Original Article

The impact of age and education level in the linguistic validation of the Acute Cystitis Symptom Score (ACSS) Questionnaire

Konstantinos Stamatiou, Evangelia Samara, Jakhongir F. Alidjanov[1], Kurt G. Naber[2], Adrian Pilatz[1], Florian M. Wagenlehner[1]

Department of Urology, Tzaneio General Hospital of Piraeus, Piraeus, Greece, [1]Clinic for Urology, Pediatric Urology and Andrology, Justus Liebig University, Giessen, [2]Department of Urology, Technical University of Munich, Munich, Germany

Abstract

Introduction/Purpose: The Acute Cystitis Symptom Score (ACSS) was developed as a simple and self-reporting questionnaire for diagnosing and monitoring acute uncomplicated cystitis in female patients. It consists of 18 questions placed in four subcategories: (1) typical symptoms, (2) differential diagnosis, (3) quality of life and (4) coexisting gynecological conditions. It has been translated into many languages. The purpose of this work is the linguistic evaluation of ACSS in the Greek language. **Materials and Methods:** The translation of ACSS into Greek was carried out in accordance with international standards and guidelines. The process consisted of 4 stages: in the 1st and 2nd stage a translation was made into the target language (Greek) from the original (Russian, English) by native speakers, while reverse translation and re-evaluation was made by experts whose mother tongue language is the target language. In stage 3, a cognitive assessment was performed by female subjects with and without a history of uncomplicated urinary tract infection. At this stage, based on the degree of understanding, the final draft was chosen between the two drafts of different origins (Russian or English). In stage 4: the final clinical evaluation was performed by female subjects with acute episode of uncomplicated cystitis (Arm 1 - Patients) and female subjects undergoing treatment for any other diseases (Arm 2 - Control). The Memorandum of Understanding between the Greek Study Group of ACSS and the copyright holders of ACSS was made on 17 November 2019 while it has been approved by the Ethics Committee of the Hospital. The diagnosis of acute uncomplicated cystitis was made based on the history and results of laboratory findings. **Results:** The two pre-final versions in Greek were randomly applied to 15 healthy women aged between 89 and 22 years. The mean age of the final sample was 23.84 years. The level of education differed between a doctorate and a primary school diploma with most participants graduating from universities (8/30) and high school (8/30). According to the answers, 20 women would prefer the English standard translation, compared to 10 women, who preferred the Russian translation. The 2: 1 ratio was similar whether the participants had higher education or not. No significant difference was observed in the mean age of the participants who chose one or the other version. **Conclusion:** The process of translating and adapting a study instrument such as a questionnaire for a different ethnic group is a difficult task since it requires to adapt it in a culturally relevant and comprehensible form despite peculiarities of the target language. Considering these difficulties, we were able to develop a linguistically validated Greek version of the ACSS, which now can be used for clinical and research purposes in a multidisciplinary fashion.

Keywords: *Age, education level, linguistic validation, medical questionnaire*

Submitted: 29-Apr-2021
Revised: 21-May-2021
Accepted: 07-Jun-2021
Published: 15-Feb-2022

Address for correspondence:
Dr. Konstantinos Stamatiou, Department of Urology, Tzaneio General Hospital of Piraeus, Piraeus, Greece.
E-mail: stamatiouk@gmail.com

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 10.4103/HUAJ.HUAJ_19_21

Quick Response Code:

Introduction

Acute cystitis, an infection of the urinary bladder, is the most frequent bacterial infection in women.[1] It most commonly affects young, sexually active women (between the ages of 16 and 35 years), with 10% of women getting an infection yearly and more than 40%–60% having an infection at some point in their lives.[2] The classic clinical symptoms of cystitis consist of dysuria, urinary frequency, urinary urgency, and suprapubic pain. Frequency, length, and intensity of symptoms vary from patient to patient.[3] In several patients (most often the very old and the very young), symptoms may be vague or nonspecific; however, the majority of symptoms are bothersome.[3] Clinical evaluation of the bothersome is somehow controversial, given that improvements assessed in patient interview may be subjective and may be affected by recall biases. The acute cystitis symptom score (ACSS) was developed and validated as a simple and

How to cite this article: Stamatiou K, Samara E, Alidjanov JF, Naber KG, Pilatz A, Wagenlehner FM. The impact of age and education level in the linguistic validation of the acute cystitis symptom score (acss) questionnaire. Hellenic Urol 2021;33:1-4.

self-reporting questionnaire for diagnosing and monitoring acute uncomplicated cystitis (AUC) in female patients, by assessing typical and differential symptoms and additional health conditions, which may play an important role in such a clinical setting.[4] Additionally to the detection and evaluation of the severity of acute cystitis symptoms, the ACSS questionnaire can assess the impairment of everyday activities and quality of life caused by the symptoms and differentiates AUC from other disorders that present with similar symptoms.[5] In most guidelines' antibiotics are recommended as first-line treatment[6,7] although; symptomatic therapy also has shown similar good results.[8,9] The necessity to shift from symptomatic therapy to antibiotics, the actual duration of antibiotic treatment, and the addition of other drugs to the treatment regimen (such as urinary tract pain reliever) depend often on the level of discomfort and symptoms persistence[10] and therefore, the ACSS questionnaire is the ideal tool to manage the above issues. The ACSS questionnaire can also serve to predict transition to pyelonephritis. In fact, infection of the kidney usually occurs in a retrograde, ascending fashion from the bladder and in most of cases, symptoms of cystitis such as dysuria and hematuria precede those of renal infection (fever, flank pain, and nausea or vomiting). Young sexually active women are the patients that are most often affected by both acute cystitis and acute pyelonephritis.[11] Since AUCs recurrences are common, with up to 40% of patients getting a second infection within a year, the ACSS questionnaire can also be used to monitor recurrences. To our knowledge, the ACSS has been ultimately used in a larger prospective phase III trial comparing the outcome of an antibacterial agent with that of herbal treatment in women with AUC.[12] This study is aiming to translate the ACSS questionnaire from the original Russian language and American English as a new master version into the Greek language and to validate the Greek version linguistically in female patients with Greek as their first language.

Materials and Methods

To create a Greek version of the ACSS questionnaire using a cross-cultural adaptation process, we appointed two independent translators, of native Greek language origin, both experts in English and Russian language, respectively, and two English and Russian native-speaking translators. The first group of translators had to translate the original Russian version and American English as the new master version into the target Greek language. The second group of translators had to back-translate the translated versions (Russian to Greek [RG] and English to Greek [EG]) into the original languages. Translators had then to compare the original and back-translated versions to correct any discrepancies compared to the original text and provide the first draft of each questionnaire in the Greek language (RG and EG) after applying any necessary modifications.[13] These drafts had to be printed and distributed to randomly selected females of different educational levels who had to be asked whether they prefer either the RG or the EG version and had to score the different items of each version. After careful discussion within the scientific committee the final Greek version composed from both translations considering the item scoring had further to undergo evaluations including face to face validation and internal consistency.[13] A statistical analysis using the (p) Pearson correlation coefficient had then to be performed. A $P \leq 0.05$ was considered statistically significant.

Results

We have initially interviewed 15 randomly selected females, of different ages (30–89 years old) and of different levels of education (from elementary school to postgraduate studies). All were asked to choose their favorite translation. Eight of them have chosen the EG translation, whereas 7 have chosen the RG version. No significant differences existed in the median age (50 vs. 54 years) and educational level between the two groups although the number of the technical school and university graduates was slightly higher among those having chosen the RG translation as compared to those, who preferred the translated EG questionnaire (5/7 vs. 4/8). Of note, EG translation considered more the spoken language, while that of RG questionnaire resembled the written formal language. Reasons explaining this result were attributed to the translators and the languages' characteristics: While no difference in the level of education (postgraduate studies) between translators existed, age of the RG questionnaire translator was significantly higher than that of the EG questionnaire (76 vs. 38 years). On the other hand, differences between spoken and written language are prominent in both Greek and Russian, compared to American English.[14] To achieve a reliable comparison, we repeated the process for the Russian version of the ACSS questionnaire with another translation from the Russian version to Greek, this time from a younger translator (not related to the previous ones). This version of the RG questionnaire still resembled written language but was somehow closer to the EG translation. The two prefinal

Table 1: Level of education, age, and preferred translated version

Level of education	*n*	Mean age	Preferred version	
			R	AE
PhD	2	46	1	1
Master's degree	1	33	0	1
University	8	61.1	5	3
Technical school	6	32.1	2	4
High school	8	37.8	2	6
Primary/elementary school	5	52	0	5

AE: American English, R: Russian

versions in the Greek language were randomly applied to 30 healthy women aged between 22 and 89 years [Table 1]. Education level varied between Ph.D. and Elementary School degree. Participants were invited to compare the two versions and indicate the most comprehensive version of each item. According to the responses, 20 females would have preferred the translated EG questionnaire, as compared to 10 females, who preferred the translated RG questionnaire. The proportion of 2:1 was similar regardless of the participant's age. The difference in the educational level between participants was significant since most of the respondents in higher education (university graduates) preferred the translated RG questionnaire rather than the EG questionnaire (6/10 vs. 4/20).

As many of the responders suggested that they would prefer specific translated questions from each questionnaire, we afterward created a questionnaire providing both translations for each individual question, asking the participants to choose their preferred translated question. Responders were also asked to comment on the given choices. Thirty participants responded, including female patients as well as healthcare professionals (urologists, gynecologists, nurses, pharmacists). The consensus version was based mainly on the last survey's results and was composed by the items of both translations assigned to the grade of understanding and clarity as reported by the respondents. For this procedure, a scoring system from 1 (low) to 10 (highest) was used. This consensus version underwent a process of cognitive assessment. A link was sent by mail to Greek physicians and other healthcare professionals (pharmacists, nurses) and acute cystitis patients.[15] The first 30 respondents of each group consisted of the study group. The sample size was considered adequate for safe results to be extracted since; previously published articles on the topic refer to similar numbers.[4,5,16,17] Subjects have been asked to comment if they understood each question and write whatever comment they would like to make on each question of the questionnaire. Several acute cystitis patients commented that they would prefer descriptive sentences instead of medical terms. As it was proved to be understood and accepted by both healthcare professionals and patients, this version was constituted as final version [Appendix 1].

Discussion

By translating the ACSS into the Greek language and then to validate it in Greek-speaking patients we encountered challenges not priorly described among common translation issues regarding questionnaires. The difficulties are probably connected to the peculiarities of the modern Greek language. In fact, in the modern era, the Greek language entered a state of diglossia: The coexistence of vernacular and archaizing written forms of the language. What came to be known as the Greek language question was a polarization between two competing varieties of Modern Greek: Dimotiki, the vernacular form of Modern Greek proper, and Katharevousa, meaning "purified," a compromise between Dimotiki and Ancient Greek, which was developed in the early 19th century, and was used for literary and official purposes in the newly formed Greek state. In 1976, Dimotiki was declared the official language of Greece, having incorporated features of Katharevousa and giving birth to Standard Modern Greek, which is used today for all official purposes and in education.[18] Several of these incorporated features of Katharevousa are used in formal language which is more common in written communication, especially in public documents including medical forms. These features are usually filtered down into the vernacular, though often in a changed from, which is generally used by sophisticated persons or certain professionals, for example, lawyers.[19] Of note, formal language and informal language are associated with particular choices of grammar and vocabulary. Differences between formal language and informal language-which are more common in oral communication-are prominent in the modern Greek language. As shown in this study, a questionnaire with an old-fashioned style such as the RG version of ACSS is better acceptable by persons with tertiary education who are familiar with formal written communication. Currently, most uses of American English are rather informal than formal.[20] As a result, the consensus version which was mainly resulted from the EG prefinal version was more informal, more descriptive, and longer than the RG prefinal version, and uses more words and explanatory sentences to explain medical terms. After the publication of its clinical validation, the Greek ACSS can be widely used as a suitable instrument for patient-reported outcome assessment, for clinical and research purposes in a multidisciplinary fashion. The impact of AUC on everyday activities and quality of life, the role of co-morbidities in the development and outcome of AUC, the ideal duration of antibiotic treatment, and the necessity and the timing of treatment regimen modification are some issues that could be further investigated with the use of the Greek ACSS in both everyday practice and research. To our knowledge, the current study was performed at a single center, which may be considered a limitation. Nevertheless, the results of clinical validation (will be presented in a future paper) suggest, that the questionnaire can describe the dynamics of this particular clinical condition very well.

Conclusions

The process of translating and adapting a study instrument such as a questionnaire for a different ethnic group is a difficult task since it requires to adapt it in a culturally relevant and comprehensible form despite peculiarities of the target language. Considering these difficulties, we were able to develop a linguistically validated Greek version of the ACSS, which now can be used for clinical and research purposes in a multidisciplinary fashion.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Colgan R, Williams M. Diagnosis and treatment of acute uncomplicated cystitis. Am Fam Physician 2011;84:771-6.
2. Nicolle LE. Epidemiology of urinary tract infection. Infect Med 2001;18:153-62.
3. Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection? JAMA 2002;287:2701-10.
4. Di Vico T, Morganti R, Cai T, Naber KG, Wagenlehner FM, Pilatz A, *et al*. Acute cystitis symptom score (ACSS): Clinical validation of the Italian version. Antibiotics (Basel) 2020;9:104.
5. Alidjanov JF, Naber KG, Abdufattaev UA, Pilatz A, Wagenlehner FM. Reevaluation of the acute cystitis symptom score, a self-reporting questionnaire. Part II. Patient-reported outcome assessment. Antibiotics (Basel) 2018;7:43.
6. Anger J, Lee U, Ackerman AL, Chou R, Chughtai B, Clemens JQ, *et al.* Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. J Urol 2019;202:282-9.
7. Kang CI, Kim J, Park DW, Kim BN, Ha US, Lee SJ, *et al.* Clinical practice guidelines for the antibiotic treatment of community-acquired urinary tract infections. Infect Chemother 2018;50:67-100.
8. Gágyor I, Bleidorn J, Kochen MM, Schmiemann G, Wegscheider K, Hummers-Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: Randomised controlled trial. BMJ 2015;351:h6544.
9. Kronenberg A, Bütikofer L, Odutayo A, Mühlemann K, da Costa BR, Battaglia M, *et al.* Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: Randomised, double blind trial. BMJ 2017;359:j4784.
10. Cai T, Mazzoli S, Mondaini N, Meacci F, Nesi G, D'Elia C, *et al.* The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: To treat or not to treat? Clin Infect Dis 2012;55:771-7.
11. Kim B, Myung R, Kim J, Lee MJ, Pai H. Descriptive epidemiology of acute pyelonephritis in Korea, 2010-2014: Population-based Study. J Korean Med Sci 2018;33:e310.
12. Wagenlehner FM, Abramov-Sommariva D, Höller M, Steindl H, Naber KG. Non-Antibiotic Herbal Therapy (BNO 1045) versus Antibiotic Therapy (Fosfomycin Trometamol) for the Treatment of Acute Lower Uncomplicated Urinary Tract Infections in Women: A double-blind, parallel-group, randomized, multicentre, non-inferiority phase III trial. Urol Int 2018;101:327-36.
13. Ervin S, Bower RT. Translation problems in international surveys. Public Opin Q 1952;16:595-604.
14. Ogiermann E, Bella S. An interlanguage study of request perspective: Evidence from German Greek, Polish and Russian learners of English. Contrastive Pragmatics 2020;1:180-209.
15. Available from: https://docs.google.com/forms/d/1NHLeMl6UERPbk5Kfa3MpyDZXz2UTsdZ_KKjVLAFc390/close. [Last accessed on 2021 Apr 10].
16. Magyar A, Alidjanov J, Pilatz A, Nagy K, Arthanareeswaran VK, Póth S, *et al*. The role of the acute cystitis symptom score questionnaire for research and antimicrobial stewardship. Validation of the Hungarian version. Cent European J Urol 2018;71:134-41.
17. Alidjanov JF, Pilatz A, Abdufattaev UA, Wiltink J, Weidner W, Naber KG, *et al*. German validation of the acute cystitis symptom score. Urologe A 2015;54:1269-76.
18. Available from: https://wiki2.org/en/Greek_language_question. [Last accessed on 2021 Apr 10].
19. Gkaragkouni OM. The Sociolinguistic Phenomenon of Modern Greek Diglossia: The outcome of conflicts between high and low Variety and the National language question in 19th – 20th c.Greece: An Historico - Sociolinguistic perspective. ITB J 2009;10:3.
20. Available from: https://www.yuqo.com/british-vs-american-english-important-specific/.[Last accessed on 2021 Apr 10].

Appendix 1

Ερωτηματολόγιο ACSS
Πρώτη επίσκεψη - Μέρος Α: "διαγνωστική" φόρμα Ώρα: Ημερομηνία αξιολόγησης: (ηη/μμ/εεεε)
Παρακαλώ σημειώστε αν είχατε τα παρακάτω συμπτώματα κατά τη διάρκεια των τελευταίων 24 ωρών και πόσο έντονα ήταν (Παρακαλώ επιλέξτε μόνο μια απάντηση για κάθε σύμπτωμα): 0 1 2 3
Τυπικά συμπτώματα 1 Συχνή ούρηση με μικρή ποσότητα ούρων (πηγαίνω στην τουαλέτα πολύ συχνά) □ Καθόλου
έως 4 φορές την ημέρα Ναι, ήπια
5-6 φορές/ημέρα □ Ναι, μέτρια
7-8 φορές/ημέρα □ Ναι, έντονα
9 φορές/ημέρα και πλέον
2 Έπειξη για ούρηση (ξαφνική και ανεξέλεγκτη ανάγκη για ούρηση) □ Καθόλου □Ναι, ήπια □ Ναι, μέτρια □ Ναι, έντονα 3 Πόνος και καύσος κατά την ούρηση □ Καθόλου □Ναι, ήπια □ Ναι, μέτρια □ Ναι, έντονα
4 Αίσθημα ατελούς κένωσης της κύστης (εξακολουθείτε να αισθάνεστε ότι θα μπορούσατε να ουρήσετε ξανά μετά την ούρηση). □ Καθόλου □Ναι, ήπια □ Ναι, μέτρια □ Ναι, έντονα
5 Αίσθημα πόνου που δε σχετίζεται με την ούρηση στην κάτω κοιλία (κάτω από τον ομφαλό) □ Καθόλου □Ναι, ήπια □ Ναι, μέτρια □ Ναι, έντονα
6 Παρουσία αίματος στα ούρα (χωρίς έμμηνο ρύση) □ Καθόλου □Ναι, ήπια □ Ναι, μέτρια □ Ναι, έντονα
Σύνολο "Τυπικών" = βαθμοί
Διαφορικά συμπτώματα 7 Πόνος χαμηλά στη πλάτη/μέση στη μία ή και τις δύο πλευρές □ Καθόλου □Ναι, ήπια □ Ναι, μέτρια □ Ναι, έντονα 8 Ασυνήθεις κολπικές εκκρίσεις (ποσότητα, χρώμα και/ή οσμή) □ Καθόλου □Ναι, ήπια □ Ναι, μέτρια □ Ναι, έντονα 9 Εκκρίσεις από το στόμιο της ουρήθρας, ανεξάρτητες από την ούρηση □ Καθόλου □Ναι, ήπια □ Ναι, μέτρια □ Ναι, έντονα 10 Πυρετός/ Ρίγος □ Καθόλου □Ναι, ήπια □ Ναι, μέτρια □ Ναι, έντονα (αν μετρήθηκε, παρακαλώ σημειώστε την ένδειξη) <37.5° C 37.6-37.9° C 38.0-38.9° C >39.0° C Σύνολο "Διαφορικών" = βαθμοί
Ποιότητα ζωής 11 Παρακαλώ σημειώστε πόση δυσφορία έχετε βιώσει εξαιτίας των συμπτωμάτων σας τις τελευταίες 24 ώρες (Σημειώστε μόνο μια απάντηση, αυτή που σας εκφράζει καλύτερα)
0. Κανένα αίσθημα δυσφορίας (Καθόλου συμπτώματα. Αισθάνομαι τόσο καλά, όπως συνήθως)
1. Αίσθημα ήπιας δυσφορίας (Αισθάνομαι λίγο χειρότερα από ό,τι συνήθως)
2. Αίσθημα μέτριας δυσφορίας (Αισθάνομαι αρκετά άσχημα)
3. Αίσθημα έντονης δυσφορίας (Αισθάνομαι απαίσια).
12 Παρακαλώ σημειώστε κατά πόσο τα συμπτώματά σας εμπόδισαν τις καθημερινές σας δραστηριότητες/ εργασία τις τελευταίες 24 ώρες (Σημειώστε μόνο μια απάντηση, αυτή που σας εκφράζει καλύτερα):
0. Καθόλου (Εργασία ως συνήθως μια εργάσιμη ημέρα)
1. Λίγο (Εργασία σχετιζόμενη με λίγη δυσφορία
2. Μέτρια (Η καθημερινή εργασία απαιτεί προσπάθεια)
3. Έντονα (Η καθημερινή εργασία ή οι δραστηριότητες είναι σχεδόν αδύνατες)
13 Παρακαλώ σημειώστε κατά πόσο τα συμπτώματά σας εμπόδισαν τις κοινωνικές σας δραστηριότητες (επισκέψεις, συναντήσεις με φίλους κλπ) τις τελευταίες 24 ώρες (Σημειώστε μόνο μια απάντηση, αυτή που σας εκφράζει καλύτερα):
0. Καθόλου (Μπορώ φυσιολογικά να απολαύσω τις κοινωνικές δραστηριότητες)
1. Λίγο (Λιγότερες δραστηριότητες από ό,τι συνήθως)
2. Μέτρια (Πρέπει να παραμείνω στο σπίτι για κάποιο χρόνο)
3. Έντονα (Τα συμπτώματα με εμποδίζουν να βγω από το σπίτι)
Σύνολο απαντήσεων "ποιότητας ζωής"= βαθμοί
Επιπλέον 14 Παρακαλώ σημειώστε αν έχετε κάτι από τα παρακάτω τη στιγμή της συμπλήρωσης του ερωτηματολογίου
1. Εμμηνόρροια (περίοδος)
2. Προεμμηνορυσιακό Σύνδρομο
3. Σημεία εμμηνοπαυσιακού συνδρόμου (π.χ. εξάψεις)
4. Εγκυμοσύνη
5. Διαγνωσμένο σακχαρώδη διαβήτη (υψηλό σάκχαρο) □ Όχι
□ Όχι
□ Όχι
□ Όχι
□ Όχι □ Ναι
□ Ναι
□ Ναι
□ Ναι

 Ναι
Μην ξεχάσετε να επιστρέψετε το συμπληρωμένο ερωτηματολόγιο στον ιατρό σας. Ευχαριστώ για την συνεργασία
Επίσκεψη ελέγχου - Μέρος Β: φόρμα παρακολούθησης Ώρα: Ημερομηνία αξιολόγησης: (ηη/μμ/εεεε)
 Παρακαλώ, σημειώστε αν έχετε βιώσει αλλαγές στα συμπώματά σας από την πρώτη φορά που συμπληρώσατε αυτό το ερωτηματολόγιο.
Αποτέλεσμα 0 Ναι, αισθάνομαι φυσιολογικά (Όλα τα συμπτώματα έχουν υποχωρήσει)
 1 Ναι, αισθάνομαι πολύ καλύτερα (Τα περισσότερα συμπτώματα έχουν υποχωρήσει)
 2 Ναι, αισθάνομαι λίγο καλύτερα (Μόνο κάποια συμπτώματα έχουν υποχωρήσει)
 3 Όχι, δεν υπάρχει σχεδόν καμία αλλαγή (Έχω ακόμη περίπου τα ίδια συμπτώματα)
 4 Ναι, αισθάνομαι χειρότερα (Η κατάστασή μου έχει χειροτερέψει)
 Παρακαλώ σημειώστε αν είχατε τα παρακάτω συμπτώματα κατά τη διάρκεια των τελευταίων 24 ωρών και πόσο έντονα ήταν (Παρακαλώ επιλέξτε μόνο μια απάντηση για κάθε σύμπτωμα): 0 1 2 3
Τυπικά συμπτώματα 1 Συχνή ούρηση με μικρή ποσότητα ούρων (πηγαίνω στην τουαλέτα πολύ συχνά) Καθόλου
έως 4 φορές την ημέρα Ναι, ήπια
5-6 φορές/ημέρα Ναι, μέτρια
7-8 φορές/ημέρα Ναι, έντονα
9 φορές/ημέρα και πλέον
2 Έπειξη για ούρηση (ξαφνική και ανεξέλεγκτη)

Original Article

Robotic Partial Nephrectomy for Multiple Renal Masses: A Case Series

Abstract

Background: Partial nephrectomy is strongly recommended by the EAU guidelines as the primary treatment option for T1 Renal Cell Carcinoma. Robotic assisted partial nephrectomy has been gaining ground as an approach with similar oncological results to open and laparoscopic approaches, while outperforming them in secondary endpoints, such as functional and perioperative results. **Materials and Methods:** We present our cohort of multiple renal tumors treated with robotic partial nephrectomy. 4 patients were treated for double kidney tumours. We demonstrate patients' demographics and tumour preoperative assessment, our surgical technique, operative details, such as the perioperative outcomes and complications. **Conclusion:** Our experience in the treatment of multiple renal masses with robotic partial nephrectomy suggests favourable outcomes for our patients extending the oncological, functional and perioperative results of RAPN.

Keywords: *Multiple masses, partial nephrectomy, robot*

Konstantinos G Stravodimos, Napoleon Moulavasilis, Emmanouil Manousakis, Evangelos Fragkiadis

Department of Urology, National and Kapodistrian University of Athens, Greece

Introduction

Partial nephrectomy is strongly recommended by the EAU guidelines as the primary treatment option for T1 renal cell carcinoma,[1-9] as robotic technology plays an increasingly important role in surgery worldwide. Surgical patterns in Greece confirm the rapid adoption of the technique in everyday practice, as in the rest of the world.[10] Concerning the treatment of renal masses, oncological outcomes such as progression-free survival are comparable between radical and nephron-sparing approach, while partial nephrectomy better preserves kidney function and protects from cardiovascular disorders and mortality. Nonetheless, a slightly higher complication rate is associated with nephron-sparing techniques. Anatomic considerations regarding tumor site, size, multifocality, and complexity are also important factors in decision-making.

Robotic-assisted partial nephrectomy (RAPN) has been gaining ground as an approach with similar oncological results to open and laparoscopic approaches,[1,11] while outperforming them in secondary endpoints such as warm ischemia time (WIT), intraoperative blood loss, transfusion rates, minor and major complications, and hospital stay.[12-15]

Multiple tumors in the same kidney, comprise a somewhat niche cohort of patients of increased complexity and special surgical challenges, that has been scarcely reported in the literature.[16-19] The increased dexterity of the Da Vinci robotic system (Intuitive Surgical, USA) allows to offer the full benefits of the robotic approach while treating multiple tumors in the same kidney. We would like to present our case series of multiple renal tumors treated with robotic partial nephrectomy.

Materials and Methods

From 2013 to 2021, a total of 76 robotic partial nephrectomies were performed in our Department, while four among them were for double kidney tumors. All RAPNs were performed by an experienced surgeon (K. S.) through a transperitoneal approach. Patients were placed in a modified flank position at 60°. Three robotic arms were used and two extra ports for the bedside assistant were placed (5 and 12 mm). The AirSeal system (ConMed, USA) was used to provide stable pneumoperitoneum, continuous smoke evacuation, and valve-free access to the abdominal cavity. After mobilization of the colon and the identification of the hilum, the renal vessels were prepared and positively identified. Tumor was identified

How to cite this article: Stravodimos KG, Moulavasilis N, Manousakis E, Fragkiadis E. Robotic partial nephrectomy for multiple renal masses: A case series. Hellenic Urol 2021;33:5-8.

Submitted: 07-Jun-2021
Revised: 22-Jun-2021
Accepted: 28-Jun-2021
Published: 15-Feb-2022

Address for correspondence:
Dr. Napoleon Moulavasilis, Department of Urology, Laiko Hospital, National and Kapodistrian University of Athens, Agiou Thoma Street, Athens, 115 27, Greece.
E-mail: napomoul@hotmail.com

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 10.4103/HUAJ.HUAJ_24_21

Quick Response Code:

and the boundaries were marked with cautery; only the renal artery was clamped using a bulldog and tumors were excised. A combination of cold and cautery excision was used. A two-stage renorrhaphy was performed on the defect using the sliding-clip technique.[20]

We declare that we have obtained the consent of the participants to make the data public.

Results

Four patients (two females and two males, and one with Von Hippel-Lindau [VHL] disease) of a mean age of 52.5 (35–73) were treated for double kidney tumors and are presented in our cohort. We present the patients' demographics and tumor preoperative assessment utilizing the RENAL score in Table 1. The average value for body mass index was 26.85 kg/m^2.

Tumor characteristics and final pathology report (all patients had at least one malignant tumor) are presented in Table 2. The size of the tumors excluded was from 6 mm to 45 mm and the RENAL score was valued 4–8. Two left and two right kidneys were operated. Only one tumor was recorded as T1b stage at the histology report, while all other tumors were recorded as T1a. None positive margins were found at any tumor excision. The histopathology findings include papillary tumors for patient 1, clear cell renal cell carcinoma (CRCC) and angiomyolipoma (AML) for patient 2, both CRCC for patient 3, and for patient 4 chromophobe renal cell carcinoma and AML.

Operative details, including operative time, WIT, and blood loss are presented in Table 3. No use of hemostatic agents was needed and a drain was placed upon completion of all cases. No conversion to open procedure or radical nephrectomy (lap or open) was necessary. No blood transfusion was needed, while only one patient had a prolonged hospital stay due to respiratory infection treated with antibiotics and having a delayed discharged at 9 days postoperative. Hemoglobin and creatinine level changes, postoperative complications graded with the Clavien-Dindo system and hospital stay are presented in Table 4. We took into account, the laboratory values of the preoperative examination performed 1 day before the surgery and the laboratory values on the 1st postoperative day. The fluctuation of the estimated glomerular filtration rate value that showed a decrease or an increase was attributed to the different conditions (fasting time) for each case under which the preoperative examination was performed. During follow-up, three patients are free of recurrence while the patient with VHL disease has a new tumor and is under active surveillance.

Table 1: Demographics

Patient	Gender	Age	BMI (kg/m^2)
1	Male	48	24.7
2	Female	54	28.3
3	Male	35	29
4	Female	73	25.4

BMI: Body mass index

Discussion

Robotic partial nephrectomy offers the combined advantages of excellent long-term oncological results, less intra and postoperative complications, and the fast recovery time of a minimal approach surgery.[21,22] Multiple factors attributing to those excellent results have been identified by various groups, such as the three-dimensional visualization, the effect of pneumoperitoneum on blood loss, but the most substantial factor is the increased dexterity and high precision of robotic instrument movements toward expanding the indication of partial nephrectomies to more complex cases. Therefore, we have a rapidly growing literature regarding case series of larger T2 tumors, of advanced complexity and higher RENAL score tumors.[23,24] Complicated combined surgeries, such as partial nephrectomy and cholecystectomy, have been performed by our team owing to the same reasons.[25]

Multifocality of renal cell carcinoma may range between 4.3% and 25%.[26] Radical nephrectomy or nephron-sparing surgery does not contribute to differences in cancer-specific survival in this subgroup of patients with renal carcinoma.[27] Multiple tumors are definitely a smaller group of patients and difficult to be studied in large numbers, but could also comprise younger patients and patients of hereditary syndromes, as patient 3 in our series (35 years old with VHL disease). These patients would benefit the most from renal function preservation and decrease of cardiovascular disorders. Cohorts similar to ours,[16-19] report encouraging results, with comparable operative time (mean 183.75 min in our series) and WIT (mean 24.25 min in our series). With developing experience, all the techniques described to reduce WIT (early unclamping, select clamping, and off-clamp)[18] can be facilitated when operating multiple tumors. In our cases, early unclamping was achieved in

Table 2: Tumor characteristics

Patient	Size (mm)	Location	Renal score	Stage	Histopathology	Surgical margins
1	16 and 13	L	4 and 4	T1a both	Papillary	(−) and (−)
2	20 and 45	R	5 and 5	T1a and T1b	CRCC and AML	(−) and (−)
3	20 and 25	L	8 and 8	T1a both	CRCC both	(−) and (−)
4	30 and 6	R	6 and 6	T1a both	Chromophobe and AML	(−) and (−)

CRCC: Clear cell renal cell carcinoma, AML: Angiomyolipoma

Table 3: Operative details

Patient	Operative time (min)*	WIT (min)	Blood loss (cc)
1	230	27	250
2	210	28	180
3	180	27	190
4	115	15	140

*Includes port-placement, docking, and console time. WIT: Warm ischemia time

Table 4: Perioperative outcomes and complications

Patient	Hb decrease (g/dl)	eGFR decrease (ml/min/1.73m^2)	Clavien–Dindo	Hospitalization (days)
1	2.8	−14	2	9
2	2.3	−31.3	0	3
3	1.3	24.1	0	2
4	1.6	6	0	2

eGFR: Estimated glomerular filtration rate, Hb: Hemoglobin

one patient where the tumors were excised consecutively and the inner renorrhaphy was performed for both before unclamping and performing the approximation of the renal parenchyma.

The RENAL score is a well-accepted method that can be used to correlate with intra and postoperative complications in nephron-sparing surgery although tumor size may be used equally for the same purpose.[28]

Due to the small size of our series, we did not attempt any correlation between scores or tumor size and outcomes. Nonetheless. multiplicity poses by itself a significant factor of surgical complexity. Robotic assistance helps to avoid surgical complications[18,19] and in our series, we did not have any intra or postoperative surgical complication or conversion.

Robotic assistance has been proven to achieve equal trifecta results in multifocal tumors with less morbidity when compared to open partial nephrectomy and be safe and feasible even in cases in solitary kidneys.[29,30]

We would like to stress that RAPN, although easier than the laparoscopic counterpart, is an operation with a difficult learning curve, especially in such complicated cases requires a well experienced team of surgeons, bedside assistants, nurses, and anesthesiologists. Meticulous preoperative assessment with contrast-enhanced computed tomography or Magnetic Resonance Imaging is of utmost importance regarding hilum anatomy, tumor anatomy, and preoperative planning in all of partial nephrectomy cases.

Conclusion

Our experience in the treatment of multiple renal masses with robotic partial nephrectomy suggests favorable outcomes for our patients extending the oncological, functional, and perioperative results of RAPN to a very special group of patients that may benefit the most. These complicated cases although demanding, should not be excluded from the robotic approach, but a dedicated and experienced surgical team is needed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. MacLennan S, Imamura M, Lapitan MC, Omar MI, Lam TB, Hilvano-Cabungcal AM, *et al.* Systematic review of perioperative and quality-of-life outcomes following surgical management of localised renal cancer. Eur Urol 2012;62:1097-117.
2. Kunath F, Schmidt S, Krabbe LM, Miernik A, Dahm P, Cleves A, *et al.* Partial nephrectomy versus radical nephrectomy for clinical localised renal masses. Cochrane Database Syst Rev 2017;5:CD012045.
3. Thompson RH, Boorjian SA, Lohse CM, Leibovich BC, Kwon ED, Cheville JC, *et al.* Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. J Urol 2008;179:468-71.
4. Huang WC, Elkin EB, Levey AS, Jang TL, Russo P. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors – is there a difference in mortality and cardiovascular outcomes? J Urol 2009;181:55-61.
5. Miller DC, Schonlau M, Litwin MS, Lai J, Saigal CS; Urologic Diseases in America Project. Renal and cardiovascular morbidity after partial or radical nephrectomy. Cancer 2008;112:511-20.
6. Capitanio U, Terrone C, Antonelli A, Minervini A, Volpe A, Furlan M, *et al.* Nephron-sparing techniques independently decrease the risk of cardiovascular events relative to radical nephrectomy in patients with a T1a-T1b renal mass and normal preoperative renal function. Eur Urol 2015;67:683-9.
7. Scosyrev E, Messing EM, Sylvester R, Campbell S, Van Poppel H. Renal function after nephron-sparing surgery versus radical nephrectomy: Results from EORTC randomized trial 30904. Eur Urol 2014;65:372-7.
8. Kates M, Badalato GM, Pitman M, McKiernan JM. Increased risk of overall and cardiovascular mortality after radical nephrectomy for renal cell carcinoma 2 cm or less. J Urol 2011;186:1247-53.
9. Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A,

Borkowski A, *et al*. A prospective randomized EORTC intergroup phase 3 study comparing the complications of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol 2007;51:1606-15.

10. Deligiannis D, Anastasiou I, Mygdalis V, Fragkiadis E, Stravodimos K. Change of practice patterns in urology with the introduction of the Da Vinci surgical system: The Greek NHS experience in debt crisis era. Arch Ital Urol Androl 2015;87:56-61.
11. Chang KD, Abdel Raheem A, Kim KH, Oh CK, Park SY, Kim YS, *et al.* Functional and oncological outcomes of open, laparoscopic and robot-assisted partial nephrectomy: A multicentre comparative matched-pair analyses with a median of 5 years' follow-up. BJU Int 2018;122:618-26.
12. Alimi Q, Peyronnet B, Sebe P, Cote JF, Kammerer-Jacquet SF, Khene ZE, *et al.* Comparison of short-term functional, oncological, and perioperative outcomes between laparoscopic and robotic partial nephrectomy beyond the learning curve. J Laparoendosc Adv Surg Tech A 2018;28:1047-52.
13. Masson-Lecomte A, Yates DR, Hupertan V, Haertig A, Chartier-Kastler E, Bitker MO, *et al*. A prospective comparison of the pathologic and surgical outcomes obtained after elective treatment of renal cell carcinoma by open or robot-assisted partial nephrectomy. Urol Oncol 2013;31:924-9.
14. Peyronnet B, Seisen T, Oger E, Vaessen C, Grassano Y, Benoit T, *et al.* Comparison of 1800 robotic and open partial nephrectomies for renal tumors. Ann Surg Oncol 2016;23:4277-83.
15. Choi JE, You JH, Kim DK, Rha KH, Lee SH. Comparison of perioperative outcomes between robotic and laparoscopic partial nephrectomy: A systematic review and meta-analysis. Eur Urol 2015;67:891-901.
16. Abreu AL, Berger AK, Aron M, Ukimura O, Stein RJ, Gill IS, *et al.* Minimally invasive partial nephrectomy for single versus multiple renal tumors. J Urol 2013;189:462-7.
17. Boris R, Proano M, Linehan WM, Pinto PA, Bratslavsky G. Initial experience with robot assisted partial nephrectomy for multiple renal masses. J Urol 2009;182:1280-6.
18. Laydner H, Autorino R, Spana G, Altunrende F, Yang B, Khanna R, *et al.* Robot-assisted partial nephrectomy for sporadic ipsilateral multifocal renal tumours. BJU Int 2012;109:274-80.
19. Yang J, Xia JD, Xue JX, Song NH, Liang C, Xi D, *et al.* Robotic-assisted partial nephrectomy with sequential clamping of segmental renal arteries for multiple ipsilateral renal tumors: Initial outcomes. BMC Urol 2019;19:31.
20. Benway BM, Wang AJ, Cabello JM, Bhayani SB. Robotic partial nephrectomy with sliding-clip renorrhaphy: Technique and outcomes. Eur Urol 2009;55:592-9.
21. Gul ZG, Tam A, Badani KK. Robotic partial nephrectomy: The current status. Indian J Urol 2020;36:16-20.
22. Bertolo R, Garisto J, Dagenais J, Sagalovich D, Stein R, Fareed K, *et al.* Transperitoneal robot-assisted partial nephrectomy with minimum follow-up of 5 years: Oncological and functional outcomes from a single institution. Eur Urol Oncol 2019;2:207-13.
23. Abdel Raheem A, Alatawi A, Kim DK, Sheikh A, Alabdulaali I, Han WK, *et al*. Outcomes of high-complexity renal tumours with a Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) score of ≥10 after robot-assisted partial nephrectomy with a median 46.5-month follow-up: A tertiary centre experience. BJU Int 2016;118:770-8.
24. Hennessey DB, Wei G, Moon D, Kinnear N, Bolton DM, Lawrentschuk N, *et al.* Strategies for success: A multi-institutional study on robot-assisted partial nephrectomy for complex renal lesions. BJU Int 2018;121 Suppl 3:40-7.
25. Stravodimos K, Katafigiotis I, Pournaras C, Dimitroulis D, Kousournas G, Fragkiadis E, *et al*. Combined robot assisted right partial nephrectomy and cholecystectomy with single docking. J Robot Surg 2019;13:167-9.
26. Tsivian M, Moreira DM, Caso JR, Mouraviev V, Madden JF, Bratslavsky G, *et al.* Predicting occult multifocality of renal cell carcinoma. Eur Urol 2010;58:118-26.
27. Minervini A, Serni S, Giubilei G, Lanzi F, Vittori G, Lapini A, *et al.* Multiple ipsilateral renal tumors: Retrospective analysis of surgical and oncological results of tumor enucleation vs radical nephrectomy. Eur J Surg Oncol 2009;35:521-6.
28. Khene ZE, Mazouin C, Larcher A, Peyronnet B, Gasmi A, Roumiguié M, *et al.* Predicting Complications After Robotic Partial Nephrectomy: Back to Simplicity. Eur Urol Focus. 2021:S2405-4569(21)00123-1. doi: 10.1016/j.euf.2021.04.017. Epub ahead of print. PMID: 33958318.
29. Yerram NK, Dagenais J, Bryk DJ, Nandanan N, Maurice MJ, Mouracade P, *et al.* Trifecta outcomes in multifocal tumors: A comparison between robotic and open partial nephrectomy. J Endourol 2018;32:615-20.
30. Miyake H, Motoyama D, Matsushita Y, Watanabe H, Ito T, Sugiyama T, *et al*. Robot-assisted partial nephrectomy for patients with multifocal renal tumors arising in a solitary kidney: Report of three cases. J Endourol Case Rep 2020;6:370-3.

Review Article

Minimal Invasive Treatment of Locally Advanced Renal Cancer

Abstract

Despite the progress in diagnosis and treatment, renal cancer still represents one of the deadliest malignancies of the urogenital tract. Surgically wise, one could certainly make the case that locally advanced renal cancer, especially with vena cava involvement, is the most challenging operable tumor. Conventionally, these patients have been operated with open approach. Nowadays, the contribution of advanced technology (both laparoscopy and robotics) as well as the increasing experience of the surgeons has led to the usage of minimal invasive (MI) techniques in increasingly complex cases. The purpose of this review is to highlight the most important data in the literature as far as usage of MI techniques in the treatment of locally advanced RC is concerned.

Keywords: *Laparoscopy, locally advanced renal cancer, robotics*

Periklis Giannakis, Panagiotis Prodromos Papadopoulos, Panagiotis Mourmouris, Ioannis Varkarakis, Charalambos Deliveliotis

2nd Department of Urology, National Kapodistrian University of Athens, Sismanoglio General Hospital, Athens, Greece

Introduction

Renal carcinoma (RC) is still one of the deadliest urogenital tumors in the modern era of diagnostics and treatment.[1] Interestingly enough, the most challenging tumors to resect are without a doubt the locally advanced ones, including the ones who infiltrate the renal vein (renal vein) or with vena cava (VC) involvement.[2] In the past, locally advanced RC as well as tumors with size >7 cm were considered as strong contraindications for the use of minimal invasive (MI) techniques. However, the unneglectable advantages of MI (i.e., three-dimensional [3D] vision and flexible tools) and the undisputed rise of surgical expertise have led to the incorporation of these techniques in increasingly advanced cases.[3] This is not just an assumption, as the literature on laparoscopic partial nephrectomy for T3a tumors[4] and robotic nephrectomy with additional excision of inferior vena cava (IVC) thrombus above the diaphragm is constantly enriched.[5] In conclusion, MI techniques are already a part of locally advanced RC excision and it seems like its use will follow an ascending trajectory.

Material and Methods

We conducted a thorough search in PubMed for articles written only in English and from inception to 2021. We reviewed only studies with at least one abstract. We used the terms "T3a renal tumors", "IVC thrombus", "laparoscopic nephrectomy", "robotic nephrectomy", "locally advanced renal tumors".

Renal vein or branch infiltration (T3a)

Even from the very first studies, laparoscopic excision of T3a tumors provided very encouraging results. More than a decade ago, a large study was conducted at John Hopkins with 37 patients diagnosed with RC and thrombosis of the RV. Despite the large mean size (7.5 cm), transfusions were only needed in 16% of cases, the mean postoperative hospital stay was 3 days, and complications occurred in 19% of the cases. It is noteworthy that only one case was converted to open surgery.[6] In a more recent study, survival rates of patients who were treated with laparoscopic radical nephrectomy (LRN) were compared and contrasted to those of the ones treated with an open approach. In a sample of more than 1000 patients, neither single nor multivariable statistical analysis showed worse prognosis in the laparoscopic approach.[7] Confirmatory results for the efficacy of LRN for locally advanced RC were provided by a smaller but prospective study of 25 patients, in which there were no conversions to open approach, and no statistically significant differences in complications ($P < 0.52$) as well as better results in blood loss ($P < 0.001$) and hospitalization ($P < 0.001$) were reported.[8]

How to cite this article: Giannakis P, Papadopoulos PP, Mourmouris P, Varkarakis I, Deliveliotis C. Minimal invasive treatment of locally advanced renal cancer. Hellenic Urol 2021;33:9-11.

Submitted: 30-Aug-2021
Revised: 20-Sep-2021
Accepted: 09-Oct-2021
Published: 15-Feb-2022

Address for correspondence:
Dr. Panagiotis Mourmouris, 2nd Department of Urology, National and Kapodistrian University of Athens, 1 Sismanogleiou Str Marousi, Athens, Greece.
E-mail: thodoros13@yahoo.com

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 10.4103/HUAJ.HUAJ_32_21

Quick Response Code:

Furthermore, the scientific leaps in robotics quickly changed the landscape in the treatment of locally advanced RC, offering robotic partial nephrectomy (RPN) as another MI alternative. One of the largest studies in the literature includes 157 patients who underwent RPN for T3 tumors, of which 34 involved the RV or a branch. During the operation, tumor excision (mean size 7 cm) as well as thrombectomy were performed. The trifecta was achieved, with 95% negative surgical margins, 76% warm ischemia time, and 85% no postoperative complications.[9]

The aforementioned promising results of RPN could only lead to its comparison to another MIS modality, and robotic radical nephrectomy (RRN) as far as T3 tumors are concerned. In a 140 patient study, Andrade *et al*. showed that RPN achieved the same oncological results without a burden on survival, and in contrast with RRN, renal function was better preserved.[4] It is worth mentioning, however, that studies indicate optimal preoperative staging as a prerequisite for success in robotic excision of locally advanced RC. A large meta-analysis shows worse outcomes on patients that underwent robotic nephrectomy and were staged as pT1 and cT3 relative to patients with the same clinical and pathology staging.[10]

Inferior vena cava thrombus

Laparoscopic approach

It is only logical to assume that MI IVC thrombectomy was first tested below the diaphragm, with classic laparoscopy. In 2002, Sundaram *et al*. first reported their experience from a patient with a 12 cm RC and a level 2 IVC thrombus. Not only were the results promising, with EBL 500 mL and a 3-day postoperative hospital stay[11] but also other researchers managed to report increasingly encouraging results in the following years as well.[12-14] Increasing experience and confidence led to larger patient samples, with Martin *et al*. reporting a study of 14 patients, 4 of which had an IVC thrombus. All tumors and thrombi were excised on negative margins, with only one complication (PE that was treated with anticoagulants) and no recurrence in the 4 years of follow-up.[15] The most recent study regarding laparoscopy was published in 2015 and includes patients with more advanced level 4 IVC thrombi; mean operation time was 275 min, mean EBL was 850 mL with no patient having a complication Clavien >3.[16]

Robotic approach

The emergence of robotic systems has vastly renovated the field of angioplasty procedures by bringing tools for fast suturing and 3D vision. Robotics were used pretty early in simple renal procedures, so there should be no surprise that they are now being used in much more complex scenarios. The first report of robotic nephrectomy with concurrent IVC thrombectomy was published by Abaza *et al*., who for the first time performed side-clamping and thrombectomy simultaneously, thus sparing IVC flow.[17] The same technique was used in the first multicenter study concerning 32 patients, 2 of which had level 3 IVC thrombi; mean thrombus size was 4.2 cm (2–11 cm), mean operational time was 292 min (largely shorter than laparoscopic approach), and no operation was converted to open approach.[18] In the following years, more studies on robotic thrombectomy were published, with increases in both the complexity of cases and the number of patients. Short hospital stays (1–5 days) were achieved, with no conversions to open surgery and complication rates that did not exceed 25%.[19-22]

Level 4 IVC thrombectomies are without a doubt the most technically demanding procedure as far as locally advanced RC is concerned and traditionally require an open approach. However, Wang *et al*. very recently presented their attempt to deal with such thrombi (right side) using robotic surgery.[23] In cooperation with cardiac surgeons, cardiopulmonary bypass was initiated, the proximal IVC was then clamped, and RA thrombectomy was performed. Moving on, the IVC was clamped below the diaphragm along with the LRV and the hepatic vein, allowing IVC thrombectomy above the diaphragm. On the upside, despite a mean EBL of 2800 mL and a mean duration of 510 min, 60% of the patients did not show major complications, which makes this technique a success considering the complexity of the case. On the downside, the aforementioned technique requires highly experienced robotic surgeons and frequent repositioning of trocars and robotic arms, which significantly increase the operational time and skill requirement.

Comparison of open and minimal invasive approaches

Inevitably, advancements in MIS led to its comparison with the open approach, which is still the first-line treatment for T3 RC. The first multivariable analysis between open and MI approaches for level 1 and 2 thrombi proved that surgical technique is not influential in the overall survival rates. That being said, robotics showed favorable results in terms of hospitalization time, intraoperative blood loss, operational time, and overall complications.[24] However, due to the low number of patients, these results present some limitations, which were put to rest by an 872 patient study, in which open approach was associated with greater blood loss, longer hospital stays, and no advantage in postoperative complications.[25]

At this point, it is worth mentioning that surgeons who managed to perform such demanding operations, such as robotic IVC thrombectomy, have a much greater experience than the normal learning curve (over 1000 operations). This review demonstrates perhaps the most basic benefits of MI as a treatment modality for locally advanced RC. Although the series are relatively small, the smaller blood losses and the reduction in hospitalization time are evident.[7,24] At the same time, the reduced or even zero need for sedatives[18]

leads to faster recovery as well as faster initiation of adjuvant therapy, when indicated.

Despite the encouraging results, it is important to recognize the significant limitations of the studies that offer them. Most of the studies are retrospective and therefore characterized by significant selection bias. In addition, prospective randomized trials are almost impossible to carry in such a clinical entity. Furthermore, these operations require extremely experienced robotic surgeons, and therefore, they cannot be easily widespread, but even so, the latter should have experience in open surgeries, in case a conversion is required.

Conclusions

The treatment of locally advanced RC with MIS techniques proves feasible and safe and offers corresponding oncological results with the classic open approach in combination with more favorable peri- and postoperative results. However, the use of these techniques requires extensive surgical experience and given the low level of evidence from the existing literature, larger and better organized studies are needed to determine the patients who will benefit from the use of these methods.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
2. Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernández-Pello S, *et al.* European Association of Urology guidelines on renal cell carcinoma: The 2019 update. Eur Urol 2019;75:799-810.
3. Murphy C, Abaza R. Complex robotic nephrectomy and inferior vena cava tumor thrombectomy: An evolving landscape. Curr Opin Urol 2020;30:83-9.
4. Andrade HS, Zargar H, Akca O, Kara O, Caputo PA, Ramirez D, *et al.* Is Robotic partial nephrectomy safe for T3a renal cell carcinoma? Experience of a high-volume center. J Endourol 2017;31:153-7.
5. Wang B, Li H, Huang Q, Liu K, Fan Y, Peng C, *et al.* Robot-assisted retrohepatic inferior vena cava thrombectomy: First or second porta hepatis as an important boundary landmark. Eur Urol 2018;74:512-20.
6. Guzzo TJ, Schaeffer EM, McNeil BK, Pollock RA, Pavlovich CP, Allaf ME. Laparoscopic radical nephrectomy for patients with pathologic T3b renal-cell carcinoma: The Johns Hopkins experience. J Endourol 2009;23:63-7.
7. Bensalah K, Salomon L, Lang H, Zini L, Jacqmin D, Manunta A, *et al.* Survival of patients with nonmetastatic pT3 renal tumours: A matched comparison of laparoscopic vs open radical nephrectomy. BJU Int 2009;104:1714-7.
8. Laird A, Choy KC, Delaney H, Cutress ML, O'Connor KM, Tolley DA, *et al.* Matched pair analysis of laparoscopic versus open radical nephrectomy for the treatment of T3 renal cell carcinoma. World J Urol 2015;33:25-32.
9. Yim K, Aron M, Rha KH, Simone G, Minervini A, Challacombe B, *et al.* Outcomes of Robot-assisted Partial Nephrectomy for Clinical T3a Renal Masses: A Multicenter Analysis. Eur Urol Focus. 2021;7:1107-14.
10. Veccia A, Falagario U, Martini A, Marchioni M, Antonelli A, Simeone C, *et al.* Upstaging to pT3a in patients undergoing partial or radical nephrectomy for cT1 renal tumors: A systematic review and meta-analysis of outcomes and predictive factors. Eur Urol Focus 2021;7:574-81.
11. Sundaram CP, Rehman J, Landman J, Oh J. Hand assisted laparoscopic radical nephrectomy for renal cell carcinoma with inferior vena caval thrombus. J Urol 2002;168:176-9.
12. Disanto V, Pansadoro V, Portoghese F, Scalese GA, Romano M. Retroperitoneal laparoscopic radical nephrectomy for renal cell carcinoma with infrahepatic vena caval thrombus. Eur Urol 2005;47:352-6.
13. Romero FR, Muntener M, Bagga HS, Brito FA, Sulman A, Jarrett TW. Pure laparoscopic radical nephrectomy with level II vena caval thrombectomy. Urology 2006;68:1112-4.
14. Varkarakis IM, Bhayani SB, Allaf ME, Inagaki T, Gonzalgo ML, Jarrett TW. Laparoscopic-assisted nephrectomy with inferior vena cava tumor thrombectomy: Preliminary results. Urology 2004;64:925-9.
15. Martin GL, Castle EP, Martin AD, Desai PJ, Lallas CD, Ferrigni RG, *et al.* Outcomes of laparoscopic radical nephrectomy in the setting of vena caval and renal vein thrombus: Seven-year experience. J Endourol 2008;22:1681-5.
16. Shao P, Li J, Qin C, Lv Q, Ju X, Li P, *et al.* Laparoscopic radical nephrectomy and inferior vena cava thrombectomy in the treatment of renal cell carcinoma. Eur Urol 2015;68:115-22.
17. Abaza R. Initial series of robotic radical nephrectomy with vena caval tumor thrombectomy. Eur Urol 2011;59:652-6.
18. Abaza R, Shabsigh A, Castle E, Allaf M, Hu JC, Rogers C, *et al.* Multi-institutional experience with robotic nephrectomy with inferior vena cava tumor thrombectomy. J Urol 2016;195:865-71.
19. Bratslavsky G, Cheng JS. Robotic-assisted radical nephrectomy With retrohepatic vena caval tumor thrombectomy (Level III) combined with extended retroperitoneal lymph node dissection. Urology 2015;86:1235-40.
20. Chopra S, Simone G, Metcalfe C, de Castro Abreu AL, Nabhani J, Ferriero M, *et al.* Robot-assisted Level II-III inferior vena cava tumor thrombectomy: Step-by-Step technique and 1-year outcomes. Eur Urol 2017;72:267-74.
21. Gill IS, Metcalfe C, Abreu A, Duddalwar V, Chopra S, Cunningham M, *et al.* Robotic Level III inferior vena cava tumor thrombectomy: Initial series. J Urol 2015;194:929-38.
22. Wang B, Li H, Ma X, Zhang X, Gu L, Li X, *et al.* Robot-assisted laparoscopic inferior vena cava thrombectomy: Different sides require different techniques. Eur Urol 2016;69:1112-9.
23. Wang B, Huang Q, Liu K, Fan Y, Peng C, Gu L, *et al.* Robot-assisted Level III-IV Inferior vena cava thrombectomy: Initial series with step-by-step procedures and 1-yr outcomes. Eur Urol 2020;78:77-86.
24. Gu L, Ma X, Gao Y, Li H, Li X, Chen L, *et al.* Robotic versus open level I-II Inferior vena cava thrombectomy: A matched group comparative analysis. J Urol 2017;198:1241-6.
25. Beksac AT, Shah QN, Paulucci DJ, Lo JZ, Okhawere KE, Elbakry AA, *et al.* Trends and outcomes in contemporary management renal cell carcinoma and vena cava thrombus. Urol Oncol 2019;37:576.e17-23.

Review Article

Is *Trichomonas vaginalis* a Risk Factor for Prostate Cancer? A Systematic Review and Meta-analysis

Abstract

Clinical studies have shown that patients exposed to the protozoan *Trichomonas vaginalis* (TV) may present an increased risk to develop prostate cancer (PCa). However, since data from other studies and meta-analyses did not provide so far univocal results this issue remains controversial. In this systematic review, we examined the current molecular, cellular and clinical evidence in favor or against a possible association between TV prostatitis and the incidence of PCa. Electronic database search, title/abstract screening and full-text reading yielded a total of 17 clinical articles and meta-analyses and 12 articles showing the results of preclinical investigations. Preclinical evidence points to the involvement of TV in proliferative disorders in prostate cells, involving an array of immune cell mediators. Five clinical case-control studies documented a significantly increased odds for PCa in patients with a positive TV serostatus, whereas seven other studies showed nonsignificant results. Our meta-analysis including 12 studies retrieved up to June 1, 2021, did not evidence a significant association between a positive TV serostatus and PCa of any grade (odds ratio [OR], 1.14; 95% confidence interval [CI]: 0.84–1.53). Moreover, we could not find a significant association between advanced/lethal PCa and TV exposure (OR, 1.18; 95% CI: 0.70–2.00). In conclusion, the association between a positive TV serostatus and PCa remains uncertain. Studies focused on a large sample of documented cases of symptomatic, clinical TV chronic prostatitis are warranted to make a conclusive statement in this regard.

Keywords: *Carcinogenesis, oncogenesis, prostate, prostate cancer, prostatitis, Trichomonas vaginalis*

Gianpaolo Perletti[1,2], Vittorio Magri[3], Louise Beckers-Perletti[2], Alberto Trinchieri[4], Konstantinos Stamatiou[5]

[1]Department of Biotechnology and Life Sciences, Section of Medical and Surgical Sciences, University of Insubria, Varese, [3]Urology Secondary Care Clinic, ASST-Nord, [4]Department of Urology, University of Milan-Ca' Granda Foundation, Policlinico, of Milan, Milan, Italy, [2]Faculty of Medicine and Medical Sciences, Ghent University, Ghent, Belgium, [5]Department of Urology, Tzaneio General Hospital, Piraeus, Greece

Introduction

Chemical or physical genotoxic agents can cause-together with epigenetic modulators-the vast majority of human cancers.[1] However, carcinogenesis may also occur when human tissues are colonized by microorganisms which may cause chronic infection and sustained inflammation. This is known to occur in a significant fraction of cancer cases (up to 20%).[2,3] Among viruses, the Human Papillomavirus, the Epstein-Barr virus, the Hepatitis B and C virues, the Kaposi's sarcoma-associated herpesvirus and others are the cause of several forms of cancer.[4] Among bacteria, the linkage between *Helicobacter pylori* and gastric cancer or mucosa-associated lymphoid tissue lymphoma is well established.[5]

The persistent seroprevalence of protozoans such as *Cryptosporidium parvum, Toxoplasma gondii, Blastocystis hominis, Plasmodium falciparum* and *Trichomonas vaginalis* (TV) is also reputed to be involved in the genesis of human cancers.[6]

TV is a flagellated anaerobic protozoan parasite that can infect male and female mucosae. TV is the causative agent of the most common nonviral sexually transmitted infection (STI), affecting over 150 million people worldwide.[7] In women, TV can cause vaginitis, characterized by vaginal discharge, and *colpitis macularis*, a herythematous, micro-hemorragic inflammation of the cervix. In addition, trichomonal infection has been suggested to concur to the onset of cervical cancer, likely by enhancing the oncogenic potential of Human Papillomavirus.[8] In men, TV can cause symptomatic or asymptomatic infections of the lower urinary tract and accessory glands, and trichomonal prostatitis is an occasional finding in a fraction of patients.[9] Notably, prostatitis is suspected to be a risk factor for prostate cancer (PCa).[10,11]

How to cite this article: Perletti G, Magri V, Beckers-Perletti, L, Trinchieri A, Stamatiou K. Is *Trichomonas vaginalis* a risk factor for prostate cancer? A systematic review and meta-analysis. Hellenic Urol 2021;33:12-23.

Submitted: 04-Jun-2021
Revised: 20-Jun-2021
Accepted: 29-Jun-2021
Published: 15-Feb-2022

Address for correspondence:
Prof. Gianpaolo Perletti, Department of Biotechnology and Life Sciences, University of Insubria, Via Manara, 7, 21052 Busto Arsizio (Varese), Italy. E-mail: gianpaolo.perletti@uninsubria.it

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 0.4103/HUAJ.HUAJ_23_21

Quick Response Code:

The role of TV in the genesis of PCa is still controversial and data from clinical studies and meta-analyses did not provide so far univocal results.[12]

In this systematic review, we examined the current molecular, cellular and clinical evidence in favor or against a possible association between TV prostatitis and the incidence and severity of PCa. Wherever possible, we performed a meta-analysis of clinical data.

Patients and Methods

Eligibility criteria

In the preclinical section of the review, we included only full-text articles written in English reporting the results of laboratory investigation focusing on TV, PCa, carcinogenesis and proliferative disorders. In the clinical section of the review we included only full-text articles written in English, reporting case-control studies evaluating the relationship between exposure to TV, assessed with serological methods, and a diagnosis of PCa. Patients of any ethnicity with a history of PCa of any grade, lethal or nonlethal, were eligible for the present review.

Outcomes

The single clinical outcome considered for this review is the association between the serological evidence of exposure to TV and a documented diagnosis of PCa of any grade.

Search strategy and study selection

Retrieval of published reports of case-control studies and preclinical reports was performed by searching international databases (e.g. Medline, Embase, etc., for PubMed: (Trichomonas [Title/Abstract]) AND (Prostate [Title/ Abstract]) AND (Cancer [Title/Abstract] OR carcinoma [Title/ Abstract]). All searches were assessed as up to date on June 1, 2021. Articles included in the present review are referred to by the first author and year of publication.

Quality assessment

The quality of individual clinical studies was assessed by two researchers using the case-control study version of the Newcastle–Ottawa Scale (NOS). The thresholds for converting NOS scores to Agency for Healthcare Research and Quality (AHRQ) standards were:

- Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/ exposure domain.

Publication bias was investigated by visually assessing funnel plots and by performing both the Egger's regression test and the Begg's rank correlation analysis.

We outlined the results of our meta-analyses on a summary of findings table, rating as well the quality of the pooled evidence according to GRADE criteria.[13]

Clinical data collection and statistical analysis

Data extraction was performed using standard extraction forms by two authors. To analyze dichotomous data we calculated crude (unadjusted) odds ratios (OR), the 95% confidence intervals (CIs) and Z statistics. For meta-analysis, we adopted a random-effects model and the inverse variance weighting method. Heterogeneity was assessed by calculating the I^2 value.

The *Meta-Essentials* Excel workbook 1.5 (Erasmus Research Institute of Management, Erasmus University, Rotterdam, The Netherlands) was used to perform pooled analyses, heterogeneity calculations, the Egger's/Begg's tests, and to draw funnel and forest plots.

Results

A simple term search of electronic databases, up to June 1, 2021, retrieved 47 citations. After title and abstract screening 32 records were selected. After full-text reading, we included 17 articles reporting the outcome of clinical studies and meta-analyses and 12 articles showing the results of preclinical investigations.

Preclinical evidence

The hypothesis of a link between the exposure to TV and PCa, derived from clinical observations, has fostered in the last decade extensive investigation at the cellular and molecular levels. Since inflammation is a known contributor to carcinogenesis, TV-induced activation of inflammatory cells and of inflammatory mediator release have been investigated.

It is recognized that inflammation caused by TV may involve the activation of the innate immune response receptor toll-like receptor 4 (TLR4) and inflammatory cytokine release.[14] Chen *et al*. investigated whether the expression of a TLR4 single-nucleotide polymorphism (rs4986790) generating the 896A>G (Asp299Gly) mutation, which decreases the inflammatory response, could modify the association between TV infection and PCa risk. This large nested case–control study, performed on 1382 subjects, provided evidence that PCa patients carriers of the 896A>G variant showed a higher odds (OR, 4.16; 95% CI, 1.32–13.1) of being seropositive for TV compared to homozygous carriers of the wild-type genotype.[15] The authors concluded that SNP carriers may mount a weak immune response against TV, thus increasing the likelihood of establishing sustained TV inflammatory prostatitis.

The human macrophage migration inhibitory factor (MIF), a pro-inflammatory regulator of innate immunity involved in cancer growth and invasion, seems to be implicated in TV-induced changes in prostate cells. MIF acts by protecting

macrophages from activation-induced apoptosis, thus promoting sustained inflammation. A major breakthrough in research was the finding that TV secretes TvMIF, a protozoan homolog (47% homology) of human MIF.[16] It was also demonstrated that TvMIF binds the human CD74 receptor with high affinity and is as potent as HuMIF in activating extracellular-signal-regulated kinase (ERK) in both benign prostatic hyperplasia (BPH)-1 cells and PC3 human metastatic PCa cells. Moreover, TvMIF promoted both the growth and invasive phenotypes of these cell lines.[16]

Han *et al*. demonstrated that prostate epithelial cells can promptly respond to the presence of TV by producing the cytokines interleukin (IL)-6, CCL2 and CXCL8, by inducing polarization of tumor-associated M2 macrophages, which in turn upregulate M2 markers such as IL-10, transforming growth factor-β, CD36, CD206, and arginase-1, finally promoting the proliferation and migration of a panel of human PCa cells (PC3, DU145 and LNCaP). In addition, TV-conditioned TRAMP-C2 PCa cells stimulated the accumulation of M2 macrophages in the prostate of mice *in vivo,* thus supporting a pivotal role of M2 in this process.[17]

Interestingly, the interplay between TV and macrophages may involve adipocytes, which are paracrine secretors of adipokines and other inflammatory mediators involved in cancer development and progression.[18,19]

Which cellular processes may be involved in the signaling pathways activated in the prostate by TV infection? The hypothesis that TV could act by inducing epithelial-mesenchymal transition (EMT) in prostate cells was investigated by Han *et al*. EMT is a process whereby cells of the epithelial lineage loose polarity and adhesion properties, thus acquiring the capacity to migrate and invade surrounding tissues, and to gain survival capacity and resistance to apoptosis. In oncogenesis, cells that undergo EMT can evolve into cancer stem cells by acquisition of stem cell-like properties. In an elegant study, Han *et al*. could demonstrate that human prostate epithelial cells stimulated with TV produced IL-6 in a pathogen load-dependent fashion. Expression of TLRs 2 and 4 also increased upon TV stimulation, which in turn triggered the expression of downstream TLR effectors like MAPKs p38, c-JUN N-terminal kinase, ERK, of nuclear factor-kappa B (NF-κB), and of JAK2 and STAT3 proteins. Concurrently, the authors documented a pathogen load-dependent decrease of epithelial markers (E-cadherin, cytokeratin, ZO-1) coupled to an increase of mesenchymal markers (N-cadherin, vimentin, fibronec-tin-1, β-catenin, snail1, matrix metalloproteinase-9). This was associated with expression of EMT-associated STAT3 and p-IκB proteins.[20] A subsequent study by the same research group provided additional information about the molecular mechanism of TV-triggered EMT. It was shown that stimulation by TV induced in human prostate epithelial RWPE-1 cells the production of IL-1 β, IL-6, CCL2, CXCL8, prostaglandin-E2, and COX2. The TV-conditioned medium of RWPE-1 cells was then able to markedly increase the malignant phenotype of a panel of PCa cells (PC3, DU145, and LNCaP) by enhancing their proliferation, migration and invasiveness. This effect was accompanied by EMT, demonstrated by a reduction in epithelial markers and an increase in mesenchymal markers. *In vivo*, xenograft tumors exposed to the TV-conditioned medium showed increased expression of cyclin D1 and PCNA, as well as features of EMT.[21]

The key role of IL-6 as a mediator of TV was also confirmed by Sutcliffe *et al*., who, as a result of their and others' evidence, proposed a model whereby TV-induced production of IL-6 leads to transcriptional activation of the STAT3-PIM1-HMGA1 cascade. Activation of the PIM1 effector HMGA1 proto-oncogene would then be a principal actor in prostate carcinogenesis through pathways involving COX2 and prostate-specific membrane antigen.[22]

The signaling responses characterized by Han *et al*. and Sutcliffe *et al*. were consistently confirmed by cytokine array, Reactome, and STRING analyses. Up to 23 cytokines were upregulated within 24 h of exposure of RWPE-1 cells to TV. Among the cytokines, upregulation of IL-6 was confirmed, together with IL-8, NF-κB, STAT3 and COX2. STRING further confirmed the role of MIF described above, and of PIM-1. Tumor proliferation markers Ki67, PCNA, and Bcl-2 were also upregulated. Finally, EMT was confirmed by assessment of downregulation of E-cadherin, upregulation of vimentin, and activation of focal adhesion kinase. Interestingly, human DU145 PCa cells were more sensitive to TV-activated signaling compared to normal, nontumorigenic, nonneoplastic human RWPE-1 prostatic epithelial cells.[23]

Although macrophages appear to play a key role in prostate cell growth and progression, neutrophils are also involved in the inflammatory response to TV and in inflammatory tissue damage. It was shown that neutrophils can activate *trogocytosis* to kill and clear TV infection in response to various inflammatory mediators.[24] However, this may involve inflammatory tissue damage and the release of mediators that may concur to neoplastic transformation. In addition to macrophages and neutrophils, activated mast cells were found to play a role in the stimulation of cellular proliferation in the prostate in the presence of TV. Kim *et al*. demonstrated that trichomonads could stimulate BPH-1 benign prostate hyperplasia cells to produce various chemokines (CCL2, IL-1b, IL-6, CXCL8), that activated mast cells, which in turn stimulated the proliferation of prostate stromal cells.[25]

Taken together, the evidence emerging from preclinical investigation performed so far supports a model whereby IL-6, secreted by polarized M2 macrophages in response

to stimuli exerted by TV, would be part of a complex signaling pathway also involving innate immune system pattern recognition receptors such as TLR4. The cascade would include transcriptional activation of the HMGA1 oncogene, directly contributing to cancer progression via pathways involving COX-2. The phenotypic expression of these molecular events would be inflammation, EMT, and promotion of various steps in prostatic oncogenesis.

Despite the fact that several experts demonstrated that TV can trigger a number of molecular and cellular events leading to the acquisition of phenotypic features highly suggestive of neoplastic transformation, others have provided experimental evidence of an anti-proliferative and pro-apoptotic effect of TV on PCa cells. Zhu *et al*. showed that the TV-conditioned medium inhibits the growth of two human PCa cell lines (PC-3 and DU145) and that this effect correlated with upregulation of p21, downregulation of Bcl-2, and induction of apoptosis. The authors concluded that TV may not be associated with the development of PCa, but rather that TV infection might be potentially beneficial and therapeutic to patients in an early neoplastic state.[26] Although these considerations are in contrast with the evidence provided by other research groups, they are worthy of careful thought and suggest the existence of some controversy in this matter.

Clinical evidence, meta-analysis, and quality assessment of clinical data

Table 1 summarizes the characteristics and outcomes of the clinical studies included in the present review.

The Sutcliffe 2006, Al-Mayah 2013, and Saleh 2021 case-control studies, based on a broad array of sample sizes, demonstrated a significant association between seropositivity to TV and PCa of any grade.[27-29] The Stark 2009 study, a follow-up analysis of previous findings demonstrating a higher risk for advanced disease upon exposure to TV,[27] demonstrated a significant association between a positive serostatus and advanced, metastatic, and lethal disease.[30] Accordingly, Saleh *et al*. could demonstrate a positive and significant correlation between the TV-IgG density and the stage of PCa [Table 1].[29]

In 2019 The Kim *et al*. study presented a significant association between TV seropositivity and a cumulative PCa/benign prostate hyperplasia endpoint. From the study report, we could extract the PCa data; according to our own calculation, a significant OR for the PCa-TV association was found in this small study (OR, 12.6; 95% CI, 1.51–105.56, P = 0.004). Notably, the study was likely biased by a marked difference in the mean age at presentation (controls: 40 y, cases, 73 y).[31]

The remaining studies, which also included two analyses focusing on men of African descent, known to have an increased predisposition to PCa,[32,33] failed to demonstrate an association between TV seropositivity and any grade, high-grade or lethal PCa.[15,34-36] Incidentally, a study performed in 2008 on PCa tissue specimens obtained from a group of 30 patients allowed to identify, by 16S rDNA amplification or by organism-specific polymerase chain reaction, diverse viral and bacterial species, but failed to detect the presence of TV.[37]

Contrary to any other finding, the Shui *et al*. 2016 study documented a protective activity of TV exposure against PCa (adjusted OR, 0.51; 95% CI, 0.28–0.93, P = 0.03).[38]

Meta-analysis

Twelve case–control studies (nested or nonnested) showed sufficient homogeneity and were included in a meta-analysis.[15,27-36,38] The PCa cases were 4752, of which 878 were previously exposed to TV (seropositive cases), whereas controls were 6369, of which 1133 had a history of TV exposure (seropositive controls). Pooled analysis resulted in a nonsignificant crude OR of 1.14 (95% CI: 0.84–1.53; Z = 0.94, P = 0.34). Figure 1a shows the forest plot of this meta-analysis. We calculated an I^2 value of 68%, indicating "substantial" heterogeneity according to Cochrane criteria.

Visual inspection of the funnel plot [Figure 2 Panel A] suggested asymmetry of the data distribution, which was confirmed by the Egger's and Begg's tests (P = 0.013 and P = 0.02, respectively).

The median score of the NOS was 6* (range: 0–9), and the mode was 6*. When the NOS scores were converted to AHRQ standards, 2 studies were rated as "poor," 1 study were rated as "fair" and 9 studies were rated as "good" [Table 2].

Since some studies evidenced a significant OR for a history of TV exposure in lethal or bone-metastatic cases (e.g. 30), we performed a subgroup analysis by extracting from five studies the data relative to highly advanced, bone-metastatic or lethal cases.[29,30,32,33,38] The lethal/metastatic PCa cases were 485, of which 127 were previously exposed to TV, whereas controls were 2424, of which 690 had a history of TV exposure. Again, analysis resulted in a nonsignificant OR (OR, 1.18; 95% CI: 0.70–2.00, Z = 0.88, P = 0.37), and substantial heterogeneity (I^2 = 51.83%) [Figure 1, Panel B]. The funnel plot and asymmetry tests did not indicate the presence of significant publication bias (Egger's test: P =0.5; Begg's test: P =0.32) [Figure 2, Panel B].

The findings of this meta-analysis are summarized in Table 3. According to GRADE criteria, the quality of the evidence is poor, mainly due to the retrospective design of the included studies and to the presence of risk of bias.

Discussion

TV is a common infective agent of the urogenital tract. It is transmitted through sexual intercourse and may cause symptoms similar to those of other STIs within a month

Table 1: Characteristics, assessments and outcomes of the clinical studies included in this review

Author (reference)	*n* total	*n* cohorts	Method	Results and statistical significance (*P*)
Sutcliffe 2006	1382	691 prostate cancer patiens 691 controls PSA tested	ELISA for detection of anti-TV IgG PSA testing Questionnaire data	TV (+) PCa versus control (0.07) TV (+) PCa/race versus control (<0.05) TV (+) PCa/familial PCa versus control (<0.05) TV (+) PCa/STI versus control (<0.05) TV (+) PCa/prostatitis versus control (<0.05) TV (+) PCa and irregular aspirin (<0.05) TV (+) PCa and age of diagnosis (>0.05) TV (+) PCa and screening (>0.05)
Stark 2009	1346	673 prostate cancer patients 673 matched controls	ELISA for detection of anti-TV IgG Questionnaire data	TV (+) and total PCa risk (>0.05) TV (+) and risk of advanced PCa (<0.05) TV (+) and death from cancer risk (<0.05) TV (+) and metastasis risk (<0.05) TV (+) and lethal PCa risk (<0.05)
Groom 2012	158	96 prostate cancer patients 62 matched controls	ELISA for detection of anti-TV IgG Questionnaire data	TV (+) PCa versus control (>0.05)
Shui 2016	327	146 metastatic or fatal PCa 181 age-matched control	ELISA for detection of anti-TV IgG	TV (+) and metastasis risk (>0.05) TV (+) and lethal PCa risk (>0.05) TV (+) and decreased risk of advanced PCa (<0.05)
Sutcliffe 2009	1232	616 PCa diagnosed on any biopsy after visit 2 616 controls matched by age, treatment arm, and family history of PCa	ELISA for detection of anti-TV IgG	TV (+) PCa versus control (>0.05) TV (+) PCa and aspirin use (>0.05) TV (+) PCa and minerals use (>0.05) TV (+) PCa and ethnicity/race (>0.05) TV (+) PCa and family history (>0.05)
Fowke 2016	793	296 PCa cases 497 race-matched controls	ELISA for detection of anti-TV IgG PSA testing Questionnaire data	TV (+) PCa versus control (>0.05) TV (+) PCa/race versus control (>0.05) TV (+) and Gleason score 7–10 (>0.05) TV (+) and Stage 2–4 PCa (>0.05)
Marous 2017	2342	Caucasians (c) 438 Gleason 7 487≥Gleason 8/Stage III and IV African-Americans (a) 109<Gleason 7 92≥Gleason 7 1216 controls	ELISA for detection of anti- TV IgG PSA testing Questionnaire data DRE	TV (+) PCa (a) versus PCa (c) (<0.0001) (c) TV (+) and Gleason score>7 (>0.05) (a) TV (+) and total PCa risk (>0.05) TV (+) PCa and ethnicity/race (>0.05)
Vicier 2019	307	189 localized PCa 118 metastatic PCa	ELISA for detection of anti-TV IgG	TV (+) and lethal PCa (>0.05) TV (+) and high-grade PCa (>0.05) TV (+) and stratification risk of local PCa prostate cancer (>0.05)
Tsang 2019	1485	736 PCa patients (PHS) 749 PCa patients (HPFS)	ELISA for detection of anti-TV IgG	TV (+) and death of PCa risk (>0.05) TV (+) and any cancer death risk (>0.05)

Contd...

Table 1: Continued

Author (reference)	*n* total	*n* cohorts	Method	Results and statistical significance (*P*)
Breyer 2016	38340	Men with possible BPH without PCa	ELISA for detection of anti-TV IgG PSA testing Questionnaire data DRE	prevalent nocturia and (+) TV (<0.05) large prostate and (+) TV(<0.05) prevalent BPH/LUTS and (+) TV (<0.05)
Kim 2019	241	139 BPH patients 44 PCa patients 58 controls	ELISA for detection of anti-TV IgG radiologic evaluation (MRI and bone scan) Questionnaire data	TV (+) PCa versus BPH (>0.05) TV (+) PCa/BPH versus control (<0.05)
Langston 2019	732	732 healthy young men	ELISA for detection of anti-TV IgG PSA testing	TV (+) and levels of PSA (>0.05)
Saleh 2013	246	126 PCa patients 120 matched controls	ELISA for detection of anti-TV IgG PSA testing	TV (+) and PCa (0.0150) TV-IgG density score and PSA correlation, r=0.7, (<0.0001) TV-IgG density score and PCa stage correlation, r=0.5, (<0.05)
Al-Mayah 2021		50 PCa patients 40 matched controls	ELISA for detection of anti-TV IgG PCR of TV DNA in PCa specimens	TV (+) PCa versus controls (<0.05) TV DNA (+) PCa versus controls (>0.05)

Pca: Prostate cancer, TV: *Trichomonas vaginalis*, PSA: Prostate specific antigen, STI: Sexually transmitted infections, PHS: Polygenic hazard score, HPFS: Health professional's follow-up study, DRE: Digital rectal examination, IgG: Immunoglobulin G, PCR: Polymerase chain reaction, MRI: Magnetic resonance imaging, BPH: Benign prostatic hyperplasia, LUTS: Lower urinary tract symptoms

after exposure. Up to 50% of patients will not develop any symptom but will remain infectious. Although the prostate gland is believed to serve as a parasite reservoir in men's trichomoniasis, the association between trichomonads and prostatic diseases has been under discussion.

In this review, we summarized the data emerging from preclinical investigations performed both at the cellular and molecular level. In general, these data are suggestive of a possible link between the exposure to TV and the onset of growth abnormalities in prostate cells-including EMT-that may be linked to the development of a neoplastic phenotype.

Early research by Sutcliffe *et al*. documented a statistically significant association between a TVs serostatus and prostate inflammation[34] in men, confirming previous laboratory observations. In 1986, Gardner *et al*., positively identified trichomonads in the prostatic urethra, glandular lumina, submucosa, and stroma. Concomitant foci of nonspecific acute and chronic inflammation, as well as intraepithelial vacuolization, suggested an association with the infection.[39]

In the clinical practice, cases of acute or chronic prostatitis related to TV are infrequently reported. Probably, TV prostatitis may be overlooked due to limited culture-based assays routinely performed in hospital microbiology laboratories.[40] In fact, by using specific tests researchers found a 16%–18% incidence of TV prostatitis.[41]

Worldwide investigation to assess an association between a positive TV serostatus (a marker of exposure to the protozoan) and PCa was fostered by the findings of Sutcliffe *et al*. on a large population of patients, showing a significantly increased odds for PCa of any grade on exposure to TV.[27] These results were confirmed by the same group in later studies focusing on advanced/lethal PCa,[30] as well as by other independent studies performed more recently in smaller patient populations.[28,29,31] However, other clinical studies failed to find a significant increase of the risk for PCa in patients with a positive TV serostatus.[15,32-36] Thus, clinical data were not univocal, the issue has remained controversial and meta-analyses-including ours-have been performed to obtain additional information in this respect.

Summary of the main results

Our meta-analysis including 12 studies retrieved up to June 1, 2021, did not evidence a significant association between a positive TV serostatus and PCa of any grade. Moreover, we could not find a significant association between advanced/lethal PCa and TV exposure. Thus, the involvement of TV in the genesis of PCa remains unknown. However, once foci of chronic infection are

Table 2: Assessment of the quality of studies included in the meta-analysis according to the Newcastle-Ottawa Scale

Study ID (first author, year)	Selection				Comparability	Exposure			Score, AHRQ rating
	Is PCa definition adequate?	Representativeness of cases	Selection of controls (hospital control bias)	Definition of controls	Comparability cases- controls	Ascertainment of exposure (recall bias)	Same method of ascertainment for cases and controls	Nonresponse rate	
Sutcliffe 2006	Questionnaire- based assessment of PCa. In most cases data also extracted from cancer registry, with no independent validation	Obviously representative*	No hospital controls*	No history of PCa*	Age- matched, adjusted for a number of different covariates*	De novo serological assessment of exposure (seropositivity)*	Yes*	Unknown	6*, good
Stark 2009	PCa assessment not disclosed	Obviously representative*	No hospital controls*	No history of PCa*	Controls were matched to cases by age, smoking status and follow-up time*	Serologically assessed seropositivity*	Yes*	Unknown	6*, good
Sutcliffe 2009	Cases were men with a pathologically confirmed diagnosis of PCa. Independent validation was performed*	Consecutive accrual (randomized study)*	No hospital controls*	A negative prostate biopsy at end of study*	Age -matched, adjusted for a number of different covariates*	De novo serological assessment of exposure (seropositivity)*	Yes*	Unknown	7*, good
Al-Mayah 2013	Cases were men with a pathologically confirmed diagnosis of PCa*	Obviously representative*	No hospital controls*	No history of PCa*	Significant age difference between cases and controls	Serologically assessed seropositivity*	Yes*	Unknown	6*, good
Chen 2013	Cases were men with a pathologically confirmed diagnosis of PCa*	Obviously representative*	No hospital controls*	No history of PCa*	Matched for age, PSA test frequency and date	Serologically assessed seropositivity*	Yes*	Unknown	6*, good
Shui 2016	Cases were men with a pathologically confirmed diagnosis of PCa*	Obviously representative*	Community controls*	No history of PCa*	Age -matched, adjusted*	Serologically assessed seropositivity*	Yes*	Unknown	7*, good
Fowke 2016	Cancer and death registry, no independent validation	Obviously representative*	Community controls*	No history of PCa*	Age and ethnicity-matched, adjusted for age at diagnosis, race, income*	Serologically assessed seropositivity*	Yes*	Unknown	6*, good
Marous 2017	Cases were men with a pathologically confirmed diagnosis of PCa*	Consecutive accrual (randomized study)*	Community controls*	No history of PCa*	Age and ethnicity-matched, adjusted*	Serologically assessed seropositivity*	Yes*	Unknown	7*, good

Contd...

Table 2: Continued

Study ID (first author, year)	Selection				Comparability	Exposure			Score, AHRQ rating
	Is PCa definition adequate?	Representativeness of cases	Selection of controls (hospital control bias)	Definition of controls	Comparability cases- controls	Ascertainment of exposure (recall bias)	Same method of ascertainment for cases and controls	Nonresponse rate	
Vicier 2019	Cases were extracted from various studies and registries, no independent validation	Unclear	Controls might include cases with low-stage PCa	Controls might include cases with low-stage PCa	Unclear	Serologically assessed seropositivity*	Yes*	Unknown	2*, poor
Tsang 2019	Cases were extracted from various studies and registries, no independent validation	Unclear	No hospital controls*	No history of PCa*	Unclear	Serologically assessed seropositivity*	Unclear: Seroprevalences evaluated with different cutoffs	Unknown	3*, poor
Kim 2019	Cases were men with a pathologically confirmed diagnosis of PCa or BPH*	Obviously representative*	Hospital controls	No history of PCa*	Controls included both healthy subjects and patients with BPH; significant age difference between cases and controls	Serologically assessed seropositivity*	Yes*	Unknown	5*, fair
Saleh 2021	Cases were men with a pathologically confirmed diagnosis of PCa*	Obviously representative*	Hospital controls	No history of PCa*	Age-matched, adjusted*	Serologically assessed seropositivity*	Yes*	Unknown	6*, good

AHRQ: Agency for Healthcare Research and Quality, Pca: Prostate cancer

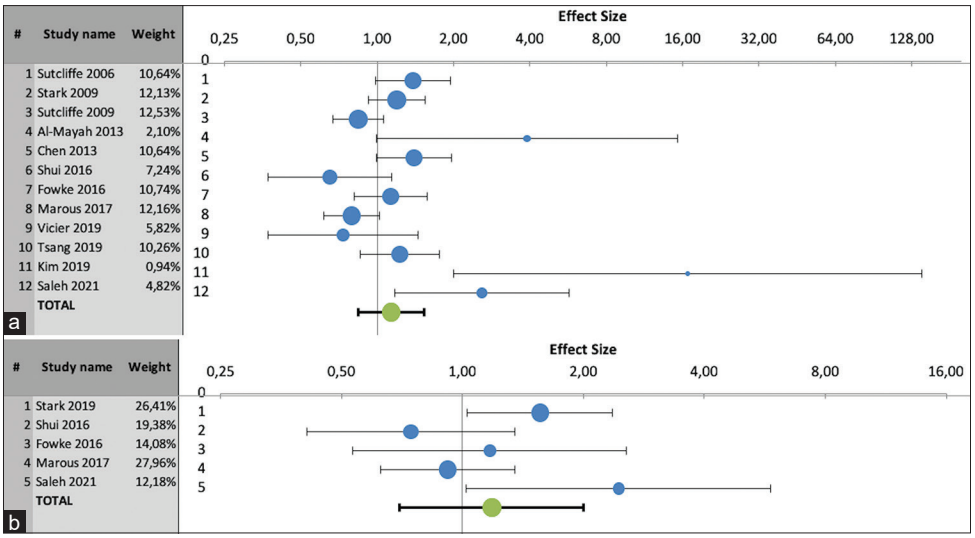

Figure 1: (a) Forest plot showing the association between a diagnosis prostate cancer (any grade or stage) and seropositivity for *Trichomonas vaginalis* in twelve case-control studies included in this review. (b) Subgroup analysis showing the association between a diagnosis of lethal or bone-metastatic prostate cancer and seropositivity for *Trichomonas vaginalis* in five case-control studies. Data to the right of the vertical no-effect line represent increased odds for prostate cancer in patients exposed to *Trichomonas vaginalis*

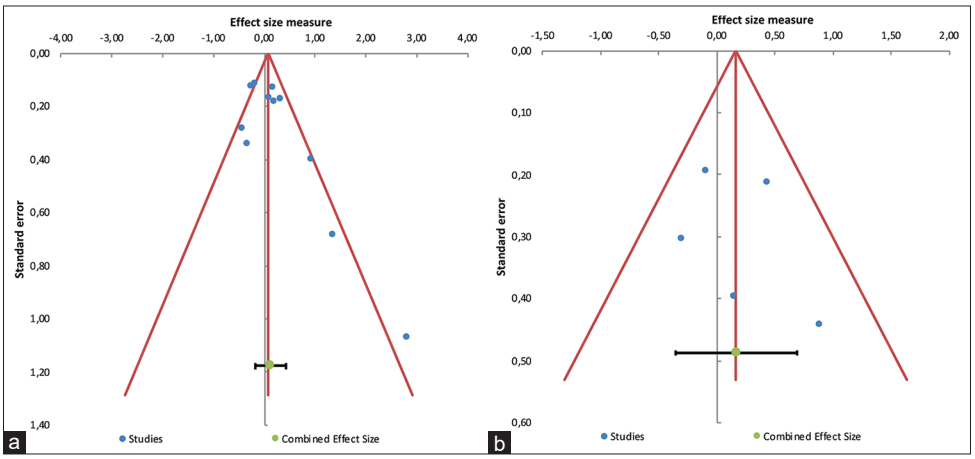

Figure 2: Funnel plots for publication bias analysis. (a) Association between any grade or stage of prostate cancer and exposure to *Trichomonas vaginalis*; (b) Subgroup analysis on the association between a diagnosis of lethal or bone-metastatic prostate cancer and exposure to *Trichomonas vaginalis*. In these plots the effect size is expressed as the natural logarithm of the odds ratio

established, the prostate microenvironment is prone to the neoplastic process, which is largely orchestrated by inflammatory cells via deregulation of the cell proliferation mechanisms, predisposing to the development of cancer and promoting all stages of tumorigenesis. Cancer cells, as well as surrounding stromal and inflammatory cells, engage in well-orchestrated reciprocal interactions to form an inflammatory tumor microenvironment.[42] Given that TV infection frequently represents as nonspecific or asymptomatic, it is conceivable that the risk of PCa may increase as a consequence of low intensity, untreated inflammation. Meta-analyses have indeed suggested that a history of CBP might be a risk factor for the subsequent development of PCa.[10,11] Yet, synergistic conditions such as excessive or low immune responses may be needed in order to trigger inflammation-induced damage to cell DNA and to affect the way cells grow and divide. This particular connection explains differences between various epidemiological studies regarding TV's tumorigenic potential and the need for new studies at the epidemiological and molecular levels.

Overall applicability of the evidence

The applicability of the evidence generated with this meta-analysis may be affected by issues of biologic variation due to ethnicity. In particular, between Caucasians and men of African descent there exist biologic differences that are likely to affect the pathogenesis of cancer, with the latter showing increased predisposition and higher proneness to high-grade disease when compared with the former.[43]

Moreover, patients of different nationalities or social groups may be subjected to socioeconomic conditions or attitudes

Table 3: Summary of findings (grading of recommendations assessment, development and evaluation criteria)

Patient or population: Male subjects

Settings: Case-control study

Cases: A documented diagnosis of PCa

Controls: Healthy individuals (no history of PCa)

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (studies or comparisons)	Quality of the evidence (GRADE)	Comments
	Assumed risk (placebo)	Corresponding risk (antidepressants)				
PCa of any grade or stage	177.89/1000	202.79/1000 (149.42–272.17)	OR: 1.14 (0.84–1.53)	11,121 (12)	⊕⊖⊖⊖ (very low)	Reasons for downgrading Risk of bias Publication bias Observational, no ROBINS-I Reasons for upgrading None
Advanced stage PCa (lethal, bone-metastatic, etc)	284.65/1000	335.88/1000 (199.25–569.3)	OR: 1.18 (0.70–2)	2909 (5)	⊕⊕⊖⊖ (low)	Reasons for downgrading Risk of bias Observational, no ROBINS-I Reasons for upgrading None

The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE working group quality of evidence, high quality: Further research is very unlikely to change our confidence in the estimate of effect, Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate, low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate, very low quality: We are very uncertain about the estimate. GRADE: Grading of recommendations assessment, development and evaluation, CI: Confidence interval; OR: Odds ratio, Pca: Prostate cancer

that make some forms of screening (e.g. frequent PSA testing) or care (e.g. CBP prolonged courses of therapy) less accessible or less feasible in some settings, such as in developing countries.

Quality of the evidence

According to GRADE criteria, the overall quality of the evidence is low, mainly due to the retrospective design of the included studies and to the presence of risk of bias.

Potential biases and confounders

Publication bias was detected by funnel plot inspection and statistics. Moreover, we hypothesize that additional generators of systematic biases may be linked to the diversity of the design of the studies included in this review. Among possible bias generators we may include the duration of exposure to TV and the assessment of TV seropositivity in patients. Moreover, no information was available concerning the time-course of cancer development. Which latency period between protozoan infection and PCa development may be considered indicative of a link between exposure and disease? In addition, a number of risk factors such as smoking, exposure to prostatic carcinogens (e.g. frequent consumption of charred meat containing the prostate carcinogen PhIP) may be additional confounders and bias generators.

It is also possible that TV infection of the prostate may be restricted to a specific patient population. Notably, Skuhala *et al*. found that TV is a major pathogen of chronic prostatitis in elderly men, suggesting that chronic decline of the immune system may also be required to propagate and provoke TV-induced constrictive pericarditis.[44] On the other side, younger, sexually-active men may be preferential targets of TV infection which might be responsible for sustained inflammation and prostate tissue alterations. Thus, in-depth research focused on different age subgroups may remove potential age-related biases.

Agreements and disagreements with other studies

A 2019 meta-analysis by Najafi *et al*., including 6 clinical studies, resulted in a OR of 1.17 (95% CI: 1.01–1.36), indicating a borderline-significant association between TV and PCa.[45]

In contrast, our updated meta-analysis including 12 studies retrieved up to June 1, 2021 did not evidence a significant association between a positive TV serostatus and PCa of any grade.

Since Stark *et al*. reported a highly significant association between advanced/lethal PCa and TV exposure in a population of in 1346 patients,[30] we performed a subgroup analysis by pooling five studies from which data about advanced/lethal disease could be extracted. Also in this case, we failed to find a significant exposure-disease association.

Conclusions

In conclusion, our meta-analysis did not provide conclusive evidence of a possible link between exposure to TV and an increased risk of PCa of any grade, as the crude OR for cancer in patients exposed to TV versus unexposed patients was not statistically significant.

Implications for practice

As far as the clinical practice is concerned, our results do not support for the moment the indication for increased surveillance of patients previously exposed to TV. However, this statement is only provisional and new clinical data from powered studies may overturn our opinion.

Implications for research

The reason underlying the different results of clinical studies may be manifold. The size of patient populations, the patients' age, the length of exposure to TV, the different ways in which PCa was staged and the ethnicity of enrolled subjects may have played a role in these discrepant findings.

Thus, whereas the results of previous trials performed by independent international research groups demonstrating a carcinogenic risk in men infected with TV should not be overlooked, novel confounder-adjusted studies performed on very large populations are warranted to provide a conclusive answer to this research question. In this regard, we believe that the simple serological assessment of a generic "exposure" to TV may act as a major confounder in such kinds of studies. In our opinion, instead of a simple serological demonstration of TV exposure, a documented history of symptomatic, clinical chronic prostatitis caused by TV may increase the likelihood of finding patients that have been truly subjected to pathological alterations of the prostatic glandular tissue caused by the protozoan. Such stringent selection may allow to exclude occasional exposure to the protozoan which may be unrelated to persistent, chronic inflammatory damage of the prostate and neoplastic transformation.

Moreover, future trials should ideally take into consideration certain potential biases and confounders, such as ethnicity, age-related issues, the degree of exposure to dietary and nondietary prostate carcinogens, and the length of a hypothetic latency period between protozoan exposure and PCa development.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Feinberg AP, Koldobskiy MA, Göndör A. Epigenetic modulators, modifiers and mediators in cancer aetiology and progression. Nat Rev Genet 2016;17:284-99.
2. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006;118:3030-44.
3. Blaser MJ. Understanding microbe-induced cancers. Cancer Prev Res (Phila) 2008;1:15-20.
4. Morales-Sánchez A, Fuentes-Pananá EM. Human viruses and cancer. Viruses 2014;6:4047-79.
5. Hatakeyama M. Malignant *Helicobacter pylori*-associated diseases: Gastric cancer and MALT lymphoma. Adv Exp Med Biol 2019;1149:135-49.
6. El-Gayar EK, Mahmoud MM. Do protozoa play a role in carcinogenesis? Parasitol United J 2014;7:80-5.
7. Van Gerwen OT, Muzny CA. Recent advances in the epidemiology, diagnosis, and management of *Trichomonas vaginalis* infection. F1000Res. 2019;8:F1000 Faculty Rev-1666.
8. Yang S, Zhao W, Wang H, Wang Y, Li J, Wu X. *Trichomonas vaginalis* infection-associated risk of cervical cancer: A meta-analysis. Eur J Obstet Gynecol Reprod Biol 2018;228:166-73.
9. Vickovic N, Skerk V, Granic J, Vargovic M, Pasini M, Turcic P, *et al.* Metronidazole 1.5 gram dose for 7 or 14 days in the treatment of patients with chronic prostatitis caused by *Trichomonas vaginalis*: A randomized study. J Chemother 2010;22:364-5.
10. Perletti G, Monti E, Magri V, Cai T, Cleves A, Trinchieri A, *et al.* The association between prostatitis and prostate cancer. Systematic review and meta-analysis. Arch Ital Urol Androl 2017;89:259-65.
11. Jiang J, Li J, Yunxia Z, Zhu H, Liu J, Pumill C. The role of prostatitis in prostate cancer: Meta-analysis. PLoS One 2013;8:e85179.
12. Hrbacek J, Urban M, Hamsikova E, Tachezy R, Heracek J. Thirty years of research on infection and prostate cancer: No conclusive evidence for a link. A systematic review. Urol Oncol 2013;31:951-65.
13. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, *et al.* GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol 2013;66:158-72.
14. Zariffard MR, Harwani S, Novak RM, Graham PJ, Ji X, Spear GT. *Trichomonas vaginalis* infection activates cells through toll-like receptor 4. Clin Immunol 2004;111:103-7.
15. Chen YC, Huang YL, Platz EA, Alderete JF, Zheng L, Rider JR, *et al.* Prospective study of effect modification by Toll-like receptor 4 variation on the association between *Trichomonas vaginalis* serostatus and prostate cancer. Cancer Causes Control 2013;24:175-80.
16. Twu O, Dessí D, Vu A, Mercer F, Stevens GC, de Miguel N, *et al. Trichomonas vaginalis* homolog of macrophage migration inhibitory factor induces prostate cell growth, invasiveness, and inflammatory responses. Proc Natl Acad Sci U S A 2014;111:8179-84.
17. Han IH, Song HO, Ryu JS. IL-6 produced by prostate epithelial cells stimulated with *Trichomonas vaginalis* promotes proliferation of prostate cancer cells by inducing M2 polarization of THP-1-derived macrophages. PLoS Negl Trop Dis 2020;14:e0008126.
18. Chung HY, Kim JH, Han IH, Ryu JS. Polarization of M2 macrophages by interaction between prostate cancer cells treated with *Trichomonas vaginalis* and adipocytes. Korean J Parasitol 2020;58:217-27.
19. Park J, Euhus DM, Scherer PE. Paracrine and endocrine effects of adipose tissue on cancer development and progression. Endocr Rev 2011;32:550-70.

20. Han IH, Kim JH, Kim SS, Ahn MH, Ryu JS. Signalling pathways associated with IL-6 production and epithelial-mesenchymal transition induction in prostate epithelial cells stimulated with *Trichomonas vaginalis*. Parasite Immunol 2016;38:678-87.
21. Han IH, Kim JH, Jang KS, Ryu JS. Inflammatory mediators of prostate epithelial cells stimulated with *Trichomonas vaginalis* promote proliferative and invasive properties of prostate cancer cells. Prostate 2019;79:1133-46.
22. Sutcliffe S, Neace C, Magnuson NS, Reeves R, Alderete JF. Trichomonosis, a common curable STI, and prostate carcinogenesis – A proposed molecular mechanism. PLoS Pathog 2012;8:e1002801.
23. Kushwaha B, Devi A, Maikhuri JP, Rajender S, Gupta G. Inflammation driven tumor-like signaling in prostatic epithelial cells by sexually transmitted *Trichomonas vaginalis*. Int J Urol 2021;28:225-40.
24. Bhakta SB, Moran JA, Mercer F. Neutrophil interactions with the sexually transmitted parasite *Trichomonas vaginalis:* Implications for immunity and pathogenesis. Open Biol 2020;10:200192.
25. Kim JH, Kim SS, Han IH, Sim S, Ahn MH, Ryu JS. Proliferation of prostate stromal cell induced by benign prostatic hyperplasia epithelial cell stimulated with *Trichomonas vaginalis* via crosstalk with mast cell. Prostate 2016;76:1431-44.
26. Zhu Z, Davidson KT, Brittingham A, Wakefield MR, Bai Q, Xiao H, *et al. Trichomonas vaginalis*: A possible foe to prostate cancer. Med Oncol 2016;33:115.
27. Sutcliffe S, Giovannucci E, Alderete JF, Chang TH, Gaydos CA, Zenilman JM, *et al.* Plasma antibodies against *Trichomonas vaginalis* and subsequent risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2006;15:939-45.
28. Al-Mayah QS, Al-Saadi MA, Jabbar RN. *Trichomonas vaginalis* infection as a risk factor for prostate cancer. Int J Curr Microbiol Appl Sci 2013;2:105-13.
29. Saleh NE, Alhusseiny SM, El-Zayady WM, Aboelnaga EM, El-Beshbishi WN, Saleh YM, *et al. Trichomonas vaginalis* serostatus and prostate cancer risk in Egypt: A case-control study. Parasitol Res 2021;120:1379-88.
30. Stark JR, Judson G, Alderete JF, Mundodi V, Kucknoor AS, Giovannucci EL, *et al.* Prospective study of *Trichomonas vaginalis* infection and prostate cancer incidence and mortality: Physicians' health study. J Natl Cancer Inst 2009;101:1406-11.
31. Kim JH, Moon HS, Kim KS, Hwang HS, Ryu JS, Park SY. Comparison of seropositivity to *Trichomonas vaginalis* between men with prostatic tumor and normal men. Korean J Parasitol 2019;57:21-5.
32. Marous M, Huang WY, Rabkin CS, Hayes RB, Alderete JF, Rosner B, *et al. Trichomonas vaginalis* infection and risk of prostate cancer: Associations by disease aggressiveness and race/ethnicity in the PLCO Trial. Cancer Causes Control 2017;28:889-98.
33. Fowke JH, Han X, Alderete JF, Moses KA, Signorello LB, Blot WJ. A prospective study of *Trichomonas vaginalis* and prostate cancer risk among African American men. BMC Res Notes 2016;9:224.
34. Sutcliffe S, Alderete JF, Till C, Goodman PJ, Hsing AW, Zenilman JM, *et al.* Trichomonosis and subsequent risk of prostate cancer in the prostate cancer prevention trial. Int J Cancer 2009;124:2082-7.
35. Vicier C, Werner L, Chipman J, Harshman LC, Patil DH, Fichorova RN, *et al.* Elevated serum cytokines and *Trichomonas vaginalis* serology at diagnosis are not associated with higher gleason grade or lethal prostate cancer. Clin Genitourin Cancer 2019;17:32-7.
36. Tsang SH, Peisch SF, Rowan B, Markt SC, Gonzalez-Feliciano AG, Sutcliffe S, *et al.* Association between *Trichomonas vaginalis* and prostate cancer mortality. Int J Cancer 2019;144:2377-80.
37. Sfanos KS, Sauvageot J, Fedor HL, Dick JD, De Marzo AM, Isaacs WB. A molecular analysis of prokaryotic and viral DNA sequences in prostate tissue from patients with prostate cancer indicates the presence of multiple and diverse microorganisms. Prostate 2008;68:306-20.
38. Shui IM, Kolb S, Hanson C, Sutcliffe S, Rider JR, Stanford JL. *Trichomonas vaginalis* infection and risk of advanced prostate cancer. Prostate 2016;76:620-3.
39. Gardner WA Jr., Culberson DE, Bennett BD. *Trichomonas vaginalis* in the prostate gland. Arch Pathol Lab Med 1986;110:430-2.
40. Kline KA, Lewis AL. Gram-positive uropathogens, polymicrobial urinary tract infection, and the emerging microbiota of the urinary tract. Microbiol Spectr Microbiol Spectr. 2016;4:10.1128 /microbiolspec.UTI-0012-2012.
41. Skerk V, Schönwald S, Krhen I, Markovinović L, Beus A, Kuzmanović NS, *et al.* Aetiology of chronic prostatitis. Int J Antimicrob Agents 2002;19:471-4.
42. Greten FR, Grivennikov SI. Inflammation and cancer: Triggers, mechanisms, and consequences. Immunity 2019;51:27-41.
43. Powell IJ, Dyson G, Land S, Ruterbusch J, Bock CH, Lenk S, *et al.* Genes associated with prostate cancer are differentially expressed in African American and European American men. Cancer Epidemiol Biomarkers Prev 2013;22:891-7.
44. Skuhala T, Desnica B, Jurina K. *Trichomonas vaginalis*-Major pathogen of chronic prostatitis in elderly men. Int J Infect Dis 2012;16:e333-4.
45. Najafi A, Chaechi Nosrati MR, Ghasemi E, Navi Z, Yousefi A, Majidiani H, *et al.* Is there association between *Trichomonas vaginalis* infection and prostate cancer risk? A systematic review and meta-analysis. Microb Pathog 2019;137:103752.

Leiomyoma of the Bladder Neck

Abstract

Benign bladder tumors represent a rare entity of bladder neoplasms and include tumors such as leiomyomas. Female preponderance is characteristic, and patients usually present with bladder outlet obstruction, dysuria, hematuria, and urinary tract infections; symptoms that are not disease specific and can be overlooked. Bladder leiomyomas can be easily diagnosed during imaging tests or/and cystoscopy evaluation and they are mainly treated with transurethral surgical excision. We present a case of a female patient with urinary obstruction due to missed on previous ultrasound examinations large leiomyoma located at the bladder neck and expanded into the proximal urethra.

Keywords: *Benign bladder tumor, bladder leiomyoma, bladder obstruction, transurethral resection*

Petros Gorgoraptis[1], Dimitrios Papaioannou[2], Ioannis Kazanis[1], Kostas Chondros[1,3]

[1]Department of Urology, Creta InterClinic HHG Group, [3]Urological Office, Iatriko Kritis (Affidea), Heraklion, [2]Department of Pathology, Hygeia Hospital, Athens, Greece

Introduction

Benign bladder tumors represent only 1% of all bladder neoplasms.[1] They mainly consist of papillomas, leiomyomas, hemangiomas, neurofibromas, and lipomas. Patients typically present with urinary tract infections, pain, and voiding dysfunction caused by obstruction and rarely gross hematuria. Endoscopic evaluation and transurethral excision are usually mandatory. Women are at higher risk of developing such tumors than men, especially leiomyomas.[2] We present a case of a female patient who was diagnosed with a large bladder leiomyoma located in the right aspect of the bladder neck, expanded to the urethra and causing a valve-like outflow obstruction. The patient remained undiagnosed for several months perhaps due to the unusual tumor location.

Case Report

A 61-year-old female patient presented with lower urinary tract (LUT) symptoms indicating urinary infection. The patient was afebrile, and the urine tests revealed typical cystitis caused by *Escherichia coli* which was treated with a short-term course of oral fosfomycin due to resistance to other common antibiotics. The patient had a significant surgical history including thyroidectomy, tonsillectomy, appendicectomy, double cesarean incisions, and several uterine curettages and a medical history of hypertension and chronic pulmonary disease. She was also a heavy smoker (approximately 40 pack-years). The clinical examination was normal, and no urethral pathology, vaginal lesions, or pelvic organ prolapse were present. Furthermore, the patient reported several urinary infections in the past 2 years and prolonged voiding dysfunction. However, no bladder pathology was ever demonstrated despite a series of ultrasound evaluations the recent years. Because of the high suspicion of bladder malignancy, the patient submitted to further imaging investigation. A circumstantial ultrasound investigation revealed a 3 cm mass located at the trigone [Figure 1a]. Subsequently, the patient submitted to computed tomography (CT) urography which showed a normal upper urinary tract, no other visceral lesions, and no lymph node involvement. The bladder mass had a size of 2.7 cm × 3.1 cm, and it was located right at the bladder neck approximately 1.5 cm away from both ureteral orifices. The lesion was solid, moderately enhanced after the contrast injection, and created a characteristic filling deficit during the urography [Figure 1b-d]. No conclusion could be made about the degree of urethral involvement. Urine cytology was also negative for any malignancy. Eventually, the patient was submitted to transurethral resection (TURB) 1 week later, where a large proximal urethral mass was recognized that was attached to the right side, caused

How to cite this article: Gorgoraptis P, Papaioannou D, Kazanis I, Chondros K. Leiomyoma of the bladder neck. Hellenic Urol 2021;33:24-7.

Submitted: 10-Mar-2021
Revised: 31-Mar-2021
Accepted: 12-Apr-2021
Published: 15-Feb-2022

Address for correspondence:
Dr. Kostas Chondros, Urological Office, Iatriko Kritis (Affidea), Eleftherias Sq. 45, Heraklion, Crete, Greece.
E-mail: ckurology@gmail.com

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 10.4103/HUAJ.HUAJ_10_21

Quick Response Code:

an almost complete obstruction of the bladder neck, and had extensive intravesical protrusion [Figure 2a]. There was no involvement of the trigone itself, yet a biopsy of the mucosa was sent separately for pathological evaluation. The tumor was completely excised carefully using a pure bipolar resectoscope with low power settings to minimize the trauma on the urethral sphincter [Figure 2b]. The patient was discharged the next day and 1 week later reported impressive voiding function improvement. The pathological examination showed a benign tumor of smooth muscle cells with no mitotic activity, no significant atypia, and no necrosis, consistent with bladder leiomyoma [Figure 3]. Immunohistochemical evaluation included stains for Cytokeratin, h-Caldesmon, and Ki67 and resulted in a very low proliferation rate (<1%) which corroborated the diagnosis. Finally, the patient was scheduled for endoscopic follow-up after multidisciplinary consultation without any additional treatment. The cystoscopy at 3 months was negative for any signs of residual tumor or recurrence and the mucosa of the urethra, bladder neck, and bladder was normal [Figure 4a and b].

Discussion

Leiomyomas of the urinary bladder are very rare neoplasms, with only ~250 cases previously reported in the literature.[3] Although rare, they are the most common benign mesenchymal tumors of the bladder. They usually affect patients in their third to sixth decade with a female preponderance (70%).[4] According to their location, leiomyomas are classified as endovesical, intramural, and extravesical. Endovesical leiomyomas are the most common and constitute 63%–86% of the cases, while intramural leiomyomas are present in 3%–7% and extravesical in 11%–30%. The most common symptoms at presentation are obstructive (49%), followed by irritative (38%) and hematuria (11%), while in larger masses, flank pain may present due to ureteric obstruction.[5] LUT leiomyomas should always be considered in the differential diagnosis of an anterior vaginal mass. Ultrasound is most commonly the first imaging step. Magnetic resonance imaging (MRI) and CT may also be performed. The ultrasound will typically detect a smooth-walled solid lesion with numerous internal echoes and homogenous texture of medium echogenicity. Cystoscopy can show a characteristic bladder mass with a smooth and regular mucosa. CT generally shows a smooth-walled bladder filling defect with an attenuation coefficient of 25–50 Hounsfield units.[6] MRI shows an intermediate signal intensity on T1-weighted images, giving good contrast compared with the low-intensity signal of urine. On T2-weighted images, it gives areas of high and low intensity at the same time, giving excellent contrast, as opposed to the intermediate-low intensity of the bladder

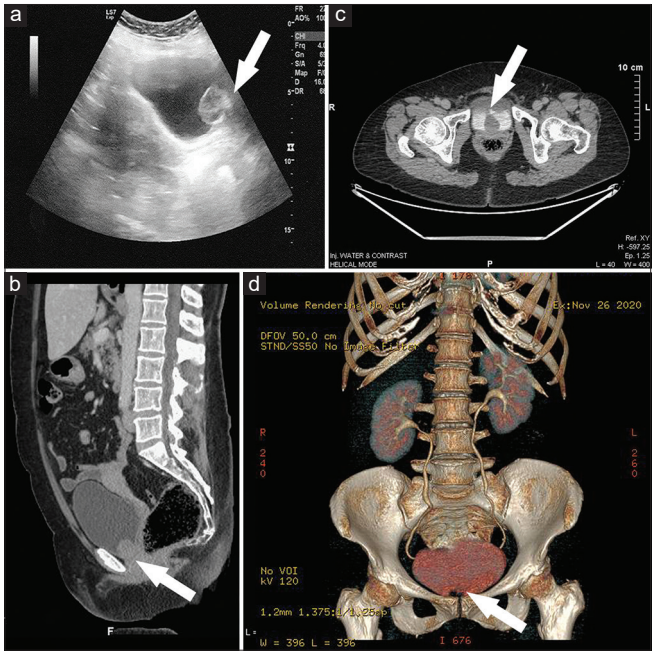

Figure 1: Imaging evaluation of the patient. (a) Ultrasonographic image identifying the solid mass at the bladder neck. (b) Coronal plane of the computed tomography scan demonstrating the urethral involvement. (c) Axial plane of the computed tomography urography showing the characteristic filling deficit into the bladder (white arrow). (d) Three-dimensional reconstruction of the urinary tract demonstrating a deficit (white arrow) at the level of the pubic symphysis

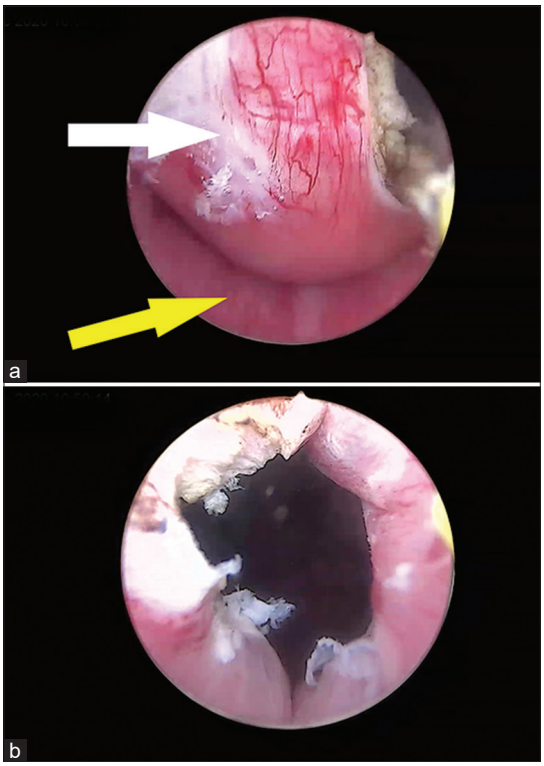

Figure 2: Intraoperative images of the transurethral resection of the tumor. (a) The bladder neck leiomyoma inside the urethra causing a complete obstruction (white arrow). The tumor was attached to the right side and the resection began on the left side toward the base of the tumor. The yellow arrow is pointing at the normal posterior urethral mucosa. (b) Final endoscopic view after complete resection at the level of the bladder neck

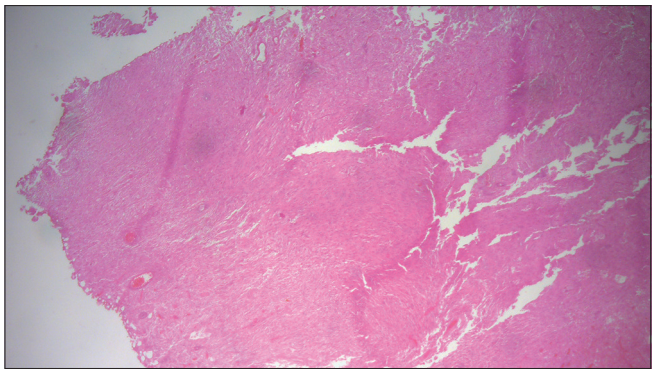

Figure 3: Histopathological image of the specimen under H and E, ×100. Irregular fascicles of smooth muscle cells with no significant atypia or mitotic activity, covered by normal urothelium indicative of benign bladder leiomyoma and mild chronic cystitis inflammation findings

muscle, facilitating the diagnosis of an extravesical extension.[7] TURB represents the main treatment in almost 90% of cases unless a large intramural or an extravesical leiomyoma is encountered requiring a wider excision such as a partial cystectomy or a transvaginal resection.[5,8] Surgical treatment is usually effective since bladder leiomyomas have generally a good prognosis, and the recurrence rate is extremely low. However, a residual tumor may be present in 18% of the cases after TURB and these patients will require a re-operation.[5] Therefore, a cystoscopic follow-up schedule is recommended in these patients. Notwithstanding, the knowledge of urinary leiomyomas is limited to only a few case reports or small case series to recommend standard treatment and follow-up options.

The pathophysiology of these lesions remains unknown but four theories have been proposed: (1) Hormonal disturbances cause these tumors to develop; (2) dysontogenesis, for example, embryonic rests of tissue residing in the bladder that transforms into leiomyomas; (3) perivascular inflammation leading to a metaplastic transformation of the bladder vascular supply; and (4) bladder musculature infection leading to inflammation and the development of these benign tumors.[9] More studies and research are needed to elucidate the mechanism of their growth. Leiomyomas of the urinary bladder share common histopathological features with leiomyomas of the uterus, i.e., round gray-white nodules with a spiral appearance of smooth muscle fibers gathered in small fascicles and separated by varying amounts of fibrous connective tissue, and fewer than two mitotic figures per high-power field.[8] Interestingly, bladder leiomyomas during pregnancy increase more obviously in size and recur more frequently.[10,11] This observation suggests that bladder leiomyomas may be dependent on hormonal changes as uterine leiomyomas. The use of gonadotropin-releasing hormone (GnRH) may be another choice for the treatment of bladder leiomyomas as in uterine leiomyomas. GnRH analogs can be effective for uterine leiomyomas because

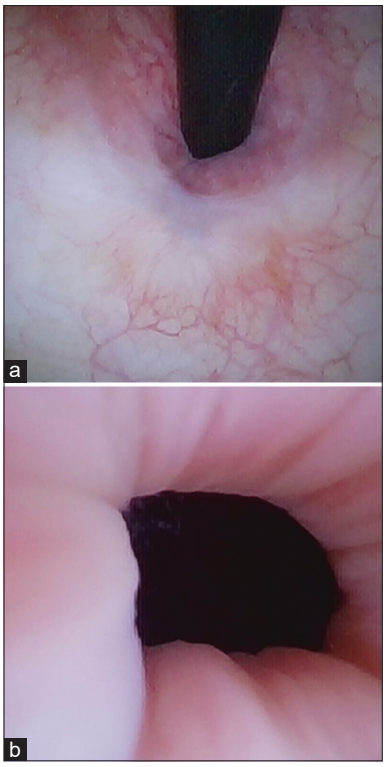

Figure 4: Three-month postoperative flexible video-cystoscopy of the patient. (a) 210° flexion image of the bladder neck demonstrating normal mucosal scarring with no signs of residual tumor or recurrence (whitish area at 10,11 and 12 o'clock, upside-down image). (b) Endoscopic view of the previously obstructed bladder neck with normal appearance after complete surgical excision of the leiomyoma

they can influence hypothalamus–pituitary–gonadal axis and play a role as medical oophorectomy. GnRH treatment has been predicted to be effective for bladder leiomyomas as well, since bladder leiomyomas have also been reported to be associated with hormonal changes.[12,13]

In conclusion, bladder leiomyoma is a rare nonmalignant tumor that can present with typical LUT symptoms and/or hematuria. Imaging and endoscopic evaluation are mandatory since the tumor can be effectively managed with transurethral resection only.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Campbell EW, Gislason GJ. Benign mesothelial tumors of the urinary bladder: Review of literature and a report of a case of leiomyoma. J Urol 1953;70:733-41.
2. Silva-Ramos M, Massó P, Versos R, Soares J, Pimenta A. Leiomyoma of the bladder. Analysis of a collection of 90 cases. Actas Urol Esp 2003;27:581-6.
3. Khater N, Sakr G. Bladder leiomyoma: Presentation, evaluation and treatment. Arab J Urol 2013;11:54-61.
4. Cornella JL, Larson TR, Lee RA, Magrina JF, Kammerer-Doak D. Leiomyoma of the female urethra and bladder: Report of twenty-three patients and review of the literature. Am J Obstet Gynecol 1997;176:1278-85.
5. Goluboff ET, O'Toole K, Sawczuk IS. Leiomyoma of bladder: Report of case and review of literature. Urology 1994;43:238-41.
6. Bryckaert PE, Ceccaldi PF, Bancheri F, Staerman F. Pelvic pain caused by bladder leiomyoma: Diagnostic and radiologic difficulties. Prog Urol 2002;12:1299-301.
7. Maya MM, Slywotzky C. Urinary bladder leiomyoma: Magnetic resonance imaging findings. Urol Radiol 1992;14:197-9.
8. Knoll LD, Segura JW, Scheilhauer BW. Leiomyoma of the bladder. J Urol 1986;136:906-13.
9. Teran AZ, Gambrell RD. Leiomyoma of the bladder. Int J Fertil 1989;34:289-92.
10. Núñez Mora C, Julve Villalta E, Hardisson Hernáez D, Jiménez de León J, Picazo García ML, Hidalgo Togores L, *et al*. Leiomioma vesical durante el embarazo [Bladder leiomyoma during pregnancy]. Arch Esp Urol 1999;52:510-3.
11. Kulkarni JN, Kamat MR, Chinoy RF. Bladder leiomyoma in pregnancy: A case report. Tumori 1992;78:414-6.
12. Furuhashi M, Suganuma N. Recurrent bladder leiomyoma with ovarian steroid hormone receptors. J Urol 2002;167:1399-400.
13. Matsuo H, Maruo T. GnRH analogues in the management of uterine leiomyoma. Nihon Rinsho 2006;64 Suppl 4:75-9.

Literature Review of an Adult Woman with Wilms' Tumor

Abstract

Wilms' tumor (WT), also known as nephroblastoma, is considered as an embryonal tumor due to nephrogenesis and histologic mimics of the early-onset age. WT is the most common renal tumor in children, but it is extremely rare in adults. WT is known to be a very chemosensitive tumor, and modern clinical trials aim to improve risk classification to reduce the burden of treatment. Diagnosis of WT is usually made after nephrectomy, so the possibility of preoperative chemotherapy is only possible in patients diagnosed with biopsy. A 48-year-old female with a history of 3-week left upper quadrant and left flank pain applied to a general practitioner. There was no previous trauma, hematuria, or other systemic symptoms. Further investigation with computed tomography (CT) scan of the abdomen with intravenous contrast revealed enlarged left kidney mass lesion within the left lower pole measuring up to 7.4 cm × 7.5 cm × 9.2 cm [Figure 1]. The patient underwent open radical left nephrectomy, retroperitoneal lymph node dissection, and partial excision [Figure 2]. Radical nephrectomy was performed, and when nephroblastoma was detected in histopathological examination, she was consulted with medical oncology. After positron emission tomography-CT examination revealed a thyroid involvement, a biopsy was performed, and it was diagnosed as papillary thyroid carcinoma. Total thyroidectomy was performed by the ear, nose, and throat and papillary thyroid carcinoma was diagnosed. Then, the patient started on vincristine dactinomycin therapy. There was no recurrence at the 3rd, 6th, 12th, and 36th month controls of the patient.

Keywords: *Adult, nephroblastoma, Wilms' tumor*

Basri Cakiroglu[1], Tuncay Tas[1,2], Mustafa Solak[3], Süleyman Hilmi Aksoy[4,5], Lora Ates[6]

Departments of [1]Urology, [3]Oncology, [4]Radiology, and [6]Pathology, Hisar Intercontinental Hospital, [2]Nişantaşı University, [5]Department of Medical Imaging, Galata University, Istanbul, Turkey

Introduction

Wilms' tumor (WT), also known as nephroblastoma, is the most common pediatric cancer of the kidney, most often occurring in the first 5 years of life and with the highest incidence between 3 and 4 years of age.[1] Adult WTs (AWT) are extremely rare and have been presented in the literature in about 500 cases or case series to date.[2] WT is an embryonic tumor that is thought to be originated from primitive metanephric blastemal.[1] Histologically, it is consists of three-phase model including epithelial, stromal, and blastemal components with varying degrees of expression. Histopathologically, AWT is not different from the pediatric group.[3]

Case Report

A 48-year-old female, 172 cm tall and 68 kg in weight, presented with weakness, fatigue, weight loss, and abdominal distension for 3 weeks. In her examination, her blood pressure revealed 130/70 mmHg, heart rate revealed: 78/min, her temperature was 36.5, the patient was slightly pale in appearance, CVAT(Costa Vertebra Angle Tenderness) −/left+ (CVAH−/left+), she was presented with tenderness in the left upper quadrant.

There was no previous trauma and hematuria. She has been treated for 4 years due to severe depression. She had no history of other systemic disease. There was no family history of medical problems or cancer. She was a nonsmoker, had no allergies, and was not taking any regular medications.

Infection parameters were found normal in blood tests (C-reactive protein 48 mg/L, leukocytes 6.79 × 10^9/L) with signs of anemia (hemoglobin 11.3 g/dL, hematocrit 33.3%, and thrombocytes 285 × 10^9/L). Kidney functions were normal (creatinine 0.64 mg/dL, blood urea nitrogen 11.6 mg/mg/dL). Renal ultrasound revealed a hyperechoic mass measuring 9 cm in the lower pole of the left kidney. Further investigation with computed tomography (CT) scan of the abdomen with intravenous contrast revealed enlarged left kidney mass lesion within the left lower pole measuring up to 7.4 cm × 7.5 cm × 9.2 cm [Figure 1].

How to cite this article: Cakiroglu B, Tas T, Solak M, Aksoy SH, Ates L. Literature review of an adult woman with Wilms' Tumor. Hellenic Urol 2021;33:28-31.

Submitted: 26-Jun-2021
Revised: 07-Jul-2021
Accepted: 08-Jul-2021
Published: 15-Feb-2022

Address for correspondence:
Prof. Basri Cakiroglu, Saray Mh. Siteyolu Cd. No. 7, 34768, Ümraniye, İstanbul, Turkey.
E-mail: drbasri@gmail.com

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 10.4103/HUAJ.HUAJ_27_21

Quick Response Code:

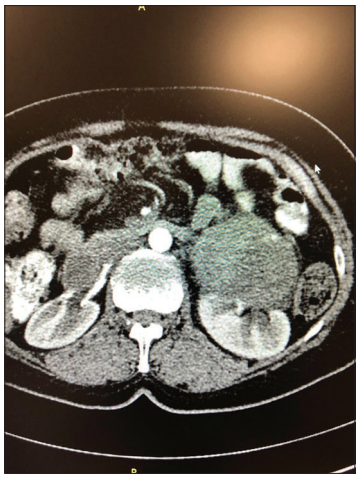

Figure 1: Computed tomography scan – axial view. Left kidney a mass lesion within the left lower pole measuring up to 7.4 cm × 7.5 cm × 9.2 cm

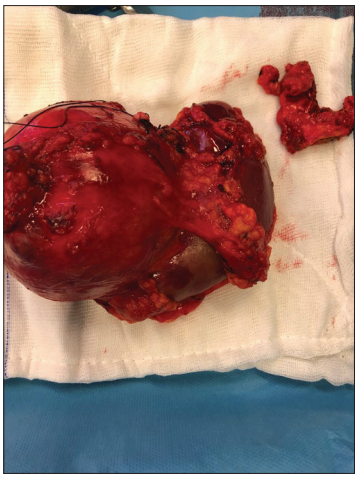

Figure 2: Macroscopical nephrectomy material sized 14 cm × 9.5 cm × 7.5 cm

At the end of the examinations, the patient was diagnosed with renal cancer, and open radical left nephrectomy and retroperitoneal lymph node dissection were performed. Macroscopically, nephrectomy material sized 14 cm × 9.5 cm × 7.5 cm diameter. On the cross-sectional surface, a 9 cm × 8 cm tumor showing hemorrhage and cystic areas, with solid and soft components were demonstrated [Figure 2].

Tumoral capsule invasion was detected. There was no invasion in the pelvis. In addition, the sample from the surreal tissue was 6 cm × 2 cm × 0.7 cm diameter. Microscopically, a 9 cm diameter malignant tumor formation consisting of round-oval tubular structures formed by cells with hyperchromatic nuclei, rosette structures, cord structures, papillary structures, and solid areas were observed [Figure 3]. Vascular invasion, necrosis, and hemorrhage were observed in the tumor. Capsule invasion and extracapsular soft-tissue invasion were demonstrated, although the tumor penetrated the gerota, it did not exceed to perirenal soft tissues. There was no invasion in the renal hilus either.

There was an invasion in the pelvis. Adrenal gland invasion was not detected. Surgical margins were tumor free. Histologically, the tumor consisted of blastemal, stromal, and anaplastic elements. Blastemal elements were present in nodular form and there was a syncytial pattern without diffuse infiltrative components. Anaplastic elements and stromal elements (nucleus three times bigger than tumor cells and tripolar mitosis) were demonstrated. Tumor tissue was consisting of round and oval cells, forming cords, and clusters. Furthermore, glomeruloid structures and focal papillary structures were demonstrated.

Fluorescent *in situ* hybridization analysis showed no loss of heterogeneity for 1p 16q, which was associated with poor outcomes in pediatric WT. Pathological staging was pT3a, pN0, and cM0 (pT3a – tumor invading renal capsule, but not beyond Gerota's fascia, pN0 – no metastasis in the regional lymph node, cM0 – not specified).

The patient was consulted with medical oncology. After positron emission tomography-CT examination revealed a thyroid involvement, a biopsy was performed, and it was diagnosed as papillary thyroid carcinoma. Total thyroidectomy was performed by the ear, nose, and throat. Group UH-1 protocol with early radiotherapy to the tumor bed and multiagent chemotherapy including actinomycin D, vincristine, and doxorubicin was applied to the patient. Radiotherapy and chemotherapy were started concomitantly within 3 weeks after surgery. The intensity of chemotherapy was maintained according to the protocol with granulocyte support. The patient was followed at regular intervals with CT scan and routine blood tests.

The findings of the patient's 3rd, 6th, 12th, 24th, and 36th-month control images were compared to each other and there were no signs of compatible with recurrence or metastases.

Discussion

Although WT is the most common renal tumor accounting for 85% of renal neoplasms in children, it is extremely rare in adults, and <500 cases have been reported in the literature.[1,2] WT is the most common kidney cancer in childhood with an annual incidence of 8–10/million.[4] WT has been reported as only 3% of kidney tumors in adults, which explains the difficulties in the diagnostic procedure and management of the treatment strategies in this age group.[5]

WT is characterized histologically by three types of cells: it consists of stromal, epithelial, and blastemal cells. In adults, blastemal component, which is possibly the most malignant component, is predominant. It is rare to find three patterns of cells at the same time.[6,7] In a study conducted by the European Cancer Registry between 1983 and 1994, they found that the average age of AWT patients at the time of diagnosis was 34.[8]

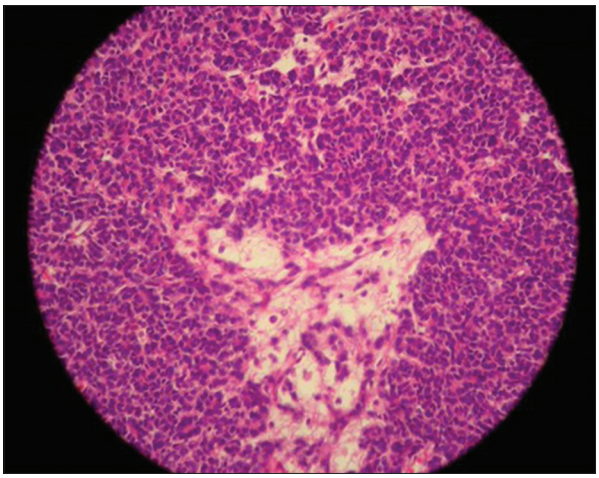

Figure 3: Blastemal area with tubular and small papillary structures (H and E, ×10)

Clinical and radiographic findings of WT in adults are indistinguishable from kidney tumors such as renal cell carcinoma. As a result, correct identification is usually not made until after nephrectomy, thus eliminating the possibility of neoadjuvant chemotherapy.[9] In our patient, concerning clinical and radiological findings, we concluded that the patient may have a kidney cancer and performed nephrectomy directly without biopsy. Yet, biopsy material revealed WT.

The clinical course of adults with WTs is different from that of children. While pediatric patients usually present with a painless abdominal mass, adults complain of flank, and abdominal pain, but few of them have symptoms. Some patients may present with complaints of hematuria, chest pain, back pain, abdominal mass, and hypertension. Adult patients may also present with other nonspecific symptoms such as weight loss, loss of appetite, and sudden decrease in performance.[5,9] Our patient also presented with the complaints of weakness, fatigue, weight loss, and abdominal bloating.

Metastasis is more common in adults than in children. It is most common in the lungs, followed by the liver, bone, lymph nodes, skin, orbital, and contralateral kidney.

A wide variety of syndromes, congenital abnormalities, and structural chromosomal abnormalities have been associated with an increased risk of WT in children. Although one case of an AWT patient with a germline WT1 mutation and another with hypospadias and cryptorchidism has been identified, these syndromes do not appear to be responsible for WT in adulthood. The genetic changes that underlie WT in children contain approximately 40 cancer genes.[10]

AWT is a treatable disease. Chemotherapy is an effective treatment method, together with surgery and radiation therapy.[1]

Pediatric WT treatment is complex in itself and managed by Children's Oncology Group (COG) and International Society of Pediatric Oncology (SIOP) protocols. The two main approaches for the treatment of WTs in pediatric patients belong to the Pediatric Oncology Group and SIOP. One of the main differences between the two is that the COG approach advocates anterior nephrectomy, SIOP recommends a 4–6-week period of neoadjuvant chemotherapy for all patients older than 6 months, which allows to phase down and prevent intraoperative tumor shedding.[11]

In a study of 27 patients, four patients were Stage III, as in our patient, one of these patients received AMD + VCR, two of them AMD + VCR + ADR, and the remaining patient received postoperative chemotherapy with AMD + VCR + ADR + CPM. Three patients were treated with postoperative radiation therapy: one patient was given full abdominal radiation therapy at 4440 cGy to the tumor bed and the other two at 1080 and 1100 cGy doses, respectively. Group UH-1 protocol including radiotherapy was applied. Our patient responded objectively to this treatment. It has been stated that the role of actinomycin D in the long-term survival of patients is also unclear.

Gender is not an important prognostic factor in the pediatric age group, and only metastatic disease has been reported to have worse survival with stage-specific treatment. However, in the adult group, 5-year relative survival (61%) has been reported to be almost 30% higher in women compared to men.[8]

In a series of 27 patients, 2-year survival was reported as 67%. Depending on the tumor stage and histology, they recommend treating risk-adapted adults.[12] Our patient is now being checked for the 3rd year, and no relapse was detected during this period.

Conclusion

Unlike children, WT is seen rarely in adult patients. There are no established protocols for the treatment of this age group. The diagnosis is usually made in postoperative histopathological examination.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that their name and initial will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Modi S, Tiang KW, Inglis P, Collins S. Adult Wilms' tumour: Case report and review of literature. J Kidney Cancer VHL 2016;3:1-7.
2. Ferreira E, Mohaghegh M, Venkat S, Drachenberg D, Battistuzzi S, Ji S. A case of an adult wilms tumour in a patient with velocardiofacial syndrome. Urology 2020;137:e8-9.
3. Babaian RJ, Skinner DG, Waisman J. Wilms' tumor in the adult patient: Diagnosis, management, and review of the world medical literature. Cancer 1980;45:1713-9.
4. Spreafico F, Bellani FF. Wilms' tumor: Past, present and (possibly) future. Expert Rev Anticancer Ther 2006;6:249-58.
5. Reinhard H, Aliani S, Ruebe C, Stöckle M, Leuschner I, Graf N. Wilms' tumor in adults: Results of the Society of Pediatric Oncology (SIOP) 93-01/Society for Pediatric Oncology and Hematology (GPOH) Study. J Clin Oncol 2004;22:4500-6.
6. Caramanti RL, Aprígio RM, de Moraes DF, Rocha CE, Meguins LC, Goes MJ, *et al.* Brain metastasis of Wilms tumor in adult. World Neurosurg 2020;138:422-4.
7. Coppes MJ, Pritchard-Jones K. Principles of Wilms' tumor biology. Urol Clin North Am 2000;27:423-33.
8. Mitry E, Ciccolallo L, Coleman MP, Gatta G, Pritchard-Jones K; EUROCARE Working Group. Incidence of and survival from Wilms' tumour in adults in Europe: Data from the EUROCARE study. Eur J Cancer 2006;42:2363-8.
9. Bradtke M, Rink M, Büscheck F, Sauter G, Dahlem R, Fisch M, *et al.* Current therapies of wilms tumors in the adult: Diagnostic considerations and treatment challenges. Clin Genitourin Cancer 2019;17:e522-5.
10. Treger TD, Chowdhury T, Pritchard-Jones K, Behjati S. The genetic changes of Wilms tumour. Nat Rev Nephrol 2019;15:240-51.
11. Dome JS, Graf N, Geller JI, Fernandez CV, Mullen EA, Spreafico F, *et al*. Advances in Wilms tumor treatment and biology: Progress through international collaboration. J Clin Oncol 2015;33:2999-3007.
12. Arrigo S, Beckwith JB, Sharples K, D'Angio G, Haase G. Better survival after combined modality care for adults with Wilms' tumor. A report from the National Wilms' tumor study. Cancer 1990;66:827-30.

An Infected Urachal Cyst Mimicking a Lower Urinary Tract Infection in a Young Adult

Abstract

Urachus is an embryologic remnant of allantois, which in adults presents as medial umbilical ligament connecting the dome of the bladder to the umbilicus. Defective obliteration of the urachus results in various urachal abnormalities. An infected urachal cyst is one of the urachal abnormalities, all of which are rare in adult life. The clinical presentation of an infected urachal cyst in adults is heterogeneous, and therefore, the diagnosis may be occasionally challenging. We present and discuss a case of a 25-year-old man with an infected urachal cyst, mimicking a lower urinary tract infection.

Keywords: *Abdominal pain, laparotomy, lower urinary tract infection, urachal cyst*

Kristiana Gkeka, Georgios Tsampoukas[1], Maria Tsimara[2], Panagiotis Kartsaklis

Departments of Urology and [2]Radiology, General Hospital of Patras, Patras, Greece, [1]Department of Urology, Princess Alexandra Hospital, Harlow, UK

Introduction

Urachus is an embryologic remnant, developed by the obliteration of the allantois. It forms the medial umbilical ligament, which connects the bladder dome to the umbilicus. If the obliteration fails, it will result in various urachal abnormalities: patent urachus, urachal cyst, urachal sinus, and vesicourachal diverticulum. Although those are quite rare, urachal cysts might be encountered in urological practice if they become complicated. In our paper, we present the case of a young man presenting with an infected urachal cyst, initially considered a lower urinary tract infection.

Case Report

A 25-year-old man was referred to the emergency department after several days of progressively worsening infraumbilical pain, dysuria, and fever. The diagnosis of lower urinary tract infection had been previously made in the community, and the patient had been treated with levofloxacin for 5 days with no response. On physical examination, a midline mass along with tenderness in the lower abdomen was noticed. The patient was tachycardic, body temperature was 38.5°C, and the blood pressure was 120/80 mmHg. Laboratory data showed a white blood cell count of 15.500/μL and a C-reactive protein level of 8.5 mg/dL. An urgent ultrasound illustrated a cystic-like mass (7.6 cm × 5 cm ×4.3 cm in diameter) located at the superior part of the bladder [Figure 1]. A computed tomography (CT) of the abdomen and pelvis showed a hypodense mass in the midline of the abdominal wall, with an indentation at the superior part of the bladder and a fibrous band ending up to the umbilicus, setting the diagnosis of an infected urachal cyst [Figure 2]. A decision for surgical intervention was made, and intravenous antibiotics (ciprofloxacin, amikacin) were administrated 24 h before the procedure. A laparotomy was performed, which revealed the urachal cyst as an extraperitoneal mass full of purulent fluid located at the superior part of the bladder. Firm adhesions between anterior abdominal wall and bladder were noticed; therefore, the cyst was extracted along with part of the bladder dome [Figure 3]. The postoperative course was uneventful, and the patient was discharged 7 days after surgery. The culture of the fluid of the mass revealed the growth of a Gram-negative bacterium (*Citrobacter braakii*). Pathological examination confirmed the histological characteristics of an infected urachal cyst [Figure 4].

Discussion

The incidence of the congenital anomalies of the urachus is rather unknown, whereas the same applies for the complications. The presentation of an infected urachal cyst as acute abdominal pain is quite rare; a study reported that the urachal remnants were

How to cite this article: Gkeka K, Tsampoukas G, Tsimara M, Kartsaklis P. An infected urachal cyst mimicking a lower urinary tract infection in a young adult. Hellenic Urol 2021;33:32-4.

Submitted: 18-Jun-2021
Revised: 05-Jul-2021
Accepted: 04-Aug-2021
Published: 15-Feb-2022

Address for correspondence:
Dr. Kristiana Gkeka, 53, Samothrakis Street, Patras, Greece. E-mail: kristianagkeka@gmail.com

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 10.4103/HUAJ.HUAJ_25_21

Quick Response Code:

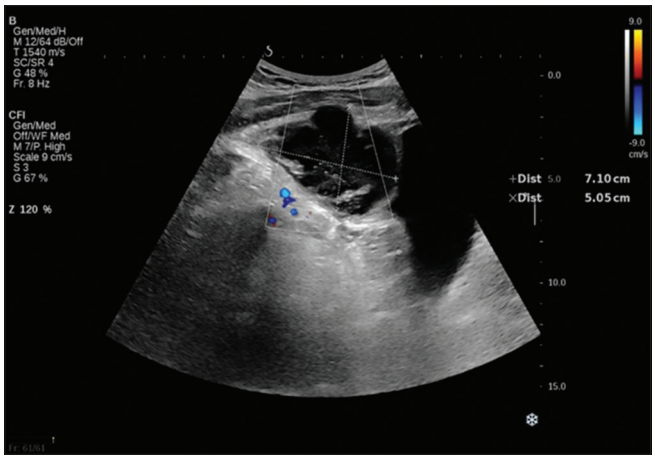

Figure 1: Ultrasound showing an irregular, lobulated, cystic lesion with content of mixed echogenicity located at the dome of the bladder

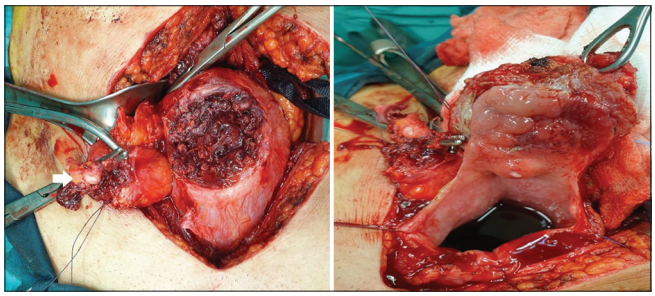

Figure 3: Intraoperative urachal cyst excision along with the dome of the bladder (white arrow: Urachal remnant)

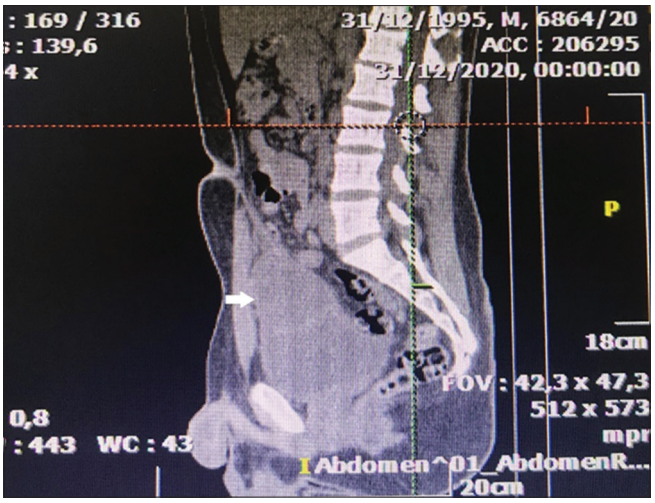

Figure 2: Abdominopelvic computed tomography showing the infected urachal cyst, lying upon the dome of the bladder (sagittal view, white arrow)

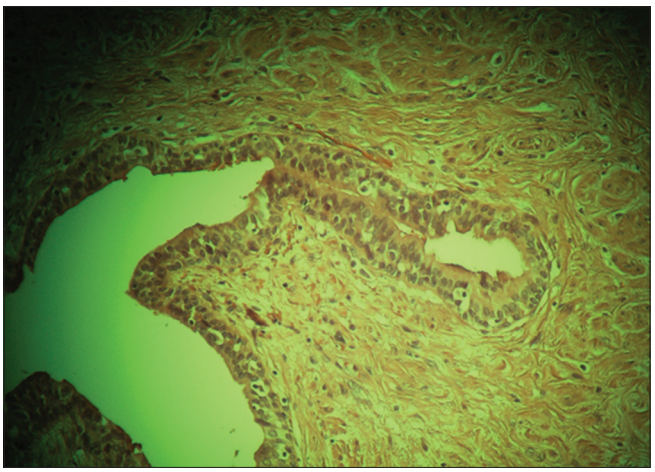

Figure 4: H and E image showing the duct lined by benign urothelium and cuboidal epithelium

responsible for 0.03% of acute abdominal presentation in the emergency department. Examination of the ages revealed a trimodal distribution: in the neonatal period, the early 20s, and the mid-50s.[1]

The majority of urachal cysts remain asymptomatic unless get complicated. They present with a wide range of symptoms including abdominal pain, fever, umbilical discharge, midline mass, and dysuria. Usually, the diagnostic process focuses on other common conditions such as acute appendicitis, Meckel's diverticulitis, urinary tract infection, and tumors of the bladder. Due to the heterogeneous presentation, patients might be initially misdiagnosed, like in our case. However, urachal anomalies should be considered in the differential diagnosis of patients with atypical, abdominal pain or an abdominal mass in the midline presenting with acute abdomen, due to infection of the cyst, intracystic bleeding, intraperitoneal rupture, intestinal obstruction, obstructive uropathy, or bowel fistula.[2]

Secondary infection, rupture, fistula formation, hemorrhage, urinary or intestinal obstruction, and the development of cancer have been reported as long-term complications.[3] Regarding the latter one, the majority of urachal carcinomas are adenocarcinomas corresponding to 0.1%–0.3% of all bladder malignancies and 20%–39% of bladder adenocarcinomas, with a mean age of presentation of 61 years.[4,5] Abdominal pain, a suprapubic mass, discharge of blood or pus from the umbilicus, and especially hematuria should raise the suspicion of urachal adenocarcinoma, whereas the presence of lower fatty infiltration of the retzius space in imaging is associated with benign disease.[6]

Multiple bacterial species have been isolated from the infected cysts, including *Staphylococcus aureus*, *Streptococcus viridans*, *Escherichia coli*, and *Bacteroides* species.[4] Like seen in our case, uncommon bacterial growth in the infected content of the cysts might reflect previous failed treatments.

Although the diagnosis of infected urachal cysts is primarily clinical, imaging is mandatory to confirm the diagnosis. Urachal cyst might be seen as a complex cystic mass in the midline above the bladder in ultrasonography, whereas CT with contrast illustrates the cyst as a supravesical heterogenous collection with enhancing irregular walls and

a central nonenhancing low attenuation content. Magnetic resonance imaging might also assist. To our experience, CT should be considered the imaging of choice, as it is accurate and available in the emergency setting, excluding also other pathologies. However, imaging might not be able to differentiate benign from malignant urachal pathology. Although the majority of malignancies are solid, up to 27% can demonstrate a cystic component, and similarly, the "pathognomonic" of urachal cancer intrinsic calcification can also been seen in approximately 20% of urachal cysts.[7]

Should the surgical treatment have been decided, open or minimally invasive approaches can be considered with similar efficacy. A two-stage approach with preoperative antibiotic therapy and later intervention should be followed because of the shorter hospital stay and the lower complications rate. This approach was proven quite efficient in our case. Due to the high risk of recurrence and the future risk of malignancy, the complete resection of the cyst is preferred compared to the radiological drainage.[8] The traditional surgical technique is the open excision of urachal remnants with a midline infraumbilical incision, but laparoscopic excision can also be performed.[9] A robotically-assisted laparoscopic approach, if available, can also be followed with remarkable results.[10]

To sum up, urachal anomalies are a rare condition in adulthood but may result in severe illness necessitating surgical intervention. Although clinical presentation is nonspecific, the medical history, physical examination, and early imaging will result in the prompt diagnosis. When the surgical treatment is indicated, the excision of the cyst, open or laparoscopically, should be regarded as the treatment of choice.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Schiffman JS. Urachal remnants in patients presenting to the emergency department with abdominal pain. J Emerg Med 2018;55:333-8.
2. Mrad Daly K, Ben Rhouma S, Zaghbib S, Oueslati A, Gharbi M, Nouira Y. Infected urachal cyst in an adult: A case report. Urol Case Rep 2019;26:100976.
3. Allen JW, Song J, Velcek FT. Acute presentation of infected urachal cysts: Case report and review of diagnosis and therapeutic interventions. Pediatr Emerg Care 2004;20:108-11.
4. Ashley RA, Inman BA, Routh JC, Rohlinger AL, Husmann DA, Kramer SA. Urachal anomalies: A longitudinal study of urachal remnants in children and adults. J Urol 2007;178:1615-8.
5. Hassanbhai DH, Ng FC, Koh LT. Is excision necessary in the management of adult urachal remnants? A 12-year experience at a single institution. Scand J Urol 2018;52:432-6.
6. Bi X, Wu Z, Han H, Zhou F. Clinical comparison of patients with benign urachal masses versus urachal carcinomas. Chin J Cancer 2017;36:2.
7. Das JP, Vargas HA, Lee A, Hutchinson B, O'Connor E, Kok HK, *et al.* The urachus revisited: multimodal imaging of benign and malignant urachal pathology. Br J Radiol 2020;93:20190118.
8. Yoo KH, Lee SJ, Chang SG. Treatment of infected urachal cysts. Yonsei Med J 2006;47:423-7.
9. Li Destri G, Schillaci D, Latino R, Castaing M, Scilletta B, Cataldo A Di. The urachal pathology with umbilical manifestation: Overview of laparoscopic technique. J Laparoendosc Adv Surg Tech 2011;21:809-14.
10. Madeb R, Knopf JK, Nicholson C, Donahue LA, Adcock B, Dever D, *et al.* The use of robotically assisted surgery for treating urachal anomalies. BJU Int 2006;98:838-42.