RUC
Revista Urología Colombiana

Volume 32 • Number 1 • 2023
Urol Colomb

ISSN: 0120-789X / eISSN: 2027-0119
www.urologiacolombiana.com

Indexada/*Indexed in*: SCImago, Publindex Colciencias Clase C, Latindex, Redalyc, Ulrichs Directory, Urology Green List

Atarraya. Dr. Luis Enrique Abuchaibe Sedo

SCU
Sociedad Colombiana de Urología®

PERMANYER
www.permanyer.com

REVISTA UROLOGÍA COLOMBIANA

PERMANYER

EDITORIAL

Urología de precisión: conceptualización desde el cáncer de próstata

Precision urology: a view from prostate cancer

Andrés F. Gutiérrez-Rojas

Servicio de Urología, Hospital Universitario San Ignacio, Bogotá DC, Colombia

No hay duda de que la práctica diaria de la urología es un constante ejercicio de ajustar factores, variables o determinantes demográficos, clínicos, paraclínicos, histopatológicos e imagenológicos para lograr clasificar a un paciente en determinado grupo de partida para definir su ruta o plan de manejo. Es en ese punto donde la semántica de los términos medicina o cuidado personalizado y medicina de precisión de encuentran y a su vez divergen. Hemos adoptado el término de la medicina de precisión desde la perspectiva de la aplicación clínica de la farmacogenómica, entendida como el desarrollo de moléculas a dianas o alteraciones de las denominadas «ómicas» (genómica, transcriptómica y proteómica, entre otras). La medicina de precisión abarca o agrupa los determinantes del cuidado personalizado que corresponde a la adaptación metódica y meticulosa de los resultados de los estudios de investigación (medicina basa en evidencia) actuales a las condiciones clínicas, circunstancias de la atención médica, tecnología disponible, acceso a servicios y habilidades clínicas, sumado al perfilamiento biológico del tumor por medio de la información obtenida de diferentes plataformas, incluidas nuevas tecnologías en diagnostico por imágenes (por ejemplo), por lo que podríamos definirlo como una aproximación o integración de datos obtenidos de una forma más precisa con el fin de ajustar el tratamiento[1]. El término también abarca un control del «daño colateral», entendido como la disminución de los efectos secundarios o no deseados por una intervención, una denominación ampliamente usada en la terapia antibiótica o citotóxica en cáncer[2,3]. Este daño puede ocurrir por acciones como una identificación errónea o subóptima de la severidad o significancia de una lesión, emplear estrategias de tratamiento inadecuadas por ser insuficientes o exageradas para una enfermedad determinada.

La atención en cáncer de próstata se ha visto marcadamente revolucionada por esta nueva aproximación al cuidado de la enfermedad.

La integración de la resonancia multiparamétrica y la biopsia por fusión han permitido identificar pacientes con lesiones clínicamente significativas susceptibles de terapia curativa de órgano completo, evitando así la toma de biopsias innecesarias con sus riesgos y el tratamiento de la enfermedad indolente[4], pudiéndole sumar el beneficio demostrado en la selección de pacientes basado en clasificadores genómicos para encaminar a pacientes hacia la vigilancia activa[5]. La integración de los hallazgos o caracterización imagenológica de los tumores de próstata en la resonancia magnética y su asociación a ciertas alteraciones genómicas abrió el campo a una disciplina de la medicina de precisión: la radiogenómica[6]. Uno de los campos más prometedores de la radiogenómica y las biopsias por fusión es la identificación de la denominada lesión índice, cuya identificación correcta y en concordancia al origen monoclonal

Correspondencia:
Andrés F. Gutiérrez-Rojas
E-mail: afgutierrez@husi.org.co

Fecha de recepción: 02-02-2023
Fecha de aceptación: 07-02-2023
DOI: 10.24875/RUC.23000026

Disponible en internet: 23-03-2023
Urol. Colomb. 2023;32(1):01-02
www.urologiacolombiana.com

de las metástasis[7], lo que podría impulsar el uso de la terapia focal o preservadoras de órgano[8]. Son bien conocidas las ventajas oncológicas funcionales de la disección quirúrgica precisa de la cirugía laparoscópica asistida por robot o de la radioterapia guiada por imágenes de resonancia (MRI-Linac)[9], como estrategias con intención curativa radicales. La determinación de la carga tumoral total mediante la identificación por imágenes de tomografía por emisión de positrones del antígeno de membrana específico de la próstata (PSMA) tanto en la enfermedad localizada de alto riesgo como la recaída bioquímica son determinantes pronósticos y predictivos, permitiendo la reclasificación y redefinición de la terapia que escoger, un ejemplo de esto es evitar la terapia sistémica en pacientes con recaída bioquímica solo identificada en el lecho en recaída bioquímica o enfermedad metastásica *de novo* hormonosensible[10,11]. El uso de clasificadores genómicos en la recaída bioquímica ha demostrado su papel predictivo en la respuesta a la radioterapia de salvamento y la necesidad o no de uso de la terapia de deprivación androgénica[12]. La expresión identificable del PSMA como diana terapéutica para llevar radiofármacos como el lutecio 177 en pacientes con enfermedad metastásica en estadio castración (CPCRm) resistente es otro claro ejemplo de la medicina de precisión en cáncer de próstata[13]. Las nuevas tecnología o plataformas de secuenciación genética en pacientes, especialmente en CPCRm, han permitido identificar blancos accionables y mecanismos de resistencia a la terapia sistémica. Las alteraciones de la vía de la recombinación homologa (BRCA1/2), la pérdida funcional de PTEN-hiperactividad vía del PI3K, la inestabilidad microsatelital o defectos en genes de reparación han ampliado el panorama de las opciones de terapia sistémica de una forma exponencial como inhibidores PARP, inhibidores de AKT e inmunoterapia[14]. La identificación de variantes del receptor de andrógenos en células tumorales circulantes ARV7 en paciente en resistencia a la castración se asoció a resistencia a la enzalutamida/abiraterona, sugiriendo que existe un grupo de pacientes en los que la terapia citotóxica en ese momento pudiese ser la estrategia de tratamiento más conveniente[15].

La medicina de precisión en urología a la que podríamos llamar también urología de precisión desde el cuidado del cáncer de próstata como ejemplo, pretende generar capacidad de anticipación a los desenlaces, ajuste las intervenciones por medio de una «medicina guiada por datos», como la define Pino Villarreal[16], en donde la evaluación, recolección y análisis de los datos obtenidos de diferentes plataformas de información (imágenes, patología, perfiles genómicos, analítica de sangre, etc.) y en diferentes momentos de la enfermedad amparado en protocolos o asistida por la inteligencia artificial, nos permitirán llevar con seguridad al paciente por una mejor ruta de atención con resultados más efectivos y menos adversos.

Bibliografía

1. McAlister FA, Laupacis A, Armstrong PW. Finding the right balance between precision medicine and personalized care. CMAJ. 2017;189(33): E1065-E1068.
2. Hoban DJ. Antibiotics and collateral damage. Clin Cornerstone. 2003; Suppl 3:S12-20.
3. Chen Y, Jungsuwadee P, Vore M, Butterfield DA, St Clair DK. Collateral damage in cancer chemotherapy: oxidative stress in nontargeted tissues. Mol Interv. 2007;7(3):147-56.
4. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al.; PRECISION Study Group Collaborators. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med. 2018;378(19):1767-77.
5. Jairath NK, Dal Pra A, Vince R Jr, Dess RT, Jackson WC, Tosoian JJ, et al. A systematic review of the evidence for the decipher genomic classifier in prostate cancer. Eur Urol. 2021;79(3):374-83.
6. Thenault R, Gasmi A, Khene ZE, Bensalah K, Mathieu R. Radiogenomics in prostate cancer evaluation. Curr Opin Urol. 2021;31(4):424-9.
7. Liu W, Laitinen S, Khan S, Vihinen M, Kowalski J, Yu G, et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nat Med. 2009;15(5):559-65. Erratum in: Nat Med. 2009;15(7):819.
8. Elkhoury FF, Simopoulos DN, Marks LS. MR-guided biopsy and focal therapy: new options for prostate cancer management. Curr Opin Urol. 2018;28(2):93-101.
9. Sritharan K, Tree A. MR-guided radiotherapy for prostate cancer: state of the art and future perspectives. Br J Radiol. 2022;95(1131):20210800.
10. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al.; proPSMA Study Group Collaborators. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet. 2020;395(10231):1208-16.
11. Morris MJ, Rowe SP, Gorin MA, Saperstein L, Pouliot F, Josephson D, et al.; CONDOR Study Group. Diagnostic performance of ^{18}F-DCFPyL-PET/CT in men with biochemically recurrent prostate cancer: Results from the CONDOR Phase III, multicenter study. Clin Cancer Res. 2021;27(13):3674-82.
12. Dal Pra A, Ghadjar P, Hayoz S, Liu VYT, Spratt DE, Thompson DJS, et al. Validation of the Decipher genomic classifier in patients receiving salvage radiotherapy without hormone therapy after radical prostatectomy - an ancillary study of the SAKK 09/10 randomized clinical trial. Ann Oncol. 2022;33(9):950-8.
13. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al.; VISION Investigators. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med. 2021;385(12):1091-103.
14. Ku SY, Gleave ME, Beltran H. Towards precision oncology in advanced prostate cancer. Nat Rev Urol. 2019;16(11):645-54.
15. Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roeser JC, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med. 2014;371(11):1028-38.
16. Pino Villarreal LE. Moviéndonos hacia la urología híbrida. Rev Colomb Urol. 2022;31(04):e141-e142.

REVISTA UROLOGÍA COLOMBIANA

PERMANYER

Check for updates

ORIGINAL ARTICLE

Diagnostic accuracy of uroflowmetry parameters to predict infravesical obstruction

Exactitud diagnóstica delos parámetros de la flujometría para predecir la obstrucción infravesical

José Gaona, Daniel Romero, Pablo Robles, Diego Bravo, Raúl Rueda, Jairo Ortiz, Daniel Sánchez, César González, Fabio González, Angélica Rueda, Sebastián Ortiz, and Carlos Camargo*

Urology Research Group, Department of Surgery, Uromédica Institute, Universidad de Santander, Bucaramanga, Santander, Colombia

Resumen

Objetivo: *evaluar las estadísticas de desempeño del flujo promedio (Qave), el tiempo de evacuación (Vtime) y el tiempo hasta el flujo máximo (TQmax), además del flujo máximo (Qmax), para el diagnóstico de obstrucción infravesical.* **Métodos:** *revisamos urodinamias realizadas en hombres > 40 años. La obstrucción se consideró un grado 3-6 en el nomograma de Schäfer. Se calcularon la sensibilidad, la especificidad, la razón de verosimilitud positiva (LR +), la razón de verosimilitud negativa (LR-) y la curva característica operativa del receptor (ROC) para los diferentes componentes de la flujometría libre.* **Resultados:** *analizamos 443 estudios. Los pacientes con obstrucción tenían valores más bajos de Qmax y Qave, y valores más altos de Vtime y TQmax. Considerando diferentes umbrales, el Qmax tuvo valores de sensibilidad, especificidad, LR + y LR- de 12-83%, 50-97%, 1.7-4.46 y 0.32-0.9, respectivamente; Qave tuvo valores de sensibilidad, especificidad, LR + y LR- de 65-95%, 21-66%, 1.22-1.94 y 0.19-0.53, respectivamente; Vtime tuvo valores de sensibilidad, especificidad, LR + y LR- de 49-85%, 26-67%, 1.15-1.54 y 0.57-0.74, respectivamente; TQmax tuvo una sensibilidad, especificidad, LR + y LR- de 36-81%, 22-72%, 1.04-1.33 y 0.85-0.87, respectivamente. Las áreas bajo las curvas ROC para Qmax, Qave, Vtime y TQmax fueron 0,75 (95% CI = 0.71-0.79, p < 0,001), 0.71 (95% CI = 0.66-0.75, p < 0,001), 0.62 (95% CI = 0.57-0.67, p < 0,001) y 0.55 (95% CI = 0.5-0.6, p = 0.03), respectivamente.* **Conclusiones:** *Qave, Vtime y TQmax mostraron una capacidad discriminatoria estadísticamente significativa para predecir la obstrucción infravesical, por lo que tienen valor clínico como complemento de la información proporcionada por el Qmax.*

Palabras clave: *Flujo medio. Flujo máximo. Tiempo hasta el flujo máximo. Uroflujometría. Estudio de urodinamia. Tiempo de evacuación.*

Abstract

Objective: *to evaluate the performance statistics of average flow (Qave), voiding time (Vtime), and time to maximum flow (TQmax), in addition to maximum flow (Qmax), for diagnosis of infravesical obstruction.* **Methods:** *we reviewed urodynamic studies performed in men > 40 years. Obstruction was considered a grade 3-6 in the Schäfer nomogram. Sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), and the receiver operator characteristic (ROC) curve were calculated for the different components of free uroflowmetry.* **Results:** *we analyzed 432 studies. Patients with obstruction had lower values of Qmax and Qave, and higher values of Vtime and TQmax. Considering different thresholds, Qmax*

***Correspondencia:**
José Gaona
E-mail: gaonapinilla@gmail.com

Fecha de recepción: 11-01-2023
Fecha de aceptación: 07-02-2023
DOI: 10.24875/RUC.23000004

Disponible en internet: 23-03-2023
Urol. Colomb. 2023;32(1):03-08
www.urologiacolombiana.com

had sensitivity, specificity, LR + and LR- values of 12-83%, 50-97%, 1.7-4.46 and 0.32-0.9, respectively; Qave had sensitivity, specificity, LR + and LR- values of 65-95%, 21-66%, 1.22-1.94 and 0.19-0.53, respectively; Vtime had sensitivity, specificity, LR + and LR- values of 49-85%, 26-67%, 1.15-1.54, and 0.57-0.74, respectively; TQmax had a sensitivity, specificity, LR + and LR- of 36-81%, 22-72%, 1.04-1.33 and 0.85-0.87, respectively. The areas under the ROC curves for Qmax, Qave, Vtime and TQmax were 0.75 (95% CI = 0.71-0.79, p < 0.001), 0.71 (95% CI = 0.66-0.75, p < 0.001), 0.62 (95% CI = 0.57-0.67, p < 0.001) and 0.55 (95% CI = 0.5-0.6, p = 0.03), respectively. **Conclusions:** *Qave, Vtime, and TQmax showed a statistically significant discriminatory capacity to predict infravesical obstruction, and therefore they have clinical value as a complement to the information provided by Qmax.*

Keywords: *Average flow. Máximum flow. Time to maximum flow. Uroflowmetry. Voiding time. Study of urodynamics.*

Introduction

Free uroflowmetry is a diagnostic tool recommended by different management guidelines for men with lower urinary tract symptoms (LUTS)[1,2,3]. Its non-invasive nature, simplicity, and low cost make it a first-line screening test, more attractive than the flow/pressure study, even though the latter is the gold standard for diagnosing infravesical obstruction[4,5,6,7].

Maximum flow (Qmax) is regarded as the most important uroflowmetric element for diagnostic accuracy and has been extensively studied[8,9]. Other uroflowmetry parameters such as average flow rate (Qave), voiding time (Vtime), and time to maximum flow (TQmax) have received less attention in the literature, and are frequently underestimated in clinical practice. However, Qave is a valuable "radiograph" of the total evacuation, in contrast to the isolated point described by Qmax[10,11]. Its relevance may increase in cases of intermittent flow or in patients who strain to start urination[11]. In addition, Vtime and TQmax may support the diagnosis of infravesical obstruction, especially in cases of prolonged urination[12,13,14,15,16].

Since few studies have simultaneously measured and compared the discriminative capacity of uroflowmetric variables different from Qmax in terms of infravesical obstruction, we set out to measure them in a cohort of men who underwent urodynamics due to lower urinary tract symptoms.

Materials and methods

We carried out a retrospective evaluation of all urodynamic studies performed in our Institute between January 2012 and February 2021. Information was collected with the following inclusion criteria: men older than 40 years, storage or voiding symptoms, no history of neuropathic bladder, no history of prostate cancer, and evacuated volumes between 150 ml and 500 ml during free uroflowmetry and during pressure-flow studies. We recorded in all cases the value of Qmax, Qave, Vtime, TQmax, evacuated volume, post-void residual (RPM), detrusor pressure at Qmax (PdetQmax), and the result of the Schäfer nomogram. The Institutional Ethics Committee approved the research protocol.

Urodynamic studies were performed following the recommendations of the International Continence Society (ICS)[4,17,18]. Patients performed free flowmetry in their preferred position and were asked not to squeeze the penis, not push, and not move the urinary stream around the funnel. Qmax measurement was done with artifact correction. Vtime measurement was made by moving the marker towards the actual end of urination, avoiding errors due to dripping associated with the patient´s coughing or movements. Cistometry and pressure-flow studies were performed after free flowmetry.

Pressure-flow studies´ interpretation was based on the passive urethral resistance relationship (Passive Urethral Resistance Relation, LinPURR, Schäfer´s nomogram)[6,7,19]. Obstructive pattern was defined as a LinPUR 3,4,5, or 6. No obstruction was considered a LinPURR 0 or 1. Patients with a LinPURR 2 were excluded, as it was considered equivocal.

Statistical analysis: variables are presented with means and standard deviations. The Kolmogorov-Smirnov test was used to determine the normality of continuous variables. The differences between the two groups were made using the Student's t-test for variables with normal distribution and the Mann-Whitney U for variables without normal distribution. The values of sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR-) were calculated for the different cutoff points of the flowmetric variables. The performance values of Qmax, Qave, Vtime, and TQmax were calculated as areas under the curve (AUC) on the receiver operator characteristic (ROC) curves. An AUC of 1.0 was considered perfect discrimination, and a value of 0.5 was considered the absence of discriminatory power. A p lower than 0.05 was considered a statistically significant difference. The difference between the ROC curves was obtained

Table 1. Age and voiding parameters

	Group 1: LinPUR	Group2: LinPUR	
	0 or 1	3-6	*p*
	n = 211	n = 221	
	Mean (+/– 1 ds)	Mean (+/– 1 ds)	
Age (years)	62,6 (+/– 12,0)	64,9 (+/– 8,7)	0.02
Qmax (ml/s)	16,3 (6,8)	10,4 (+/– 4,6)	< 0,001
Qave (ml/s)	7,5 (+/– 3,7)	4,9 (+/– 2,7)	< 0,001
Vtime (s)	51,4 (+/– 37,6)	67,4 (+/– 50,3)	< 0,001
TQmax (s)	15,4 (+/– 12,7)	20,0 (+/– 20,7)	0.04
PdetQmax (cmH2O)	28,4 (+/– 10,0)	68,7 (+/– 19,0)	< 0,001
PVR (ml)	72,3 (+/– 83,2)	117,7 (+/– 118,4)	< 0,001
Evacuated volume (ml)	316,3 (+/– 128)	260,9 (+/– 108,0)	< 0,001

Qmax: maximum flow; Qave: average flow; Vtime: voiding time; Tqmax: time to maximum flow; PdetQmax: detrusor pressure at maximum flow; PVR: post-void residual; ds: standard deviation; s: seconds; ml: mililiters.

by applying the DeLong test with the statistical software Medcalc (Mariakerke, Belgium). The other statistical calculations were made with the software The Statistical Package for the Social Sciences (SPSS version 17.0, Chicago, USA).

Results

We obtained information from 5.434 consecutive urodynamic studies performed from January 2012 to February 2021. According to the selection criteria, we identified 432 studies for inclusion in our study. Table 1 depicts the distribution of age and uroflowmetry variables in two groups according to the degree of obstruction in the Schäfer nomogram: group 1, patients with LinPUR 0 or 1, and group 2, patients with LinPUR 3,4,5 or 6. The mean age showed statistically significant differences and was 63.6 years for group 1 and 64.8 years for group 2 (p = 0.02). Group 1 had statistically superior results compared to group 2 in terms of Qmax (16.3 versus 10.4 ml/s, respectively, p < 0.001), Qave (7.5 versus 4.9 ml/s, respectively, p < 0.001), and evacuated volume (316.3 versus 260.9 ml, respectively, p < 0.001). The values of group 1 were statistically lower than those of group 2 in terms of Vtime (51.4 versus 67.4 seconds, respectively, p < 0.001), TQmax (15.4 versus 20.0 seconds, respectively, p < 0.001), PdetQmax (28.4 versus 68.7 cmH20, respectively, p < 0.001), and PVR (72.3 versus 117.7 ml, respectively, p < 0.001).

Table 2. Sensitivity, specificity

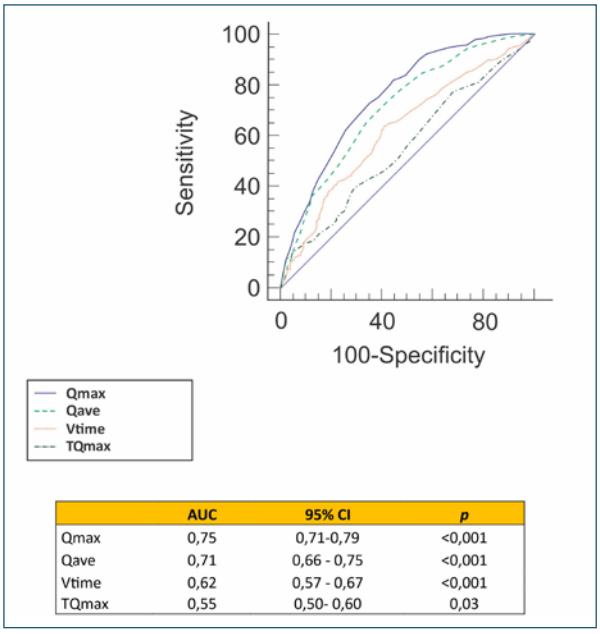
	Sensitivity %	Specificity %	LR +	LR –
Qmax (mls/s)				
≤ 5	12	97	4.46	0.9
≤ 10	53	78	2.5	0.59
≤ 15	83	50	1.7	0.32
Qave (ml/s)				
≤ 10	95	21	1.22	0.19
≤ 7	84	45	1.53	0.35
≤ 5	65	66	1.94	0.53
Vtime (s)				
> 30	85	26	1.15	0.57
> 40	66	53	1.41	0.64
> 50	49	67	1.54	0.74
TQmax (s)				
> 8	81	22	1.04	0.85
> 12	49	54	1.11	0.91
> 16	36	72	1.33	0.87

LR+ y LR- for different cutoffs. Qmax: maximum flow; Qave: average flow; Vtime: voiding time; TQmax: time to maximum flow; LR+: positive likelihood ratio; LR-: negative likelihood ratio; s: seconds; ml: mililiters.

Table 2 presents the sensitivity, specificity, and likelihood ratio for the different cutoffs of Qmax, Qave, Vtime, and TQmax. The highest sensitivity values for each variable were 83% for a Qmax less than or equal to 15 ml/s, 95% for a Qave less than or equal to 10 ml/s, 85% for a Vtime greater than 30 seconds, and 81% for a TQmax greater than 8 seconds. The highest specificity values for each variable were 97% for a Qmax less than or equal to 5 ml/s, 66% for a Qave less than or equal to 5 ml/s, 67% for a Vtime greater than 50 seconds, and 72% for a TQmax greater than 16 seconds. The highest likelihood ratio for obstruction was 4.46 and corresponded to a Qmax less than or equal to 5 ml/s. The best likelihood ratio for non-obstruction was 0.19, related to a Qave less than or equal to 10 ml/s.

The ROC curves for Qmax, Qave, Vtime and TQmax showed an AUC of 0.75 (95% confidence interval = 0.71-0.79, p < 0.001), 0.71 (95% confidence interval = 0.66-0.75, p < 0.001), 0.62 (95% confidence interval = 0.57-0.67, p < 0.001) and 0.55 (95% confidence interval = 0.50-0.60, p = 0.03) respectively, as displayed in Figure 1.

The difference between areas of the ROC curves was in favor of Qmax compared to Qave (difference = 0.04, p = 0.005), Vtime (difference = 0.12; p < 0.001),



	AUC	95% CI	p
Qmax	0,75	0,71-0,79	<0,001
Qave	0,71	0,66 - 0,75	<0,001
Vtime	0,62	0,57 - 0,67	<0,001
TQmax	0,55	0,50- 0,60	0,03

Figura 1. ROC curves comparison and area under the ROC curve (AUC) for different uroflowmetry parameters.

Qmax: maximum flow; Qave: average flow; Vtime: voiding time; TQmax: time to maximum flow; AUC: area under the curve. Described p-values refer to the comparison between each AUC and AUC: 0,5.

and TQmax (difference = 0.19; p < 0.001). Likewise, it was significantly higher in Qave than in Vtime (difference = 0.08; p < 0.001) and TQmax (difference = 0.15; p < 0.001). There was no statistically significant difference between areas of the ROC curves of Vtime and TQmax (difference = 0.06, p = 0.02).

Discussion

Uroflowmetry is recommended as part of LUTS workup during the initial evaluation or when considering a surgical correction[1,3]. Its main shortcomings are intra-individual variability, dependence on evacuated volume, and a questionable accuracy in predicting infravesical obstruction[5,20]. Different recommendations have been proposed to optimize its predictive ability, such as the realization of multiple measurements, obtaining evacuated volumes greater than 150 ml and less than 500 ml, the application of home devices, the introduction of nomograms, and the use of volume corrected flow rats[18,21,22,23,24,25].

Qmax has been the most evaluated flowmetric parameter. The multicenter ICS BPH study evaluated 1271 men between 45 and 88 years old and found that a Qmax cutoff of 10ml/s had a 47% sensitivity and a 70% specificity for diagnosing infravesical obstruction, defined as a Schäffer 3-6 category[9]. A meta-analysis that included 16 publications found that a Qmax cutoff of 10ml/s had mean sensitivity and specificity of 68.3% and 70.5% to diagnose infravesical obstruction, respectively, with observed sensitivity ranges between 16-100% and specificity between 26-100%[8]. The values we obtained in the present study (sensitivity of 53% and a specificity of 78% for a Qmax threshold less than or equal to 10 ml /s) are within the ranges described in the literature and are very similar to those in the ICS BPH study[9].

The mentioned limitations inherent to flowmetry and the suboptimal values described for Qmax sensitivity and specificity justify the analysis and consideration of other flowmetric parameters proposed in our study. Qave, for instance, may be more representative than Qmax in some patients in whom a “normal” Qmax is accompanied by a low Qave[10,11]. The situation can be seen in patients who strain to evacuate or in cases of intermittent flows, where Qmax as a sole parameter may lead to erroneous interpretations[11].

There are few publications with direct comparisons between Qmax and Qave. Shoukry et al. evaluated prospectively 173 patients and found that the correlation with obstructive symptoms was better with Qmax than with Qave[26]. However, the study was descriptive, and a flow-pressure assessment was not available as a reference. Oelke et al. compared in 168 men the two variables´ discriminative capacity to diagnose infravesical obstruction and reported an AUC in the ROC curves of 0.84 for Qmax and 0.82 for Qave[27]. The present study is in line with the mentioned publications, as the area under the ROC curve was greater for Qmax than for Qave (0.75 versus 0.71, p = 0.005). Still, individual values of the Qave can be beneficial in the clinical context. For instance, the diagnosis of obstruction will be more plausible in a patient with a Qave less than or equal to 5 ml/s because, according to our study, this cutoff has a sensitivity, specificity, LR + and LR- of 65%, 66%, 1.94, and 0.53, respectively.

The evaluation of Vtime and TQmax has been limited in the literature. Plateau, intermittent, or “saw tooth” flow patterns, all with prolonged urination times, are commonly described as suggestive of an obstructive pattern, but this classification has not been correlated with Vtime[15]. Varderbrink et al. found that children undergoing meatoplasty achieved shorter evacuation times than before surgery (19.5 sec vs. 29.3 sec, p = 0.03)[28]. Nishimoto et al. conducted evaluations in 105 patients, including five who underwent transurethral surgery[12]. According to their work, obstruction was associated with prolonged evacuation times, and a Qmax/time ratio less than or equal to 0.78 indicated

inappropriate urination. Shimizu et al. evaluated the flowmetry of 171 men with and without infravesical obstruction, finding that the Qmax/Vtime ratio was a better predictor of an obstruction than the Qmax and that its value was not affected by the volume evacuated[29]. Similarly, our study supports the notion that infravesical obstruction is associated with longer Vtime and TQmax. In particular, a Vtime greater than 50 seconds and a TQmax greater than 16 seconds showed the highest LR + (1.54 and 1.33, respectively).

Our study demonstrated statistically significant discriminative power for Qave, Vtime, and TQmax, with AUC values of 0.71 ($p < 0.001$), 0.62 ($p < 0.001$) and 0.55 ($p = 0.03$), respectively. Therefore, these parameters have clinical applicability and may complement Qmax for predicting infravesical obstruction. The benefit can be more evident in cases of Qmax located in the "gray zone" between 10 ml/s and 15 ml/s or cases with misleading symptomatology. For instance, for a patient with prostatic enlargement, voiding symptoms, and Qmax of 14 ml/s, the obstruction diagnosis will be more plausible if Qave is lower than 5 ml/s and TQmax is higher than 16 seconds. In another hypothetical case, a patient with a 30 ml prostate, storage symptoms, no voiding symptoms, and Qmax of 9 ml/s will be more likely diagnosed with infravesical obstruction if Qave is lower than 5ml/s and Vtime is greater than 50 seconds.

The present study has strengths and limitations. Each group included more than 200 patients, which is proper to estimate any AUC with a marginal error of 0.07[30]. We excluded cases with evacuated volumes lower than 150 ml or higher than 500 ml to prevent non-representative results[4]. LinPUR 2 patients were excluded to get a clear contrast between the obstructive pattern group and the non-obstructive group pattern: there was a statistically significant difference between the groups in terms of flowmetric parameters, PdetQmax, and PVR. Limitations that need to be mentioned are 1) its retrospective nature carried a higher risk of selection and information bias; 2) the precision could be affected because only one free flowmetry was done instead of several different measurements; 3) we did not include clinical and imaging variables that would have enriched the obstruction diagnosis, such as the International Prostate Symptom Score and the ultrasound measurement of intravesical protrusion and detrusor thickness[8]; finally, 4) the sample size of 211 patients in each group might not have the power to find differences lower than 10% between areas of the ROC curves[30].

Conclusion

Our study demonstrated that Qave, Vtime, and TQmax have a statistically significant discriminatory power to predict infravesical obstruction and complement the information provided by Qmax. Although Qmax is the flowmeter variable with the best area under the ROC curve, in daily practice, the clinician should interpret the flowmetry by evaluating all the flowmetry variables and not just Qmax.

Funding

This research has not received any specific grants from public, commercial, or for-profit sector agencies.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

References

1. Homma Y, Gotoh M, Kawauchi A, Kojima Y, Masumori N, Nagai A, et al. Clinical guidelines for male lower urinary tract symptoms and benign prostatic hyperplasia. Int J Urol. 2017;24(10):716–29.
2. Gratzke C, Bachmann A, Descazeaud A, Drake MJ, Madersbacher S, Mamoulakis C, et al. EAU guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol. 2015;67(6):1099–109.
3. Foster HE, Dahm P, Kohler TS, Lerner LB, Parsons JK, Wilt TJ, et al. Surgical Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA Guideline Amendment 2019. J Urol. 2019;202(3):592–8.
4. Gammie A, Drake MJ. The fundamentals of uroflowmetry practice, based on International Continence Society good urodynamic practices recommendations. Neurourol Urodyn. 2018;37(April):S44–9.
5. Gammie A, Rosier P, Li R, Harding C. How can we maximize the diagnostic utility of uroflow?: ICI-RS 2017. Neurourol Urodyn. 2018;37(November):S20–4.
6. Onyishi SE, Twiss CO. Pressure flow studies in men and women. Urol Clin North Am. 2014;41(3):453–67.
7. Nitti VW. Pressure flow urodynamic studies: the gold standard for diagnosing bladder outlet obstruction. Rev Urol. 2005;7 Suppl 6:S14–21.

8. Malde S, Nambiar AK, Umbach R, Lam TB, Bach T, Bachmann A, et al. Systematic Review of the Performance of Noninvasive Tests in Diagnosing Bladder Outlet Obstruction in Men with Lower Urinary Tract Symptoms. Eur Urol. 2017;71(3):391–402.
9. Reynard JM, Yang Q, Donovan JL, Peters TJ, Schafer W, De La Rosette JJMCH, et al. The ICS-'BPH' Study: Uroflowmetry, lower urinary tract symptoms and bladder outlet obstruction. Br J Urol. 1998;82(5):619–23.
10. Agarwal M, Choudhury S, Mandal A, Mavuduru R, Singh S. Are urine flow-volume nomograms developed on Caucasian men optimally applicable for Indian men Need for appraisal of flow-volume relations in local population. Indian J Urol. 2010;26(3):338–44.
11. Agarwal MM, Patil S, Roy K, Bandawar M, Choudhury S, Mavururu R, Sharma SK, et al. Rationalization of interpretation of uroflowmetry for a non-caucasiona (Indian) population: conceptual development and validation of volume-normalized flow rate index. Neurourol Urodyn. 2014;33: 135–41.
12. Nishimoto K, Iimori H, Ikemoto S, Hayahara N. Criteria for differentiation of normal and abnormal uroflowmetrograms in adult men. Br J Urol. 1994;73(5):494–7.
13. Nishimoto K, Tashiro K, Yoshida N, Harimoto K, Nishikasa K, Tanaka T, et al. Study on the relation of the shape of the uroflowmetrogram and the uretrhal loss coefficient calculated from the uroflowmetrogram. Hinyokika Kiyo. 2006;52:7–10.
14. Karl C, Gerlache R, Hannappel J, Lehnen H. Uroflow measurements: Their information yield in a long-term investigation of pre-and postoperative measurements. Urol Int. 1986;41(4):270–5.
15. Jarvis TR, Tse V, Chan L, Tse V. Practical uroflowmetry BJU Int. 2012; 101 Suppl 4:28–9.
16. Reynard JM, Lim C, Abrams P. Significance of intermittency in men with lower urinary tract symptoms. Urology. 1996;47(4):491–6.
17. Rosier PFWM, Schaefer W, Lose G, Goldman HB, Guralnick M, Eustice S, et al. International continence society good urodynamic practices and terms 2016: Urodynamics, uroflowmetry, cystometry, and pressure-flow study. Neurourol Urodyn. 2017;36(5):1243–60.
18. Schafer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spangberg A, et al. Good Urodynamic Practices: Uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn. 2002;21(3):261–74.
19. Sekido N. Bladder contractility and urethral resistance relation: What does a pressure flow study tell us? Int J Urol. 2012;19(3):216–28.
20. Veeratterapillay R, Pickard RS, Harding C. The role of uroflowmetry in the assessment and management of men with lower urinary tract symptoms - revisiting the evidence. J Clin Urol. 2014;7(3):154–8.
21. Reynard JM, Peters TJ, Lim C, Abrams P. The value of multiple free-flow studies in men with lower urinary tract symptoms. Br J Urol. 1996;77(6):813–8.
22. Chan CK, Yip SKH, Wu IPH, Li ML, Chan NH. Evaluation of the clinical value of a simple flowmeter in the management of male lower urinary tract symptoms. BJU Int. 2012;109(11):1690–6.
23. Bray A, Harding C, Pickard R, Drinnan M. Individualized volume-corrected maximum flow rate correlates with outcome from bladder outlet surgery in men with lower urinary tract symptoms. Int J Urol. 2016;23(7): 587–92.
24. Haylen BT, Maximum and Average Urine Flow Rates in Normal Male and Female Populations—the LiverposI Nomograms. Br J Urol. 1989;64(1):30–8.
25. Siroky MB, Olsson CA, Krane RJ. The flow rate nomogram: I. Development. J Urol. 1979;122(5):665–8.
26. Shoukry I, Susset JG, Elhilali MM, Dutartre D. Role of Uroflowmetry in the Assessment of Lower Urinary Tract Obstruction in Adult Males. Br J urol. 1975;47: 559–66.
27. Oelke M, Höfner K, Jonas U, de la Rosette JJ, Ubbink DT, Wijkstra H. Diagnostic Accuracy of Noninvasive Tests to Evaluate Bladder Outlet Obstruction in Men: Detrusor Wall Thickness, Uroflowmetry, Postvoid Residual Urine, and Prostate Volume. Eur Urol. 2007;52(3):827–35.
28. VanderBrink BA, Gitlin J, Palmer LS. Uroflowmetry Parameters Before and After Meatoplasty for Primary Symptomatic Meatal Stenosis in Children. J Urol. 2008;179(6):2403–6.
29. Shimizu K, Takahashi Y, Nakai K, et al. A new method of analysing uroflowmetric studies in low voided volumen males with obstructive diseases of the lower urinary tract. Jpn J Urol. 1984; 75:1964–9.
30. Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. J Biomed Inform. 2014; 48:193–204.

REVISTA UROLOGÍA COLOMBIANA

PERMANYER

Check for updates

ARTÍCULO DE REVISIÓN

Manejo del cáncer de vejiga invasor de músculo con enfoque preservador de órgano: terapia trimodal

Management of muscle-invasive bladder cancer with an organ-sparing approach: trimodal therapy

Carlos H. Abonía-Velasco[1,2] y Herney A. García-Perdomo[3,4]*

[1]Unidad de Urología, Departamento de Cirugía, Universidad Nacional de Colombia, Bogotá D.C; [2]Grupo de Investigación e Innovación en Urología, Universidad Nacional de Colombia, Bogotá D.C; [3]Unidad de Urología y Urooncología, Departamento de Cirugía, Escuela de Medicina, Universidad del Valle, Cali; [4]Grupo de investigación UROGIV, Escuela de Medicina, Universidad del Valle, Cali. Colombia

Resumen

Introducción: *El cáncer de vejiga es una patología frecuente del tracto genitourinario, cuyo tratamiento acarrea morbilidad y alteración de la calidad de vida y en particular en el subgrupo de pacientes con tumores vesicales clasificados como invasores de músculo. En los últimos años se han venido buscando alternativas terapéuticas para la cistectomía radical + linfadenectomía pélvica extendida, que es en la actualidad el estándar de manejo para los pacientes con carcinoma de vejiga invasor de músculo. Con el advenimiento de perfiles de manejo oncológico menos ablativos pero sin sacrificar resultados oncológicos y con las nuevas técnicas de radioterapia y quimioterapia, las modalidades terapéuticas preservadoras de órgano como la terapia trimodal (resección transuretral de tumor vesical + quimioterapia + radioterapia) se convierte en una alternativa terapéutica viable y con resultados oncológicos satisfactorios a largo plazo.* **Objetivo y metodología:** *Con esta revisión se pretende mostrar la actualidad de la terapia trimodal en el manejo de los tumores vesicales con invasión muscular, definir los mejores pacientes a considerar para recibir esta terapia, exponer los resultados oncológicos comparados con el estándar de manejo y los resultados en calidad de vida. También se propone un algoritmo de manejo y se presentar las recomendaciones al respecto en guías de práctica clínica.* **Conclusiones:** *La terapia trimodal es una alternativa al estándar de manejo que conduce a resultados oncológicos aceptables y puede considerarse una opción de tratamiento en pacientes bien seleccionados.*

Palabras clave: *Terapia trimodal. Cáncer de vejiga invasor de músculo. Cistectomía radical. Resección transuretral. Radioterapia. Quimioterapia.*

Abstract

Introduction: *Bladder cancer is a frequent pathology of the genitourinary tract, whose treatment causes morbidity and impaired quality of life, particularly in the subgroup of patients with bladder tumors classified as muscle invaders. In recent years, therapeutic alternatives have been sought for radical cystectomy + extended pelvic lymphadenectomy, which is currently the standard of care for patients with muscle-invasive bladder carcinoma. With the advent of less ablative oncological management profiles but without sacrificing oncological results and with new radiotherapy and chemotherapy techniques, organ-sparing therapeutic modalities such as trimodal therapy (transurethral resection of bladder tumor + chemotherapy + radiotherapy)*

***Correspondencia:**
Herney A. García-Perdomo
E-mail: herney.garcia@correounivalle.edu.co

Fecha de recepción: 14-01-2023
Fecha de aceptación: 19-01-2023
DOI: 10.24875/RUC.23000007

Disponible en internet: 23-03-2023
Urol. Colomb. 2023;32(1):09-14
www.urologiacolombiana.com

becomes a viable therapeutic alternative with satisfactory long-term oncological results. **Objective and methodology:** *This review aims to show the current status of trimodal therapy in the management of muscle-invasive bladder tumors, define the best patients to consider for receiving this therapy, present the oncological results compared with the management standard and the results in quality of life. A management algorithm is also proposed and recommendations in this regard are presented in clinical practice guidelines.* **Conclusions:** *Trimodal therapy is an alternative to standard management that leads to acceptable oncological outcomes and can be considered a treatment option in well-selected patients.*

Keywords: *Trimodal therapy. Muscle-invasive bladder cancer. Radical cystectomy. Transurethral resection. Radiotherapy. Chemotherapy.*

Introducción

El cáncer de vejiga es una de las neoplasias más frecuentes del tracto urinario, con un estimado de 80.500 nuevos casos y 17.600 muertes durante el 2019 en los EE.UU.[1,2]. Es la novena malignidad más común en el mundo y la cuarta más común en hombres, con una relación hombre:mujer 3-4:1[1-3].

Al diagnóstico, aproximadamente en el 25% de los pacientes con cáncer de vejiga estos se presentan como invasores de músculo[2]. Actualmente, la cistectomía radical (CR) en conjunto con la linfadenectomía pélvica extendida se consideran como la terapia estándar para el tratamiento del cáncer de vejiga invasor de músculo (MIBC, por sus siglas en inglés)[1,3,4]. Sin embargo, algunos pacientes no están dispuestos o no son aptos para este procedimiento, y la preservación de la vejiga se convierte en su opción preferida[1].

El objetivo de este manuscrito fue realizar una revisión de la información más reciente respecto a la terapia trimodal (TTM) como una opción de tratamiento de preservación vesical, en los pacientes con MIBC.

Métodos

Para identificar la información relevante publicada, se realizó una búsqueda en PubMed, utilizando combinaciones únicas o diferentes de las siguientes palabras clave: *trimodal therapy, trimodal therapy for bladder cancer, bladder preservation, bladder preserving therapy* y *bladder sparing therapy*. Inicialmente, los artículos se revisaron por título y resumen para identificar publicaciones adecuadas para la revisión de texto completo; se seleccionaron los artículos en inglés publicados en los últimos 10 años. Se excluyeron editoriales y reportes de casos.

¿Qué es la terapia trimodal?

La TTM se define como aquella que combina resección transuretral del tumor vesical (RTUV) completa más quimioterapia radiosensibilizante y radioterapia (RT). El objetivo es la preservación de la vejiga sin comprometer el resultado oncológico en pacientes no aptos para cistectomía o que no desean cistectomía[1,5,6].

En general, hay dos poblaciones de pacientes distintas a las que se les ofrece TTM, aquellos que no son aptos para la cistectomía y aquellos que la rechazan. Estos grupos tienen resultados muy diferentes. Los pacientes que no son elegibles para CR en general tienen opciones de tratamiento limitadas. Para estos pacientes, la TTM ofrece el mejor enfoque curativo; sin embargo, su supervivencia depende en gran medida de sus comorbilidades iniciales, la enfermedad avanzada al diagnóstico y la incapacidad para recibir quimioterapia basada en cisplatino. La segunda población de pacientes consiste a menudo en pacientes más jóvenes y con menor comorbilidad, que son elegibles para CR pero que desean firmemente un enfoque de conservación de la vejiga; sus resultados son generalmente más favorables[6].

Resección transuretral del tumor vesical

La RTUV visualmente completa es el predictor más fuerte tanto del control oncológico como del éxito de la TTM. Con un aumento documentado del 20% en la respuesta completa y la preservación de la vejiga a largo plazo en aquellos que reciben RTUV completa. El beneficio terapéutico de la RTUV probablemente sea secundario a la resección directa de toda la enfermedad con invasión muscular fácilmente identificable. También puede estar relacionada con un impacto en la agresividad de la enfermedad[7]. En diferentes series se ha demostrado que la RTUV visiblemente completa se asoció con una tasa significativamente más alta de respuesta completa (79%) comparado con un 57% sin ella[8-10].

Radioterapia

Se ha evaluado la RT para MIBC desde la década de 1980, con tasas de respuesta completa después de

RT sola de alrededor del 30% y tasas de supervivencia global (OS, por sus siglas en inglés) a 3 y 5 años de ~50 y 20-45%. Para mejorar estos resultados, en la década de 1990 se utilizó un radiosensibilizador para que las células tumorales fueran más sensibles a la RT. Convencionalmente, los quimioterápicos incluían las fluoropirimidinas, la gemcitabina y los análogos del platino. En la actualidad se considera la quimiorradiación como el tratamiento estándar para TTM en MIBC[11].

Aunque el estándar histórico corresponde a técnicas de RT conformada tridimensional, actualmente la RT de intensidad modulada es común y puede ser útil en la mejor cobertura de los lugares que irradiar y disminuyendo la dosis de órganos adyacentes en riesgo[12,13].

La dosis total de radiación usual es de 64-65 Gy con fracciones diarias de 1.8 a 2.0 Gy. En la mayoría de los estudios del *Radiation Therapy Oncology Group* (RTOG) se utiliza una RT de intervalo con una fase de inducción de 40 Gy seguida por una evaluación por cistoscopia. En caso de evidenciarse una respuesta clínica completa se realiza un curso de radiación de consolidación hasta completar la dosis total (mayor de 60 Gy). Sin embargo, por la desventaja radiobiológica de permitir repoblación de células tumorales, por la interrupción del tratamiento, muchos centros se encuentran realizando un curso continuo único de RT[12].

Quimioterapia

La quimioterapia funciona tanto como agente radiosensibilizador como en el tratamiento sistémico de cualquier enfermedad micrometastásica[14]. No existe un régimen de quimioterapia estándar. Sin embargo, la basada en cisplatino, establecida por el Instituto Nacional del Cáncer de Canadá (NCIC) y el RTOG es el agente más utilizado. Otro de los regímenes quimioterapéuticos utilizados es 5-fluorouracilo (5-FU) + mitomicina C (MMC). Además, la gemcitabina en dosis bajas es otra alternativa y se tolera bien[15]. Los enfoques alternativos, particularmente para los pacientes que no son elegibles para la quimioterapia concurrente basada en cisplatino o la rechazan, incluyen gemcitabina o paclitaxel como agente único[12]. Si bien el beneficio oncológico de la quimioterapia neoadyuvante antes de la CR en pacientes con MIBC es claro, esta relación puede no ser cierta para los pacientes que se someten a preservación vesical con TTM[7]. Fahmy et al. mostraron resultados similares cuando compararon quimioterapia neoadyuvante + TTM vs. TTM sola; respuesta completa (76,2 frente a 73,0%; p = 0,33), supervivencia cáncer-específica (CSS por sus siglas en inglés) (72,4 vs. 62,2%; p = 0,13) y OS a cinco años (53,8 frente a 50,4%; p = 0,078)[16].

El beneficio de la quimioterapia concurrente en TTM se ha demostrado en dos ensayos prospectivos aleatorizados. El primero asignó al azar a 99 pacientes a RT con o sin cisplatino semanal simultáneo, las tasas de fracaso se redujeron del 59 al 40% a los cinco años (p = 0,038). El segundo, BC2001, asignó al azar a 360 pacientes a RT con o sin 5-FU y MMC concurrentes, la quimioterapia concurrente mejoró significativamente la supervivencia libre de enfermedad (*hazard ratio* [HR]: 0,68, a favor de la quimioterapia simultánea; p = 0,03)[12].

Respuesta de la terapia trimodal y costos

La selección cuidadosa de los pacientes es de suma importancia para la aplicación segura y exitosa de esta opción terapéutica. Las tasas de respuesta tumoral completa y supervivencia logradas con la TTM fueron similares a las de cohortes sometidas a CR (60-80%)[15].

La CSS y OS a cinco años fue del 50-82% y 36-74%, respectivamente. Con tasas de cistectomía de rescate del 10 al 30%. Las recurrencias no invasivas después de TTM se encuentran alrededor del 25%. En caso de cistectomía de rescate, las tasas de complicaciones mayores no aumentan[5].

Ding et al.[1] compararon la diferencia entre TTM y CR. Analizaron 5.721 pacientes del grupo TTM y 48.262 pacientes del grupo CR. En este estudio se reportó que la TTM no es inferior a la cistectomía en < 10 años de OS. De igual manera, Tseng et al.[17] encontraron que no hubo diferencias significativas entre la CR y la TTM en la OS a cinco años.

Por otro lado, Gofrit et al.[4] incluyeron 105 pacientes tratados con TTM con tumores de vejiga T2-T4aN0M0. Se les realizó RTUV completa más quimioterapia con cisplatino 40 mg/m^2 semanales y en pacientes con función renal comprometida se usó carboplatino semana más RT de intensidad modulada (IMRT) de intervalo. Los resultados obtenidos fueron que el diámetro del tumor (< 3 cm) antes de la RTUV es el mejor predictor preoperatorio de la respuesta a la TTM y la combinación del diámetro del tumor con la elegibilidad para cisplatino crea un poderoso perfil predictivo.

García-Perdomo et al.[18] realizaron un metaanálisis con el objetivo de determinar la efectividad de la TTM como tratamiento de primera línea; se analizaron 39.836 pacientes tratados con CR y 4.198 tratados con TTM. Se encontró que no hubo diferencias en la OS

ni en la supervivencia libre de progresión. En cuanto a la CSS, favoreció a la CR.

Con respecto a los costos asociados, Williams et al.[19] encontraron que la TTM se asoció con una OS (HR: 1,49; intervalo de confianza del 95% [IC 95%]: 1,31-1,69) y una CSS inferiores (HR: 1,55; IC 95%: 1,32-1,83), junto con un gasto superior (USD$ 63.771 a los 180 días). Además, se identificó que la TTM tuvo un costo medio mayor ($136.935 (IC 95%: $122.131-$152.115)) comparado con la CR un año después del diagnóstico. La atención ambulatoria, la radiología, los gastos de medicamentos y los costos de patología/laboratorio contribuyeron en gran medida a los costos más altos asociados con la TTM[20].

Toxicidad y calidad de vida

La TTM se tolera bien, con tasas de finalización del 80 a 90%. La toxicidad aguda se produce en el 10-36% de los pacientes. En un análisis de cuatro ensayos del RTOG con una mediana de seguimiento de 5,4 años, el 7% de los pacientes experimentó toxicidad de grado 3 a largo plazo, el 5,7% de toxicidad urinaria y el 1,9% de toxicidad gastrointestinal[6,21]. En cuanto a la calidad de vida, no está bien dilucidado su impacto en la literatura, pero es probable que la TTM sea superior en calidad de vida[6], esto se debe en gran medida a la capacidad de los pacientes para conservar sus vejigas nativas[21].

¿Cuáles son los pacientes elegibles para la terapia trimodal?

La selección de pacientes es de suma importancia para el éxito de la TTM[22]. La OS y CSS a cinco años en pacientes tratados con TTM oscilan entre el 36-74% y 50-82%, respectivamente. Es probable que este rango se deba al diseño de los estudios, los criterios de inclusión/exclusión y la duración del seguimiento[7].

Múltiples centros han mostrado mejores resultados a medida que refinaron sus criterios de selección. Giacalone et al. mejoraron la OS a cinco años del 53 al 75% y disminuyeron su tasa de cistectomía de rescate del 29 al 16% al ser más selectivos (100% sin hidronefrosis, 97% cT2, 82% tenían RTUV completa, 81% sin CIS). En el análisis multivariante el estadio T2 (HR: 0,57), la respuesta completa a la quimiorradiación (HR: 0,61), la hidronefrosis (HR: 1,51) y la presencia de CIS (HR: 1,56) fueron predictores de una mejor OS[22].

Tabla 1. Criterios de selección para la terapia trimodal (TTM)

Paciente ideal para TTM*	Paciente no ideal para TTM (características de alto riesgo)
cT2	cT3-cT4a
RTUV completa	Imposibilidad de realizar RTUV completa
No hidronefrosis	Presencia de hidronefrosis
No CIS	Presencia de CIS
Tumor unifocal	Enfermedad multifocal
Función y capacidad vesical adecuada	

*Para ser considerado un TTM ideal, todas las características deben estar presentes y no tener características de alto riesgo.
RTUV: resección transuretral de tumor vesical; CIS: carcinoma *in situ*.
Adaptada de Tholomier et al., 2020[22].

Se han definido un conjunto de características que convierten a un paciente en ideal o no ideal para TTM (Tabla 1)[15,22,23].

Seguimiento

Se propone el siguiente esquema de seguimiento[6]:

- Cistoscopias:
  - Cada tres meses durante uno a dos años.
  - Luego cada seis meses durante los siguientes dos años.
  - Luego anualmente.
- Citología urinaria:
  - Se puede utilizar como complemento de la cistoscopia.
- Imágenes:
  - Tomografía computarizada de tórax, abdomen y pelvis cada tres a seis meses durante dos años.
  - Luego a intervalos crecientes, o según esté clínicamente indicado.

Recomendaciones de las guías de práctica clínica

European Association of Urology (EAU)-European Society for Medical Oncology (ESMO)[5]

- En una población de pacientes muy seleccionada, las tasas de supervivencia a largo plazo del tratamiento multimodal son comparables con las de la cistectomía temprana.
- Un determinante importante para la elegibilidad del paciente en caso de tratamiento conservador de la vejiga es la ausencia de carcinoma *in situ*.

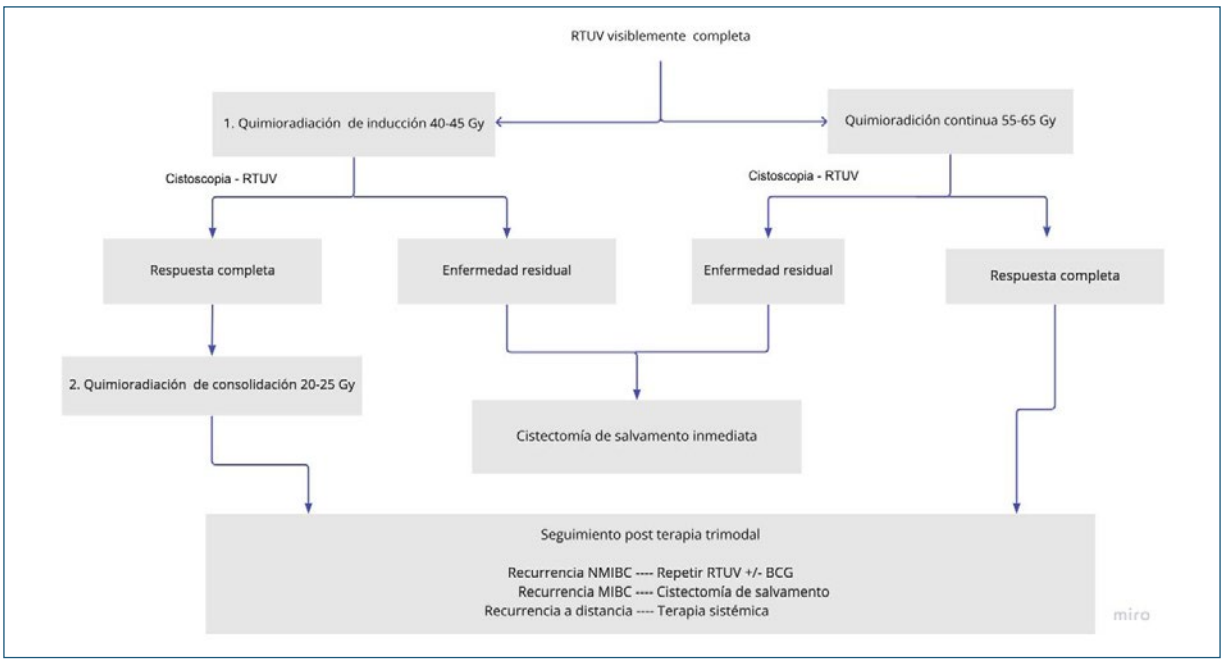


Figura 1. Algoritmo propuesto en la literatura para la terapia trimodal.

*2 Gy/día dirigida a la vejiga y ganglios pélvicos.
RTUV: resección transuretral de tumor vesical; NMIBC: cáncer de vejiga no invasor de músculo; MIBC: cáncer de vejiga invasor de músculo; BCG: bacilo de Calmette-Guerin.

- Un determinante importante para la elegibilidad del paciente en caso de tratamiento de preservación de la vejiga es la ausencia de hidronefrosis.
- Al evaluar la elegibilidad del paciente para la preservación de la vejiga, se debe tener en cuenta la probabilidad de éxito de la cirugía de citorreducción (reducción óptima).
- En caso de preservación vesical con RT, siempre se recomienda la combinación con un radiosensibilizador para mejorar los resultados clínicos, como cisplatino, 5-FU/MMC, carbógeno/nicotinamida o gemcitabina.
- La RT para la preservación de la vejiga se debe realizar con IMRT o radioterapia guiada por imágenes para reducir los efectos secundarios.

Canadian Urological Association (CUA)[24]

- La TTM se puede ofrecer a pacientes seleccionados que no acepten el manejo con la cistectomía radical + linfadenectomía pélvica extendida y/o aquellos que no sean aptos para la cistectomía (Nivel de evidencia [NE] 3, recomendación moderada).
- Las características ideales del tumor y del paciente para TTM son las siguientes: pequeño (< 5 cm), unifocal, sin CIS, sin hidronefrosis, buena función vesical, paciente motivado para la preservación de la vejiga (NE 3, recomendación moderada).
- Con TTM, se debe realizar una RTUV máxima/radical para eliminar todo el tumor visible antes de iniciar la quimiorradiación (NE 3, recomendación moderada).
- La RT como monoterapia en el tratamiento de MIBC localizado solo es aceptable en pacientes que no son elegibles para CR y quimioterapia. De lo contrario, la radiación debe ofrecerse en combinación con cisplatino o quimioterapia con 5-FU/MMC (NE 1, recomendación fuerte) o gemcitabina (NE 2, recomendación fuerte).
- Actualmente no existe un papel bien definido para la RT neoadyuvante o adyuvante en el contexto de MIBC localizado (NE 3, recomendación moderada).

Conclusiones

Ante las tendencias actuales del manejo oncológico menos intervencionista, la TTM es una alternativa al estándar de manejo que conduce a resultados oncológicos aceptables y puede considerarse una opción de tratamiento en pacientes bien seleccionados.

Esta estrategia multimodal de preservación de la vejiga requiere una cooperación multidisciplinaria estrecha y una adecuada adherencia por parte del paciente.

Financiamiento

La presente investigación no ha recibido ninguna beca específica de agencias de los sectores públicos, comercial o con ánimo de lucro.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que en este artículo no aparecen datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

Bibliografía

1. Ding H, Fan N, Ning Z, Ma D. Trimodal therapy vs. radical cystectomy for muscle-invasive bladder cancer: A meta-analysis. Front Oncol. 2020;10:564779.
2. Hurle R, Casale P, Morenghi E, Saita A, Buffi N, Lughezzani G, et al. Intravesical gemcitabine as bladder-preserving treatment for BCG unresponsive non-muscle-invasive bladder cancer. Results from a single-arm, open-label study. BJUI Compass. 2020;1(4):126-32.
3. Polo-Alonso E, Kuk C, Guruli G, Paul AK, Thalmann G, Kamat A, et al. Trimodal therapy in muscle invasive bladder cancer management. Minerva Urol Nefrol. 2020;72(6):650-62.
4. Gofrit ON, Meirovitz A, Frank S, Rabinovich I, Luwisch H, Yutkin V, et al. Trimodal therapy in T2-4aN0M0 bladder cancer--How to select the best candidate? Cancer Med. 2020;9(22):8491-7.
5. Witjes JA, Bruins HM, Cathomas R, Compérat EM, Cowan NC, Gakis G, et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. Eur Urol. 2021;79(1):82-104.
6. Jiang DM, Chung P, Kulkarni GS, Sridhar SS. Trimodality therapy for muscle-invasive bladder cancer: Recent advances and unanswered questions. Curr Oncol Rep. 2020;22(2):14.
7. Russell CM, Lebastchi AH, Borza T, Spratt DE, Morgan TM. The role of transurethral resection in trimodal therapy for muscle-invasive bladder cancer. Bladder Cancer. 2016;2(4):381-94.
8. Mak RH, Hunt D, Shipley WU, Efstathiou JA, Tester WJ, Hagan MP, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: A pooled analysis of Radiation Therapy Oncology Group Protocols 8802, 8903, 9506, 9706, 9906, and 0233. J Clin Oncol. 2014;32(34):3801-9.
9. Rödel C, Grabenbauer GG, Kühn R, Papadopoulos T, Dunst J, Meyer M, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: Long-term results. J Clin Oncol. 2002;20(14):3061-71.
10. Efstathiou JA, Spiegel DY, Shipley WU, Heney NM, Kaufman DS, Niemierko A, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: The MGH Experience. Eur Urol. 2012;61(4):705-11.
11. Kimura T, Ishikawa H, Kojima T, Kandori S, Kawahara T, Sekino Y, et al. Bladder preservation therapy for muscle invasive bladder cancer: the past, present and future. Jpn J Clin Oncol. 2020;50(10):1097-107.
12. Konieczkowski DJ, Efstathiou JA, Mouw KW. Contemporary and emerging approaches to bladder-preserving trimodality therapy for muscle-invasive bladder cancer. Hematol Oncol Clin North Am. 2021;35(3):567-84.
13. Pham A, Ballas LK. Trimodality therapy for bladder cancer. Curr Opin Urol. 2019;29(3):210-5.
14. Lenis AT, Lec PM, Chamie K, MSHS M. Bladder cancer. JAMA. 2020;324(19):1980.
15. Mathes J, Rausch S, Todenhöfer T, Stenzl A. Trimodal therapy for muscle-invasive bladder cancer. Expert Rev Anticancer Ther. 2018;18(12):1219-29.
16. El-Achkar A, Souhami L, Kassouf W. Bladder preservation therapy: Review of literature and future directions of trimodal therapy. Curr Urol Rep. 2018;19(12):108.
17. Tseng WH, Huang S, Liu CL, Kuo JR, Hun SH, Chen CH, et al. Comparison of trimodal therapy versus radical cystectomy for each stage of muscle-invasive bladder cancer. Urol Sci. 2021;32(4):164.
18. García-Perdomo HA, Montes-Cardona CE, Guacheta M, Castillo DF, Reis LO. Muscle-invasive bladder cancer organ-preserving therapy: systematic review and meta-analysis. World J Urol. 2018;36(12):1997-2008.
19. Williams SB, Shan Y, Jazzar U, Mehta HB, Baillargeon JG, Huo J, et al. Comparing survival outcomes and costs associated with radical cystectomy and trimodal therapy for older adults with muscle-invasive bladder cancer. JAMA Surg. 2018;153(10):881.
20. Williams SB, Shan Y, Ray-Zack MD, Hudgins HK, Jazzar U, Tyler DS, et al. Comparison of costs of radical cystectomy vs. trimodal therapy for patients with localized muscle-invasive bladder cancer. JAMA Surg. 2019;154(8):e191629.
21. Hamad J, McCloskey H, Milowsky MI, Royce T, Smith A. Bladder preservation in muscle-invasive bladder cancer: a comprehensive review. International Braz J Urol. 2020;46(2):169-84.
22. Tholomier C, Souhami L, Kassouf W. Bladder-sparing protocols in the treatment of muscle-invasive bladder cancer. Transl Androl Urol. 2020;9(6):2920-37.
23. Feldman AS, Kulkarni GS, Bivalacqua TJ, Black PC, Delacroix S, Lerner SP, et al. Surgical challenges and considerations in Tri-modal therapy for muscle invafigsive bladder cancer. Urol Oncol. 2022;40(10):442-50.
24. Kulkarni GS, Black PC, Sridhar SS, Kapoor A, Zlotta AR, Shayegan B, et al. Canadian Urological Association guideline: Muscle-invasive bladder cancer. Can Urol Assoc J. 2019;13(8):230-8.

REVISTA UROLOGÍA COLOMBIANA

PERMANYER

Check for updates

REVIEW ARTICLE

Metabolic studies and calculi analysis in urinary lithiasis, how to stop recurrence?

Estudios metabólicos y análisis del cálculo en litiasis urinaria, ¿cómo detener la recurrencia?

Catalina Barco-Castillo[1,2], Camila Uribe[2], Angela Bohórquez[3], Carlos Gustavo Trujillo[1,2], and Adolfo Serrano[1,2]*

[1]Department of Urology, Hospital Universitario Fundación Santa Fe de Bogotá; [2]School of Medicine, Universidad de los Andes; [3]Nutrition Program, Hospital Universitario Fundación Santa Fe de Bogotá. Bogota DC, Colombia

Resumen

La litiasis urinaria es la consulta urológica más frecuente para la sala de emergencias debido al cólico renoureteral. Las complicaciones incluyen hematuria, anuria debido a la obstrucción bilateral o unilateral en el riñón solitario y la sepsis. La recurrencia ocurre en hasta el 50% de los pacientes después de 5 años desde el primer episodio, y aquellos paciente requieren estudios metabólicos y análisis del cálculo. El manejo farmacológico y las modificaciones dietéticas evitarán nuevos episodios. Nuestro objetivo es describir cada trastorno metabólico asociado con su respectivo tipo de cálculo y su manejo basado en la prevención de la recurrencia de la litiasis urinaria.

Palabras clave: *Litiasis urinaria. Cólico renoureteral. Recurrencia. Prevención. Estudios metabólicos. Análisis del cálculo.*

Abstract

Urinary lithiasis is the most frequent urological consultation to the emergency room due to renoureteral colic. Complications include hematuria, anuria due to bilateral or unilateral obstruction in solitary kidney, and sepsis. Recurrence occurs in up to 50% of patients after 5 years from the first episode, and those will need metabolic studies and calculi analysis. Pharmacological management and dietary measures will prevent new episodes. We aim to describe each metabolic disorder associated with its respective type of calculi, and its management based on prevention of recurrence of urinary lithiasis.

Keywords: *Urinary lithiasis. Renal colic. Recurrence. Prevention. Metabolic work-up. Calculi analysis.*

***Correspondence:**
Catalina Barco-Castillo
E-mail: c.barco2320@uniandes.edu.co

Fecha de recepción: 20-12-2022
Fecha de aceptación: 19-01-2023
DOI: 10.24875/RUC.22000003

Disponible en internet: 23-03-2023
Urol. Colomb. 2023;32(1):15-22
www.urologiacolombiana.com

Introduction

Lithiasis of the urinary tract is one of the most frequent urological pathologies, with a prevalence that reaches up to 10% in developed countries in the general population[1,2]. Comparing by sex, up to 16% of men and 8% of women will develop at least one episode of renoureteral colic in their lives[3]. Moreover, of those patients who have presented a first episode, 11 to 39% will present a recurrence in the following 2 to 15 years, a figure that increases to 56% in patients with personal risk factors for urolithiasis[4].

The prevalence and recurrence of this pathology contributes to a high socioeconomic impact associated with treatment costs and work days lost[5]. In the United States, in the year 2000 alone, the disease burden had an estimated annual cost of 5 billion US dollars, a figure that doubled in 2012 and will be estimated at 15 billion dollars by 2030[6–8].

Currently, the prevalence of urinary lithiasis has increased from 3.2% in 1980 to 5.2% in 1994 and to 8.8% in 2010[1]. This increase is closely related to dietary changes including a rise in consumption of animal protein, salt, carbonated beverages and high fructose foods[3,4]. Also, climate change and global warming might be contributing.

Several extrinsic and intrinsic factors are associated with urinary tract lithogenesis. Among the extrinsic factors are geographical location and weather, with a higher prevalence of lithiasic disease in arid, dry, and tropical regions[9]. There is also an increased risk in those working in environments with high temperatures (e.g. kitchens and machine rooms) or have sedentary jobs[9]. Diet is another influential factor, since a high consumption of sodium, animal protein, and foods high in fructose/sucrose, as well as low water intake, all increase the risk of calculi[10].

Consistent with the factors outlined previously, populations located at lower latitudes are at greater risk of urolithiasis than those at higher latitudes[8]. This variation in prevalence according to geographical location has been associated with higher ambient temperature and sun exposure[1], causing high levels of dehydration. Furthermore, within each region there are variations in disease pattern associated to seasonal changes, presenting a higher prevalence during the summer[1,8]. Thus, with the rising concern of climate change, urolithiasis prevalence is predicted to increase in susceptible populations from 40% in the year 2000 to 56 and 70% for the years 2050 and 2095, respectively[8].

Moreover, there are modifiable risk factors associated with over half of documented urolithiasis cases: body mass index (BMI) greater than 25 Kg/m^2, daily fluid intake less than 2 liters, inadequate consumption of fruits and vegetables, and consumption of more than four servings of sugary drinks per week[11]. Nonetheless, these factors may be mitigated by other factors shown to have a protective effect, such as the adequate dietary intake of calcium, potassium and natural diuretic drinks such as coffee and tea[12], suggesting that lithiasic disease of the urinary tract has a high potential for prevention.

Regarding intrinsic factors, the maximum incidence of urolithiasis has been reported in individuals between 20 and 60 years of age, with an average age of diagnosis of 44.8 years in men and 40.9 in women[1,9]. There is also a documented male predominance worldwide, with an overall ratio of 1.5-2.5 men for each affected woman[8,9]. However, this difference has decreased in recent years from 3.1:1 to 1.3:1 associated with lifestyle homogenization between sexes[1]. Moreover, an increase in metabolic syndrome, obesity and diabetes has also been shown to play an important contributing factor in both sexes[1].

High-risk patients for this disease are defined as those having an increased chance of recurrence or growth of existing calculi. Therefore, these patients should be considered candidates for preventive pharmacologic therapy (Table 1)[13]. The risk of recurrence depends on both the type of stone and disease severity.

This review of the literature seeks to provide urologists with a comprehensive understanding of the metabolic implications behind urinary stone formation, as well as provide recommendations regarding its study and management beyond surgical interventions. Of note, the factors mentioned above and further detailed in the following pages, generally do not present themselves in these patients with a complete and elaborate disorder, but instead present with a combination of elements that coincide, thus creating a high urolithitic risk.

Calculi formation mechanism

The urolithiasis process begins with the nucleation of crystals and their peripheral aggregation with matrix-forming proteins[9]. Nucleation occurs as solutes reach the point of urinary supersaturation for homogeneous nucleation, or around other structures such as crystals, cell membranes, protein aggregates and foreign bodies for heterogeneous nucleation[6,7]. Stone growth occurs according to the etiology of the stone; the amount of protein is

Table 1. Risk factors for recurrent urolithiasis in adults

General	Early episode of urinary lithiasis Family history of nephrolithiasis Calcium phosphate calculi Infectious calculi
Associated comorbidities	Hyperparathyroidism Metabolic syndrome Nephrocalcinosis Gastrointestinal disease: – Crohn's disease – Malabsorption Bariatric surgery Sarcoidosis Spinal cord injury Neurogenic bladder
Genetic	Cystinuria: Type A, B and AB Primary hyperoxaluria Renal tubular acidosis type I 2,8-dihydroxyadenuria Xanthinuria Lesch-Nyhan Syndrome Cystic fibrosis
Anatomical	Renal medullary spongiosis Ureteropelvic obstruction Diverticulum or calyceal cyst Ureteral stenosis Vesicoureteral reflux Ureterocele Horseshoe kidney

inversely proportional to the probability of an underlying metabolic disorder, while the amount of matrix is in turn associated with an infectious disease[6,14].

The initial histopathologic and macroscopic manifestation of crystal deposition is visualized as Randall's plaques[9,15,16]. These are micro- and macroscopic deposits of calcium that originate in the basement membrane of the loop of Henle, which extend into the interstitium below the urothelium of the renal papilla[17,18].

Types of calculi and composition

I. Calcium stones

Calcium calculi account for 80% of stones in adults (19) we performed an ambulatory metabolic protocol with diagnostic purposes. From the total sample 79% of stones were made of calcium salts (oxalate and phosphate. Its formation begins in the medullary interstitium, where the calcium phosphate molecules are deposited before passing to the papilla and forming the Randall's plaques. Subsequently, the superposition of phosphate and calcium oxalate crystals form the stones themselves[17,20].

The most frequent composition of urinary stones is calcium oxalate (CaOx), present in either monohydrate (COM) or dihydrate (COD) forms, and characterized by calcium and oxalate excess in depletion of citrate and magnesium[14,16]. The COM calculi are characterized by a smooth surface and occur in hyperoxaluric states[2] metabolic evaluation of stone formers and preventive medical therapy is underutilized. The causes for this are multifactorial. Recent technological advances, including extracorporeal shock-wave lithotripsy (ESWL, while the COD calculi are morphologically characterized by a spiculate surface and tend to occur in hypercalciuric states[2,4] metabolic evaluation of stone formers and preventive medical therapy is underutilized. The causes for this are multifactorial. Recent technological advances, including extracorporeal shock-wave lithotripsy (ESWL. While COD stones are more frequent in young people, the concentration of COM increases progressively with age, reaching a peak between 40 and 70 years[8]. The main reported risk factors for calcium oxalate stones are hyperoxaluria, hypercalciuria and hypocitraturia.

Of note, calcium oxalate and calcium phosphate stones differ in their saturation points, precipitating at acidotic and alkalotic pH, respectively. Increases of urine pH to values higher than 6.5-7.5 lead to greater conversion of monobasic to dibasic phosphate, thus increasing risk of calcium phosphate stones, particularly in the presence of hypocitraturia (described below). Moreover, patients with mixed calcium oxalate/calcium phosphate stones have lower urine citrate and higher pH when compared with calcium oxalate stone formers alone[21].

II. Hyperoxaluria

Oxalate is a salt that is obtained both exogenously (directly from food intake) as well as endogenously, after hepatic metabolism of glyoxylate, glycine, hydroxyproline, and ascorbic acid[22]. In a healthy person, only 2 to 10% of the dietary oxalate enters the bloodstream, and the rest is used as energy source by the intestinal microbiota[23,24]. The dianionic oxalate is chelated by the metal cation calcium, this being the main regulator of its intestinal absorption[22,25]. Conditions that increase the absorption of oxalate or its production are thus predisposing factors to develop urolithiasis: dietary habits, enteric diseases and genetic conditions[26].

Oxalate excretion occurs in the kidneys: the breakdown of ascorbic acid and glyoxylate accounts for 80-90% of losses, and the exogenous oxalate for the

remaining 10-20%[27]. Urinary oxalate is directly proportional to its serum concentration (hyperoxaluria > 40 mg/day)[28].

The main oxalate sources are plants and their products, especially seeds and leafs[29]. Although oxalate is ubicous in diet, its biodisponibility varies among different foods groups. The highest immediate rise in urinary oxalate happens after consuming spinach, while a delayed rise occurs after consuming products such as chocolate, tea, and cranberry and orange juice[28].

Ethylene glycol is used primarily as a component in antifreeze and is associated with nephrolithiasis, nephrocalcinosis, renal failure and death[30]. Its provoked or accidental ingestion results in the production of oxalic acid that binds to calcium leading to urine oxalate crystals[31].

Avoiding foods rich in oxalate, particularly spinach an rhubarb (limiting overall daily consumption to 100 mg/day), and increasing dietary calcium intake (1000-1200 mg/day), may help in the prevention of urinary tract stones associated with hyperoxaluria[23].

Enteric hyperoxaluria occurs due to extensive intestinal resections with intact colon and inflammatory bowel diseases, such as Crohn's disease[32] This conditions lead to bowel acidification and an increase in oxalate's permeability through the endothelium lining[30,33,34] Furthermore, these diseases are associated with bacterial decolonization of Oxalobacter formigenes, a Gram negative anaerobic bacillus that resides as part of the body's normal intestinal flora and is responsible for metabolizing excess oxalate, leading to an hyperoxaluric state[32,35]. Also, abscense of Oxalobacter formigenes leads to greater levels of urinary calcium[36].

Other oxalate-degrading bacteria include Enterococcus faecalis, Providencia rettgeri, Eubacterium lentum, Escherichia coli, Lactobacillus spp. and Bifidobacterium spp[37]. The extensive use of antibiotics also leads to bacterial decolonization of the gut and increases the risk of urinary lithiasis[37].

Furthermore, primary hyperoxaluria (PHO) is a genetic disease characterized by urolithiasis and severe renal damage[30]. The most common variant is PHO type I, which occurs due to enzymatic damage of hepatic peroxisomes responsible for oxalate degradation, leading to excessive oxalate renal elimination and injury through nephrocalcinosis and recurrent nephrolithiasis. While PHO type II and III are less severe forms of the disease, their association to stone formation has likewise been reported[30]. Treatment of the cause of hyperoxaluria will prevent secondary urinary lithiasis.

III. Hypercalciuria

Hypercalciuria (> 300 mg/day) is defined as an increase in urinary calcium excretion, independent on serum calcium levels[38]. While, 99% of the body's calcium stores is found in the skeleton, only 1% remains in the intra and extracellular spaces[39]. This balance relies on the normal interplay between intestinal absorption, renal reabsorption, and bone resorption[39].

Serum calcium is found in ionized form (48%), bound to proteins (46%) and in fractionated complexes (7%)[39]. These complexes bind to larger molecules, such as citrate and phosphate, and are thus responsible for stone formation[39]. Approximately 60 to 70% of the filtered calcium is reabsorbed in the proximal convoluted tubule, 20% in the loop of Henle and 10% in the distal convoluted tubule[39]. This last portion is the main regulatory site due to the expression of hormone-sensitive receptors, and as such, disruptions in its function is associated with nephrolithiasis[39].

While calcitriol and parathyroid hormone are hypercalcemic hormones that promote bone resorption, calcitonin is hypocalcemic, and therefore stimulates bone accumulation[40]. Moreover, vitamin D favors calcium fixation at physiological levels and bone resorption at higher doses[40,41]. Primary hyperparathyroidism, prolonged immobilization, multiple myeloma, solid cancers and hyperthyroidism causes unbalanced bone remodeling, a pathological state in which resorption generates a hypercalciuric state[39,41,42]. Moreover, patients with vitamin D hypovitaminosis (be it from inadequate sun exposure, limited oral intake, or impaired intestinal absorption) may develop a secondary hyperparathyroid state, compounding the risk of hypercalciuria and kidney stone formation risk[41,43]. Management of hypercalciuria includes loop diuretics and thiazides to increase renal excretion and bisphosphonates to inhibit bone resorption[39–41,44].

In patients with underlying intestinal disease and malabsorption, hypercalciuria occurs due to metabolic acidosis and intraluminal calcium sequestration[42]. The sequestration in turn causes hyperoxaluria[30,40], increasing nephrolithiasis incidence.

Additionally, hypernatremia (> 144 mg/dL) increases calciuria due to the decrease in calcium reabsorption at the level of the proximal convoluted tubule and the loop of Henle[44]. As such, low-sodium diets reduce the risk of urolithiasis in patients with recurrent CaOx stones[44].

I.iii. Hypocitraturia

Urinary citrate binds calcium and/or phosphorus in the renal tubular lumen, decreasing the concentration of free

calcium[45,46]. Thus, hypocitraturia (< 170 mg/day) favors the precipitation of CaOx crystals despite normal levels of urinary calcium[34]. The most frequent causes of hypocitraturia are intestinal malabsorption, renal failure, distal renal tubular acidosis, hypocalcemia, use of thiazides and carbonic anhydrase inhibitors (acetazolamide and topiramate), and urinary tract infections[45,47]).

In distal renal tubular acidosis, impaired urinary acidification leads to increased citrate reabsorption (for the formation of bicarbonate). Furthermore, as a consequence of metabolic acidosis, calcium bone resorption increases, generating a hypercalciuric and hypocitraturic environment that predisposes to CaOx calculi formation[48]. Moreover, a low urinary pH causes the precipitation of calcium phosphate salts, thus further increasing nephrolithiasis[48].

As metabolic acidotic states in turn lead to decreased citrate excretion combined with an increased calcium and uric acid excretion, a favourable (physiologic) milieu for stone formation is produced[49]. This leads to the consideration of other, often overlooked, conditions associated with mild acitodic states, including (but not limited to) being overweight/obese, diabetic, and metabolic syndrome; all of which constitute intrinsic risk for nephrolithiasis[49–51].

I.iv. Hypomagnesuria

In urine, magnesium ions inhibit stone formation by destabilizing CaOx molecules[52]. This inhibitory role (along with the action of citrate), is effective even in states of low urinary pH[52]. In other words, low urinary magnesium increases free oxalate in the urine, increasing stone-formation propensity[53].

Under normal conditions, 96% of the filtered magnesium is reabsorbed in the tubular system[39]. As such, hypomagnesuria (excretion < 50 mg/day) results directly from hypomagnesemic states. The main causes of hypomagnesemia include gastrointestinal losses (chronic diarrhea and chronic use of proton pump inhibitors) and renal losses (use of loop diuretics, uncontrolled diabetes, hypercalcemia and alcohol consumption)[39,54–56].

I.v. Hyperphosphatemia

Hyperphosphatemia, through the formation of Randall's plaques, is a risk factor for the formation of calcium stones[39]. The body's equilibrium of phosphorus is determined by the balance between the excretion of phosphate and the dietary intake[39]. Once in plasma, the phosphate is either transported into the intracellular space or stored in the skeletal system[39]. In this way, the regulation of this ion is closely related to calcium concentrations: parathyroid hormone decreases renal reabsorption of phosphate in the proximal convoluted tubule and causes phosphaturia[39]. The management of hyperparathyroidism includes phosphate binders, vitamin D analogues, and calcimimetics[39].

II. Uric acid stones

Hyperuricemia is classified as primary and secondary, and in turn, in hyperproduction and uric acid hypoexcretion[24,57]. In the lithiasic patient, hyperuricosuria may occur due to elevated or normal levels of uric acid in the blood. When associated with hyperuricemia, it is suggestive of gout and metabolic alterations, whereas associated with normouricemia is suggestive of purine-rich diets[24,57]. The hyperuricosuria with normouricemia resolves once the consumption of red meat, alcohol and seafood has decreased.

In addition, hyperuricosuria (> 990 mg / day) causes greater elimination of uric acid decreasing urinary pH and triggering the formations of stones nuclei[24,57]. A pH lower than 5.7 increases the precipitation of CaOx crystals and the aggregation of these on crystals of uric acid, forming stones[24,57,58]. In addition, it has been described that insulin resistance, associated or not with metabolic syndrome, directly affects the ammoniogenesis and the ammonium that previously worked as a urinary buffer, will now acidify it[59] in the normouricemic, normouricosuric patient. Of particular importance in this group, are those patients consuming excess animal protein and specialized diets (e.g. Atkins, keto and other low-carbohydrate/high-protein diets), as animal protein has been shown to boost urinary excretion of oxalate, which then combines with calcium and other compounds to form kidney stones[60].

The treatment is based on urinary alkalinization with potassium citrate and the decrease of uric acid levels from the restriction of purine-rich animal proteins[58] due to the high capacity of urinary acidification they possess[59] calcium phosphate (US-CaP, and allopurinol[61].

III. Struvite stones

Struvite stones are composed of phosphate crystals hydrated by magnesium ammonium and calcium apatite[57]. These stones are characterized by rapid growth over a period of weeks to months, forming staghorn calculi that occupy the space of the collecting system and thus often obstructing the urinary tract[57,61,62].

Urine usually maintains low concentrations of ammonium phosphate, however, an alkalinization of urinary pH leads to lower phosphate solubility[9,57,62] and, thereof, a greater urinary availability. This happens because as urease-producing bacteria, such as Proteus spp., Klebsiella spp., and Pseudomonas spp. colonize the urinary tract[57], urea is metabolized into ammonia and combines with water to form ammonium and thus increases urine pH[63]. The treatment includes surgery and acetohydroxamic acid (reversible inhibitor of urea), which prevents the crystallization of struvite and apatite carbonate[2].

IV. Cystine stones

Cystine is an amino acid that, due to its insolubility at normal urinary pH, precipitates to form crystals in patients with cystinuria[2,64]. Cystinuria is a genetic disease of autosomal recessive inheritance, characterized by the inadequate reabsorption of cystine and other dibasic amino acids in the proximal tubule of the nephron and in the gastrointestinal epithelium, causing recurrent urolithiasis[64].

This condition has an overall incidence of 1 per 7000 live births and corresponds to 1% of urinary tract stones in adults[65]. The majority of cases of cystinuria are caused by mutations in two genes that code for subunits of the cystine transporter (SLC3A1 and SLC7A9)[64]. The treatment consists mainly in preventing the formation of stones through adequate hydration, dietary restriction of foods rich in methionine (e.g. meat, pork and dairy), decreased salt intake, urinary alkalinization and drugs with cystine reuptake (e.g. thiols)[2,64].

Metabolic studies and calculi analysis

After complete resolution of renal colic, a 4- to 6-week waiting period (during which the patient is expected to resume habitual diet) is recommended prior to proceeding with the metabolic study[66]. Metabolic study should include the following aspects: medical history directed to the underlying pathology, nutritional evaluation, and urine and blood studies.

The clinical history includes the following:

- Relevant comorbidities: diabetes mellitus, hyperuricemia, sarcoidosis, hyperparathyroidism, osteoporosis, inflammatory disease or intestinal malabsorption, and previous history of urinary lithiasis (and number of episodes).
- Pharmacological background: consumption of topiramate, acetazolamide, thiazide diuretics, vitamin C or vitamin D supplements, antacids, and proton pump inhibitors.
- Family history of calculi.
- Surgical history that includes intestinal resections and bariatric surgery.

Numerous studies link the growing urolithiasis incidence to BMI. Dietary modifications are essential and a comprehensive nutritional history must be undertaken in order to identify dietary elements which contribute to stone pathogenesis[10]. As mentioned previously, increased body weight is associated with mild metabolic acidosis, increasing stone formation risk and thus necessitating additional nutritional recommendations to promote weight loss in overweight to obese patients[49].

Nutritional appraisal quantifies daily consumption of lithogenic food components, such as sodium, sugar, animal protein (e.g. purines and uric acid) and oxalate. Likewise, protective factors must be quantified including calcium, water, fruits and vegetables[67]. Once dietary risk factors are identified, targeted nutritional recommendations may be endorsed.

General dietary recommendations should be considered in every patient, including:

- Increase liquid intake (at least 3 Liters/day to void 2-2.5 Liters/day)
- Dietary calcium: 1000-1200 milligrams/day
- Fiber-rich diet (increase fruits, vegetables, and whole-grain ingestion)
- Include citrate-rich food sources into diet (e.g. citric fruits)
- Decrease consumption of oxalate-rich foods (e.g. spinach)
- Limit salt intake to 5 grams/day or its equivalent in sodium (2 g/day), including added nitrates to most processed food
- Limit daily animal protein consumption to 1 gram per patient's ideal weight (in kilograms).

A thorough metabolic study should include two 24-hour urine collections, blood analysis and physical-chemical analysis of the stone. X-ray diffraction and infrared spectroscopy by Fourier transformation are the recommended tests for the physical study of the calculi[59,68]. These methods permit correct identification of the type of calcium stone present and other associated stone components, such as cystine, xanthine, uric acid, urates, struvite, proteins, lipids, and/or drugs[2,6].

Management in each scenario

Conclusions

Urinary lithiasis can be a recurrent disease in patients with risk factors causing high costs to the healthcare

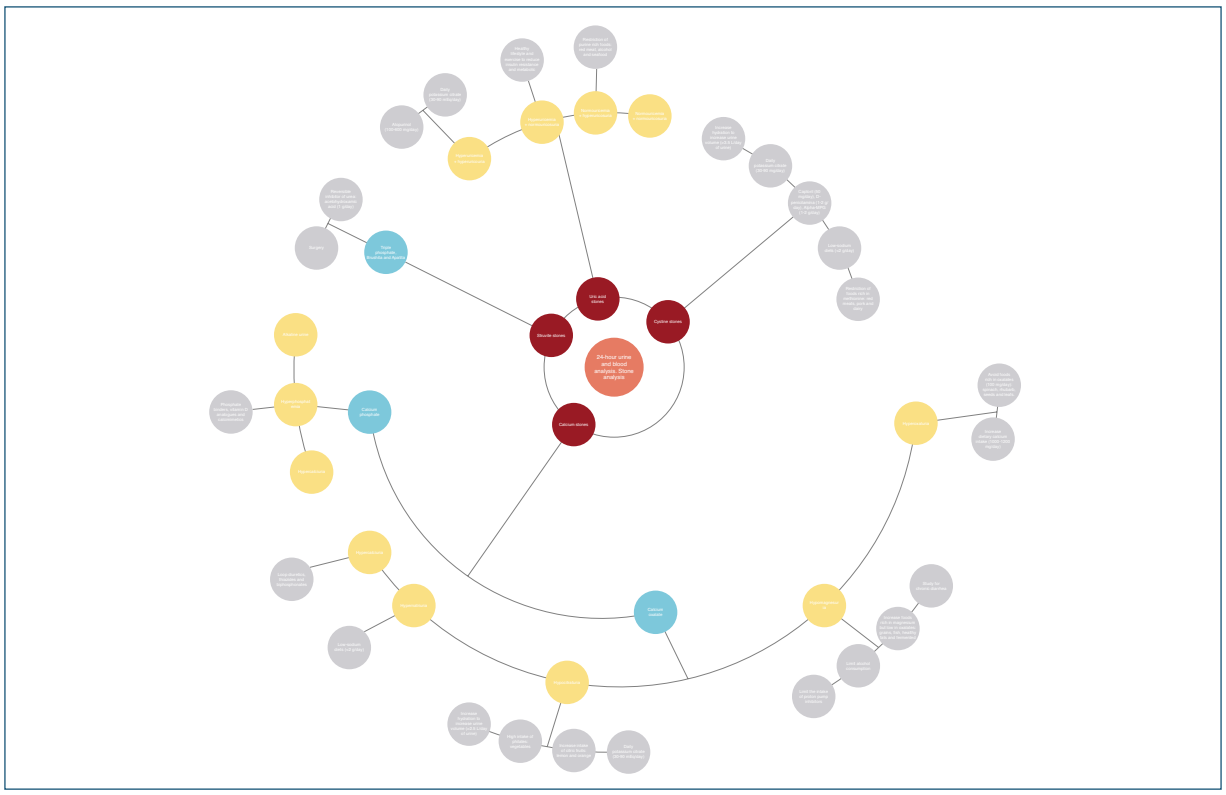


Figure 1. Subfoveal, temporal and nasal to foveal choroidal thickness measurement.

system. Is important to look for the etiology of the calculi to focus treatment on the prevention of new episodes. All physicians and urologists should counsel patients with the general recommendations and according to their metabolic studies and calculus analysis.

Funding

This research has not received any specific grant from public, commercial, or non-profit sector agencies.

Conflicts of interest

The authors declare that there is no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Ziemba JB, Matlaga BR. Epidemiology and economics of nephrolithiasis. Investig Clin Urol. 2017;58(5):299.
2. Rivers K, Shetty S, Menon M. WHEN AND HOW TO EVALUATE A PATIENT WITH NEPHROLITHIASIS. Urol Clin. 2000 May 1;27(2):203–13.
3. Scales CD, Smith AC, Hanley JM, Saigal CS, Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol. 2012 Jul;62(1):160–5.
4. Rule AD, Lieske JC, Li X, Melton LJ, Krambeck AE, Bergstralh EJ. The ROKS nomogram for predicting a second symptomatic stone episode. J Am Soc Nephrol JASN. 2014 Dec;25(12):2878–86.
5. Lipkin ME, Preminger GM. Demystifying the Medical Management of Nephrolithiasis. Rev Urol. 2011;13(1):34–8.
6. Litwin MS, Saigal CS, Yano EM, Avila C, Geschwind SA, Hanley JM, et al. Urologic diseases in America Project: analytical methods and principal findings. J Urol. 2005 Mar;173(3):933–7.
7. Pearle MS, Calhoun EA, Curhan GC, Urologic Diseases of America Project. Urologic diseases in America project: urolithiasis. J Urol. 2005 Mar;173(3):848–57.
8. Sorokin I, Pearle MS. Medical therapy for nephrolithiasis: State of the art. Asian J Urol. 2018 Oct;5(4):243–55.
9. Margaret S. Pearle, Jodi A. Antonelli, Yair Lotan. Urinary Lithiasis: Etiology, Epidemiology, and Pathogenesis. In: Campbell - Walsh Urology. Eleventh edition. Elsevier Saunders; 2016. p. 2425–61.
10. Taylor EN, Curhan GC. Diet and fluid prescription in stone disease. Kidney Int. 2006 Sep;70(5):835–9.
11. Ferraro PM, Taylor EN, Gambaro G, Curhan GC. Dietary and Lifestyle Risk Factors Associated with Incident Kidney Stones in Men and Women. J Urol. 2017 Oct;198(4):858–63.
12. Friedlander JI, Antonelli JA, Pearle MS. Diet: from food to stone. World J Urol. 2015 Feb;33(2):179–85.
13. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Diagnosis and Conservative Management of Urolithiasis. Eur Urol. 2016 Mar;69(3):468–74.
14. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int. 2003 May;63(5):1817–23.
15. Ratkalkar VN, Kleinman JG. Mechanisms of Stone Formation. Clin Rev Bone Miner Metab. 2011 Dec;9(3–4):187–97.

16. Dissayabutra T, Kalpongkul N, Rattanaphan J, Boonla C, Srisa-Art M, Ungjaroenwathana W, et al. Urinary stone risk factors in the descendants of patients with kidney stone disease. Pediatr Nephrol Berl Ger. 2018 Mar 28;
17. Evan AP, Lingeman JE, Coe FL, Parks JH, Bledsoe SB, Shao Y, et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. J Clin Invest. 2003 Mar 1;111(5):607–16.
18. Chung H-J. The role of Randall plaques on kidney stone formation. Transl Androl Urol. 2014 Sep;3(3):251–4.
19. Spivacow FR, Del Valle EE, Lores E, Rey PG. Kidney stones: Composition, frequency and relation to metabolic diagnosis. Medicina (Mex). 2016;76(6):343–8.
20. Matlaga BR, Williams JC, Kim SC, Kuo RL, Evan AP, Bledsoe SB, et al. Endoscopic Evidence of Calculus Attachment to Randall's Plaque. J Urol. 2006 May;175(5):1720–4.
21. Goldfarb DS. A Woman with Recurrent Calcium Phosphate Kidney Stones. Clin J Am Soc Nephrol. 2012 Jul;7(7):1172–8.
22. Knight J, Jiang J, Assimos DG, Holmes RP. Hydroxyproline ingestion and urinary oxalate and glycolate excretion. Kidney Int. 2006 Dec;70(11):1929–34.
23. Sadaf H, Raza SI, Hassan SW. Role of gut microbiota against calcium oxalate. Microb Pathog. 2017 Aug;109:287–91.
24. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. N Engl J Med. 1992 Oct 15;327(16):1141–52.
25. von Unruh GE. Dependence of Oxalate Absorption on the Daily Calcium Intake. J Am Soc Nephrol. 2004 Jun 1;15(6):1567–73.
26. Coe FL. Kidney stone disease. J Clin Invest. 2005 Oct 1;115(10):2598–608.
27. Williams HE, Wandzilak TR. Oxalate Synthesis, Transport and the Hyperoxaluric Syndromes. J Urol. 1989 Mar;141(3 Part 2):742–7.
28. Brinkley LRD, MgGuire JMD, Gregory JMD, Pak CYC. Bioavailability of oxalate in foods. Urology. 1981 Jun;17(6):534–8.
29. Holmes RP, Kennedy M. Estimation of the oxalate content of foods and daily oxalate intake. Kidney Int. 2000 Apr;57(4):1662–7.
30. Victor Lorenzo, Eduardo Salido, Armando Torres. Hiperoxaluria primaria. Nefrología [Internet]. 2014 Apr [cited 2018 Apr 12];(34). Available from: http://www.revistanefrologia.com/modules.php?name=articulos&idarticulo=12335&idlangart=ES
31. Hodgman M, Marraffa JM, Wojcik S, Grant W. Serum Calcium Concentration in Ethylene Glycol Poisoning. J Med Toxicol. 2017 Jun;13(2):153–7.
32. Stewart CS, Duncan SH, Cave DR. Oxalobacter formigenes and its role in oxalate metabolism in the human gut. FEMS Microbiol Lett. 2004 Jan 15;230(1):1–7.
33. Fargue S, Milliner DS, Knight J, Olson JB, Lowther WT, Holmes RP. Hydroxyproline Metabolism and Oxalate Synthesis in Primary Hyperoxaluria. J Am Soc Nephrol JASN. 2018 Mar 27;
34. Baggio B, Gambaro G, Favaro S, Borsatti A. Prevalence of Hyperoxaluria in Idiopathic Calcium Oxalate Kidney Stone Disease. Nephron. 1983;35(1):11–4.
35. Allison MJ, Dawson KA, Mayberry WR, Foss JG. Oxalobacter formigenes gen. nov., sp. nov.: oxalate-degrading anaerobes that inhabit the gastrointestinal tract. Arch Microbiol. 1985 Feb;141(1):1–7.
36. Ravikumar Y, Begum RF, Velmurugan R. Oxalobacter formigenes reduce the risk of kidney stones in patients exposed to oral antibiotics: a case–control study. Int Urol Nephrol. 2021 Jan;53(1):13–20.
37. Abratt VR, Reid SJ. Oxalate-Degrading Bacteria of the Human Gut as Probiotics in the Management of Kidney Stone Disease. In: Advances in Applied Microbiology [Internet]. Elsevier; 2010 [cited 2019 Aug 21]. p. 63–87. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0065216410720037
38. Gouru V, Pogula V, Vaddi S, Manne V, Byram R, Kadiyala L. Metabolic evaluation of children with urolithiasis. Urol Ann. 2018;10(1):94.
39. Blaine J, Chonchol M, Levi M. Renal Control of Calcium, Phosphate, and Magnesium Homeostasis. Clin J Am Soc Nephrol. 2015 Jul 7;10(7):1257–72.
40. Boulanger H, Flamant M. Hipercalciuria. EMC - Apar Locomot. 2013 Jun;46(2):1–6.
41. Letavernier E, Daudon M. Vitamin D, Hypercalciuria and Kidney Stones. Nutrients. 2018 Mar 17;10(3).
42. Felsenfeld A, Rodriguez M, Levine B. New insights in regulation of calcium homeostasis: Curr Opin Nephrol Hypertens. 2013 Jul;22(4):371–6.
43. Kennel KA, Drake MT, Hurley DL. Vitamin D Deficiency in Adults: When to Test and How to Treat. Mayo Clin Proc. 2010 Aug;85(8):752–8.
44. Nouvenne A, Meschi T, Prati B, Guerra A, Allegri F, Vezzoli G, et al. Effects of a low-salt diet on idiopathic hypercalciuria in calcium-oxalate stone formers: a 3-mo randomized controlled trial. Am J Clin Nutr. 2010 Mar 1;91(3):565–70.
45. Gilberto González V. Litiasis renal: estudio y manejo endocrinológico. Rev Médica Clínica Las Condes. 2013 Sep;24(5):798–803.
46. Kok DJ, Papapoulos SE, Bijvoet OLM. Crystal agglomeration is a major element in calcium oxalate urinary stone formation. Kidney Int. 1990 Jan;37(1):51–6.
47. Del Valle Elisa E, Spivacow Francisco R, Negri Armando L. Citrato y litiasis renal. Med B Aires. 2013 Ago;363–8.
48. Buckalew VM. Nephrolithiasis in renal tubular acidosis. J Urol. 1989 Mar;141(3 Pt 2):731–7.
49. Hou J. The Role of Claudin in Hypercalciuric Nephrolithiasis. Curr Urol Rep. 2013 Feb;14(1):5–12.
50. Taylor EN. Obesity, Weight Gain, and the Risk of Kidney Stones. JAMA. 2005 Jan 26;293(4):455.
51. Souto G, Donapetry C, Calviño J, Adeva MM. Metabolic Acidosis-Induced Insulin Resistance and Cardiovascular Risk. Metab Syndr Relat Disord. 2011 Aug;9(4):247–53.
52. Riley JM, Kim H, Averch TD, Kim HJ. Effect of Magnesium on Calcium and Oxalate Ion Binding. J Endourol. 2013 Dec;27(12):1487–92.
53. Han H, Segal AM, Seifter JL, Dwyer JT. Nutritional Management of Kidney Stones (Nephrolithiasis). Clin Nutr Res. 2015;4(3):137.
54. Tong GM, Rude RK. Magnesium Deficiency in Critical Illness. J Intensive Care Med. 2005 Jan;20(1):3–17.
55. Hess MW, Hoenderop JGJ, Bindels RJM, Drenth JPH. Systematic review: hypomagnesaemia induced by proton pump inhibition. Aliment Pharmacol Ther. 2012 Sep;36(5):405–13.
56. Elisaf M, Merkouropoulos M, Tsianos EV, Siamopoulos KC. Pathogenetic Mechanisms of Hypomagnesemia in Alcoholic Patients. J Trace Elem Med Biol. 1995 Dec;9(4):210–4.
57. Cloutier J, Villa L, Traxer O, Daudon M. Kidney stone analysis: "Give me your stone, I will tell you who you are!" World J Urol. 2015 Feb;33(2):157–69.
58. Khan A. Prevalence, pathophysiological mechanisms and factors affecting urolithiasis. Int Urol Nephrol. 2018 Mar 22;
59. Esperto F, Miano R, Marangella M, Trinchieri A. Impact of food quantity and quality on the biochemical risk of renal stone formation. Scand J Urol. 2018 Apr 1;1–5.
60. Gottlieb S. High protein diet brings risk of kidney stones. BMJ. 2002 Aug 24;325(7361):408d–408.
61. Dardamanis M. Pathomechanisms of nephrolithiasis. Hippokratia. 2013;17(2):100–7.
62. Griffith DP. Struvite stones. Kidney Int. 1978 May;13(5):372–82.
63. Lingeman JE, Siegel YI, Steele B. Metabolic Evaluation of Infected Renal Lithiasis: Clinical Relevance. J Endourol. 1995 Feb;9(1):51–4.
64. Mattoo A, Goldfarb DS. Cystinuria. Semin Nephrol. 2008 Mar;28(2):181–91.
65. Chillarón J, Font-Llitjós M, Fort J, Zorzano A, Goldfarb DS, Nunes V, et al. Pathophysiology and treatment of cystinuria. Nat Rev Nephrol. 2010 Jul;6(7):424–34.
66. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, et al. Medical management of kidney stones: AUA guideline. J Urol. 2014 Aug;192(2):316–24.
67. Prezioso D, Strazzullo P, Lotti T, Bianchi G, Borghi L, Caione P, et al. Dietary treatment of urinary risk factors for renal stone formation. A review of CLU Working Group. Arch Ital Urol E Androl. 2015 Jul 7;87(2):105.
68. Sun X-Y, Xue J-F, Xia Z-Y, Ouyang J-M. Component analyses of urinary nanocrystallites of uric acid stone formers by combination of high-resolution transmission electron microscopy, fast Fourier transformation, energy dispersive X-ray spectroscopy, X-ray diffraction and Fourier transform infrared spectroscopy. IET Nanobiotechnol. 2015 Jun;9(3):114–21.

REVISTA UROLOGÍA COLOMBIANA

PERMANYER

CARTA AL EDITOR

Trauma renal cerrado de alto grado: el rol de la angioembolización en el manejo secuencial

High-grade blunt renal trauma: the role of angioembolization in the sequential management

María P. Gómez-Bueno[1] y Herney A. García-Perdomo[2]*

[1]Grupo de Investigación UROGIV; [2]Unidad de Urología y Urooncología. Departamento de Cirugía. Escuela de Medicina, Universidad del Valle, Cali, Colombia

El trauma renal corresponde a un 10% de todos los traumas abdominales; de ellos, un 90% comprende el trauma cerrado. Con respecto a las intervenciones asociadas, el manejo secuencial conservador o «paso a paso» ha logrado disminuir las tasas de nefrectomía innecesarias, ubicándose en un 28% en la actualidad[1,2]. Una de las herramientas disponibles en la actualidad como parte del tratamiento del paciente con trauma renal cerrado de alto grado es la angioembolización[2]. Consecuentemente, vale la pena conocer cuáles son los factores predictores para realizar una intervención temprana con fines de detener el sangrado, las tasas de éxito de la primera o segunda angioembolización y los predictores de falla.

La angioembolización de primera vez tiene un éxito de hasta el 85% y una efectividad del 100% en los pacientes que requieren una segunda angioembolización[2]. Entre los hallazgos radiográficos considerados como factores de riesgo se ubica el tamaño de hematoma perirrenal (> 3,5 cm), la extravasación del contraste y una lesión compleja (abarca porción lateral y medial del riñón simultáneamente)[3]. Adicionalmente existe un nomograma propuesto por *The American Association for the Surgery of Trauma* que determina el riesgo de requerir intervención para detener el sangrado, y los factores tenidos en cuenta son diámetro del hematoma, mecanismo del trauma, extravasación de contraste, lesión concomitante de otro órgano o inestabilidad hemodinámica[4].

Actualmente la recomendación de las guías americanas respecto a intervención (cirugía o angioembolización) se mantiene para tamaño del hematoma perirrenal > 4 cm con o sin extravasación del medio de contraste y en pacientes con inestabilidad hemodinámica[5]. No obstante, se debe considerar que se han descrito predictores de falla de la angioembolización tales como trauma renal grado V con riesgo relativo (RR) 4,05 (1,14-14,4), *Injury Severity Score* (ISS) con RR 1,03 (1,0-1,06) y un mecanismo penetrante con RR 3,04 (1,60-5,79)[6]. También se han planteado la hematuria macroscópica, *odds ratio* (OR) 2,15 (intervalo de confianza [IC]: 1,02-4,74), y la inestabilidad hemodinámica, OR 3,76 (IC: 1,79-8,04) como factores asociados a la falla de esta intervención[7].

Por lo anterior, consideramos que ante un trauma renal cerrado de alto grado (III-V) y signos radiográficos tales como el tamaño del hematoma, la extravasación del medio de contraste y la complejidad de la lesión, es posible y aceptable realizar una angioembolización como una medida menos invasiva y mórbida

***Correspondencia:**
Herney A. García-Perdomo
E-mail: herney.garcia@correounivalle.edu.co

Fecha de recepción: 15-01-2023
Fecha de aceptación: 19-01-2023
DOI: 10.24875/RUC.23000008

Disponible en internet: 23-03-2023
Urol. Colomb. 2023;32(1):23-24
www.urologiacolombiana.com

para el paciente. Esto puede permitir la disminución en la tasa de nefrectomías innecesarias por trauma renal. Además, se abre la puerta a una línea de investigación fundamental en el manejo del paciente con trauma genitourinario; área en la que todos debemos participar dada la epidemiología del trauma en nuestro contexto.

Financiamiento

La presente investigación no ha recibido ninguna beca específica de agencias de los sectores públicos, comercial o con ánimo de lucro.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que en este artículo no aparecen datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

Bibliografía

1. Chien LC, Herr KD, Archer-Arroyo K, Vakil M, Hanna TN. Review of multimodality imaging of renal trauma. Radiol Clin North Am. 2020;58(5):965-79.
2. Liguori G, Rebez G, Larcher A, Rizzo M, Cai T, Trombetta C, et al. The role of angioembolization in the management of blunt renal injuries: a systematic review. BMC Urol. 2021;21(1):104.
3. Dugi DD, Morey AF, Gupta A, Nuss GR, Sheu GL, Pruitt JH. American Association for the Surgery of Trauma Grade 4 Renal Injury Substratification Into Grades 4a (Low Risk) and 4b (High Risk). J Urol. 2010;183(2):592-7.
4. Keihani S, Rogers DM, Putbrese BE, Moses RA, Zhang C, Presson AP, et al. A nomogram predicting the need for bleeding interventions after high-grade renal trauma: Results from the American Association for the Surgery of Trauma Multi-institutional Genito-Urinary Trauma Study (MiGUTS). J Trauma Acute Care Surg. 2019;86(5):774-82.
5. Morey AF, Broghammer JA, Hollowell CMP, McKibben MJ, Souter L. Urotrauma Guideline 2020: AUA Guideline. J Urol. 2021;205(1):30-5.
6. Hotaling JM, Sorensen MD, Smith TG, Rivara FP, Wessells H, Voelzke BB. Analysis of diagnostic angiography and angioembolization in the acute management of renal trauma using a national data set. J Urol. 2011;185(4):1316-20.
7. Baboudjian M, Gondran-Tellier B, Panayotopoulos P, Hutin M, Olivier J, Ruggiero M, et al. Factors predictive of selective angioembolization failure for moderate- to high-grade renal trauma: A French multi-institutional study. Eur Urol Focus. 2022;8(1):253-8.