the information available is very limited. Its presentation, management, and outcome, as well as pathology and immunohistochemical findings will be discussed in this report.

2. Presentation of the case

A 79-year-old male patient was referred to the Urology Department of National Medical Center Northeast Specialty Hospital in July 2020, with macroscopic hematuria that persisted for 6 months, amorphous clots were formed intermittently, and the patient was non-anemic, with no other associated symptoms. When questioned about his history, he reported that he was a smoker for 50 years, at a rate of 60 packs per year, but stopped smoking 6 years ago. He also reported 15 years of occupational exposure to different types of

solvents, such as petrol, thinner and acetone, and his hereditary family history of cancer was denied.

As part of his study protocol, a computed tomography (CT) scan with intravenous contrast was performed on the chest, abdomen, and pelvis, which revealed multiple bilateral pulmonary nodules of peripheral predominance, with an average diameter of 8 mm each, which suggested a metastatic disease (**Figure 1**). At the bladder level, posterior wall thickening was observed with enhancement to 76 Hounsfield Units (HU) in the arterial phase, and a 12 mm filling defect in the elimination phase (**Figure 2**).

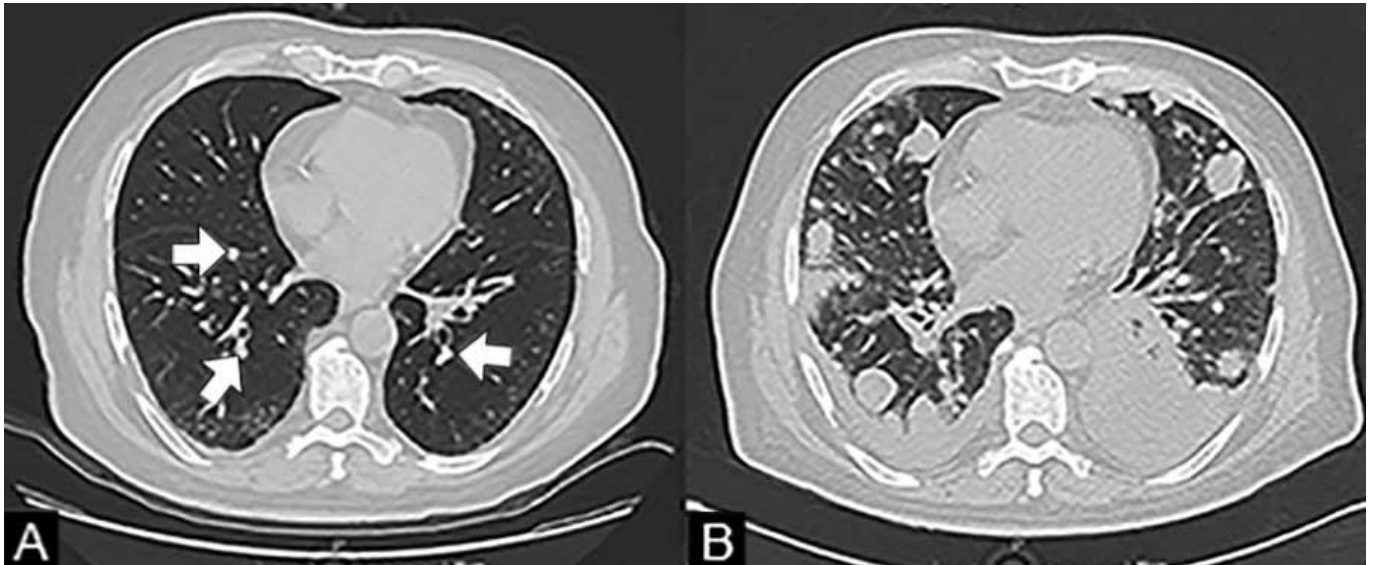


Figure 1. Chest CT scan with lung window in axial reconstruction. Panel A: Initial CT scan with multiple bilateral nodules of 8 mm diameter each (arrows). Panel B: Same CT scan segment months after transurethral resection of the bladder, indicating rapid progression of metastatic disease, as well as bilateral pleural effusion and interstitial pattern secondary to COVID-19 infection in the patient at that time.



Figure 2. CT scan of the abdomen and pelvis with elimination phase in axial (panel A) and coronal (panel B) reconstruction. A 12 mm filling defect in the posterior wall of the bladder (arrow). No evidence of extension into the upper urinary tract or adjacent structures.

Based on the findings in **Figures 1 & 2**, an urgent transurethral resection of the bladder (TURBT) was

performed, and a tumor of 1.5 cm in diameter with a sessile appearance was found at the trigone level, with extensive and friable necrosis. The tumor was resected completely. Following the surgical procedure, complete remission of the hematuria was achieved, and the patient was discharged after 48 hours, with an outpatient follow-up plan.

Pathology analysis of the surgical specimen revealed a composition of two cell populations through hematoxylin and eosin (H&E) staining: the first one was composed of mononuclear cells with scant eosinophilic cytoplasm and a spindle-shaped morphology, their nucleus contained vesicle-shaped chromatin and discrete nucleoli (**Figure 3A**); the second population was composed of giant cells with multiple nuclei, compatible with osteoclast-like giant cells, with obvious atypia (**Figure 3B**). Both cell populations were surrounded by a highly vascularized stroma, with areas of erythrocyte extravasation and extensive necrosis.

Immunohistochemistry was positive for epithelial markers cytokeratins AE1/AE3, EMA and P53 in the mononuclear cells and CD68 in the osteoclast-like giant cells (**Figure 3C**). Both cell populations were positive for vimentin (**Figure 3D**).

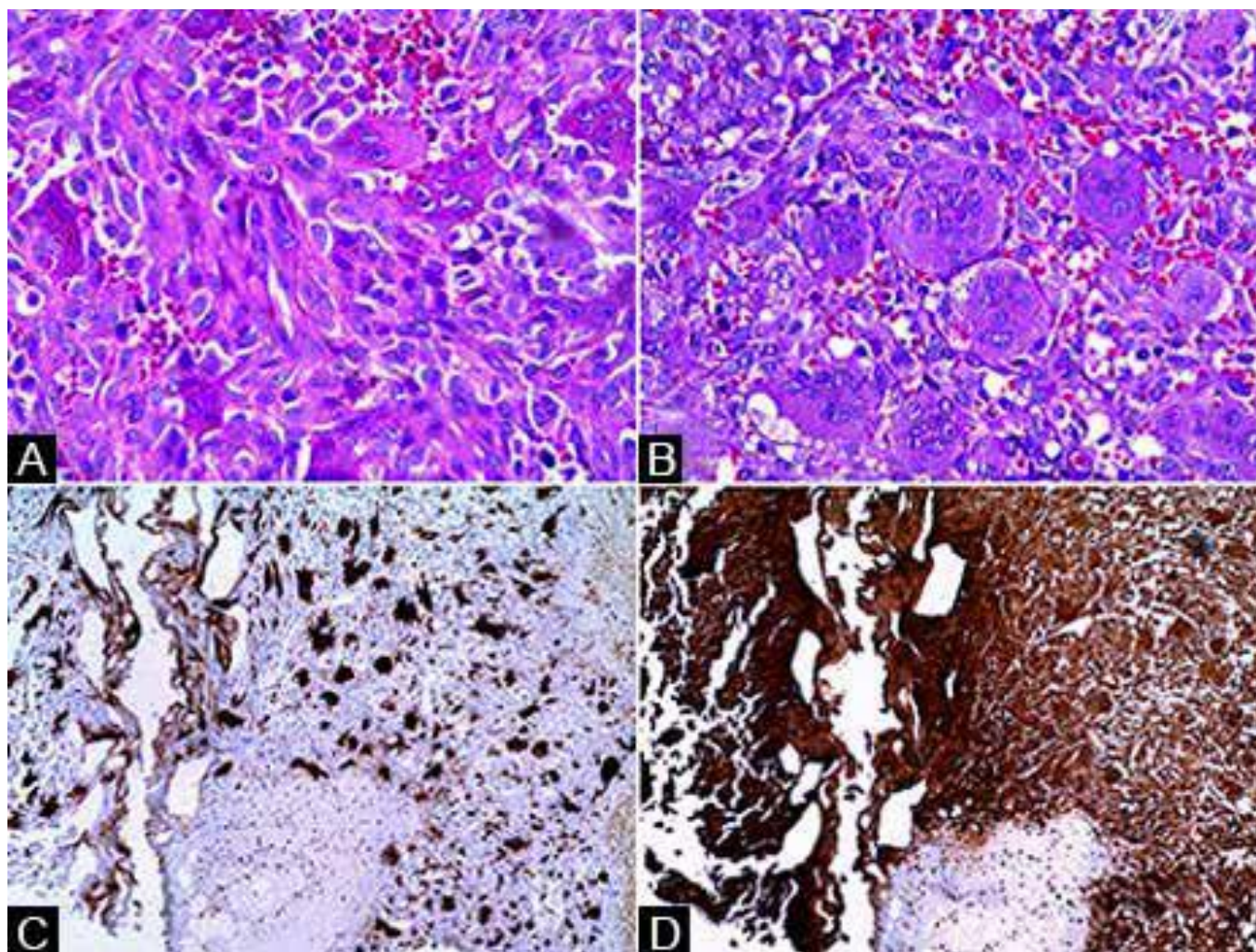


Figure 3. Osteoclast-like giant cell carcinoma identified through H & E staining and immunohistochemical analysis. Panel A (H&E, 40x): proliferation of mononuclear cells with scant eosinophilic cytoplasm, spindle morphology and presence of mitoses. Panel B (H&E, 40x): osteoclast-like giant cells without obvious atypia. Panel C (immunohistochemistry, 10x): osteoclast-like giant cells with CD68 expression. Panel D (immunohistochemistry, 10x): both cell populations with vimentin expression.

The patient was assessed an oncologist, who stated that the patient was not suitable for cisplatin-based chemotherapy due to his poor functional status (Eastern Cooperative Oncology Group, ECOG 2). For the same reason, the Urology department decided not to perform a radical cystectomy but instead to keep him under close surveillance, and further trans urethral resection of bladder tumor (TURBT) was performed if needed as palliative treatment. Two months after surgery, our patient was hospitalized due to a COVID-19 infection. The chest CT scan performed at that time revealed bilateral pleural effusion, interstitial pattern, and rapid progression of the metastatic disease (**Figure 1B**). Unfortunately, he died due to complications related to COVID-19 infection and metastatic disease two months after diagnosis.

3. Discussion

According to the World Health Organization's classification of urinary tract and male genitalia trans urethral resection of bladder tumors in 2016, the urinary tract tumors are divided into urothelial and non-urothelial variants ^[1]. The latter accounts for about 25% of the total and their incidence has been increasing in recent years, mainly due to a better knowledge of them by urologists and pathologists ^[2,3].

Histological subdivisions of non-urothelial carcinomas are predominantly based on their morphology observed with H & E staining ^[4], with squamous, adenocarcinoma, and neuroendocrine features, either one or mixed ^[2,5].

Among bladder tumors, non-urothelial carcinomas are rare and present a real diagnostic challenge because only 1-5% are of primary origin ^[2,6], and initial TURBT has a low sensitivity ^[7], detecting only 53% of cases ^[8], and some histological subtypes may appear to be benign lesions ^[9].

Non-urothelial carcinomas generally occur in older patients and at later stages compared to their urothelial counterparts ^[10-12]. Their prognosis is poor, regardless of clinical stage ^[13,14], with a 2- and 5-year recurrence-free survival rate of 62.0% ± 3.0% and 57.0% ± 3.0%, respectively; and a 2- and 5-year cancer-specific survival rate of 68.0% ± 2.0% and 58.0% ± 3.0%, respectively ^[15]. The effect of neoadjuvant therapies varies in their impact on patient survival, depending largely on histological subtype ^[16,17], so radical cystectomy remains the gold standard for treatment to date ^[4,18], and it should be performed within eight weeks of diagnosis to avoid compromising patient survival ^[19].

Among the non-urothelial histological variants, osteoclast-like giant cell carcinomas of the urinary tract are extremely rare, with only 30 cases reported worldwide ^[20,21]. They are predominant in male patients and has non-specific symptoms, with hematuria being the most common ^[20,22]. They are characterized by two types of cell populations: mononuclear cells with mild to moderate atypicality and expression of epithelial markers cytokeratins AE1/AE3, CAM 5.2, CK7, and EMA, and osteoclast-like giant cells with expression of CD68, LCA, CD51, and CD54 markers ^[21,22]. Both populations are positive for vimentin and acid phosphatase ^[23].

Their pathogenesis is still unknown, but one theory suggests that these are not true bone cells because there are key differences in their immunohistochemical profile, such as the expression of parurothelial epithelial markers. It is thought that they may actually be an unusual and aggressive variant of urothelial carcinomas that subsequently differentiate into a giant bone cell morphology ^[22].

Their appearance on cystoscopy is the same as that of a urothelial carcinoma. Thus, the only way to make a diagnosis is through pathological analysis along with immunohistochemistry ^[24].

Osteoclast-like giant cell carcinomas of the urinary tract have an overall poor prognosis, with a reported median survival of less than 15 months (**Table 1**) ^[25]. Radical surgical treatment is therefore recommended because of the aggressive nature of these tumors and because there is no proven effective adjuvant treatment so far ^[20].

Table 1. Summary of similar cases reported in literature: age at presentation, gender, site, treatment, and reported survival data

Authors	Gender	Age	Site	Treatment	Survival
Park ^[20]	Male	76 years old	Distal ureter	Radical nephroureterectomy	Alive at five months post-diagnosis. No evidence of recurrence
Palazzetti et al. ^[21]	Female	54 years old	Bladder	Radical cystectomy	Alive one year after diagnosis, no evidence of recurrence.
Baydar et al. ^[22]	Male	65 years old	Pelvis renal	Radical nephroureterectomy	Died 15 months after diagnosis. Pulmonary metastases
Baydar et al. ^[22]	Male	39 years old	Pelvis renal	Radical nephroureterectomy	Died 10 months after diagnosis. Recurrence of liver and lung metastases.
Baydar et al. ^[22]	Male	82 years old	Pelvis renal	TURBT	Died 5 months after diagnosis. Pulmonary metastases
Baydar et al. ^[22]	Male	81 years old	Bladder	TURBT	No follow-up or survival is reported.
Baydar et al. ^[22]	Male	81 years old	Bladder	Radical cystectomy	Alive four months after diagnosis, with local recurrence.
Baydar et al. ^[22]	Male	67 years old	Bladder	Radical cystectomy	Died 12 months after surgery.
Wu et al. ^[24]	Male	62 years old	Bladder	Radical cystectomy and partial ureterectomy	Alive five months after diagnosis. No evidence of recurrence
Osman et al. ^[25]	Male	55 years old	Bladder	Radical cystectomy	Died 10 months after diagnosis due to a lung infection. Received four sessions of gemcitabine along with cisplatin chemotherapy.

4. Conclusion

4.1. Limitations

The main limitation of this case report is the short follow-up period given to our patient, besides the late presentation of his disease. His poor condition also precluded him from being a candidate for systemic chemotherapy as adjuvant treatment, which would have potentially extended his survival.

4.2. Summary of scientific evidence and further recommendations

After a systematic search of indexed journals, no reports of similar cases were found locally or in Latin America with which to contrast immunohistopathology findings, treatment, and patient follow-up.

The cases published in international indexed journals, which are the treatments and follow-up are summarized in **Table 1**. It is noteworthy that only two patients received a treatment similar to our case (TURBT) instead of radical surgery, one of them presenting early recurrence at four months; and the follow-up and survival are unknown. The gold standard of treatment for these patients remains early radical surgery, within eight weeks of initial diagnosis.

4.3. Strengths

The greatest strength of this article is the microphotographs of pathology and immunohistopathology presented, which, to our knowledge, are the highest quality found in literature. As this is a highly unusual pathology, we believe that these information may help in the identification of future cases.

Disclosure statement

The authors declare no conflict of interest.

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The Effect of Lower Urinary Tract Symptoms on Quality of Life and Complementary Therapies for Patients with Multiple Sclerosis

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Abstract: Multiple sclerosis patients face many physiological, psychological, and social problems depending on the type and course of the disease. One of the physiological problems is lower urinary tract symptoms (LUTS). Problems such as urinary incontinence, frequent urination, sudden urination, inability to urinate, inability to empty the bladder completely affect the daily life of the patients. These patients may avoid social interaction because of frequent urination and incontinence. Patients with multiple sclerosis refrain from shopping, meeting with friends, and other social activities due to urinary problems. In addition, they also restrict their fluid intake because they urinate frequently. Urinary tract infections associated with low fluid intake and inability to urinate are more common in multiple sclerosis patients than in the normal population. These problems restrict the patient's life and negatively affect their quality of life. These complaints can be minimized by bladder training, pelvic floor muscle exercises, nerve stimulation, or use of urinary catheter in order to eliminate these problems and improve the quality of life of the patients. While bladder training prolongs the urination intervals of patients, pelvic floor muscle exercises reduce urinary incontinence by strengthening the muscles. Neuromodulation reduces these problems by suppressing nerve impulses. Catheters are important for patients who cannot urinate or have urinary incontinence. Urinary incontinence, retention, and urinary infection can be reduced by using catheters.

Keywords: Multiple sclerosis; Lower urinary tract symptoms; Complementary applications; Quality of life

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1. Introduction

Multiple sclerosis (MS) is a disease affecting young people and it causes sequelae due to neurological deficits because the disease affects the central nervous system. This disease affects women at a rate of approximately 2–3/1. Balance problems, visual problems, tingling, numbness, fatigue, spasticity, tremor, mood changes, paresthesia, sexual problems, heat intolerance, speech difficulties, bladder problems, and bowel problems are observed in MS patients depending on the progress of the disease ^[1]. Among these symptoms, lower urinary tract symptoms (LUTS) have been reported to affect up to 97.6% of patients ^[2], and these symptoms affect the quality of life of the patients ^[3].

2. Symptoms

The International Continence Society (ICS) defines LUTS as symptoms that occur when the bladder,

prostate, urethra or the associated pelvic floor, pelvic organ, or lower ureter cannot be stimulated. These symptoms are classified as storage (increased number of urination, frequent urination during the day, nocturia, polyuria, sensory symptoms related to the bladder, urinary incontinence, and overactive bladder), voiding (delay in urination, dysuria, stranguria, intermittent urination, and urinary retention) and post-urination (feeling of not being able to empty the urine completely, desire to urinate again, incontinence after urination, pain, and urinary system infections) [4]. Patients diagnosed with multiple sclerosis face many social, physiological, and psychological problems. Among these, lower urinary tract symptoms are one of the major problems affecting the lives of patients. The urinary problems are caused by myelin sheath damage of the nerves that control micturition. The frequency of LUTS may vary according to the duration of the disease. In a study, it was found that the incidence of LUTS increased up to 97.6% in patients with a disease duration of 10 or more years [2,3]. The frequency and type of LUTS in MS patients vary. The most common symptoms include urge to urinate, frequent urination, urge incontinence, stress incontinence, dysuria, and mixed-type incontinence. Urinary problems in MS patients sometimes occur as the first symptom of the disease. Regarding LUTS, voiding problems were observed in 24%, storage symptoms in 41% and both voiding and storage symptoms in 35% of the patients [5]. In the study conducted by Wang *et al.* [6], frequent urination, urge incontinence, stress incontinence, pauses, feeling of incomplete bladder emptying, dysuria, and mixed type incontinence were observed respectively. In the same study, it was found that the severity of urological symptoms were related to EDSS (Expanded Disability Status Scale) [6]. However, complications related to LUTS may also develop, which include urinary infection and urolithiasis [7]. Detrusor overactivity is the most common bladder problem in MS patients. Detrusor dyssynergia, detrusor hypocontractility, and low bladder compliance have also been observed [6]. Although the exact time of onset of urinary symptoms has not been determined, the frequency of urinary symptoms increase with the progression and course of disease. MS plaques may be found in any part of the central nervous system. Lesions observed in the cortical region (medial prefrontal cortex, insula, and pons) causes excessive detrusor activity [8]. Afferent stimuli from the bladder are processed in the periaqueductal grey matter. The periaqueductal grey matter suppresses the pontine micturition center during bladder storage. The pontine micturition center is connected to the spinal cord and stimulates the smooth muscles to contract the bladder. Conscious voiding control is carried out by the hypothalamus, which controls the activity of the middle frontal cortex and periaqueductal grey matter. Axonal loss leads to failure of cortex, brainstem, and spinal cord functions and increase in neurological deficits [9].

3. LUTS and their relationship with quality of life

MS affects the lives of patients physiologically, psychologically, and socially. LUTS significantly affect a person's life but it is not widely discussed. In MS patients, nocturia causes interruption of sleep at night, decreased sleep quality, tiredness the next day, and low energy [10]. LUTS observed in MS also affects the quality of life of patients as it improves when LUTS are resolved [5]. In the study conducted by Kahalaf *et al.*, a relationship was found between physical health, mental health, physical function, pain, general health, social function, emotional health, motivation, and lower urinary tract symptoms. When the people with the lowest quality of life were analyzed, it was found that they had urge incontinence and urge problems [11]. When the results of the study were analyzed, it was shown that LUTS affected both physical functions and emotional status of the patients. Lucio *et al.* found that urinary problems in women diagnosed with MS decreased and their quality of life improved with pelvic floor muscle exercise [12]. LUTS also affects the sexual life in MS patients. Erectile dysfunction, sexual reluctance, and dissatisfaction with sexual intercourse have been observed in MS patients. It has been found that sexual life worsens as LUTS increase in male MS patients [2]. Conditions including detrusor overactivity, inadequacy of detrusor activity, and detrusor sphincter dyssynergia lead to erectile dysfunction in men. The quality of sexual life is lower in MS

patients with erectile dysfunction compared with patients without erectile dysfunction ^[13]. In a study, sexual satisfaction of men with detrusor overactivity was found to be significantly lower than those with normal detrusor activity. In the same study, the sexual function of women (level of sexual arousal, vaginal lubrication, orgasm), involuntary detrusor contraction, and the highest detrusor contraction levels were found to be lower than those with normal detrusor activity ^[14]. It has been reported that many factors including pain, fatigue, alcohol consumption, and cognitive status play a role in the occurrence of depression in MS patients. However, changes in brain pathology, genetic factors, psychosocial status, and immune systems have been shown to be involved in its etiology ^[15]. It has been reported that LUTS is associated with anxiety, depression, and stress ^[3]. In a study by Khalaf *et al.* ^[11], it was found that the most common comorbid conditions in MS patients were depression and anxiety. In the same study, it was found that the rate of depression was higher in patients with urge incontinence compared with those who did not have this problem or had minimal problems ^[11]. Depression rates were found to be significantly higher in patients with erectile dysfunction ^[13]. There are studies showing that depression and anxiety levels do not change in patients with detrusor overactivity compared to those with normal detrusor activity ^[14]. It has been reported that the severity of anxiety increases in MS patients after diagnosis compared to the pre-disease period ^[16]. Fatigue and other symptoms, comorbid disease, anxiety medications, childhood trauma, and self-esteem, self-efficacy, and stress coping issues are conditions that cause depression ^[17]. When these studies are considered, it was revealed that there are many physiological and psychological conditions that trigger depression in MS patients. Although there are studies suggesting that LUTS may be one of them, studies on this subject showed different results. Overactive bladder also affects MS patients socially. People with overactive bladder limit their activities, are affected psychosocially, and they also limit their social life, thus their quality of life is affected. Frequent urination, urge to urinate, and nocturia are the main problems that affect quality of life related to incontinence ^[18]. Dysfunctions in MS patients affects the daily activities of the patients. After a ten-year follow-up, it was observed that those with mild and moderate MS became dependent in individual and instrumental activities of daily living. Among them, those with moderate MS were found to have increased limitations in all daily activities at the end of ten years, except for feeding and cleaning. At the end of ten years, those with mild MS were found to have increased dependence on urination and all instrumental and individual activities of daily living. It was revealed that those with severe MS became dependent in all individual activities of daily living at the end of ten years. It was found that those with severe MS were dependent on instrumental activities of daily living both at the beginning and at the end of ten years. At the end of ten years, it was found that activities such as participating in collective activities, working life, washing dishes, preparing food, washing dishes, walking outside, and driving a car were restricted ^[19].

4. Complementary practices for lower urinary system symptoms

There are various treatment modalities for overactive bladder in MS. The first ones are behavioral treatment methods. These behavioral treatment methods include Pelvic floor muscle training, bladder training, and fluid intake management. PFMT were created by Arnold Kegel and were initially applied in patients with urinary incontinence. The basic principle of PFMT is to create an inhibition effect by contracting the detrusor muscles. However, the patient should have the ability to contract the pelvic floor muscles ^[20]. These muscle exercises should increase strength, endurance, and function in a coordinated manner ^[21]. PFMT increases endurance in MS patients, reduces urinary incontinence, nocturia, and pad use, and facilitates voiding ^[22]. PFMT can be used alone or in combination with other techniques. In the study conducted by Walker and Mohillo-Fernandez, it was found that PFMT resulted in a decrease in LUTS of MS patients at the end of 12 weeks and improved quality of life ^[23]. The severity of frequent urination and urinary incontinence is inversely proportional to the quality of life ^[24]. Bladder training starts with the

person holding urine for 30 minutes. This time is increased by half an hour every 4–5 days and the voiding intervals are increased up to 3–4 hours [25]. Bladder training decreases the number of urinations, incontinence, and sudden urination in patients with an overactive bladder, and therefore improves their quality of life [26]. In the study conducted by Yoon *et al.*, it was found that bladder training resulted in a decrease of frequency of urination and increase in the volume of urination [27]. Bladder training can be used alone or with other pharmacological or non-pharmacological methods. Bladder training alone can reduce urination frequency, nocturia, and sudden urination symptoms. However, bladder training is more effective when used with tolterodine. However, while bladder training has no side effects, at least one side effect occurs in patients who were prescribed tolterodine alone or in combination with bladder training [28]. In women with overactive bladder, bladder training reduces the frequency of urination, urinary incontinence, and sudden urination, and improves the quality of life altogether [29]. For patients with MS, electrical stimulation is also used in addition to pharmacological treatment to treat the overactive bladder. It is used especially in patients with an overactive bladder, detrusor sphincter dyssynergia, and neural lower urinary tract dysfunction [30–33]. Electrical stimulation methods include pudendal, intravesical, posterior tibial nerve stimulation, and cutaneous neuromodulation [33]. Sacral neuromodulation of S3–S4 is usually applied, and its purpose is to suppress the impulses going to the bladder or to decrease the transmission of impulses from the bladder to the spinal cord. In posterior tibial nerve stimulation, L4–S3 fibers depolarize the afferent nerves in the lumbar and sacral regions and suppress bladder activity [34]. Sacral neuromodulation reduces the urge to urinate, frequency of urination, and the number of pads used in MS patients with storage and mixed problems. Besides, it decreases intermittent catheterization and residual amount and increases the volume of spontaneous voiding [5]. In a study by Kabay *et al.* [35], it was shown that a 12-week posterior tibial nerve stimulation decreased urge to urinate, urinary incontinence, nocturia, daily urination frequency, and pad use in patients. In the same study, an increase in detrusor contraction and maximum detrusor pressure was also observed [35]. Percutaneous tibial nerve stimulation is effective in treating urinary issues and improving the quality of life of the patients. Percutaneous tibial nerve stimulation reduces urination frequency and urinary incontinence in patients with an overactive bladder and improves their quality of life [36]. LUTS in patients with MS causes urinary tract infection. In a study by Nikseresht *et al.* [37], the rate of infection was found to be significantly higher in patients with problems such as urinary retention, urinary incontinence, frequent urination, and sudden urination compared to those without these problems [37]. Treatment or management of urinary problems is important to prevent infections. One way to reduce or eliminate LUTS is through intermittent or indwelling catheterization. Twelve per cent of MS patients use a clean intermittent catheter, indwelling catheter, or suprapubic catheter. The most commonly used one is the clean intermittent catheter. The use of catheters is more common in patients with urinary incontinence. Catheters may have a positive, negative, or no effect on the quality of life of patients [38]. 81.2% of catheter users use intermittent catheters, 42.8% use permanent catheters, and 7.7% use suprapubic catheters. Catheter use is higher in patients with overactive bladder who have problems like frequent urination, sudden urination, urinary incontinence, and nocturia. Despite the use of urinary catheter, urinary leakage occurs in 24% of patients. The feeling of discomfort due to urinary incontinence is related to the catheter used. 54% of patients using intermittent catheters experience difficulties in voiding compared to 18.8% of permanent catheter users and 8.5% of suprapubic catheter users [39]. Urinary infections in patients results in economic effects and lead to renal diseases. Measures have been developed to protect patients from these infections. These measures include taking urine cultures of patients for protection against urinary infections, use of silicone catheter, insertion of the catheter according to aseptic technique, fixation of the bag to the thigh, keeping the urine bag under the bladder, and avoiding contact with the floor and removal of the catheter as soon as possible [40]. Washing the urethral meatus with soap and water, using a closed drainage system, irrigation only in case of obstruction, and monthly replacement of the catheter are recommended, but there

is no conclusive evidence on this issue. The use of antibacterials in the drainage bag has no effect, and there are different opinions regarding the separation of patients with catheter-related infections. Training of personnel who will insert catheters and caregivers is important for the prevention of infection ^[41]. Apart from these methods, other methods such as intravesical stimulation, pudendal nerve stimulation, saphenous nerve stimulation, and transcutaneous nerve stimulation can be used (42). Overactive bladder and other bladder issues significantly affect the lives of patients. There are many pharmacological and non-pharmacological methods than can be applied to eliminate urinary problems in MS patients and to prevent the development of complications. In some cases, more than one of these treatment methods are used at the same time to reduce the symptoms and improve the quality of life of the patients. In order to reduce the urinary problems of patients and the economic effects, and improve the quality of life, nurses should explain the condition of patients. It is important that patients can benefit from methods other than medication for the elimination of urinary problems to improve their quality of life.

5. Conclusion

LUTS in patients with MS significantly affect the quality of life of patients. Complementary practices should be utilized to relieve these symptoms and improve the quality of life of patients. These complementary practices include bladder training, pelvic floor muscle exercises, neuromodulation, urinary catheterization, and other methods. The use of these methods alone or in combination with pharmacological treatment helps to increase the quality of life of patients and reduce economic losses.

Disclosure statement

The authors declare no conflict of interest.

Author contributions

Conceptualization – SÖ

Literature review, manuscript writing – SÖ, ÜP

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Factors Associated with Survival in Wilms Tumor Patients

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Abstract: *Introduction:* Wilms tumor is the second most common abdominal tumor in the pediatric age group and accounts for more than 90% of renal tumors in pediatrics. Even though the described survival rate is greater than 90%, we found that it only reaches 70% among our patients. Therefore, we aim to evaluate which are the factors associated with these unfavorable results, in order to implement measures to improve the survival of our patients. *Methods:* An observational, cross-sectional study was conducted in two high-level care centers, which included a sample of 84 patients under 15 years of age, diagnosed with Wilms tumor. *Results:* Factors significantly associated with an increased likelihood of death were failure to complete the chemotherapy protocol (odds ratio [OR] = 34; 95% confidence interval [CI] = 3.7–312; $P = 0.000$) and tumor recurrence (OR = 35.7; 95% CI = 6.9–184; $P = 0.000$). Other minor factors with certain impact were bilateral presentation (OR = 4.1; 95% CI = 0.6–5.5; $P = 0.147$), surgical complications (OR = 3.2; 95% CI = 0.7–14.6; $P = 0.136$), lymph node involvement on CT scan (OR 2.4; 95% CI 0.7–8.4; $P = 0.139$), and distant metastases (OR = 2.5; 95%CI = 0.7–9; $P = 0.143$). *Discussion:* The survival of our patients with Wilms tumor is lower than that reported in literature is associated with factors like failure to complete chemotherapy, recurrence, and the need for bilateral surgery.

Keywords: Wilms tumor; Nephroblastoma; Surgery; Urology; Surgical oncology; Cancer survivors

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1. Introduction

Wilms tumor is the second most common abdominal tumors in the pediatric age group and accounts for more than 90% of renal tumors in pediatrics ^[1]. In the United States, Wilms tumor has an incidence rate of 8.1 cases per million per year ^[2,3] and in Colombia, the National Cancer Institute reports a frequency of 9.3% for nephroblastoma, with 3.2 cases per million inhabitants per year ^[4].

Survival in patients with Wilms tumor has improved in recent decades in developed countries, thanks to the studies done on multimodal chemotherapy, the development of surgical techniques, and the recognition of the role of radiotherapy, which increased from 73% in 1975 to 93% in 2012, and currently reaching 95% ^[5]. In one study, it was found that 108 months after diagnosis, survival is 71% and that the average relapse-free survival time is 97 months ^[5].

The aim of this study was to evaluate which factors are associated with unfavorable survival outcomes,

in order to implement measures to improve survival in our patients with Wilms tumor.

2. Methods

We conducted an observational, cross-sectional study that included a sample of 84 patients under 15 years of age that were diagnosed with Wilms tumor and were treated in the pediatric hemato-oncology department of two high-level care hospitals in Medellín, Colombia, between January 1, 2005, and May 31, 2018.

To define the factors associated with two-year survival, we evaluated sociodemographic variables (place of residence and sex), clinical variables (clinical presentation, laterality, history of malformation), pathological variables (tumor pathology, previous biopsy, presence of necrosis, and histology), surgical variables (resectability, procedure performed, bilaterality, tumor containment, and complications), chemotherapy (protocol used, complete termination of the protocol), radiotherapy, recurrence, and tomographic findings. As for data collection, medical records from the pediatric surgery, oncology, and pediatric nephrology department were reviewed.

As for statistical analysis, a database was constructed in Excel, with the relevant validation rules to ensure data quality, and calculations were made using SPSS 22.0. Qualitative variables were presented with absolute and relative frequencies and quantitative variables with measures of central tendency. Percentages were calculated based on the number of patients who had data on each variable.

Bivariate analysis was performed using contingency tables with a 5% independence test, to measure the relationship of the variables with two-year survival. Adjusted odds ratios (OR) were obtained using logistic regression analysis. Several models were constructed with the epidemiologically important variables, also noting the contribution of independent variables that were statistically significant with a $P < 0.25$. Independent variables whose correlations suggested collinearity were excluded from the analysis and tests were done to assess the fit through the likelihood ratio.

Informed consent: In accordance with Resolution 008430 of 1993 of the Colombian Ministry of Health, the research is classified as low risk because it is based on the review of data from medical records, so informed consent was not required. Prior authorization was requested from the research and ethics committees of both institutions, which approved the research.

3. Results

A total of 84 children with Wilms tumor were evaluated at the Pablo Tobón Uribe and San Vicente Fundación hospitals between 1 January 2005 and 31 May 2018. Only 61 of them could be followed up to establish survival at two years after diagnosis, which was 70.5 % ($n = 43$).

Forty-eight patients (57.8%) were found to be from Medellín and 43 (51.2%) were male. In 61 cases, (73.5 %) the reason for consultation was the symptom of abdominal mass, accompanied by other symptoms; the involvement was unilateral and there was no history of congenital malformations in 78 patients (92.9 %). In addition, pathology was predominantly blastemal in 23 cases (53.5 %), necrosis in eleven (17.7 %), and unfavorable histology in seven (8.8 %), as shown in **Figure 1**.

Variable	Categoría	n	%
Lugar de residencia	Medellín y área metropolitana	48	57,8
	Antioquia	25	30,1
	Otros departamentos	10	12,0
	Sin dato	1	
Sexo	Masculino	43	51,2
	Femenino	41	48,8
Presentación Clínica	Masa abdominal y otra sintomatología	61	73,5
	Dolor abdominal u otra sintomatología	22	26,5
Lateralidad	Bilateral	6	7,1
	Unilateral	78	92,9
Antecedente de malformación	Presencia de malformación	6	7,1
	Sin malformación	78	92,9
Patología tumoral	Tumor de Wilms o nefroblastoma con predominio blastemal	23	53,5
	Tumor de Wilms o nefroblastoma sin predominio blastemal	20	46,5
Biopsia previa	Si	16	25,8
	No	46	74,2
	Sin dato	22	
Patología con presencia de necrosis	Con necrosis	11	17,7
	Sin necrosis	51	82,3
	Sin dato	22	
Histología	Histología desfavorable	7	8,8
	Histología favorable	73	91,2
	Sin dato	4	

Figure 1. Characteristics of the patients with Wilms tumor in the study population

Regarding the surgical aspects (**Figure 2**), the tumor was found to be respectable in 51 (60.7 %) patients. Unilateral nephrectomy was performed in 78 cases (96.3 %), and in 51 (65.4 %) of these, the approach was unilateral prechemotherapy nephrectomy. Only three (3.7 %) patients required bilateral approach and ten (12.3 %) had complications during surgery.

Variable	Categoría	n	%
Resecabilidad quirúrgica	Tumor irresecable	33	39,3
	Tumor resecable	51	60,7
Lateralidad de la cirugía	Unilateral	78	96,3
	Bilateral	3	3,7
	Sin dato	3	
Momento de la nefrectomía unilateral	Previa a quimioterapia	51	65,4
	Posterior a quimioterapia	27	34,6
Contención tumoral	Tumor no contenido	35	43,2
	Tumor contenido	46	56,8
	Sin dato	3	
Complicaciones quirúrgicas	Cirugía con complicaciones	10	12,3
	Cirugía sin complicaciones	71	87,7
	Sin dato	3	
Protocolo de quimioterapia*	NWTS	58	70,7
	SIOP	24	29,3
	Sin dato	2	
Protocolo completo de quimioterapia	No	11	16,2
	Si	57	83,8
	Sin dato	16	
Recibió radioterapia	Si	38	46,9
	No	43	53,1
	Sin dato	3	
Presento recidiva	Si	20	27,4
	No	53	72,6
	Sin dato	11	
Presencia de trombo mural en la tomografía	Con trombo tumoral en tomografía	8	10,4
	Sin trombo tumoral en tomografía	69	89,6
	Sin dato	7	
Compromiso de ganglios linfáticos en tomografía	Compromiso ganglios linfáticos	23	31,1
	Sin Compromiso ganglios linfáticos	51	68,9
	Sin dato	10	
Presencia de metástasis a distancia	Presencia de metástasis a distancia	17	22,1
	Ausencia de metástasis a distancia	60	77,9
	Sin dato	7	
Sobrevida a dos años	Muerto	18	29,5
	Vivo	43	70,5

* NWTS: *National Wilms' Tumor Study*, SIOP: *Societe Internationale D'oncologie Pediatrique*

Figure 2. Treatment of patients with Wilms tumor in the study population

	Variables	Muerto		Vivo		OR	IC _{95%}	p
		n	%	n	%			
Lugar de residencia	Medellín y área metropolitana	10	32,3	21	67,7	1		
	Antioquia	5	26,3	14	73,7	1,3	0,4-4,7	0,657
	Otros departamentos	2	20,0	8	80,0	1,9	0,3-10,7	0,464
Sexo	Masculino	8	27,6	21	72,4	0,8	0,3-2,5	0,754
	Femenino	10	31,3	22	68,8	1		
Presentación clínica	Masa abdominal y otra sintomatología	15	30,6	34	69,4	1,2	0,3-5,1	0,827
	Dolor abdominal u otra sintomatología	3	27,3	8	72,7	1		
Lateralidad	Bilateral	3	60,0	2	40,0	4,1	0,6-27	0,147
	Unilateral	15	26,8	41	73,2	1		
Antecedente de malformación	Presencia de malformación	1	20,0	4	80,0	0,6	0,06-5,5	0,535
	Sin malformación	17	30,4	39	69,6	1		
Patología tumoral	Tumor de Wilms o nefroblastoma con predominio blastemal	5	33,3	10	66,7	3,2	0,5-20,4	0,195
	Tumor de Wilms o nefroblastoma sin predominio blastemal	2	13,3	13	86,7	1		
Biopsia previa	Si	4	30,8	9	69,2	1,2	0,3-5	0,518
	No	9	26,5	25	73,5	1		
Patología con presencia de necrosis	Con necrosis	1	14,3	6	85,7	0,4	0,05-4,1	0,414
	Sin necrosis	10	27,8	26	72,2			
Histología	Histología desfavorable	1	20,0	4	80,0	0,7	0,07-6,8	0,614
	Histología favorable	14	26,4	39	73,6			
Resecabilidad quirúrgica	Tumor irreseccable	7	26,9	19	73,1	0,8	0,3-2,5	0,703
	Tumor reseccable	11	31,4	24	68,6	1		
Momento de la nefrectomía unilateral	Previa a quimioterapia	11	31,4	24	68,6	2,6	0,6-10,7	0,178
	Posterior a quimioterapia	3	15,0	17	85,0			
Cirugía bilateral	Bilateral	2	66,7	1	33,3	5,9	0,5-69,7	0,181
	Unilateral	14	25,5	41	74,5			
Contención tumoral	Tumor no contenido	7	31,8	15	68,2	1,4	0,4-4,5	0,573
	Tumor contenido	9	25,0	27	75,0			
Complicaciones quirúrgicas	Cirugía con complicaciones	4	50,0	4	50,0	3,2	0,7-14,6	0,136
	Cirugía sin complicaciones	12	24,0	38	76,0			
Protocolo de quimioterapia	Protocolo SIOP	4	21,1	15	78,9	0,5	0,1-2	0,364
	Protocolo NWTS	13	32,5	27	67,5			
Protocolo completo de quimioterapia	No	8	88,9	1	11,1	34	3,7-312,1	0,000
	Si	8	19,0	34	81,0			
Recibió radioterapia	Si	7	25,9	20	74,1	0,8	0,3-2,5	0,708
	No	10	30,3	23	69,7			
Presento recidiva	Si	11	78,6	3	21,4	35,7	6,9-184,2	0,000
	No	4	9,3	39	90,7			
Presencia de trombo mural en la tomografía	Con trombo tumoral en tomografía	3	42,9	4	57,1	2,1	0,4-10,5	0,314
	Sin trombo tumoral en tomografía	13	26,5	36	73,5			
Compromiso de ganglios linfáticos en la tomografía	Con compromiso	7	43,8	9	56,3	2,4	0,7-8,4	0,139
	Sin compromiso	9	24,3	28	75,7			
Presencia de metástasis a distancia	Presencia de metástasis	6	46,2	7	53,8	2,5	0,7-9,1	0,143
	Ausencia de metástasis	11	25,6	32	74,4			

Figure 3. Factors associated with two-year survival in patients diagnosed with Wilms tumor

Through CT scans, 23 patients (31.1 %) were found to have lymph node involvement, 17 (22.1 %)

had distant metastases, and 8 (10.4 %) had mural thrombus. In relation to chemotherapy, the most commonly used protocol was the National Wilms Tumor Study (NWTs) in 58 patients (70.7 %). Fifty-seven patients (83.8%) completed the protocol and 20 (27.4%) had tumor recurrence.

Figure 3 shows the factors that were significantly associated with an increased fatality: failure to complete the chemotherapy protocol (OR = 34; 95% CI = 3.7–312; $P = 0.000$), and tumor recurrence (OR = 35.7; 95% CI = 6.9–184; $P = 0.000$). Other factors that increased this probability without being statistically significant but had certain impact were bilateral tumor (OR = 4.1; 95% CI = 0.6–5.5; $P = 0.147$), surgical complications (OR = 3.2; 95% CI = 0.7–14.6; $P = 0.136$), lymph node involvement on CT scan (OR = 2.4; 95% CI = 0.7–8.4; $P = 0.139$), and distant metastasis (OR = 2.5; 95% CI 0.7–9; $P = 0.143$). The other characteristics assessed were not significantly associated with fatality.

The final logistic regression model was composed of the following variables: failure to complete chemotherapy protocol (OR = 11.2; 95% CI = 0.4–329.9; $P = 0.161$), tumor recurrence (OR = 71.5; 95% CI 6.05–845; $P = 0.011$) and need for bilateral surgery (OR = 28; 95% CI = 1.2–1244; $P = 0.041$). It was calculated that 71% of the variability in survival was explained by these three factors.

4. Discussion

Prognostic factors for Wilms tumor according to the Children's Oncology Collaborative Group (COG) are tumor stage, histology, age, tumor weight, lung nodal response, and loss of heterozygosity (LOH) of 1p and 16q, while those of the International Society of Pediatric Oncology (SIOP) include age, histology, tumor volume, and response to therapy. Response to chemotherapy has been defined as decrease in tumor size, change in histology, and in stage IV cases, disappearance of metastases.

With respect to age, children younger than 2 years have better results compared to those aged 2–4 years (95 % event-free survival at 5 years vs. 88%). Other studies reported 96% survival in children under 1 year and 80% in children between 1 and 2 years [6]. However, in a paper by Aronson and Hadley from Africa, it was described that it is only during stage I with favorable histology that children under 4 years can have better results than older children [7].

Tumor volume can be considered a prognostic factor in intermediate risk tumors, excluding those with epithelial or stromal predominance [8]. In terms of tumor size, with the cut-off point of 500 mL in patients with intermediate risk tumors (excluding epithelial and stromal subtypes), the event-free survival was 88–95% in tumors smaller than 500 mL compared to 76–90% in larger tumors.

Histology is one of the most powerful prognostic factors in Wilms tumor. Anaplasia is present in 5–10% of cases, and studies have shown that blastemal predominance, as a histological subtype, and anaplasia, especially if diffuse, are poorer prognostic factors [8,9].

In our review, the factors shown to be statistically significantly associated with survival were bilateral tumor surgery, recurrence, and incomplete chemotherapy. Tumor size, stage, and histology were not found to be associated with shorter survival. It should be noted that molecular studies are not routinely performed in our setting and therefore cannot be analyzed in the results.

The factors associated with mortality have different results, which are linked to the level of development of the country studied. African studies reported a Wilms tumor incidence rate of 9% in the pediatric population aged 0–9 years, with a survival rate of 52.7%. Factors such as malnutrition, lack of access to optimal therapy and lack of health insurance have been described as factors associated with poor outcomes [10–12]. In another African study, Atanda *et al.* found that better outcomes were associated with early tumor stage at diagnosis, non-blastemal histology and receiving complete chemotherapy, the latter factor being similar to that found in our study [13]. Besides, we also found that Wilms tumor is often presented in advanced stages in Africa (up to 72%) [10,13–15].

Sangkhathat studied patients in Thailand, where the incidence rate is 2.2%, and found that the most

frequent stages of presentation were stages I and III (38%), with an overall survival of 65%. Factors associated with poor outcomes were failure of primary treatment in stage I patients, tumor size greater than 10 cm, and presentation with macroscopic hematuria. In our study, tumor size and form of presentation did not result in statistically significant differences, nor did gender, age, or histology [16].

Node status revealed a statistically significant association with overall survival. However, positive nodes may be thought to change the stage of disease, and this may represent the most important associated factor [16]. Other studies have found lymph node density to be a predictor of survival, reinforcing the importance of adequate sampling during surgery to improve staging and to achieve a possible reduction in the intensity of therapy in low-risk cases [17]. Failure of lymph node sampling during surgery has been shown to not only increase the likelihood of local relapse, but it is also an independent prognostic indicator of poorer survival [13].

In developing countries, delayed diagnosis, lack of resources such as chemotherapy and irradiation and poor therapeutic adherence to treatment (which may be associated with toxicity or poor follow-up) are crucial factors that lead to the poor outcome of children with Wilms tumor [10,19], which are similar results to those found in our review regarding incomplete chemotherapy.

In patients with stage III Wilms tumor with favorable histology, who usually have a good disease-free survival after management with chemotherapy and radiotherapy, the lymph node and LOH status have been found to be highly predictive of event-free survival, and intrarenal vessel invasion is not an independent prognostic factor [20,21].

A study in Japan found that patients with blastemal histology had a worse prognosis compared to the other histological subtypes, suggesting that in these cases treatment strategies should be different. They described that the overall 5-year survival in the epithelial type was 100%, 93% in the stromal type, and 90% in the mixed type, compared to the blastemal type which was 65%. On the other hand, the 5-year event-free survival was 100% in the epithelial type, 80% in the stromal type, 87% in the mixed type, and 52% in the blastemal type [22]. Another Japanese study found that initial stage and histological subtype were the only factors with statistically significant difference associated with tumor relapse in children with unilateral Wilms tumors and favorable histology who underwent nephrectomy followed by chemotherapy [23].

The UMBRELLA protocol validated new prognostic factors, such as tumor subtype, tumor volume, and molecular markers, in order to determine subgroups of patients with worse prognosis and increased relapse rates [24]. Surgical factors other than lymph node sampling and intraoperative rupture have also been analyzed as factors worsening prognosis, and it has been reported that leaving Gerota's fascia does not increase the risk of recurrence [25].

The need for bilateral intervention in our study was a factor that increased the likelihood of death, and if favorable histology is added, the negative impact on survival is greater. Other factors in addition to bilaterality, such as age, sex, tumor stage, and the presence of a target or synchronous tumor have not shown statistical significance [26].

The limitations of this study lie in the fact that, being a cross-sectional design, it is not possible to establish causal associations, although it is possible to establish the relationship of the variables with survival; and in the fact that it was not possible to randomize the patients.

5. Conclusion

The survival of our children with Wilms tumor is lower than that reported in literature (70 % versus more than 90 %), and the factors associated with this outcome were failure to complete the chemotherapy regimen, tumor recurrence, and bilateral surgery.

Disclosure statement

The authors declare no conflict of interest.

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Study of the Effect of Exercises on the Quality of Life, Fatigue, Sarcopenia in Breast, and Prostate and Colorectal Cancers

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Abstract: Breast, prostate, and colorectal cancers are the most common cancers and have the highest mortality rates worldwide. *Objective:* To determine the benefits of continuous training at moderate and high intensity on quality of life, fatigue and sarcopenia in breast, prostate, and colorectal cancer. *Method:* A quasi-experimental study was performed with 356 patients with stage II breast cancer. The patients were distributed in 2 groups, and EORTC QLQ C-30 scale, FACT- Fatigue Scale, quality of life test, stress test, dynamometry and others were carried out. *Results:* The study population presented with sarcopenia. At the end of the study, the prevalence of sarcopenia decreased significantly (GE1: 31 % [before] vs. 24 % [after], and GE2: 38 % [before] vs. 19 % [after]; $P \leq 0.05$). As did the values for fatigue (GE1: 17.3 ± 3.8 [before] vs. 10.4 ± 2.5 [after], and GE2: 19.6 ± 4.2 [before] vs. 9.4 ± 3.1 [after]; $P = 0.012$) and in the quality-of-life questionnaire (GE1: 61.7 ± 10.4 [before] vs. 69.5 ± 14.4 [after]; GE2: 76.5 ± 7.4 [before] vs. 106; $P = 0.005$). *Conclusion:* Continuous training at moderate and high intensity inevitably improved the variables evaluated, especially quality of life, fatigue, and sarcopenia. It should be noted that the improvements were more notable in the high intensity group.

Keywords: Cancer; Aerobic exercise; High intensity training; Strength training

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1. Introduction

Cancer is considered a systemic disease worldwide, which causes morbidity and mortality by affecting organs and tissues. More than 14 million people are diagnosed with cancer worldwide and 8 million die from it each year. The most common types of cancer are lung, breast, prostate, and colorectal cancers. Cancers are associated with various factors: genetics, age (> 40 years), sex (male: higher prevalence), race (< 40 years: white; > 40 years: African-American/black), lifestyle, environmental factors, and also human papillomavirus (HPV), human immunodeficiency virus (HIV), and Epstein-Barr virus (EBV) ^[1]. Malignant tumors are also formed, although other factors play a role in their development, such as hormones, tobacco and alcohol consumption, psychological stress, diet ^[2], and increased exposure to carcinogens ^[3].

Quality-of-life assessment depends on the progress of disease and treatment, optimistic attitudes, autonomy and rights, as well as psychosocial aspects, in addition to constant demographic and epidemiological evolution ^[3,4].

Breast cancer is a neoplasm that requires intense and continuous treatment, with physical,

physiological, mental, and psychosocial effects, negatively affecting the patient's quality of life. Likewise, the decrease muscle mass, i.e., sarcopenia, leads to fatigue (78%–96% of people), somnolence, anxiety, stress, myocardial, coronary, carotid, and ventricular alterations, which decrease ejection fraction ^[5,6].

However, colorectal cancer is the second leading cause of death worldwide and the fifth most common malignant tumor, with a higher incidence in developing countries than in developed countries, with Japan, China and Korea accounting for 60% of cases ^[7]. Besides, prostate cancer is the second leading cause of death and the most common cause of death in Chile and the USA ^[8]. Pharmacological treatments for cancers affect quality of life, endocrine system, and causes fatigue, muscle weakness, discouragement, limited sexual and cognitive desire and function, increased insulin resistance, anemia, and dyslipidemia; all this together with psychosocial problems ^[9] and many other alterations ^[10].

However, according to literature, physical exercises reduce adverse effects, and a change in eating habits helps to improve quality of life and reduce anxiety and fear of relapse ^[11]. In addition, it will improve the physical condition, weight, and muscle mass of the patient. Moreover, several studies have shown that high intensity interval training (HIIT) and moderate intensity interval training (MICT) are useful for increasing cardio-respiratory capacity, mitochondrial, muscle biogenesis, GLUT-4, HbA1c, and others ^[12-14]. Therefore, the aim of this research is to determine the benefits of MICT and HIIT on quality of life, fatigue, and sarcopenia in breast, prostate and colorectal cancer patients.

2. Methodology

A quasi-experimental descriptive study combined with analysis of quantitative variables was conducted in the city of Cúcuta, Colombia, with an initial sample of 1,573 patients within a period of 3 years and 4 months. After the different filtering, this research was conducted with 356 patients with stage II breast, prostate, or colorectal cancers. The patients were divided into 2 groups (MICT and HIIT) using basic probability sampling, which was a table of numbers, in which the order of patients was randomized through Excel. As a result, experimental group 1 (GE1) consisted of 177 participants and experimental group 2 (GE2) consisted of 179. It should be noted that this article is part of the ONCO-EXE TRIAL macro-project registered in ClinicalTrials.gov NCT03915288 (**Figure 1**).

2.1. Characteristics of participants

The participants of this study are similar in terms of cancer stage, ejection fraction, functional class, muscle percentage, fat and body mass index, abdominal circumference, prevalence of diabetes, and hypertension, and they are classified as “high risk” in terms of cardiovascular risk according to the American Association for Cardiopulmonary Rehabilitation stratification ^[15].

2.2. Inclusion criteria

Participants with stage II cancer, over 18 years of age, and who are willing to participate in the program. They signed an informed consent form and were protected by the Ethics and Research Committee of the CEI-FISICOL institution. They were also required to present a mandatory ejection fraction of 35% and above, without any impediment to present the tests, surveys, and research.

2.3. Exclusion criteria

Participants were excluded if they reported severe lower limb pain, heart rate instability or >120 bpm at rest, angina, systolic blood pressure > 190mmHg, diastolic > 120mmHg, and participants that are not of stage II cancer were excluded. Besides, the individual had the choice to leave the investigation at any time or upon showing hemodynamic instability without improvement.

2.4. The blind method

At the beginning, assessments were carried out by an external medical oncologist. Subsequently, the information was entered into the database at Microsoft Excel using a number for identification, and then randomization was carried out by an engineer from the institution and an external engineer.

The researchers carried out the forms and tests without any information about the participants or the type of cancer they had, or their intervention group. Only the lead author held periodic meetings with the physiotherapist trainers to understand training of the participants without any knowledge of the data. At the end of the program, the participants were evaluated again for quantification, comparison, and statistical analysis, in a blinded manner by the authors. After the different variables were studied, all authors were notified to generate conclusions together.

2.5. Anthropometric characteristics

The participants' personal and family history was obtained using a separate form, as well as anthropometric measurements (weight, height, body mass index (BMI), and abdominal circumference), and the percentage of muscle and adipose tissue.

To obtain the weight and the percentage of adipose and muscle tissue, a calibrated TezzioTB-30037 digital scale was used. The Adult Acrylic Halter Wall Kramer 2104 was used to obtain the height, where the participant stood in a bipedal position, facing forward, with upper limbs relaxed and close to the body, with an upright back resting on a flat surface to avoid lordosis with the feet. With these values, the BMI was determined. Subsequently, the abdominal circumference was measured using a measuring tape, while taking into account the anatomical values described by Frisancho ^[16].

2.6. Clinical and hemodynamic parameters

Each participant underwent 2-D echocardiography at baseline and at the end of the program to identify the structures involved, left ventricular ejection fraction (LVEF), and to analyze mobility in real time. In addition, physical function was assessed individually according to the New York Heart Association (NYHA) classification; and dyspnea and fatigue was assessed according to the modified Borg scale ^[17]. The patients' heart rates were measured using the Polar Multisport RS800CX system, and their respiratory rate and blood pressure were obtained manually and corroborated by a second evaluator, while a Nellcor Puritan Bennett® oximeter was used to obtain oxygen saturation.

2.7. Questionnaires, tests, and quizzes

At the beginning, the participants had to undergo an assessment by the medical oncology department which included the current status, anthropometric, and physical measurements of the participant. At the same time, the participants' exercise tolerance were also evaluated by a physiotherapist according to the ATS Statement: Guidelines for the six-minute-walk test of the American Thoracic Society ^[18,19].

The following day, participants returned for the Naughton stress test with prior advice not to drink stimulant beverages, smoke and/or ingest drugs or substances that would alter consciousness or vital signs.

2.8. Sarcopenia

We used the European Consensus on Sarcopenia (2010) ^[20], which was based on three criteria: gait examination, muscle strength, and muscle mass. For the first criterion, we used the Short Physical Performance Battery (SPPB) modified by Guralnik *et al.* ^[21]. For the second criterion, the participants' muscle strength was measured. As for the last criterion, muscle mass was assessed based on BMI and calf circumference (cut-off point 31cm) ^[20].

2.9. Strength

It was assessed by dynamometry with Hand Grip CAMRY Electronic hand dynamometer model EH101 where the participants were seated without support on the forearms, arms held laterally against the body alignment. Their elbows were flexed to a 90° angle, while their forearm and wrist remain in a neutral position. The assessment was performed on the dominant side with 3 repetitions and 1 min rest, as well as the non-dominant side. For maximal strength, a test of one repetition maximum (1RM) was performed.

2.10. Quality of life

The EORTC QLQ C-30 questionnaire ^[22] was used with appropriate modifications ^[23]. This test was requested from the EORTC Quality of Life Group website who approved its use in this study.

2.11. Fatigue

Fatigue was assessed using the FACT-Fatigue Scale (Functional Assessment of Cancer Laterapy Fatigue Scale), which is a 13-item scale that assesses the severity of cancer-associated fatigue (FAC) in the past week ^[24].

2.12. Interventions

The training program was set according to the FCM obtained in the stress test and strength test, and the result of the 1RM test was also considered. The training program lasted 36 weeks, 3 sessions a week, and 70 min per session. Patients were monitored by the Polar Multisport RS800CX system, oximetry, and the Borg scale. The incline, resistance, or speed of the exercises were assigned according to the indicative parameters (FCM, VO₂, Borg) for moderate and high intensity exercises.

2.13. Experimental group 1 (n = 177)

The 70 min sessions included a 10 min warm-up (breathing exercises, walking, and stretching), 30 min of continuous aerobic training at moderate intensity (60-80 % FCM) like cycling, rowing machine, elliptical, and recumbent. The other 20 min were for strength training (40-60 % maximal strength), and the last 10 min were for cool down (coordination exercises, balance, walking, and breathing exercises).

2.14. Experimental group 2 (n = 179)

The warm-up, strength training, and cool-down were identical to GE1. The following 30 min were HIIT intervallic exercise with a protocol created by the main author which we call 30-30. 30sec at moderate intensity (60-80% FCM) and 30sec at high intensity (80-90% FCM) on a treadmill, exercise bike, rowing, and recumbent.

2.15. Statistical analysis

A database was created in Microsoft Excel and descriptive statistical analysis was then performed to evaluate the data based on average values and their corresponding standard deviation. The normality of the data was assessed using the Kolmogorov-Smirnov test, and the indication of specificity was evident for all analyses. Furthermore, Tukey's test and analysis of variance ANOVA (two-way analysis of variance) were carried out followed by post hoc tests. In all cases, a significance level of 5 % ($P < 0.05$) was established and everything was carried out in the accordingly.

2.16. Ethical considerations

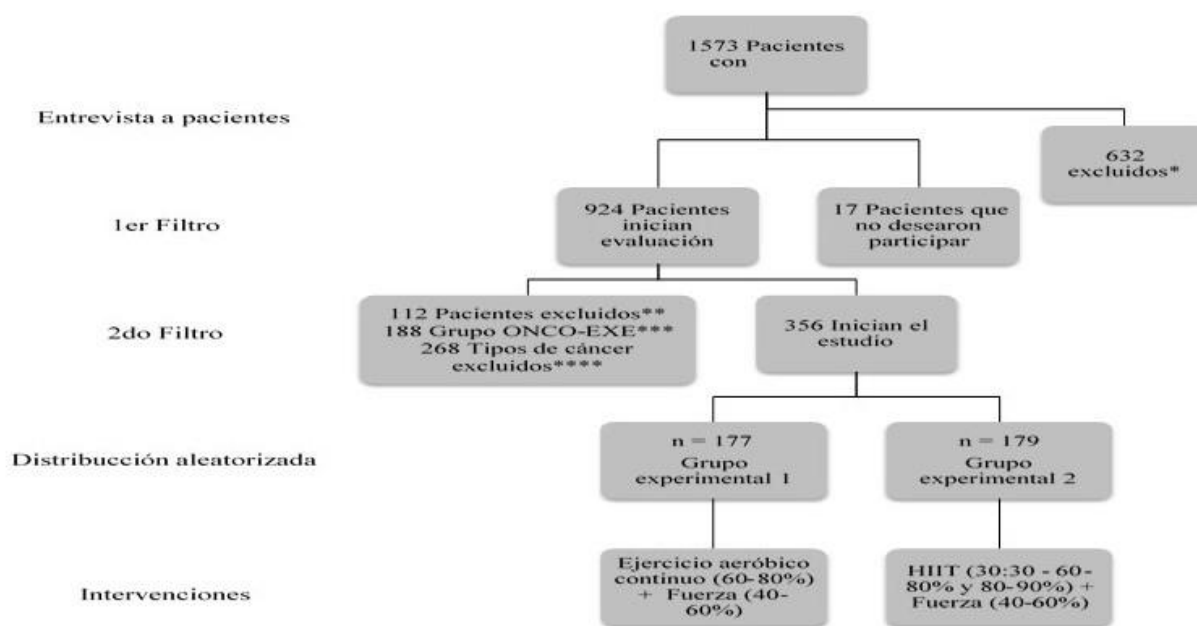
This study was designed and developed under the ethical considerations of the Helsinki Declaration, which involved signing of an informed consent by the patients, and an approval from the managers, coordinators,

and ethics committee of the institution.

3. Result

After filtering, 356 patients in 2 groups (GE1 and GE2) with stage II breast (GE1-45 % and GE2-39 %), prostate (GE1-43 % and GE2-46 %) and colorectal (GE1-12 % and GE2-15 %) cancers were included in this study.

Regarding the academic level of the participants, 43.8 % ($n = 156$) had only completed primary school, 23.5 % ($n = 84$) studied up to secondary school, 19.3 % ($n = 69$) university level, and 13.2 % ($n = 47$) have not received formal education. The oncological treatments performed were surgery (26%), radiotherapy (62%), chemotherapy (47%), and hormone therapy (43%). The most prevalent risk factors in the study population were sedentary lifestyle, obesity, malnutrition, smoking, and many others (**Table 1**).



HIIT: High Intensity Interval Training.

*632 Pacientes excluidos (132 por cáncer fase 1; 351 por cáncer fase 3; 149 por cáncer fase 4).

**112 Pacientes excluidos (5 por proceso infeccioso, 13 dificultad para el traslado al sitio de entrenamiento, 22 por alteraciones arrítmicas, 35 por hipertensión sistólica >190 mmHg, 37 dolor articular).

***188 Pacientes fueron distribuidos a un grupo control como parte del proyecto ONCO-EXE.

****268 Tipos de cáncer excluidos (48 Cervico-uterino, 70 tiroides, 37 pulmón, 29 estomago, 25 hepático, 24 páncreas, 22 renal, 13 esófago).

Figure 1. Flow chart of the distribution ($n = 1573$)

A significant percentage of the study population were diagnosed with sarcopenia based on the aforementioned criteria. After the training program, the prevalence of sarcopenia decreased significantly, with GE2 showing greater impact (GE1: 31 % [before] vs. 24 % [after], and GE2: 38 % [before] vs. 19 % [after]; $P \leq 0.05$), as shown in **Figure 2**. As for the values for cancer-associated fatigue (GE1: 17.3 [before] \pm 3.8 vs. 10.4 \pm 2.5 [after] and GE2: 19.6 \pm 4.2 [before] vs. 9.4 \pm 3.1 [after]; $P = 0.012$) and in the EORTC QLQC-30 questionnaire for quality of life (GE1: 61.7 \pm 10.4 [before] vs. 69.5 \pm 14.4 [after]; GE2: 76.5 \pm 7.4 [before] vs. 106 [after]; $P = 0.005$), as shown in **Figure 3**.

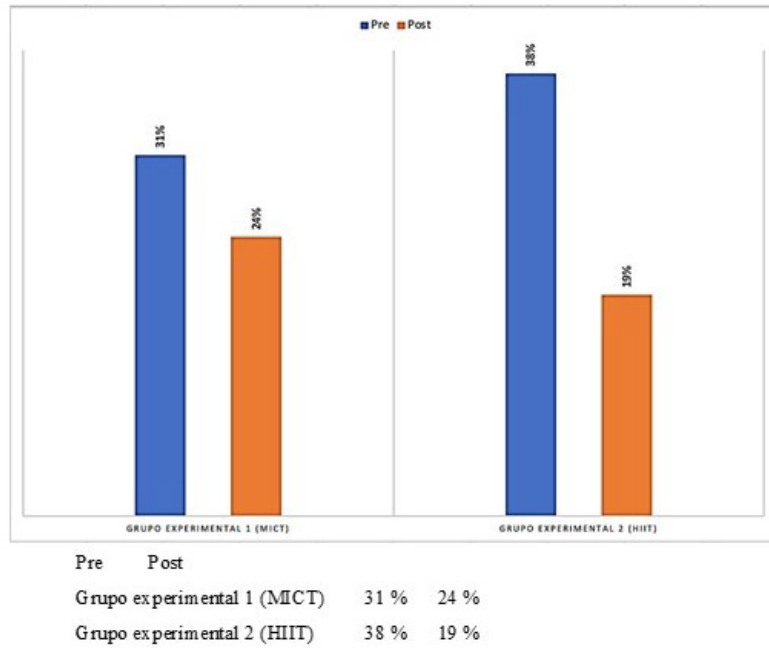


Figure 2. Prevalence of sarcopenia pre- and post-training

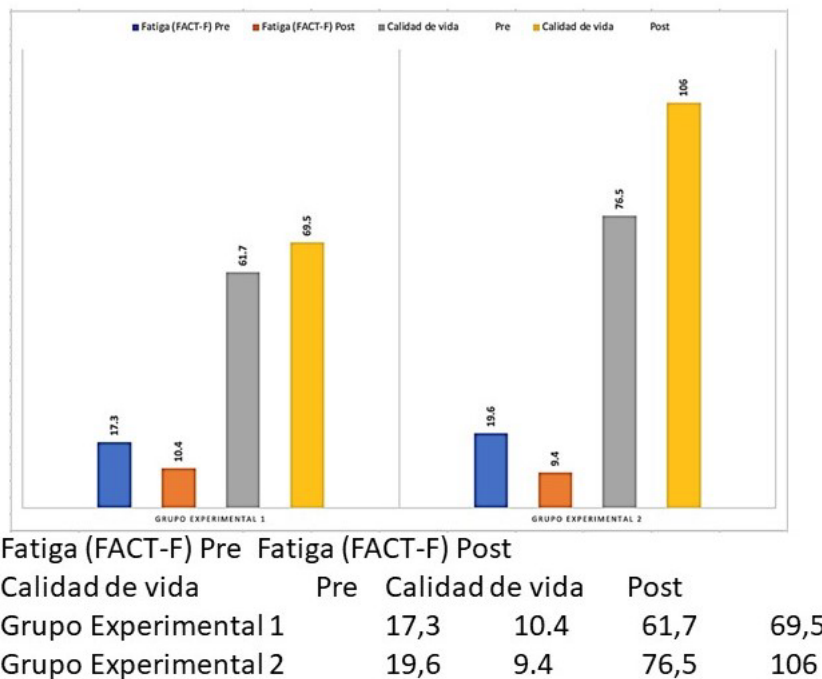


Figure 3. Fatigue and quality of life associated with post-training cancer

In terms of hemodynamic variables after the training program, we were able to determine changes in ejection fraction (GE1: 48 ± 2.7 [before] vs. 50 ± 3.2 [after]; GE2: 49 ± 1.8 [before] vs. 54 ± 2.6 [after]; $P = 0.003$) and maximum heart rate (GE1: 150 ± 4.6 vs. 152 ± 8 ; GE2: 152 ± 3.5 vs. 155 ± 7 ; $P = 0.012$) (**Table 2**). Also, it is worth mentioning that no complications or adverse events occurred during the training program. Furthermore, it is noteworthy that during the training sessions, participants reported a perceived dyspnea according to the Borg scale between 6 and 8 (moderate intensity) in groups 1 and 2, with group 2 reporting peaks between 9 and 10, as well as feelings of peri-exercise fatigue.

Table 1. Baseline characteristics of participants ($n = 356$)

Cuadro 1. Características iniciales de los participantes (n= 356).		
Características	GE 1 n= 177	GE 2 n= 179
Cáncer próstata	76 (42,9 %)	82 (45,8 %)
Cáncer mama	80 (45,1 %)	70 (39,1 %)
Cáncer Colorrectal	21 (11,8 %)	27 (15 %)
Sexo	H: 87 M: 90	H: 94 M: 85
Edad (Años)	54 ± 5	56 ± 4
Fracción de eyeción (%)	48 ± 2,7	49 ± 1,8
Altura (m)	1,54 ± 7,1	1,60 ± 9,3
Peso (kg)	80 ± 12,7	82 ± 9,7
IMC	33,7 ± 3,9	32 ± 3,1
Circunferencia abdominal (cm)	89 ± 5,5	85 ± 6,7
Porcentaje grasa (%)	19 ± 4,4	17 ± 3,8
Porcentaje muscular (%)	25 ± 5,1	23 ± 2,3
Fuerza	30,3 ± 2,7	28 ± 3,6
Sarcopenia (%)	31 %	38 %
Circunferencia pantorrilla	32 ± 9,3	31,3 ± 5,6
Vo2 estimado	13,2 ± 5,2	11,5 ± 4,7
Fatiga (FACT-F)	17,3 ± 3,8	19,6 ± 4,2
Calidad de vida	61,7 ± 10,4	76,5 ± 7,4
Distancia recorrida	363 ± 25	332 ± 20
FCM en prueba de esfuerzo	150 ± 4,6	152 ± 3,5
Sobrepeso y/u obesidad	72 %	79 %
Obesidad abdominal	51 %	58 %
Dislipidemia	25 %	30 %
Hipertensión arterial	31 %	40 %
Diabetes	12 %	17 %
Enfermedad renal	8 %	10 %
Sedentarismo*	92 %	93 %
Depresión	51 %	56 %
Ansiedad	18 %	21 %
Tabaquismo	35 %	40 %
Alcoholismo	11 %	16 %
Ingesta de comida inadecuada	40 %	51 %
Historial de IMC	3 %	4 %
Sexo femenino	51 %	47 %
Edad †	4 %	5 %

IMC: índice de masa corporal; VO2: consumo máximo de oxígeno; FCM: frecuencia cardiaca máxima; kilogramos; %: porcentaje; cm: centímetros; m: metros. IAM: infarto agudo de miocardio.

* Menos de 150 min por semana.

† Mujer > 65 años y Hombres > 40 años según *Rev Colomb Cardiol. 2011;18(4):177-182.*

Table 2. Post-training change analysis ($n = 356$)

Variables	GE 1 n= 177		GE 2 n= 179		G1 Vs G2 Valor P
	Pre	Pos	Pre	Pos	
Fracción de eyección (%)	48±2,7	50±3,2	49±1,8	54±2,6	0,003
Peso (kg)	80±12,7	76±4,1	82±9,7	75±3,5	0,001
Índice de masa corporal	33,7±3,9	32±2,8	32±3,1	29,2±1,3	0,001
CA (cm)	89±5,5	87±4,6	85±6,7	81±6,2	0,000
Porcentaje grasa (%)	19±4,4	17±3,8	17±3,8	14±1,4	0,001
Porcentaje muscular (%)	25±5,1	28±9,4	23±2,3	35±3,8	0,000
Fuerza (kg)	30,3±2,7	35,9±5,2	28±3,6	38,2±8,4	0,001
Sarcopenia (%)	31 %	24 %	38 %	19 %	0,001
Circunferencia pantorrilla (cm)	32 ± 9,3	36 ±6,4	31,3±5,6	48,2±4,2	0,003
Vo2 estimado (ml/kg/min/o2)	13,2 ± 5,2	15.7±3,3	11,5±4,7	16,9±3,3	0,002
Fatiga (FACT-F)	17,3 ± 3,8	10,4±2,5	19,6±4,2	9,4±3,1	0,012
Calidad de vida	61,7 ± 10,4	69,5±14,4	76,5±7,4	106±7,6	0,005
Distancia recorrida (m)	363±25	407±39	332±20	417±29	0,000
FCM en prueba esfuerzo (lpm)	150±4,6	152±8	152±3,5	155±7	0,012
Disnea pos (TC6M)	8±3	5±1	9±2	4±1	0,000
Fatiga pos (TC6M)	8±1	5±2	8±1	3±1	0,003

4. Discussion

Defining the correlation between existing techniques to improve quality of life, fatigue, and sarcopenia in breast, prostate, and colorectal cancers is a challenge for health professionals, because it involves an exhaustive review and interpretation of the significant findings in the theoretical and practical part of daily life. Likewise, the analysis and comparison after the implementation of two types of training such as continuous training MICT and HIIT provided information that allows a direction of training in these cases. In this order of ideas, a study of similar methodology and results carried out by Mijwel S *et al.* [25] compared the effects of resistance and interval training at high intensity and interval training at moderate aerobic and high intensity, with the study population being women with breast cancer who underwent chemotherapy. Measurements were taken at baseline and at 16 weeks. In relation to the present study, more measurements were performed in order to have more control over variables that could impact on the quality of life of patients. More tests were performed to achieve greater precision. Based on the tests' results, participants who experienced fatigue showed an improvement in their physical condition after physical training. Likewise, those who presented good conditions initially showed improvements in terms of fatigue, quality of life, and sarcopenia.

In comparison and similarity to a study conducted in Canada with breast cancer patients, using three groups: supervised aerobic interval training (AIT), supervised continuous moderate exercise training (CMT), and an unsupervised control group (NOC). For 6 weeks, AIT exercised between 70% and 100% of VO₂ peak, while CMT exercised between 60% and 70% of VO₂ peak. The results of this study showed that these programs could increase peak VO₂ and that the addition of a strength training decreased sarcopenia and improved the overall condition of the participants [26].

On the other hand, this type of physical training had already been studied previously by a team of doctors and physiotherapists in Spain in 2016, where the effects of MICT and HIIT were compared, but it was applied in patients with coronary artery disease. They HIIT should be applied because it leads to a greater increase in functional capacity compared to MICT. Hence, this logic can also be applied to our study since like cardiovascular disease, cancers is one of the main contributors of morbidity and mortality rates in different countries [27]. With that said, it is also noteworthy that most studies show that HIIT is more physically demanding than MICT, with people reporting greater enjoyment due to its time efficiency and

constantly changing stimulus, as evidenced in a study by Thum *et al.* in 2017 ^[28]. Therefore, it is clear that structured and sequenced training can be a viable approach to improving quality of life, fatigue, and sarcopenia.

However, these types of training are generally based on the cardiovascular component with little elements of strength training, which was demonstrated by Schulzy *et al.* ^[29]. Therefore, in the present study, different variables were studied in depth and followed up to analyze the long-term effects, and these could serve as parameters for future research, such as the type of training, intensity, modality, rest time, training cycles, and many other attributes related to physical training, which could be interesting lines of research to cover in order to find out the respective benefits and impact on the cancer patient.

5. Limitations of the study

It is important to highlight that it is common for certain limitations to arise in this type of research due to the multiple variables that exist around the patient's oncology. For example, pharmacological treatment and diet were not included as variables to be evaluated even though they are inevitably a predominant factor in the cardiovascular, respiratory, and metabolic response to physical exercise in this type of population. In the study population, MICT and HIIT training undoubtedly improved all the variables evaluated, especially quality of life, fatigue, and sarcopenia. The improvements were more notable in the HIIT group,

Disclosure statement

The authors declare no conflict of interest.

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Introduction

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Journal

Journal article (print) with one to three authors

[1] Yao Y., Xia B. Application of Phase Frequency Feature Group Delay Algorithm in Database Differential Access. *Computer Simulation*, 2014, 31(12): 238-241.

Journal article (print) with more than three authors

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Book

Book with one to three authors

[5] Schneider Z., Whitehead D., Elliott D. Nursing and midwifery research: methods and appraisal for evidence-based practice. 3rd edn. 2009, Elsevier Australia, Marrickville, NSW.

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No author

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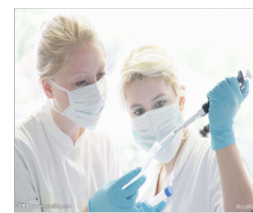
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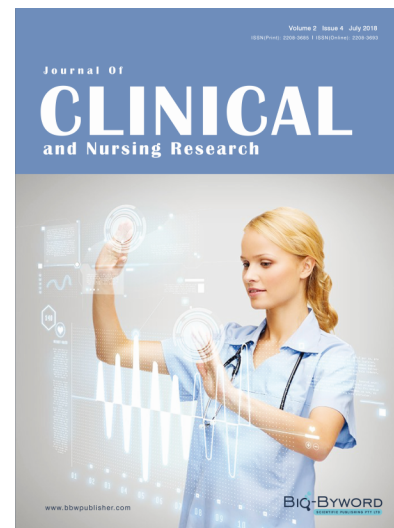
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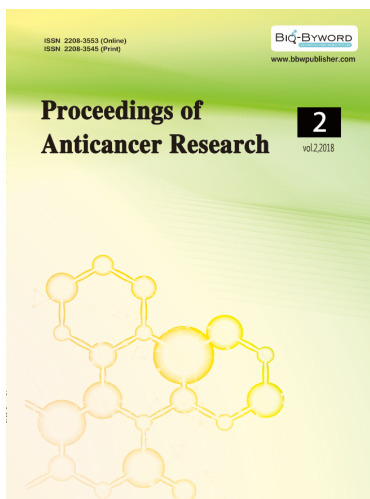
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