Original article

Abdominal pelvic radiotherapy prolongs surgical time of retrograde endoscopic treatment of upper urinary tract stones

La radioterapia abdomino-pélvica prolonga el tiempo del tratamiento endoscópico retrógrado de litiasis del tracto urinario superior

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Abstract

Objective: the main objective is to assess whether urolithiasis diagnosed in patients with previous APRT need more endoscopic procedures to reach stone-free status and if these procedures are longer. The secondary objective is to find out if these patients have more complications resulting from endourologic procedures.
Design and methodology: we designed a case-control unicentric study including patients with upper urinary tract lithiasis treated with retrograde ureterorenoscopy (URS) between 2006 and 2022. Case patients have previous history of APRT, while controls are patients without this history. We collected epidemiological, lithiasis and treatment related information in both groups.
Results: we identified 18 upper urinary tract stones in cases that underwent endoscopic retrograde treatment. We linked these urinary stones with 18 urolithiasis diagnosed in control patients. The average age in patients and the diameter of the stones diagnosed were very similar in both groups, as well as the stones' location. Longer surgical time was found for lithiasis treatment in case patients (129.6 versus 80.2 minutes in controls, p = 0.025). No significant differences were found regarding the rest of variables.
Limitations: this is a retrospective and observational study, and the sample size is small, so we need to expand to a multicentric study.
Originality and value: to our best knowledge this is the first study to provide data on how APRT may affect the effectiveness of endourological treatment of urolithiasis.
Conclusion: endourological procedures for treatment of upper urinary tract stones in patients with previous APRT are longer than in patients without this background.

Keywords:
Urolithiasis, abdominal pelvic radiotherapy, retrograde ureteroscopy

Citation: Canos-Nebot, A., Caballero-Romeu, J. P., Caballero-Pérez, P., de la Encarnación-Castellano, C., Mendiola-López, A., Galiano-Baena, J. F., *et al. Abdominal pelvic radiotherapy prolongs surgical time of retrograde endoscopic treatment of upper urinary tract stones. Rev Mex Urol.* 2024;84(4):. 2024;84(4): 1-9

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Accepted: September 7, 2024.
Received: January 29, 2024.

Resumen

Objetivos: el objetivo principal es evaluar si las litiasis urinarias diagnosticadas en pacientes con antecedentes de radioterapia abdomino-pélvica necesitan más procedimientos endoscópicos para lograr la resolución de las litiasis y si estos procedimientos son más prolongados. El objetivo secundario es conocer si estos pacientes presentan más complicaciones derivadas de los procedimientos endourológicos.
Diseño y metodología: planteamos un estudio unicéntrico de casos y controles incluyendo pacientes con litiasis del tracto urinario superior tratadas mediante ureterorrenoscopia retrógrada entre 2006 y 2022. Los pacientes caso son aquellos con historia previa de radioterapia, mientras que los controles son los pacientes sin este antecedente. Se recogió información epidemiológica, de las características de las litiasis y del procedimiento realizado.
Resultados: identificamos dieciocho litiasis del tracto urinario superior entre los pacientes casos en las que se realizó tratamiento endoscópico retrógrado. Relacionamos estas litiasis con dieciocho urolitiasis diagnosticadas en pacientes control. La edad media de los pacientes, así como el diámetro y localización fue similar en ambos grupos. Se observó mayor tiempo quirúrgico para el tratamiento en pacientes casos (129.6 versus 80.2 minutos en controles, p = 0.025). No se encontraron diferencias significativas en el resto de las variables.
Limitaciones: se trata de un estudio retrospectivo y observacional, y el tamaño muestral es pequeño, por lo que es necesario ampliar la muestra con un estudio multicéntrico.
Originalidad y valor: este es el primer estudio que aporta datos sobre como la radioterapia puede afectar a la eficacia del tratamiento endourológicos de litiasis urinaria.
Conclusiones: los procedimientos endourológicos para el tratamiento de litiasis del tracto urinario superior en pacientes con antecedentes de radioterapia son más prolongados que en pacientes sin este antecedente.

Palabras clave:
Urolitiasis, radioterapia abdomino pélvica, ureteroscopia retrógrada

Background

Radiotherapy is a treatment option for a large variety of malignant tumours.[1] Ionizing radiation have cytotoxic effects produced by DNA damage mechanisms and by reactive oxygen species generation.[1–4] These cellular changes can affect to healthy tissues the irradiated tumour causing ischaemia, fibrosis and unbalanced vascular proliferatio.[2,5,6]

In 2020, the incidence of pelvic organ cancers worldwide was 4 055 200 cases, in which radiotherapy plays a key role in their treatment. The distal portions of the ureters, the bladder, and posterior urethra can be affected by APRT due to their close anatomical relationship.[5] This can lead to complications cluding radiation cystitis,[6–10] ureteral and urethral strictures,[7,10–14] secondary malignancies and urinary fistulas.[7,15–20]

Patients with a history of abdominal pelvic radiotherapy (APRT) have a higher frequency

of readmissions (mean of 1.3 hospital admissions per year), longer admissions and a higher number of surgical interventions.[7]

Some authors have highlighted the higher frequency of complications derived from endourological procedures such as infections or ureteral perforations in patients with previous local radiotherapy.[6,7,10,12,13,21] scarce literature is limited to a few published cases describing the impossibility of spontaneous expulsion of stone fragments after extracorporeal shock wave lithotripsy (ESWL) or the difficulty in stone fragmentation by ureteroscopy (URS) in patients with previous APRT.[21]

The main objective of this study is to evaluate the results in terms of stone-free status, number of procedures needed for the treatment of urolithiasis and operating time in patients with previous history of APRT compared to those of the patients without this background.

We also sought to find out if these patients have more complications resulting from URS treatment compared to patients without a history of APRT.

Materials and methods

We conducted a retrospective case-control study of patients who underwent treatment of upper urinary tract lithiasis by means of retrograde URS between 2006 and 2022 in our centre.

25 patients with prior history of APRT and posterior treatment of renal and/or ureteral stones were initially identified. Thirty-seven stones were found in these patients, and 42 procedures performed as treatment, including 24 URS (57.14 %), 12 ESWL (28.57 %), 3 open ureterolithotomies (7.14 %), 2 laparoscopic nephrectomies (4.76 %) and one case of percutaneous nephrolithotomy (2.38 %). Twenty-four URS were needed to treat 18 stones in 14 patients. These stones form our case sample.

A random sample matched to cases by age and sex was obtained among all available patients who underwent URS in the same time period, the sample coinciding with the number of stones of case patients in order to appropriately evaluate the results.

Data collected from both cases and controls included sex, age, personal history of genitourinary abnormalities, characteristics of the stone (date of diagnosis, number, size, location, follow-up time), URS related information (duration of the procedure, presence or absence of previous urinary diversion), complications according to the adapted Clavien-Dindo classification system,[22] results of treatment (stone-free or residual fragments ≥ 4 mm) as well as the need for urinary diversion during the procedure or deferred due to some complication.

In addition, data related to APRT received prior to the URS, such as the date of treatment, reason for the radiotherapy treatment, modality, and total dose of radiation received were obtained from the case patients.

Working hypothesis were that patients with a history of APRT needed more endoscopic procedures to solve the stones, had a lower stone-free rate and/or a higher number of complications resulting from endoscopic treatment. We also considered that interventions for these patients might be more complex and therefore more prolonged.

For the statistical analysis, we used the IBM SPSS Statistics 15.0 programme. McNemar's test was used for the analysis of nominal

dichotomous variables, the sign test for ordinal variables and the mean difference calculation and Wilcoxon nonparametric test for the procedure's duration.

Results

The epidemiological data of case and control patients who underwent URS for lithiasis treatment are shown in Table 1. Table 2 shows the features of the stones diagnosed in both groups.

Table 1. Epidemiological data of case-control patients

		Case patients	Control patients
n: patients		14	18
Age (years)	Mean	68	67
	Range	54-83	54-86
Gender (n (%))	Men	9 (64.3)	11 (61.1)
	Women	5 (35.7)	7 (38.9)
Genitourinary congenital anomalies (n (%))		0 (0)	0 (0)

Table 2. Urinary stones features in case-control patients

		Case patients	Control patients
Number of lithiasis (n)		18	18
Max. diameter (mm)	Mean	10.83	10
	Range	3-27	4-19
Localisation (n (%))	Pelvis + calyces	1 (5.6)	0 (0)
	Pelvis	1 (5.6)	4 (22.2)
	Calyces	0 (0)	0 (0)
	Proximal ureter	3 (16.7)	2 (11.1)
	Middle ureter	7 (38.8)	3 (16.7)
	Distal ureter	6 (33.3)	9 (50)
Average follow-up time from diagnosis (months)		21.64	11.47

The differences in the sample size between the groups are justified since controls patients are obtained to match the 18 urinary stones diagnosed in 14 case patients. Table 3 highlights the main characteristics of treatment with APRT in 14 case patients who underwent endourological procedures. In 50 % of cases, APRT was performed as a treatment for prostate cancer, followed in frequency by rectal cancer in 28.57 %. Less frequently, we also observed cases of cervical and uterine cancer. All patients received a total dose superior 45 Gy, attending to available data.

Table 3. Data about radiotherapy treatment in 14 case patients

Reason for radiotherapy (n = 14) (n (%))	Prostate cancer	7 (50)
	Rectal cancer	4 (28.6)
	Cervical cancer	2 (14.3)
	Uterine cancer	1 (7.1)
Radiation dose (Gy) (n = 7)	Mean	62.7
	Range	45-80
Radiotherapy modality (n = 13) (n (%))	External radiotherapy	9 (69.2)
	External radiotherapy + brachytherapy	4 (30.8)

Table 4 shows the operative and complications results.

Table 4. Case-control study results comparing urinary treated with URS

URS		Stones in case patients n = 18	Stones in control patients n = 18	OR1 95% CI[2]	Paired samples p-value[*3] ◊[4]
Stone-free*		14 (77.8)	17 (94.4)	4.9 (0.5; 48.6)	0.375
Intraoperative stenting*		12 (66.7)	8 (44.4)	2.5 (0.6;9.7)	0.344
Deferred stenting*		1 (5.6)	0 (0)	1.1 (0.9;1.2)	0.999
Clavien-Dindo scale ◊[4]	Grade 0	12 (66.7)	11 (61.1)	Ref.	
	Grade I	3 (16.7)	4 (22.2)	0.7 (0.1;3.8)	
	Grade II	2 (11.1)	3 (16.7)	0.6 (0.1; 4.4)	
	Grade III	1 (5.5)	0 (0)	---	0.366
				Difference of means 95%CI[2]	
Additional endoscopic procedures		0.3 (0.8)	0.1 (0.2)	0.2 (-0.7;0.1)	0.157
Procedure duration (minutes) (mean/SD) ◊[4]		129.6 / (96.2)	80.2 (42.6)	24.8 (100; -1)	0.025

[1]OR: Odds Ratio, 295% CI: 95% confidence interval,[3*]: P-Value of McNemar's test,[4]◊: P-Value of Wilcoxon test.

The stone-free rate for URS in case patients was 77.8 % versus 94.4 % in control patients, but these differences between the two groups were not statistically significant. We also could observe in our cohort a tendency to require a greater number of endoscopic procedures to stone treatment in case patients (0.3 additional URS per stone in cases vs. 0.1 extra URS per stone in controls). However, we again found that these differences were not statistically significant (p = 0.157).

But, on the other hand, the mean duration of the procedures in cases was 129.6 minutes versus 80.2 minutes in controls, and the p-value of Wilcoxon's test was statistically significant (p = 0.025).

Regarding complications according to the Clavien-Dindo classification system, we observed a higher frequency of grade I and grade II complications in control patients (22.2 % and 16.7 % in controls vs. 16.7 % and 11.1 % in cases, respectively). We only observed one case of grade III complication in the group of case patients (5.6 % in cases vs. 0 %). Neither for complications rate nor for need of intraoperative or deferred stenting significant differences were found when comparing both groups.

Discussion

The endourological treatment of upper urinary tract stones offers good stone-free rates with low morbidity. The stone-free rate of URS for ureteral stones observed in large series such as the one published by Pérez Castro *et al.*,[23] varies between 76.6 % and 94.2 %. Our results in controls are quite similar, with a stone-free rate of 94.4 %.

The CROES ureteroscopy global study reported no intraoperative complications in up to 92 % of the procedures. In our control series,[23] in 61.1 % of the procedures no intraoperative or postoperative complications were found.

The greatest difficulties during de procedures in case patients were identified in access through the ureteral orifice, as well as in the presence of stenotic ureteral segments. Strictures hinders the expulsion of stone fragments and could reduce the stone-free rate in patients with a history of APRT. At the same time, this condition could increase the number of endoscopic procedures required to achieve the stone-free status in these patients. This trend can be seen in the results obtained in our cohort.

In our study, the longer surgical times in patients with an antecedent of APRT could be related to the presence of more difficult surgical scenarios and more complex access due to the tissue fibrosis generated by radiotherapy, requiring the use of thinner endoscopes to reach the stone. In patients with a history of APRT, there is greater tissue devitalisation and friability, as well as a higher frequency of fibrosis and strictures. This could lead to higher overall challenge in the procedures performed. The use of smaller caliber ureteroscopes could be a solution in specific cases to gain easier access to the ureteral orifice.[24–26]

Given the peculiarities of the surgical field, even for ureteral catheter placement, some authors such as Zeng *et al.*,[27] consider that combined approaches (percutaneous and endoscopic retrograde) should be the first choice in patients with post-radiotherapy ureteral strictures. This combined approach proved, in their series of 19 patients, to be a safe and effective option in patients with these characteristics. We believe that the retrograde approach is generally adequate for ureteral catheter placement, and the anterograde approach should be considered if necessary.

Regarding the complications of the procedure, we found no significant differences between cases and controls. However, the only grade III complication in the Clavien-Dindo classification system occurred in a case patient, identifying ureteral perforation during the endoscopic procedure. This case of ureteral perforation was considered grade 3 according to the PULS (Post-Ureteroscopy Lesion Scale),[28] and required placement of JJ ureteral catheter after the procedure.

Ureteral strictures are a serious complication that can develop after endourological

procedures. In patients with a history of APRT, the ureteral strictures may be more frequent in relation to the tissue changes generated by the radiation.[12,28] In our series of 14 patients in which a total of 24 URS was performed, we found the following intraoperative findings that prevented completion of endourological treatment of stones: 2 cases of severe ureteral oedema (8.3 %), 3 cases of ureteral rigidity (12.5 %) and 4 cases of ureteral stricture (16.7 %).

In patients with repetitive and complex treatments for ureteral stones and in whom we detect a ureteral injury, it is necessary to consider long-term follow-up through functional tests to evaluate the kidneys functionality.[13,29]

The main limitation of this study is its retrospective nature and the fact of being an observational study. Nevertheless, to reduce the risk of bias, we matched the case with controls attending to some parameters as age, sex, and type of intervention, to make pairs of patients with characteristics as similar as possible. In addition, the small sample size available may limit the detection of statistically significant differences between rare circumstances such as complications derived from the procedure. We need to perform a multicentric study to achieve a larger sample size.

However, to our best knowledge this is the first study to provide data on how APRT may affect the effectiveness of endourological treatment of urolithiasis. Larger prospective studies would be needed to support our results.

Conclusions

Endourological treatment of upper urinary tract stones in patients with a history of abdominal pelvic radiotherapy is longer than in patients without this background.

CRediT Taxonomy

1. **À Canós:** Project development, data collection, manuscript writing.
2. **JP Caballero:** Project development, data collection, manuscript editing.
3. **P Caballero:** Project development, data analysis.
4. **C de la Encarnación:** Data collection.
5. **A Mendiola:** Data collection.
6. **JF Galiano:** Manuscript editing.
7. **MD Montoya:** Manuscript editing.
8. **JA Galán:** Project development, manuscript editing.

Conflict of interest

None of the authors have any conflicts of interest or financial ties to disclose.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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