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Original article

Ureteral stent insertion failure in obstructive uropathy secondary to cervical cancer

Factores predictivos de derivación urinaria endourológica en uropatía obstructiva por cáncer cervicouterino

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Abstract

Introduction: To identify preoperative features that predict ureteral stent placement failure in women with obstructive uropathy secondary to cervical cancer.

Methods: Observational, descriptive, analytical study. Clinical registries of patients with diagnosis of obstructive uropathy secondary to cervical cancer were reviewed. Fifty-two patients attended between January 2017 to January 2021 were included. Diagnosis of obstructive uropathy consisted of hydronephrosis or hydroureter in imaging studies and elevation in baseline serum creatinine and blood urea nitrogen with uremic syndrome. An analysis of variables of interest was carried out to assess the association with ureteral stent placement failure.

Results: We observed that the overall rate of failed ureteral stent placement was 55.8%. We did not find any differences in baseline characteristics between patients with successful or unsuccessful ureteral stent placement. A higher percentage of patients with failed urinary diversion on admission had a decrease in urinary output (58.6% vs. 30.4%, p=0.04), uremic syndrome (51.7% vs. 21.7%, p=0.02), as well as an increased median serum creatinine (6.6 vs. 2.6 mg/dL, p=0.03) compared to patients with successful ureteral stent placement. An admission serum creatinine cut-off value of 3.4 mg/dL yielded sensitivity of 69% and specificity of 65.2% for unsuccessful ureteral stent placement (AUC=0.674, 95% CI 0-52-0.82; p=0.03).

Conclusion: Our data suggest that distal ureteral obstruction evidenced by imaging, regardless of the extent of invasion, is the most important factor related to unsuccessful ureteral stent placement.

Key words:
Cervical Cancer, malignant ureteral obstruction, ureteral catheterization, acute kidney failure, pelvic neoplasms

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Resumen

Introducción: Identificar las características preoperatorias que predicen el fracaso de la colocación de stent ureteral en mujeres con uropatía obstructiva secundaria por cáncer cervicouterino.

Métodos: Estudio observacional, descriptivo, analítico. Se revisaron los registros clínicos de pacientes con diagnóstico de uropatía obstructiva secundaria por cáncer cervicouterino. Se incluyeron 52 pacientes atendidos entre enero de 2017 y enero de 2021. El diagnóstico de uropatía obstructiva consistió en hidronefrosis o hidrouréter en estudios de imagen y elevación de la creatinina sérica basal y nitrógeno ureico en sangre con síndrome urémico. Se realizó un análisis de variables de interés para evaluar la asociación con el fracaso de la colocación de stent ureteral.

Resultados: Se observó que la tasa global de colocación fallida de stent ureteral fue del 55.8%. No encontramos diferencias en las características basales entre los pacientes con colocación exitosa o no exitosa de stent ureteral. Un mayor porcentaje de pacientes con derivación urinaria fallida al ingreso presentaron disminución de la diuresis (58.6% vs 30.4%, p=0.04), síndrome urémico (51.7% vs 21.7%, p=0.02), así como aumento en la mediana de la creatinina sérica (6.6 frente a 2.6 mg/dL, p=0.03) en comparación con pacientes con colocación exitosa de stent ureteral. Un valor de corte de creatinina sérica al ingreso de 3.4 mg/dl produjo una sensibilidad del 69 % y una especificidad del 65.2 % para la colocación fallida de un stent ureteral (AUC=0.674, IC del 95 %: 0-52-0.82; p=0.03).

Conclusión: Nuestros datos sugieren Jque la obstrucción ureteral distal evidenciada por imágenes, independientemente de la extensión de la invasión, es el factor más importante relacionado con la colocación fallida de un stent ureteral.

Palabras clave:
Cáncer cervicouterino, obstrucción ureteral maligna, cateterismo ureteral, insuficiencia renal aguda, neoplasias pélvicas

Introduction

Cervical cancer is the fourth most common cancer in women, with an incidence of 15.1 cases per 100 000 and a mortality rate of 8.2 deaths per 100 000.[1] In low-income countries, it is the fourth leading cause of death by cancer.[2] In Mexico cervical cancer has a prevalence of 38 women per 100 000 women, with an incidence of 9439 new cases in 2020.[3] Squamous cell carcinoma is the most frequent histopathological type in 80% of cases, related to human papillomavirus infection in up to 50%.[4] According to the International Federation of Gynecology and Obstetrics (FIGO), cervical cancer IIIA is defined as tumor involvement of the lower third of the vagina. When the tumor extends to the pelvic wall, and hydronephrosis or a non-functioning kidney is present the cervical cancer is staged as IIIB.[1] Obstructive uropathy related to any pelvic malignant disease is present in up to 22% of all these oncological patients, with a median survival of 255 days.[5–14] Patients who undergo percutaneous urinary diversion have shown an increase in survival, up to a median of 938 days.[14] There are no studies describing the survival of patients after ureteral stent placement. [5–7,10–18] However, failure in ureteral stent

placement in malignant obstructive uropathy, caused by a difficult ureteral meatus localization secondary to tumor invasion, persistent hematuria, and retroperitoneal lymphadenopathy or fibrosis, may decrease many favorable outcomes.[7–9] Some studies have outlined several factors associated with ureteral stent placement failure in obstructive uropathy secondary to pelvic malignancy, such as a serum creatinine >5.3 mg/dL at the moment of the identification of obstruction and a difference of >3.5 g/dL in serum creatinine between baseline and obstruction onset.[12] Other imaging features such as >30 mm hydronephrosis, tumor bladder invasion, and >3 cm distal ureteral invasion has been related to ureteral stent insertion failure in such individuals.[9–11] Our study aimed to identify preoperative features in women with obstructive uropathy secondary to cervical cancer that predicts ureteral stent placement failure.

Materials and Methods

We performed an observational, retrospective study that included patients with cervical cancer and obstructive uropathy who underwent endourological urinary diversion in a tertiary referral hospital, from January 2017 to January 2021. The Institutional Ethics Committee approved the study.

Patients

We included all patients admitted to our institution with a diagnosis of obstructive uropathy secondary to cervical cancer. Basal creatinine was defined as a random measurement of serum creatinine before diagnosis of cervical cancer or at diagnosis of cervical cancer. Diagnosis of obstructive uropathy was done by contrast-enhanced computerized tomography (CT) with delayed phase and serum creatinine levels. Criteria such as hydronephrosis or hydroureter by imaging, rise in baseline serum creatinine and blood urea nitrogen (BUN), or uremic syndrome were included in diagnosing obstructive uropathy. Uremic syndrome was considered when a rise in BUN was accompanied by uremic encephalopathy, nausea, vomit and evidence of fluid overload in absence of cardiac disease. We excluded patients with either clinical or radiologic evidence of vesicovaginal or vesicorectal fistulae, as well as those who underwent primary percutaneous urinary diversion without a prior attempt of ureteral stent placement. All imaging studies were assessed by an experienced radiologist.

Ureteral stent placement

All patients underwent endourological urinary diversion by a senior resident supervised by an associate professor. Ureteral stent insertion was indicated in patients with acute kidney injury, urinary infection associated with obstruction, and imaging findings of obstructive uropathy, such as hydronephrosis hydroureter. Ureteral stent insertion attempts were performed in the operating room under regional or general anesthesia with the Seldinger technique with a Standard-Body wire Guide with Slip Coating 0.035 inch and 3 cm angle tip configuration and 22-F sheath using a 70° lens and fluoroscopy. A radiology interventionist performed an ultrasound-guided percutaneous nephrostomy in patients with ureteral stent insertion failu-

re. Inpatient postoperative follow-up was provided with serial blood chemistry tests until serum creatine lowered or stabilized. Outpatient follow-up was assessed with monthly serum creatinine measurements.

Statistical analysis

We performed independent samples t and Mann-Whitney tests to compare continuous variables, and Pearson chi-square or Fisher's exact test for categorical data between patients with failed or successful ureteral stent placement. We identified independent clinical, radiological, and laboratory factors related to failure in ureteral stent placement after multivariate logistic regression. We performed a ROC analysis to identify a cut-off point of serum creatinine at admission related to failed ureteral stent placement. Survival analysis was performed using Ka plan–Meier method and log-rank test. We considered a p-value < 0.05 and a 95% confidence interval (95% CI) for statistical significance. All analyses were performed on IBM SPSS version 25 (IBM Corp., Armonk, NY) and MedCalc version 18.2 (MedCalc Software Ltd., Ostend, Belgium) statistical software.

Results

A total of 52 patients met the selection criteria. Patients median age was 46 years (interquartile range [IQR 25-75%], 37-52). The median time from initial cervical cancer diagnosis to development of obstructive uropathy was 12 months (IQR 25-75%, 5-24). Patient baseline characteristics are summarized in Table 1.

Table 1. Baseline clinical characteristics of patients

Characteristic, n (%)	*Overall (n = 52)*	*Failed ureteral stent (n=29)*	*Successful ureteral stent (n=23)*	*p-value*
Age (years)				0.24
≤50	36 (69.2%)	22 (75.9%)	14 (60.9%)	
>50	16 (30.8%)	7 (24.1%)	9 (39.1%)	
History of smoking	19 (36.5%)	13 (44.8%)	6 (26.1%)	0.16
Diabetes mellitus	6 (11.5%)	3 (10.3%)	3 (13%)	>0.99
Hypertension	13 (25%)	7 (24.1%)	6 (26.1%)	0.87
History of pelvic surgery	19 (36.5%)	11 (37.9%)	8 (34.8%)	*0.81*
History of abdominal surgery	16 (30.8%)	6 (20.7%)	10 (43.5%)	0.07

Continued...

Months after diagnosis†	12 (5-24)	13 (5-27)	12 (5-24)	0.50
Chemotherapy	27 (51.9%)	14 (48.3%)	13 (56.5%)	0.55
Radiotherapy	29 (55.8%)	15 (51.7%)	14 (60.9%)	0.51
Brachytherapy	23 (44.2%)	12 (41.4%)	11 (47.8%)	0.64
Histopathology				0.09
Keratinizing squamous cell carcinoma	30 (57.7%)	19 (65.5%)	11 (47.8%)	
Non-keratinizing squamous cell carcinoma	17 (32.7%)	6 (20.7%)	11 (47.8%)	
Adenocarcinoma	5 (9.6%)	4 (13.8%)	1 (4.3%)	
FIGO stage at diagnosis				0.81
I-II	19 (36.5%)	11 (37.9%)	8 (34.8%)	
III-IV	33 (63.5%)	18 (62.1%)	15 (65.2%)	
FIGO stage at stent placement				0.76
IIIB	27 (51.9%)	14 (48.3%)	13 (56.5%)	
IIIC	4 (7.8%)	2 (6.9%)	2 (8.6%)	
IV	21 (40.3%)	13 (44.8%)	8 (34.8%)	

†Median (interquartile range)

Overall, 29 patients (55.8%) had a failed ureteral stent placement. We did not find any differences in baseline characteristics between patients with successful or failed ureteral stent placement. There are no differences between the two groups of patients who received external radiotherapy or brachytherapy before obstructive uropathy (p=0.51, p=0.64).

Median surgical time was 65 minutes (IQR, 45-120) where several attempts were performed, and 38 patients (73.1%) were classified as ASA III or IV before the procedure, of which a higher proportion had failed stent placement (89.7% vs. 52.2%, p=0.002). The main cause of unsuccessful ureteral stent insertion was a failure in identifying the ureteral orifice (62.1%), followed by the presence of hematuria on cystoscopy (24.1%) due to bladder involvement, and ureteral stenosis (13.8%); p=<0.001.

We observed that a higher proportion of patients with failed urinary diversion had a decrease in urinary output (58.6% vs. 30.4%, p=0.04) and uremic syndrome (51.7% vs. 21.7%, p=0.02) on admission, as well as higher median serum creatinine (6.6 vs. 2.6 mg/dL, p=0.03), and a greater difference between serum creatinine at the moment of identification of obstructive uropathy compared to baseline creatinine measured during or before the initial cancer diagnosis (5.7 vs. 1.4 mg/dL, p=0.01). We also identified by imaging a higher proportion of failed ureteral stent insertion in patients with evidence of distal ureteral tumor invasion (92.3% vs. 47.4%, p=0.001) (Table 2).

Table 2. Factors related to failed ureteral stent placement

Variable	*Failed ureteral stent (n=29)*	*Successful ureteral stent (n=23)*	*p-value*
Symptoms, n (%)			
Renal colic	16 (55.2)	11 (47.8)	0.59
Macroscopic Hematuria	6 (20.7)	2 (8.7)	0.23
Oliguria	17 (58.6)	7 (30.4)	0.04
Urinary Tract Infection	3 (10.3)	2 (8.6)	0.99
Uremic Syndrome	15 (51.7)	5 (21.7)	0.02
Laboratory findings			
Hemoglobin (g/dL)†	8.3±2.4	9.4±2.1	0.11
Serum creatinine at admission (mg/dL)‡	6.6 (2.5-12.0)	2.6 (1.2-8.3)	0.03
Δ Creatinine admission-basal creatinine, mg/dL ‡	5.7 (1.4-11.1)	1.4 (0.4-6.6)	0.01
BUN at admission mg/dL ‡	43 (29-79.5)	48 (22-71)	0.79
Fractional Excretion of Sodium FENa % ‡	4.9 (2.1-11.5)	3.4 (2.0-10.2)	0.44
CECT[1] with delayed phase findings			
Hydronephrosis Grading, n (%)			
Grade I	1 (3.8)	1 (5.3)	0.73
Grade II	6 (23.1)	6 (31.6)	
Grade III	8 (30.8)	7 (36.8)	
Grade IV	11 (42.3)	5 (26.3)	
Bi vs Unilateral Hydronephrosis n (%)			
Unilateral	18 (67)	13 (68)	0.9
Bilateral	9 (33)	6 (31)	
Length of Ureteral Obstruction greater than 3 cm, n(%)	22(92)	9(90)	0.8
Tumoral extension through bladder wall, n (%)	8 (69.2)	8 (42.1)	0.06

On admission, a serum creatinine cut-off value of 3.4 mg/dL was associated with failed ureteral stent insertion (AUC=0.674, 95% CI 0.52-0.82; p=0.03). Median overall survival was similar between patients with successful and failed urinary diversion (7 months, 95% CI 1.2-12.7 vs. 7 months, 95% CI 1.3-12.6; p=0.648). During the 6-month follow-up, there are no differences in the remission rate of obstructive uropathy between the two groups of patients, none of the patients developed the end-stage renal disease. (p=0.79)

We performed a multivariate analysis to assess the clinical variables that were linked to failed ureteral stent implantation (uremic syndrome, evidence of distal ureteral tumor invasion, and serum creatinine >3.4 mg/dL at admission). In this regression model, distal ureteral tumor invasion in imaging studies was independently associated with a failed ureteral stent insertion (OR 12.11, CI 95% 1.91-76.61; p=0.008) (Table 3).

Table 3. Multivariate analysis of factors related to failed ureteral stent placement

Variable	*Univariate*			*Multivariate*		
	OR	*95% CI*	*p-value*	*OR*	*IC 95%*	*p-value*
Uremic Syndrome	3.85	1.12-13.19	0.03	2.98	0.54-16.37	0.20
Distal Ureteral Obstruction[1]	13.33	2.43-73.02	0.003	12.11	1.91-76.61	0.008
Serum creatinine >3.4 mg/dL at admission	4.16	1.30-13.34	0.01	2.55	0.50-12.98	0.25

OR: odds ratio; 95% CI: 95% confidence interval.,
[1]Diagnosed by contrast-enhanced CT with delayed phase

Discussion

According to our findings, we identified several clinical features among patients with failed ureteral placement, such as uremic syndrome at hospital admission and oliguria. To date, there is a lack of reports describing symptoms associated with malignant obstructive uropathy.[6–12]

In our population, the median age at diagnosis of obstructive uropathy in the context of cervical cancer was 46 years. Our observations differ from those reported by McCullough *et al.*[12] who reported that the median age at diagnosis of hydronephrosis in their study was 68 years, in patients with any pelvic malignancy in the United States. In contrast, Pradhan *et al.*[13] reported a mean age of 73.7 years in patients with advanced cervical cancer in the US, higher than the mean age of 50.3 years in China, according to Tan *et al.*[16] The reason for these shifts in age is unclear, thus, additional epidemiological research is required to identify features associated with an early or late age of obstructive uropathy development onset.

In the context of pelvic malignancies, successful ureteral stent placement in patients with obstructive uropathy has been found in 21 to 50% of patients.[9,14,15] These low success rates suggest that better patient selection is required for each type of urinary diversion to improve

clinical outcomes, increase successful rate attempts, and reduce morbidity associated with failed attempts. It seems there are no differences between patients receiving radiotherapy or brachytherapy that are related to the success of unsuccessful ureteral stent placement. Uthappa *et al.*[17] showed a failure to identify the ureteral meatus as the most common cause of unsuccessful retrograde stent placement in 88% of cases of obstructive uropathy associated with pelvic malignancy ureteral obstruction mechanisms includes extrinsic or intrinsic compression, tumor infiltration through the ureteral wall, and ureteral stricture secondary to external radiotherapy.[5,14,16]

Maguire *et al.* reported a mean basal serum creatinine in patients with cervical cancer without obstructive uropathy of 0.7 mg/dl.[11] In our study, we observed similar findings, however, we found that the mean serum creatinine on admission was significantly lower in patients who had a successful ureteral stent placement than in those who had a failed ureteral stent placement, similar to other studies.[12] Tan *et al.* reported a 71.4% success rate of ureteral stent placement in patients with cervical cancer and a mean serum creatinine on admission of less than 2.26 mg/dL. In contrast, success rate lowered to 62.5% in patients with serum creatinine over 2.26 mg/dl.[16] Moreover, the increased mean serum creatinine in obstructive uropathy could be associated with a higher grade of ureteral obstruction, thus, a higher rate of failed stent placement. We observed that a serum creatinine greater than 3.4 mg/dL at the moment of identification of obstructive uropathy was significantly associated with stent insertion failure, in agreement with other studies.[12] We did not find any significant difference in other measurements such as blood urea nitrogen, serum and urinary electrolytes, or fractional excretion of sodium between patients who had a successful and failed stent placement.

We found that the presence of distal ureteral tumor invasion diagnosed by CT was significantly higher in patients who had failed ureteral stent placement. Furthermore, a length of distal ureteral obstruction greater than 3 cm may result in a failed attempt of endourological urinary diversion. This finding is consistent with the studies by Tan *et al.* and Song *et al.*, who outlined that patients with a ureteral obstruction with a length greater than 3 cm had a lower success rate of ureteral stent placement and that distal ureteral tumor invasion was a significant risk factor for progression to percutaneous nephrostomy.[15,16] This finding confirmed that an obstruction, especially greater than 3 cm, does matter when an urologist attempts to place an endourological urinary diversion. Identification of ureteral invasion by CT can help surgeons choose percutaneous nephrostomy as the first surgical procedure options. We also explored other CT findings, such as hydronephrosis grading, tumoral extension through the bladder wall, perivesical fat stranding, bilateral hydronephrosis and anterior-posterior diameter of the renal pelvis. We did not find any statistical association of these with failure of ureteral placement. Our data differ from those reported by Wang *et al.* who found that the grade of hydronephrosis was associated with the unsuccess rate of endourological urinary diversion in patients with obstructive uropathy after gynecological malignancies.[18]

This study has some limitations, such as its retrospective design and inclusion of data from a single tertiary referral hospital. Despite

these limitations, our study has many notable strengths. It is one of the largest studies to date on obstructive uropathy due to cervical cancer focusing on several predictive factors of failed endourological urinary diversion. Further, future prospective, multicenter research is needed for the generalization of our results and to guide optimal treatment for women with obstructive uropathy due to cervical cancer.

Conclusion

The results from our study may contribute to the evidence-based decision-making process at an individual patient level to select an appropriate urinary diversion in patients with obstructive uropathy due to cervical cancer to provide better outcomes and avoid anesthetic risks related to failed ureteral stent placement. In these patients, distal ureteral tumor invasion diagnosed by CT can be the most important factor related to unsuccessful ureteral placement.

CRediT Taxonomy

Conceptualization C.M.D.E., P.M.R., V.D.B.I.S., N.O.A.A., D.L.C.C, G.G.A., A.G.G visualization C.M.D.E., P.M.R.; supervision G.G.A., A.G.G.; data management C.M.D.E., P.M.R., V.D.B.I.S., N.O.A.A., H.E.A.K.L, D.L.C.C; redaction – original draft C.M.D.E., P.M.R. writing – proofreading and editing C.M.D.E., H.A.K.L., G.G.A. and, A.G.G.

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Conflict of interest

The authors declare no conflicts of interest.

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