ISSN 2219-2816 (online)

World Journal of *Clinical Urology*

World J Clin Urol 2017 March 24; 6(1): 1-33

Published by Baishideng Publishing Group Inc

WJCU

World Journal of Clinical Urology

A peer-reviewed, online, open-access journal of clinical urology

Editorial Board

2016-2019

The *World Journal of Clinical Urology* Editorial Board consists of 201 members, representing a team of worldwide experts in urology. They are from 32 countries, including Australia (2), Austria (1), Belgium (2), Brazil (4), Canada (2), Chile (1), China (19) , Czech Republic (1), Egypt (7), France (3), Germany (7), Greece (7), Hungary (1), India (3), Iran (1), Israel (4), Italy (20), Japan (8), Malaysia (1), Mexico (1), Netherlands (2), Pakistan (3), Portugal (1), Romania (1), Saudi Arabia (3), South Korea (4), Spain (2), Switzerland (1), Thailand (2), Turkey (12), United Kingdom (7), and United States (68).

World Journal of Clinical Urology

Contents

Four-monthly Volume 6 Number 1 March 24, 2017

World Journal of Clinical Urology
Volume 6 Number 1 March 24, 2017

Contents

NAME OF JOURNAL
World Journal of Clinical Urology

ISSN
ISSN 2219-2816 (online)

LAUNCH DATE
December 28, 2011

FREQUENCY
Four-monthly

World Journal of Clinical Urology
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
March 24, 2017

World Journal of Clinical Urology

Submit a Manuscript: http://www.wjgnet.com/esps/

World J Clin Urol 2017 March 24; 6(1): 1-9

DOI: 10.5410/wjcu.v6.i1.1

ISSN 2219-2816 (online)

REVIEW

Contemporary management of upper tract urothelial cell carcinoma

Kellen Choi, Ryan McCafferty, Samuel Deem

Kellen Choi, Samuel Deem, Department of Urology, Charleston Area Medical Center, Charleston, WV 25304, United States

Ryan McCafferty, Department of Anesthesiology PGY-1, Larkin Community Hospital, South Miami, FL 33143, United States

Author contributions: Choi K wrote the paper; McCafferty R and Deem S performed literature review.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Manuscript source: Invited manuscript

Correspondence to: Kellen Choi, DO, Department of Urology, Charleston Area Medical Center, 3200 MacCorkle Ave, S.E., Charleston, WV 25304, United States. bchoi@alum.unthsc.edu
Telephone: +1-304-3885280
Fax: +1-304-3885291

Received: April 5, 2016
Peer-review started: April 8, 2016
First decision: July 14, 2016
Revised: November 7, 2016
Accepted: December 27, 2016
Article in press: December 29, 2016
Published online: March 24, 2017

Abstract

Upper tract urothelial cell carcinoma (UTUCC), formerly known as transitional cell carcinoma of the upper urinary tract, is a rare oncologic disease in Western countries. Thus its disease process and its management are not as well defined as other urologic cancers. We are reviewing the current evidence based literature available to develop a plan for the treatment of UTUCC. A PubMed search was completed using the key words "upper tract urothelial cell carcinoma", "epidemiology", "risk factor", "treatment" and "prognosis". Six hundred fifty two articles were found. We narrowed our search to articles published between January 2004 and June 2016 for a more contemporary review of the topic. Four hundred seventy articles were then available for review. Further detailed search was performed for relevance on the topic and hundred one articles were selected for the review. Many risk factors have been found to be associated with the development of UTUCC, including tobacco use. Patients are often asymptomatic and may only present with microscopic or gross hematuria. Tumor grade and stage are pivotal in determining the treatment options for UTUCC. Advancements in endoscopic techniques have aided in the diagnosis, grading and treatment of this disease. Treatment options include topical therapy, with combinations of methotrexate, vinblastine, doxorubicin and cisplatin or gemcitibine or cisplatin, endoscopic resection, segmental ureterectomy and ureteral implantation, and nephroureterectomy, including bladder cuff. Treatment recommendations depend on tumor grade and stage, renal function, tumor location and the patient's prognosis. There are currently no tissue or blood-based biomarkers available to accurately monitor the disease. Further studies of gene expression and biomarkers may hopefully improve the management of this disease. Although rare in many countries, UTUCC is becoming more prevalent due to exposure to carcinogenic herbal remedies and other identifiable risk factors. Numerous treatment modalities, both surgical and chemotherapeutic, have been utilized to treat both low and high grade UTUCC tumors. Additional clinical trials are necessary to further develop methods for screening, treatment, and surveillance to improve management.

Key words: Urothelial cell carcinoma; Diagnosis; Upper tract; Epidemiology; Risk factors; Treatment; Prognosis

Core tip: To review the current literature on upper tract urothelial cell carcinoma (UTUCC) and provide a contemporary management plan for treatment based on best available evidence. Large randomized controlled trials are lacking in UTUCC due to the fortunately rare occurrence of the disease. Treatment recommendations for the primary lesion, imaging, and follow-up in this review are based on the stage and grade of the tumor. Early diagnosis and aggressive treatment remains the mainstay of therapy for UTUCC.

Choi K, McCafferty R, Deem S. Contemporary management of upper tract urothelial cell carcinoma. *World J Clin Urol* 2017; 6(1): 1-9 Available from: URL: http://www.wjgnet.com/2219-2816/full/v6/i1/1.htm DOI: http://dx.doi.org/10.5410/wjcu.v6.i1.1

INTRODUCTION

Upper tract urothelial cell carcinoma (UTUCC) accounts for 95% of upper tract carcinoma, with the remaining types being squamous cell carcinoma and adenocarcinoma[1]. Although UTUCC is a rare disease in the West, with an incidence of approximately 40000 cases per year, the incidence has risen in recent years. It is more common and the incidence has risen quickly in Asian countries, especially Taiwan, along with the Balkan regions[2].

UTUCC shares a similar embryologic origin as the bladder, both being derived from the urothelium. But due to anatomic, biological, and molecular differences between upper tract urothelial carcinoma and bladder cancer, they have been referred to as "disparate twin" diseases[2,3]. Accurate local surgical staging and subsequent clinical staging (TNM) is important to help standardize treatment planning. Modern management of UTUCC includes chemotherapy, endoscopic procedures, and nephroureterectomy. We will review the epidemiology, risk factors, classification, diagnosis, staging and medical and surgical treatments of UTUCC.

EPIDEMIOLOGY

Upper tract urothelial cell cancer can be found with higher incidence in Balkan regions, and most recently in certain Asian countries especially in Taiwan[2,4,5].

Upper tract urothelial cell cancers are most commonly diagnosed later in life, mostly in the eighth decade[6]. However, it should also be considered in younger populations, especially in patients with exposure to aristolochic acid (AA) plants, which is commonly used for weight loss in Asian countries. It is a very uncommon disease, with an incidence of less than 1 case per 40000[2]. It makes up 5% of all urothelial tumors and 5% to 7% of all renal tumors[6]. Men are twice as likely to have UTUCC, compared to women[7]. Although low in incidence, UTUCC is very aggressive, as many patients are asymptomatic and tend to present later with advanced stage disease, often with metastasis. A thorough understanding of this disease is pivotal in successful diagnosis and treatment[8].

RISK FACTORS

The most well known risk factor for UTUCC is aristolochic acid plants, more commonly used in Balkan regions and in Asian countries, especially in Taiwan[4,9-12]. Balkan endemic nephropathy, associated with ingesting the aristolochic acid plants, can lead to renal failure and increased risk of UTUCC. In addition to increased exposure to aristolochic acid, Balkan populations are also known to have genetic and hereditary predisposition to UTUCC. Other risk factors are microsatellite instability and lynch syndrome type Ⅱ[13-16].

Other risk factors for UTUCC are similar to bladder urothelial cell carcinoma, with the most common risk factor being cigarette smoking[7,17,18]. Tobacco use is found to increase the relative risk exposure from 2.5 to 7[19]. Occupational exposures to chemicals such as petrochemical and plastic industries, ink solvents, coals, asphalt and aniline dye products are shared risk factors between UTUCC and bladder UCC[20,21]. Newly identified risk factors associated with UTUCC include inverted papilloma which are found in the bladder[22].

UTUCC can be associated with bladder urothelial cell carcinoma but occurs in less than 5%, although nearly 25% in patients with carcinoma *in situ* (CIS). Environmental exposures unique to upper tract tumors include Blackfoot disease, Artesian well water, weight-reducing pills, well water, arsenic, organic chlorides, and Ergot alkaloids[5,23]. Phenacetin-based analgesics and cyclophosphamide have also been found to be causative agents in UTUCC.

PRESENTATION

UTUCC has been associated with significant delays in presentation, as many cases are asymptomatic. However, these cancers tend to be very aggressive once they present. Typically, it presents with microscopic or gross hematuria. Flank pain can be present in up to 30% of patients. This is often attributed to urinary tract obstruction by the tumor.

The most common locations for this tumor are the renal pelvis and less often the ureter. Ureteral tumors are located most commonly in the lower ureter and least commonly in the upper ureter. Incidence based on location is as follows: distal ureter in 70%, mid ureter in 25% and then proximal ureter in 5%[24-26].

DIAGNOSIS

Contrasted imaging of the collecting systems and ureters with CT urogram or retropyelogram is necessary along with cystoscopy to diagnose UTUCC. UTUCC is most frequently identified as an obstruction or filling defect,

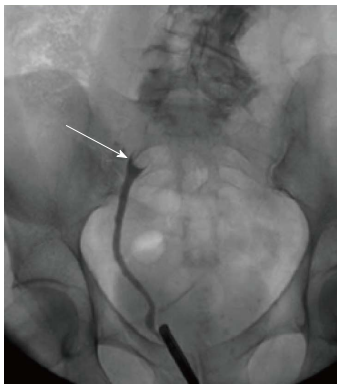

Figure 1 Filling defect on retropyelogram, showing typical "goblet sign" due to R ureteral urothelial cell carcinoma.

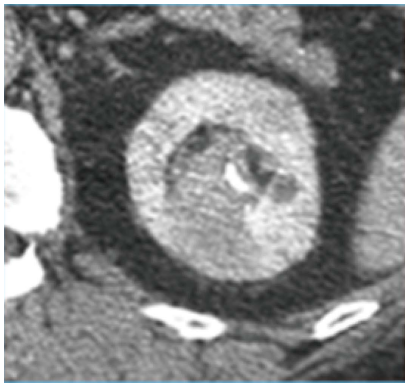

Figure 2 Central mass of upper tract urothelial cell carcinoma on left kidney, seen as renal sinus mass.

often known as the "goblet sign" when found in the ureter (Figure 1). CT urogram is the gold standard for both staging and diagnosis, with the sensitivity of 0.67-1 and specificity of 0.93[19,27-31]. If the patient has renal failure or another reason to avoid intravenous contrast, a retrograde pyelogram can be performed. Suspect UTUCC if a central renal tumor is seen, as the mass grows into the renal sinus (Figure 2).

Physicians must have a high index of suspicion for UTUCC when faced with a positive cytology despite having a negative cystoscopy, especially high grade UCC and CIS[32,33]. In this scenario, ureteral barbotage, also known as selective ureteral catherization is performed[34]. Ureteral washing has 80% sensitivity and ureteral brushing has 90% sensitivity. Of note, such selective collection of urine samples should occur prior to retrograde pyelography, as high-osmolar contrast agents may alter the cytologic features of the urine sample.

Once UTUCC is suspected, ureteropyeloscopy and biopsy is indicated[35-37]. Coupled with biopsy, ureteropyeloscopy is the method of choice for diagnosis of UTUCC[38-40]. However, due to the small size of the ureteral scopes, thin walled ureter and small biopsy forceps, staging is limited. Nevertheless, concordance between biopsy and final pathology is as high as 90% to 92%.

The TNM Staging System for UTUCC provided in Figure 3 and Table 1 defines the locations and extent of disease.

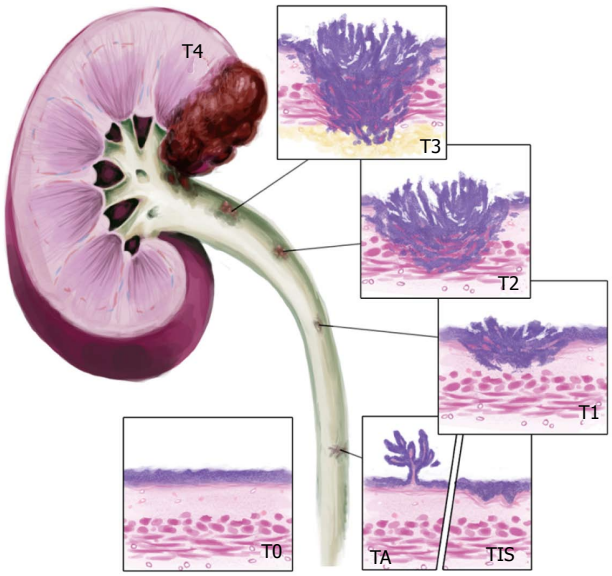

Figure 3 Pathologic stage of upper tract urothelial cell carcinoma. Courtesy of third year medical student at West Virginia University, Mike Tran.

The staging system begins at T0, which is no evidence of primary tumor and progresses to T4, where the tumor invades adjacent organs or through the kidney into the perinephric fat. Of note, tumor stage was identified as the most important determinant in predicting recurrence and survival. There for all efforts to obtain an accurately staged tissue is crucial[41].

Lymph node involvement for renal pelvis tumors may include renal hilar, paracaval, aortic, and retroperitoneal nodes. For ureteral lymph node involvement, renal hilar, iliac, paracaval, periureteral, and pelvic nodes are commonly involved.

PROGNOSTIC FACTORS

The most pivotal factors in determining prognosis are tumor stage and grade[42-46]. Invasion of the vascular, lymphatic, renal hilum and parenchyma, and perineural tissue surrounding the kidney has been shown to indicate more aggressive tumor behavior[47-52]. Multifocal disease, including areas such as the bladder, have been found to indicate a higher likelihood of recurrence and a worse overall prognosis[53]. Tumor necrosis greater than 10% is another independent risk factor indicating worse prognosis[54,55]. Age, gender and tumor location have been found to offer little information on disease course and predicting overall prognosis[56-61]. Numerous molecular markers including E-cadherin, Telomerase RNA component, hypoxia-inducible factor (HIF) 1-α, epithelial membrane protein 3, and C-erb-B2 have been investigated as possible diagnostic and prognostic tools[62-66]. More data is needed before applying the markers in a clinical setting.

TREAMENT

Stage and grade of the tumor is instrumental in de-

Table 1 TNM classification

T - primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive carcinoma
Tis	Carcinoma *in situ*
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades the muscularis
T3	(For renal pelvis only) tumor invades beyond muscularis into peripelvic fat or the renal parenchyma T3 (For ureter only) tumor invades beyond muscularis into periureteric fat
T4	Tumor invades adjacent organs, or through the kidney into the perinephric fat
N - regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node, ≤ 2 cm in greatest dimension
N2	Metastasis in a single lymph node, > 2 cm but not > 5 cm in greatest dimension; or multiple lymph nodes, none > 5 cm in greatest dimension
N3	Metastasis in a lymph node, > 5 cm in greatest dimension
M - distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

NCCN Guidelines® version 2, 2015[19]. Upper GU tract tumors.

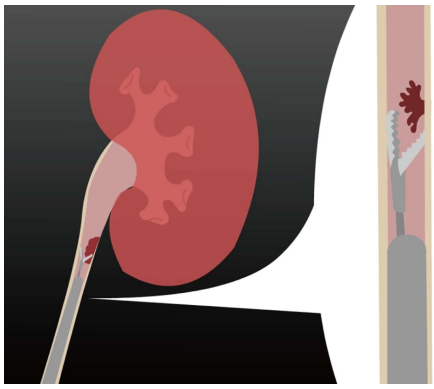

Figure 4 Obtaining tumor specimen for pathologic stage.

ciding treatment plans. Nephroureteretomy (NU) with bladder cuff has been the gold standard, and remains the treatment of choice for high grade (TA/T1, HG or CIS), invasive, or multifocal tumors, along with regional lymph node dissection[42,67].

Segmental resection or distal ureterectomy may be indicated in select cases to preserve renal function[68-70]. Tumors located in the distal third of the ureter can utilize a Psoas Hitch[71,72] which was popularized by Turner-Warwick. This method is an effective means to bridge the resultant defect of the lower third of the ureter. However, a small contracted bladder is a contraindication due to insufficient bladder capacity.

Ureteral defects proximal to the pelvic brim require more than a Psoas hitch. A lengthy ureteral tumor or diseased ureter in a patient with a need to preserve renal function can utilize an ileal ureteral substitution. Relative contraindications for ileal ureteral substitution include renal insufficiency, bladder outlet obstruction, and inflammatory bowel disease.

Endoscopic resection or ablation can be considered in patients with a solitary kidney or poor surgical candidates, especially for low grade and low stage tumors[73-78]. Holmium or Nd: Yag may be used for tumor ablation, as well as ureteral resection *via* an ureteroscope (Figures 4 and 5)[79].

A percutaneous approach may be considered in large (> 1.5 cm) renal pelvis UCC that are grade 1 and possibly grade 2[80,81]. The advantage for the percutaneous approach is that after 2-3 wk and with a normal nephrogram, BCG or mitomycin may be administered into the collecting system through the nephrostomy tube, as opposed to retrograde administration *via* reflux up a ureteral stent which is more challenging[82-85]. The disadvantage for a percutaneous approach is that 1/3 will recur and it is more invasive than other treatment options.

There is a lack of prospective studies that use of chemotherapy, whether neoadjuvant or adjuvant, due to the low incidence of this disease. The National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) suggest the use of both with patient discretion (Table 2). For muscle invasive UCC, MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) or gemcitabine and cisplatin chemotherapy are both treatment options[85-91]. Of note, BCG and mitomycin treatment for upper tract UCC is extrapolated from bladder cancer and retrospective studies. There are currently no prospective studies showing improved survival and these are difficult to construct since it is such a rare disease. A role for BCG in the management of upper tract CIS has been demonstrated in retrospective studies, although a definitive efficacy of adjuvant topical therapy after endoscopic resection of Ta/T1 tumors has not yet been proven[84,92]. Of note, immunotherapy and chemotherapy in the upper tract has limitations due to difficulty delivering them to the system, unlike bladder instillations with such agents. Currently NCCN Guidelines® support using postsurgical

Table 2 Adjuvant treatment for renal pelvis and urothelial carcinoma of ureter

Pathologic staging	Adjuvant treatment	Follow-up
pT0, pT1	None	Cystoscopy every 3 mo for 1 yr, then at increasing intervals Imaging of upper tract collecting system at 3- to 12-mo intervals, if endoscopic resection ± CT scan or MRI ± Chest X-ray
pT2, pT3 pT4, pN+	Consider adjuvant chemotherapy	Cystoscopy every 3 mo for 1 yr, then at increasing intervals Imaging of upper tract collecting system at 3- to 12-mo intervals ± CT scan or MRI ± Chest X-ray

NCCN Guidelines® version 2, 2015[19]. Upper GU tract tumors. CT: Computed tomography; MRI: Magnetic resonance imaging.

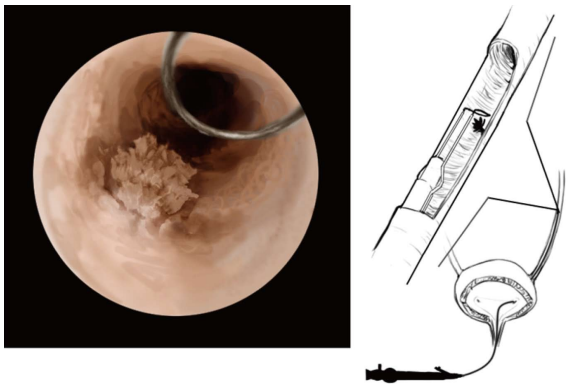

Figure 5 Tumor resection using ureteral resectoscope with loop.

intrapelvic chemotherapy or BCG for low grade UTUCC of the renal pelvis after endoscopic resection[91].

Chemotherapy for metastatic disease was studied using MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) in 184 patients from 1986 to 2004 at M.D. Anderson Center. Median recurrence-free survival was 2.4 years[75]. Patients with advanced disease should receive chemotherapy, preferably in a neoadjuvant setting. Enlarged lymph nodes should be biopsied prior to surgery, and if positive then intravenous chemotherapy should be administered, followed by surgery if no progression, as with bladder UCC.

Radiation plays a very small role in the treatment of UTUCC. Adjuvant radiotherapy may help limit local disease in a palliative setting. Although its role is limited, when combined with chemotherapy it may improve survival and disease-free survival[93,94].

MANAGEMENT/SURVEILLANCE

Management principles of UTUCC are similar to that of bladder cancer. Low grade/low stage tumors may recur, but have a low likelihood of progression and high grade/high stage tumors are more aggressive and have a higher chance to metastasize. The challenge is identifying tumors as Ta low grade and ruling out CIS and more aggressive tumors[95,96] as obtaining adequate tissue for diagnosis can be challenging. Surveillance after treatment of UTUCC comes with many options. Per the European Association of Urology guidelines, low grade/stage tumors follow up should include cystoscopy every 3 mo for 1-2 years with periodic urine cytology, then every 6 mo for 2 years[41]. If renal sparing surgery was performed, an ureteroscopy would also be required. If the tumor was high grade/stage the management would be similar to that of the low grade/stage. In addition you would recommend imaging of the pelvis and abdomen and a chest X-ray.

CONCLUSION

Upper tract urothelial cell carcinoma is a rare disease with an incidence of less than 40000 cases per year. The most common presenting symptoms of UTUCC include hematuria and ureteral obstructive symptoms such as flank pain. The work up would then include cystoscopy, urine cytology, BUN, Creatinine and a CT Urogram. Tumor stage and grade are the most important prognostic factors to help the physician determine the best treatment options for the patient. Nephroureterectomy continues to be the gold standard for treatment in high grade, high stage tumors. In patients with low grade/stage disease, an absent contralateral kidney, poor renal function, or bilateral disease, renal sparing therapies including endoscopic resection, intravesical therapy with BCG or mitomycin C, and ureteral resection with ureteroureterostomy or re-implantation should be considered as an option for treatment. With appropriate treatment, the 5 year recurrence free survival rate for low grade/stage disease can be as high as 92%. However if the disease is not caught early and the patient has high grade/stage disease the 5 year recurrence free survival can be as low as 5%-48%. Factors such as high pathological stage, lymph node metastasis and vascular invasion increase the risk of recurrence and lead to decreased overall survival. Due to the aggressive nature of this disease, and lack of large prospective studies on this topic, large multi-institutional clinical trials are necessary to further investigate options for diagnosis, treatment, and surveillance to help those diagnosed with UTUCC.

ACKNOWLEDGMENTS

Special thanks to Mike Tran MD, who drew illustrations

for this topic.

REFERENCES

1 **Ploeg M**, Aben KK, Kiemeney LA. The present and future burden of urinary bladder cancer in the world. *World J Urol* 2009; **27**: 289-293 [PMID: 19219610 DOI: 10.1007/s00345-009-0383-3]

2 **Matin SF**, Shariat SF, Milowsky MI, Hansel DE, Kassouf W, Koppie T, Bajorin D, Grollman AP. Highlights from the first symposium on upper tract urothelial carcinoma. *Urol Oncol* 2014; **32**: 309-316 [PMID: 24397995 DOI: 10.1016/j.urolonc.2013.08.029]

3 **Wang Y**, Lang MR, Pin CL, Izawa JI. Comparison of the clonality of urothelial carcinoma developing in the upper urinary tract and those developing in the bladder. *Springerplus* 2013; **2**: 412 [PMID: 24024098 DOI: 10.1186/2193-1801-2-412]

4 **Chen CH**, Dickman KG, Moriya M, Zavadil J, Sidorenko VS, Edwards KL, Gnatenko DV, Wu L, Turesky RJ, Wu XR, Pu YS, Grollman AP. Aristolochic acid-associated urothelial cancer in Taiwan. *Proc Natl Acad Sci USA* 2012; **109**: 8241-8246 [PMID: 22493262 DOI: 10.1073/pnas.1119920109]

5 **Tan LB**, Chen KT, Guo HR. Clinical and epidemiological features of patients with genitourinary tract tumour in a blackfoot disease endemic area of Taiwan. *BJU Int* 2008; **102**: 48-54 [PMID: 18445081 DOI: 10.1111/j.1464-410X.2008.07565.x]

6 **Munoz JJ**, Ellison LM. Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. *J Urol* 2000; **164**: 1523-1525 [PMID: 11025695 DOI: 10.1016/S0022-5347(05)67019-X]

7 **Rink M**, Xylinas E, Trinh QD, Lotan Y, Margulis V, Raman JD, Fisch M, Lee RK, Chun FK, Abdennabi J, Seitz C, Pycha A, Zlotta AR, Karakiewicz PI, Babjuk M, Scherr DS, Shariat SF. Gender-specific effect of smoking on upper tract urothelial carcinoma outcomes. *BJU Int* 2013; **112**: 623-637 [PMID: 23465088 DOI: 10.1111/bju.12014]

8 **Raman JD**, Shariat SF, Karakiewicz PI, Lotan Y, Sagalowsky AI, Roscigno M, Montorsi F, Bolenz C, Weizer AZ, Wheat JC, Ng CK, Scherr DS, Remzi M, Waldert M, Wood CG, Margulis V. Does preoperative symptom classification impact prognosis in patients with clinically localized upper-tract urothelial carcinoma managed by radical nephroureterectomy? *Urol Oncol* 2011; **29**: 716-723 [PMID: 20056458 DOI: 10.1016/j.urolonc.2009.11.007]

9 **Grollman AP**, Shibutani S, Moriya M, Miller F, Wu L, Moll U, Suzuki N, Fernandes A, Rosenquist T, Medverec Z, Jakovina K, Brdar B, Slade N, Turesky RJ, Goodenough AK, Rieger R, Vukelić M, Jelaković B. Aristolochic acid and the etiology of endemic (Balkan) nephropathy. *Proc Natl Acad Sci USA* 2007; **104**: 12129-12134 [PMID: 17620607 DOI: 10.1073/pnas.0701248104]

10 **Arlt VM**, Stiborová M, vom Brocke J, Simões ML, Lord GM, Nortier JL, Hollstein M, Phillips DH, Schmeiser HH. Aristolochic acid mutagenesis: molecular clues to the aetiology of Balkan endemic nephropathy-associated urothelial cancer. *Carcinogenesis* 2007; **28**: 2253-2261 [PMID: 17434925]

11 **Laing C**, Hamour S, Sheaff M, Miller R, Woolfson R. Chinese herbal uropathy and nephropathy. *Lancet* 2006; **368**: 338 [PMID: 16860704]

12 **Lord GM**, Cook T, Arlt VM, Schmeiser HH, Williams G, Pusey CD. Urothelial malignant disease and Chinese herbal nephropathy. *Lancet* 2001; **358**: 1515-1516 [PMID: 11705569 DOI: 10.1016/S0140-6736(01)06576-X]

13 **Roupret M**, Catto J, Coulet F, Azzouzi AR, Amira N, Karmouni T, Fromont G, Sibony M, Vallancien G, Gattegno B, Meuth M, Hamdy FC, Cussenot O. Microsatellite instability as indicator of MSH2 gene mutation in patients with upper urinary tract transitional cell carcinoma. *J Med Genet* 2004; **41**: e91 [PMID: 15235034 DOI: 10.1136/jmg.2003.017871]

14 **Acher P**, Kiela G, Thomas K, O'Brien T. Towards a rational strategy for the surveillance of patients with Lynch syndrome (hereditary non-polyposis colon cancer) for upper tract transitional cell carcinoma. *BJU Int* 2010; **106**: 300-302 [PMID: 20553255 DOI: 10.1111/j.1464-410X.2010.09443.x]

15 **Rouprêt M**, Yates DR, Comperat E, Cussenot O. Upper urinary tract urothelial cell carcinomas and other urological malignancies involved in the hereditary nonpolyposis colorectal cancer (lynch syndrome) tumor spectrum. *Eur Urol* 2008; **54**: 1226-1236 [PMID: 18715695 DOI: 10.1016/j.eururo.2008.08.008]

16 **Rouprêt M**, Cancel-Tassin G, Comperat E, Fromont G, Sibony M, Molinié V, Allory Y, Triau S, Champigneulle J, Gaffory C, Larré S, de la Taille A, Richard F, Hamdy FC, Cussenot O. Phenol sulfotransferase SULT1A1*2 allele and enhanced risk of upper urinary tract urothelial cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 2500-2503 [PMID: 18006944]

17 **Pommer W**, Bronder E, Klimpel A, Helmert U, Greiser E, Molzahn M. Urothelial cancer at different tumour sites: role of smoking and habitual intake of analgesics and laxatives. Results of the Berlin Urothelial Cancer Study. *Nephrol Dial Transplant* 1999; **14**: 2892-2897 [PMID: 10570093 DOI: 10.1093/ndt/14.12.2892]

18 **Hagiwara M**, Kikuchi E, Tanaka N, Matsumoto K, Ide H, Miyajima A, Masuda T, Nakamura S, Oya M. Impact of smoking status on bladder tumor recurrence after radical nephroureterectomy for upper tract urothelial carcinoma. *J Urol* 2013; **189**: 2062-2068 [PMID: 23328579 DOI: 10.1016/j.juro.2013.01.024]

19 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Bladder cancer. Version 2.2015. [accessed 2016 Feb 3]. Available from: URL: https://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf

20 **Colin P**, Koenig P, Ouzzane A, Berthon N, Villers A, Biserte J, Rouprêt M. Environmental factors involved in carcinogenesis of urothelial cell carcinomas of the upper urinary tract. *BJU Int* 2009; **104**: 1436-1440 [PMID: 19689473 DOI: 10.1111/j.1464-410X.2009.08838.x]

21 **Shinka T**, Miyai M, Sawada Y, Inagaki T, Okawa T. Factors affecting the occurrence of urothelial tumors in dye workers exposed to aromatic amines. *Int J Urol* 1995; **2**: 243-248 [PMID: 8564742 DOI: 10.1111/j.1442-2042.1995.tb00465.x]

22 **Furihata M**, Yamasaki I, Ohtsuki Y, Sonobe H, Morioka M, Yamamoto A, Terao N, Kuwahara M, Fujisaki N. p53 and human papillomavirus DNA in renal pelvic and ureteral carcinoma including dysplastic lesions. *Int J Cancer* 1995; **64**: 298-303 [PMID: 7591300]

23 **Palvio DH**, Andersen JC, Falk E. Transitional cell tumors of the renal pelvis and ureter associated with capillarosclerosis indicating analgesic abuse. *Cancer* 1987; **59**: 972-976 [PMID: 3815276 DOI: 10.1002/1097-0142(19870301)59: 5<972: : AID-CNCR2820590520>3.0.CO; 2-Y]

24 **Azémar MD**, Comperat E, Richard F, Cussenot O, Rouprêt M. Bladder recurrence after surgery for upper urinary tract urothelial cell carcinoma: frequency, risk factors, and surveillance. *Urol Oncol* 2011; **29**: 130-136 [PMID: 19762256 DOI: 10.1016/j.urolonc.2009.06.003]

25 **Raman JD**, Ng CK, Scherr DS, Margulis V, Lotan Y, Bensalah K, Patard JJ, Kikuchi E, Montorsi F, Zigeuner R, Weizer A, Bolenz C, Koppie TM, Isbarn H, Jeldres C, Kabbani W, Remzi M, Waldert M, Wood CG, Roscigno M, Oya M, Langner C, Wolf JS, Ströbel P, Fernández M, Karakiewcz P, Shariat SF. Impact of tumor location on prognosis for patients with upper tract urothelial carcinoma managed by radical nephroureterectomy. *Eur Urol* 2010; **57**: 1072-1079 [PMID: 19619934 DOI: 10.1016/j.eururo.2009.07.002]

26 **Melamed MR**, Reuter VE. Pathology and staging of urothelial tumors of the kidney and ureter. *Urol Clin North Am* 1993; **20**: 333-347 [PMID: 8388136]

27 **Dillman JR**, Caoili EM, Cohan RH, Ellis JH, Francis IR, Schipper MJ. Detection of upper tract urothelial neoplasms: sensitivity of axial, coronal reformatted, and curved-planar reformatted image-types utilizing 16-row multi-detector CT urography. *Abdom Imaging* 2008; **33**: 707-716 [PMID: 18253780 DOI: 10.1007/s00261-008-9360-3]

28 **Van Der Molen AJ**, Cowan NC, Mueller-Lisse UG, Nolte-Ernsting CC, Takahashi S, Cohan RH. CT urography: definition, indications and techniques. A guideline for clinical practice. *Eur Radiol* 2008; **18**: 4-17 [PMID: 17973110 DOI: 10.1007/s00330-007-0792-x]

29 **Wang LJ**, Wong YC, Chuang CK, Huang CC, Pang ST. Diagnostic accuracy of transitional cell carcinoma on multidetector computerized tomography urography in patients with gross hematuria. *J Urol* 2009; **181**: 524-531; discussion 531 [PMID: 19100576]

30 **Wang LJ**, Wong YC, Huang CC, Wu CH, Hung SC, Chen HW. Multidetector computerized tomography urography is more accurate

than excretory urography for diagnosing transitional cell carcinoma of the upper urinary tract in adults with hematuria. *J Urol* 2010; **183**: 48-55 [PMID: 19913253 DOI: 10.1016/j.juro.2009.08.144]

31 **Ng CK**, Shariat SF, Lucas SM, Bagrodia A, Lotan Y, Scherr DS, Raman JD. Does the presence of hydronephrosis on preoperative axial CT imaging predict worse outcomes for patients undergoing nephroureterectomy for upper-tract urothelial carcinoma? *Urol Oncol* 2011; **29**: 27-32 [PMID: 19117771 DOI: 10.1016/j.urolonc.2008.10.023]

32 **Zincke H**, Aguilo JJ, Farrow GM, Utz DC, Khan AU. Significance of urinary cytology in the early detection of transitional cell cancer of the upper urinary tract. *J Urol* 1976; **116**: 781-783 [PMID: 1003651]

33 **Highman WJ**. Transitional carcinoma of the upper urinary tract: a histological and cytopathological study. *J Clin Pathol* 1986; **39**: 297-305 [PMID: 3958217 DOI: 10.1136/jcp.39.3.297]

34 **Konety BR**, Metro MJ, Melham MF, Salup RR. Diagnostic value of voided urine and bladder barbotage cytology in detecting transitional cell carcinoma of the urinary tract. *Urol Int* 1999; **62**: 26-30 [PMID: 10436427 DOI: 10.1159/000030350]

35 **Abdel-Razzak OM**, Ehya H, Cubler-Goodman A, Bagley DH. Ureteroscopic biopsy in the upper urinary tract. *Urology* 1994; **44**: 451-457 [PMID: 8073566 DOI: 10.1016/S0090-4295(94)80116-9]

36 **Guarnizo E**, Pavlovich CP, Seiba M, Carlson DL, Vaughan ED, Sosa RE. Ureteroscopic biopsy of upper tract urothelial carcinoma: improved diagnostic accuracy and histopathological considerations using a multi-biopsy approach. *J Urol* 2000; **163**: 52-55 [PMID: 10604312]

37 **Keeley FX**, Kulp DA, Bibbo M, McCue PA, Bagley DH. Diagnostic accuracy of ureteroscopic biopsy in upper tract transitional cell carcinoma. *J Urol* 1997; **157**: 33-37 [PMID: 8976209 DOI: 10.1016/S0022-5347(01)65273-X]

38 **Brien JC**, Shariat SF, Herman MP, Ng CK, Scherr DS, Scoll B, Uzzo RG, Wille M, Eggener SE, Terrell JD, Lucas SM, Lotan Y, Boorjian SA, Raman JD. Preoperative hydronephrosis, ureteroscopic biopsy grade and urinary cytology can improve prediction of advanced upper tract urothelial carcinoma. *J Urol* 2010; **184**: 69-73 [PMID: 20478585]

39 **Lee KS**, Zeikus E, DeWolf WC, Rofsky NM, Pedrosa I. MR urography versus retrograde pyelography/ureteroscopy for the exclusion of upper urinary tract malignancy. *Clin Radiol* 2010; **65**: 185-192 [PMID: 20152273 DOI: 10.1016/j.crad.2009.11.003]

40 **Ishikawa S**, Abe T, Shinohara N, Harabayashi T, Sazawa A, Maruyama S, Kubota K, Matsuno Y, Osawa T, Shinno Y, Kumagai A, Togashi M, Matsuda H, Mori T, Nonomura K. Impact of diagnostic ureteroscopy on intravesical recurrence and survival in patients with urothelial carcinoma of the upper urinary tract. *J Urol* 2010; **184**: 883-887 [PMID: 20643446]

41 **Rouprêt M**, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, Burger M, Cowan NC, Böhle A, Van Rhijn BW, Kaasinen E, Palou J, Shariat SF. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma: 2015 Update. *Eur Urol* 2015; **68**: 868-879 [PMID: 26188393 DOI: 10.1016/j.eururo.2015.06.044]

42 **Margulis V**, Shariat SF, Matin SF, Kamat AM, Zigeuner R, Kikuchi E, Lotan Y, Weizer A, Raman JD, Wood CG. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. *Cancer* 2009; **115**: 1224-1233 [PMID: 19156917 DOI: 10.1002/cncr.24135]

43 **Sobin L**, Gospodarowicz M, Wittekind C. TNM Classification of Malignant Tumours. Urological Tumours. Renal Pelvis and Ureter. 7th revised edition. USA: Wiley-Blackwell, UICC, 2009: 258-261

44 **Langner C**, Hutterer G, Chromecki T, Winkelmayer I, Rehak P, Zigeuner R. pT classification, grade, and vascular invasion as prognostic indicators in urothelial carcinoma of the upper urinary tract. *Mod Pathol* 2006; **19**: 272-279 [PMID: 16424895]

45 **Lehmann J**, Suttmann H, Kovac I, Hack M, Kamradt J, Siemer S, Wullich B, Zwergel U, Stöckle M. Transitional cell carcinoma of the ureter: prognostic factors influencing progression and survival. *Eur Urol* 2007; **51**: 1281-1288 [PMID: 17125909 DOI: 10.1016/j.eururo.2006.11.021]

46 **Li CC**, Chang TH, Wu WJ, Ke HL, Huang SP, Tsai PC, Chang SJ, Shen JT, Chou YH, Huang CH. Significant predictive factors for prognosis of primary upper urinary tract cancer after radical nephroureterectomy in Taiwanese patients. *Eur Urol* 2008; **54**: 1127-1134 [PMID: 18243511 DOI: 10.1016/j.eururo.2008.01.054]

47 **Kikuchi E**, Margulis V, Karakiewicz PI, Roscigno M, Mikami S, Lotan Y, Remzi M, Bolenz C, Langner C, Weizer A, Montorsi F, Bensalah K, Koppie TM, Fernández MI, Raman JD, Kassouf W, Wood CG, Suardi N, Oya M, Shariat SF. Lymphovascular invasion predicts clinical outcomes in patients with node-negative upper tract urothelial carcinoma. *J Clin Oncol* 2009; **27**: 612-618 [PMID: 19075275 DOI: 10.1200/JCO.2008.17.2361]

48 **Kim DS**, Lee YH, Cho KS, Cho NH, Chung BH, Hong SJ. Lymphovascular invasion and pT stage are prognostic factors in patients treated with radical nephroureterectomy for localized upper urinary tract transitional cell carcinoma. *Urology* 2010; **75**: 328-332 [PMID: 20018349 DOI: 10.1016/j.urology.2009.07.1350]

49 **Novara G**, Matsumoto K, Kassouf W, Walton TJ, Fritsche HM, Bastian PJ, Martínez-Salamanca JI, Seitz C, Lemberger RJ, Burger M, El-Hakim A, Baba S, Martignoni G, Gupta A, Karakiewicz PI, Ficarra V, Shariat SF. Prognostic role of lymphovascular invasion in patients with urothelial carcinoma of the upper urinary tract: an international validation study. *Eur Urol* 2010; **57**: 1064-1071 [PMID: 20071073]

50 **Fujimoto H**, Tobisu K, Sakamoto M, Kamiya M, Kakizoe T. Intraductal tumor involvement and renal parenchymal invasion of transitional cell carcinoma in the renal pelvis. *J Urol* 1995; **153**: 57-60 [PMID: 7966791 DOI: 10.1097/00005392-199501000-00021]

51 **Davis BW**, Hough AJ, Gardner WA. Renal pelvic carcinoma: morphological correlates of metastatic behavior. *J Urol* 1987; **137**: 857-861 [PMID: 3573176]

52 **Rey A**, Lara PC, Redondo E, Valdés E, Apolinario R. Overexpression of p53 in transitional cell carcinoma of the renal pelvis and ureter. Relation to tumor proliferation and survival. *Cancer* 1997; **79**: 2178-2185 [PMID: 9179065 DOI: 10.1002/(SICI)1097-0142(19970601)79: 11<2178: : AID-CNCR16>3.0.CO; 2-T]

53 **Corrado F**, Ferri C, Mannini D, Corrado G, Bertoni F, Bacchini P, Lelli G, Lieber MM, Song JM. Transitional cell carcinoma of the upper urinary tract: evaluation of prognostic factors by histopathology and flow cytometric analysis. *J Urol* 1991; **145**: 1159-1163 [PMID: 2033684]

54 **Zigeuner R**, Shariat SF, Margulis V, Karakiewicz PI, Roscigno M, Weizer A, Kikuchi E, Remzi M, Raman JD, Bolenz C, Bensalah K, Capitanio U, Koppie TM, Kassouf W, Sircar K, Patard JJ, Fernández MI, Wood CG, Montorsi F, Ströbel P, Wheat JC, Haitel A, Oya M, Guo CC, Ng C, Chade DC, Sagalowsky A, Langner C. Tumour necrosis is an indicator of aggressive biology in patients with urothelial carcinoma of the upper urinary tract. *Eur Urol* 2010; **57**: 575-581 [PMID: 19959276 DOI: 10.1016/j.eururo.2009.11.035]

55 **Seitz C**, Gupta A, Shariat SF, Matsumoto K, Kassouf W, Walton TJ, Fritsche HM, Otto W, Tritschler S, Bastian PJ, Carballido J, Ficarra V, Karakiewicz PI, Artibani W, Mazzoleni G, Novara G. Association of tumor necrosis with pathological features and clinical outcome in 754 patients undergoing radical nephroureterectomy for upper tract urothelial carcinoma: an international validation study. *J Urol* 2010; **184**: 1895-1900 [PMID: 20846680 DOI: 10.1016/j.juro.2010.06.106]

56 **Fernández MI**, Shariat SF, Margulis V, Bolenz C, Montorsi F, Suardi N, Remzi M, Wood CG, Roscigno M, Kikuchi E, Oya M, Zigeuner R, Langner C, Weizer A, Lotan Y, Koppie TM, Raman JD, Karakiewicz P, Bensalah K, Schultz M, Bernier P. Evidence-based sex-related outcomes after radical nephroureterectomy for upper tract urothelial carcinoma: results of large multicenter study. *Urology* 2009; **73**: 142-146 [PMID: 18845322 DOI: 10.1016/j.urology.2008.07.042]

57 **Lughezzani G**, Sun M, Perrotte P, Shariat SF, Jeldres C, Budäus L, Latour M, Widmer H, Duclos A, Bénard F, McCormack M, Montorsi F, Karakiewicz PI. Gender-related differences in patients with stage I to III upper tract urothelial carcinoma: results from the Surveillance, Epidemiology, and End Results database. *Urology* 2010; **75**: 321-327 [PMID: 19962727 DOI: 10.1016/j.urology.2009.09.048]

58 **Shariat SF**, Favaretto RL, Gupta A, Fritsche HM, Matsumoto K, Kassouf W, Walton TJ, Tritschler S, Baba S, Matsushita K, Bastian PJ, Martínez-Salamanca JI, Seitz C, Pycha A, Otto W, Karakiewicz PI, Ficarra V, Novara G. Gender differences in radical nephroureterectomy for upper tract urothelial carcinoma. *World J Urol* 2011; **29**: 481-486

[PMID: 20886219 DOI: 10.1007/s00345-010-0594-7]
59 **Shariat SF**, Godoy G, Lotan Y, Droller M, Karakiewicz PI, Raman JD, Isbarn H, Weizer A, Remzi M, Roscigno M, Kikuchi E, Bolenz C, Bensalah K, Koppie TM, Kassouf W, Wheat JC, Zigeuner R, Langner C, Wood CG, Margulis V. Advanced patient age is associated with inferior cancer-specific survival after radical nephroureterectomy. *BJU Int* 2010; **105**: 1672-1677 [PMID: 19912201 DOI: 10.1111/j.1464-410X.2009.09072.x]
60 **Favaretto RL**, Shariat SF, Chade DC, Godoy G, Adamy A, Kaag M, Bochner BH, Coleman J, Dalbagni G. The effect of tumor location on prognosis in patients treated with radical nephroureterectomy at Memorial Sloan-Kettering Cancer Center. *Eur Urol* 2010; **58**: 574-580 [PMID: 20637540 DOI: 10.1016/j.eururo.2010.07.003]
61 **Isbarn H**, Jeldres C, Shariat SF, Liberman D, Sun M, Lughezzani G, Widmer H, Arjane P, Pharand D, Fisch M, Graefen M, Montorsi F, Perrotte P, Karakiewicz PI. Location of the primary tumor is not an independent predictor of cancer specific mortality in patients with upper urinary tract urothelial carcinoma. *J Urol* 2009; **182**: 2177-2181 [PMID: 19758662 DOI: 10.1016/j.juro.2009.07.035]
62 **Eltz S**, Comperat E, Cussenot O, Rouprêt M. Molecular and histological markers in urothelial carcinomas of the upper urinary tract. *BJU Int* 2008; **102**: 532-535 [PMID: 18384628 DOI: 10.1111/j.1464-410X.2008.07659.x]
63 **Nakanishi K**, Kawai T, Suzuki M, Torikata C. Growth factors and oncogene products in transitional cell carcinoma. *Mod Pathol* 1996; **9**: 292-297 [PMID: 8685230]
64 **Nakanishi K**, Kawai T, Torikata C, Aurues T, Ikeda T. E-cadherin expression in upper-urinary-tract carcinoma. *Int J Cancer* 1997; **74**: 446-449 [PMID: 9291437 DOI: 10.1002/(SICI)1097-0215(19970822)74: 4<446: : AID-IJC15>3.0.CO; 2-7]
65 **Nakanishi K**, Kawai T, Hiroi S, Kumaki F, Torikata C, Aurues T, Ikeda T. Expression of telomerase mRNA component (hTR) in transitional cell carcinoma of the upper urinary tract. *Cancer* 1999; **86**: 2109-2116 [PMID: 10570439]
66 **Remzi M**, Haitel A, Margulis V, Karakiewicz P, Montorsi F, Kikuchi E, Zigeuner R, Weizer A, Bolenz C, Bensalah K, Suardi N, Raman JD, Lotan Y, Waldert M, Ng CK, Fernández M, Koppie TM, Ströbel P, Kabbani W, Murai M, Langner C, Roscigno M, Wheat J, Guo CC, Wood CG, Shariat SF. Tumour architecture is an independent predictor of outcomes after nephroureterectomy: a multi-institutional analysis of 1363 patients. *BJU Int* 2009; **103**: 307-311 [PMID: 18990163 DOI: 10.1111/j.1464-410X.2008.08003.x]
67 **Remzi M**, Haitel A, Margulis V, Karakiewicz P, Montorsi F, Kikuchi E, Zigeuner R, Weizer A, Bolenz C, Bensalah K, Suardi N, Raman JD, Lotan Y, Waldert M, Ng CK, Fernández M, Koppie TM, Ströbel P, Kabbani W, Murai M, Langner C, Roscigno M, Wheat J, Guo CC, Wood CG, Shariat SF. Tumour architecture is an independent predictor of outcomes after nephroureterectomy: a multi-institutional analysis of 1363 patients. *BJU Int* 2009; **103**: 307-311 [PMID: 18990163 DOI: 10.1111/j.1464-410X.2008.08003.x]
68 **Lughezzani G**, Sun M, Perrotte P, Shariat SF, Jeldres C, Budaus L, Alasker A, Duclos A, Widmer H, Latour M, Guazzoni G, Montorsi F, Karakiewicz PI. Should bladder cuff excision remain the standard of care at nephroureterectomy in patients with urothelial carcinoma of the renal pelvis? A population-based study. *Eur Urol* 2010; **57**: 956-962 [PMID: 20018438 DOI: 10.1016/j.eururo.2009.12.001]
69 **Phé V**, Cussenot O, Bitker MO, Rouprêt M. Does the surgical technique for management of the distal ureter influence the outcome after nephroureterectomy? *BJU Int* 2011; **108**: 130-138 [PMID: 21070580 DOI: 10.1111/j.1464-410X.2010.09835.x]
70 **Zigeuner R**, Pummer K. Urothelial carcinoma of the upper urinary tract: surgical approach and prognostic factors. *Eur Urol* 2008; **53**: 720-731 [PMID: 18207315 DOI: 10.1016/j.eururo.2008.01.006]
71 **Ahn M**, Loughlin KR. Psoas hitch ureteral reimplantation in adults--analysis of a modified technique and timing of repair. *Urology* 2001; **58**: 184-187 [PMID: 11489694 DOI: 10.1016/S0090-4295(01)01144-X]
72 **Manassero F**, Mogorovich A, Fiorini G, Di Paola G, De Maria M, Selli C. Ureteral reimplantation with psoas bladder hitch in adults: a contemporary series with long-term followup. *ScientificWorldJournal* 2012; **2012**: 379316 [PMID: 22919311]
73 **Chen GL**, Bagley DH. Ureteroscopic management of upper tract transitional cell carcinoma in patients with normal contralateral kidneys. *J Urol* 2000; **164**: 1173-1176 [PMID: 10992360 DOI: 10.1016/S0022-5347(05)67136-4]
74 **Gadzinski AJ**, Roberts WW, Faerber GJ, Wolf JS. Long-term outcomes of nephroureterectomy versus endoscopic management for upper tract urothelial carcinoma. *J Urol* 2010; **183**: 2148-2153 [PMID: 20399468 DOI: 10.1016/j.juro.2010.02.005]
75 **Brown GA**, Busby JE, Wood CG, Pisters LL, Dinney CP, Swanson DA, Grossman HB, Pettaway CA, Munsell MF, Kamat AM, Matin SF. Nephroureterectomy for treating upper urinary tract transitional cell carcinoma: Time to change the treatment paradigm? *BJU Int* 2006; **98**: 1176-1180 [PMID: 17125474 DOI: 10.1111/j.1464-410X.2006.06524.x]
76 **Bagley DH**, Grasso M. Ureteroscopic laser treatment of upper urinary tract neoplasms. *World J Urol* 2010; **28**: 143-149 [PMID: 20229233 DOI: 10.1007/s00345-010-0525-7]
77 **Rouprêt M**, Hupertan V, Traxer O, Loison G, Chartier-Kastler E, Conort P, Bitker MO, Gattegno B, Richard F, Cussenot O. Comparison of open nephroureterectomy and ureteroscopic and percutaneous management of upper urinary tract transitional cell carcinoma. *Urology* 2006; **67**: 1181-1187 [PMID: 16765178 DOI: 10.1016/j.urology.2005.12.034]
78 **Cornu JN**, Rouprêt M, Carpentier X, Geavlete B, de Medina SG, Cussenot O, Traxer O. Oncologic control obtained after exclusive flexible ureteroscopic management of upper urinary tract urothelial cell carcinoma. *World J Urol* 2010; **28**: 151-156 [PMID: 20044752 DOI: 10.1007/s00345-009-0494-x]
79 **Abad PG**, Del Peso AC, Arjona MF. Holmium: YAG laser ablation of upper urinary tract transitional cell carcinoma with new Olympus digital flexible ureteroscope. *Urol Ann* 2013; **5**: 212-214 [PMID: 24049390 DOI: 10.4103/0974-7796.115748]
80 **Palou J**, Piovesan LF, Huguet J, Salvador J, Vicente J, Villavicencio H. Percutaneous nephroscopic management of upper urinary tract transitional cell carcinoma: recurrence and long-term followup. *J Urol* 2004; **172**: 66-69 [PMID: 15201739 DOI: 10.1097/01.ju.0000132128.79974.db]
81 **Rouprêt M**, Traxer O, Tligui M, Conort P, Chartier-Kastler E, Richard F, Cussenot O. Upper urinary tract transitional cell carcinoma: recurrence rate after percutaneous endoscopic resection. *Eur Urol* 2007; **51**: 709-713; discussion 714 [PMID: 16911852 DOI: 10.1016/j.eururo.2006.07.019]
82 **Irie A**, Iwamura M, Kadowaki K, Ohkawa A, Uchida T, Baba S. Intravesical instillation of bacille Calmette-Guérin for carcinoma in situ of the urothelium involving the upper urinary tract using vesicoureteral reflux created by a double-pigtail catheter. *Urology* 2002; **59**: 53-57 [PMID: 11796281 DOI: 10.1016/S0090-4295(01)01488-1]
83 **Nonomura N**, Ono Y, Nozawa M, Fukui T, Harada Y, Nishimura K, Takaha N, Takahara S, Okuyama A. Bacillus Calmette-Guérin perfusion therapy for the treatment of transitional cell carcinoma in situ of the upper urinary tract. *Eur Urol* 2000; **38**: 701-704; discussion 705 [PMID: 11111187 DOI: 10.1159/000020365]
84 **Thalmann GN**, Markwalder R, Walter B, Studer UE. Long-term experience with bacillus Calmette-Guerin therapy of upper urinary tract transitional cell carcinoma in patients not eligible for surgery. *J Urol* 2002; **168**: 1381-1385 [PMID: 12352398]
85 **Audenet F**, Yates DR, Cussenot O, Rouprêt M. The role of chemotherapy in the treatment of urothelial cell carcinoma of the upper urinary tract (UUT-UCC). *Urol Oncol* 2013; **31**: 407-413 [PMID: 20884249 DOI: 10.1016/j.urolonc.2010.07.016]
86 **Hellenthal NJ**, Shariat SF, Margulis V, Karakiewicz PI, Roscigno M, Bolenz C, Remzi M, Weizer A, Zigeuner R, Bensalah K, Ng CK, Raman JD, Kikuchi E, Montorsi F, Oya M, Wood CG, Fernandez M, Evans CP, Koppie TM. Adjuvant chemotherapy for high risk upper tract urothelial carcinoma: results from the Upper Tract Urothelial Carcinoma Collaboration. *J Urol* 2009; **182**: 900-906 [PMID: 19616245 DOI: 10.1016/j.juro.2009.05.011]
87 **Kaag MG**, O'Malley RL, O'Malley P, Godoy G, Chen M, Smaldone MC, Hrebinko RL, Raman JD, Bochner B, Dalbagni G, Stifelman

MD, Taneja SS, Huang WC. Changes in renal function following nephroureterectomy may affect the use of perioperative chemotherapy. *Eur Urol* 2010; **58**: 581-587 [PMID: 20619530 DOI: 10.1016/j.eururo.2010.06.029]

88 **Lane BR**, Smith AK, Larson BT, Gong MC, Campbell SC, Raghavan D, Dreicer R, Hansel DE, Stephenson AJ. Chronic kidney disease after nephroureterectomy for upper tract urothelial carcinoma and implications for the administration of perioperative chemotherapy. *Cancer* 2010; **116**: 2967-2973 [PMID: 20564402 DOI: 10.1002/cncr.25043]

89 **Matin SF**, Margulis V, Kamat A, Wood CG, Grossman HB, Brown GA, Dinney CP, Millikan R, Siefker-Radtke AO. Incidence of downstaging and complete remission after neoadjuvant chemotherapy for high-risk upper tract transitional cell carcinoma. *Cancer* 2010; **116**: 3127-3134 [PMID: 20564621 DOI: 10.1002/cncr.25050]

90 **Kim TS**, Oh JH, Rhew HY. The efficacy of adjuvant chemotherapy for locally advanced upper tract urothelial cell carcinoma. *J Cancer* 2013; **4**: 686-690 [PMID: 24155781 DOI: 10.7150/jca.7326]

91 **Papatsoris AG**, Chrisofos M, Skolarikos A, Varkarakis I, Lekas A, Dellis A, Koritsiadis S, Deliveliotis C. Upper urinary tract transitional cell carcinoma. A 10-year experience. *Tumori* 2008; **94**: 75-78 [PMID: 18468339]

92 **Shapiro EY**, Lipsky MJ, Cha DY, McKiernan JM, Benson MC, Gupta M. Outcomes of intrarenal Bacillus Calmette-Guérin/interferon-α2B for biopsy-proven upper-tract carcinoma in situ. *J Endourol* 2012; **26**: 1645-1650 [PMID: 22834939 DOI: 10.1089/end.2012.0229]

93 **Hall MC**, Womack JS, Roehrborn CG, Carmody T, Sagalowsky AI. Advanced transitional cell carcinoma of the upper urinary tract: patterns of failure, survival and impact of postoperative adjuvant radiotherapy. *J Urol* 1998; **160**: 703-706 [PMID: 9720526]

94 **Czito B**, Zietman A, Kaufman D, Skowronski U, Shipley W. Adjuvant radiotherapy with and without concurrent chemotherapy for locally advanced transitional cell carcinoma of the renal pelvis and ureter. *J Urol* 2004; **172**: 1271-1275 [PMID: 15371822 DOI: 10.1097/01.ju.0000137910.38441.8a]

95 **Wheat JC**, Weizer AZ, Wolf JS, Lotan Y, Remzi M, Margulis V, Wood CG, Montorsi F, Roscigno M, Kikuchi E, Zigeuner R, Langner C, Bolenz C, Koppie TM, Raman JD, Fernández M, Karakiewizc P, Capitanio U, Bensalah K, Patard JJ, Shariat SF. Concomitant carcinoma in situ is a feature of aggressive disease in patients with organ confined urothelial carcinoma following radical nephroureterectomy. *Urol Oncol* 2012; **30**: 252-258 [PMID: 20451416 DOI: 10.1016/j.urolonc.2010.01.001]

96 **Pieras E**, Frontera G, Ruiz X, Vicens A, Ozonas M, Pizá P. Concomitant carcinoma in situ and tumour size are prognostic factors for bladder recurrence after nephroureterectomy for upper tract transitional cell carcinoma. *BJU Int* 2010; **106**: 1319-1323 [PMID: 20394618 DOI: 10.1111/j.1464-410X.2010.09341.x]

P- Reviewer: Ali-El-Dein B, Creta M, Papatsoris AG, Soria F
S- Editor: Kong JX **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Clinical Urology

Submit a Manuscript: http://www.wjgnet.com/esps/

World J Clin Urol 2017 March 24; 6(1): 10-17

DOI: 10.5410/wjcu.v6.i1.10

ISSN 2219-2816 (online)

MINIREVIEWS

Chronic kidney disease after radical nephrectomy for suspected renal cancers

Tuck Y Yong, Kareeann SF Khow

Tuck Y Yong, Internal Medicine, Flinders Private Hospital, Bedford Park, South Australia 5042, Australia

Kareeann SF Khow, Adelaide Geriatrics Teaching and Research with Aged Care, the University of Adelaide, Paradise, South Australia 5075, Australia

Author contributions: Yong TY and Khow KSF designed, performed the research and wrote the paper.

Conflict-of-interest statement: The authors have no financial relationships to disclose.

Manuscript source: Invited manuscript

Correspondence to: Dr. Tuck Y Yong, FRACP, Internal Medicine, Flinders Private Hospital, Flinders Drive, Bedford Park, South Australia 5042, Australia. tyyong@hotmail.com
Telephone: +61-8-82412121
Fax: +61-8-82400879

Received: August 28, 2016
Peer-review started: September 1, 2016
First decision: November 30, 2016
Revised: December 29, 2016
Accepted: January 11, 2017
Article in press: January 13, 2017
Published online: March 24, 2017

Abstract

Nephrectomy is the treatment of choice for early stage renal cell carcinoma. However, radical nephrectomy is consistently associated with higher rates of new-onset chronic kidney disease (CKD) than the general population, regardless of the method used in measuring renal function. The higher rates of CKD are associated with worsened survival because of increased risk of cardiovascular diseases and mortality. Comorbidities and adjacent non-neoplastic kidney diseases are important risk factors for the development of CKD after nephrectomy. Partial nephrectomy has become the standard of care for patients with stage 1a tumours (diameter < 4 cm) and an attractive option for those with stage 1b (diameter 4-7 cm). Therefore stratifying the risk of postoperative CKD before surgery is important and ongoing monitoring of kidney function after radical nephrectomy is needed in addition to oncological surveillance. More research is needed to better understand the risk of CKD after radical nephrectomy and develop effective strategies to optimize kidney function after such surgery.

Key words: Nephrectomy; Renal function; Renal cell carcinoma; Chronic kidney disease; Prevention

Core tip: Chronic kidney disease (CKD) is an important complication associated with radical nephrectomy. CKD post-nephrectomy is associated with increased risk of cardiovascular diseases. Risk factors for CKD should be assessed thoroughly before radical nephrectomy. Where possible, nephron-sparing treatment should be used to mitigate the onset of CKD after tumour resection.

Yong TY, Khow KSF. Chronic kidney disease after radical nephrectomy for suspected renal cancers. *World J Clin Urol* 2017; 6(1): 10-17 Available from: URL: http://www.wjgnet.com/2219-2816/full/v6/i1/10.htm DOI: http://dx.doi.org/10.5410/wjcu.v6.i1.10

INTRODUCTION

Renal cell carcinoma (RCC) is the third most common urological cancer but has the highest mortality rate[1]. The five-year survival of late stage RCC is 5%-10%[1]. Radical or partial nephrectomy is the preferred treatment for the majority of patients with RCC or other renal malignancies. Although outcomes are favourable for early stage RCC treated with unilateral radical nephrectomy, concerns are emerging about the adverse impact on long-term renal function and survival. Nephrectomy for renal malignancies has been recognized as an independent risk factor for developing chronic kidney disease (CKD)[2,3] whilst nephrectomy for other indications such as living kidney donation has a more benign long-term renal outcome[4]. CKD is defined as kidney damage for more than 3 mo (either confirmed by indicators of kidney injury such as proteinuria, or pathological disease in biopsy samples) with or without changes in estimated glomerular filtration rate (eGFR), or eGFR < 60 mL/min per 1.73 m^2 for more than 3 mo[5].

In the United States, 75%-80% of patients with renal cancer are diagnosed incidentally with disease localized to the kidney[6]. This observation is largely attributable to a 73% rise in imaging of the abdomen with CT and MRI[6]. In parallel with increased detection of renal neoplasms, benign renal tumours such as oncocytoma, angiomyolipoma and simple renal cysts, have been diagnosed increasingly[7]. More than 20% of incidental renal masses are benign but current radiological investigations cannot accurately differentiate malignant from benign tumours[8].

In this review, we will describe the epidemiology of CKD after radical nephrectomy for renal tumours and ways to prevent the development of this condition after surgery.

EPIDEMIOLOGY

Evidence from observational studies support the finding that radical nephrectomy is associated with higher rates of CKD, regardless of the method used in measuring renal function. Klarenbach *et al*[9] used a large Canadian population-based database of subjects who underwent nephrectomy between 2002 and 2007 to evaluate kidney outcomes after a mean follow-up of 2 years and 8 mo. Among those who underwent radical nephrectomy, 106 out of 921 (11.5%) experienced adverse renal outcomes, which was defined as end-stage renal disease (ESRD), acute dialysis, CKD (eGFR < 30 mL/min per 1.73 m^2), and rapidly progressive CKD (eGFR < 60 mL/min per 1.73 m^2 and eGFR loss $\geqslant$ 4 mL/min per 1.73 m^2 per year)[9].

In the Memorial Sloan-Kettering Cancer Center (MSKCC) study, about a quarter of patients with T1a RCC (tumour diameter < 4 cm) had CKD (eGFR < 60 mL/min per 1.73 m^2) prior to surgery despite preoperative serum creatinine within the normal range[2] (Table 1). In a study of patients who had nephrectomy for T1a RCC using the linked Surveillance, Epidemiology and End Results (SEER)-Medicare database in the United States between 1998 and 2005, an increased rate of new-onset CKD was observed in patients who had radical nephrectomy (20%) compared with partial nephrectomy (11%)[10]. Using data from this study, the authors estimated that the five-year rate of new-onset CKD was 18% for radical nephrectomy and 9% for partial nephrectomy.

With variable duration of follow-up after radical nephrectomy, ESRD has been reported in 0%-4% of patients in various studies[2,9-11]. In a Canadian study involving 1151 subjects with kidney lesions who have undergone nephrectomy, 2% developed ESRD requiring dialysis within a median period of 32 mo after surgery[9]. However ESRD was not considered as a specific renal outcome due to its low incidence. In the SEER-Medicare (1988-2005) linked cohort, 2% of patients who had partial nephrectomy and 4% of radical nephrectomy developed ESRD when the data was censored in 2008[10]. However there was no statistical difference between these two treatment groups. In the subgroup analysis of the European Organisation for Research and Treatment of Cancer (EORTC) trial, the incidence of ESRD was low in the radical nephrectomy group at 1.5% and was not significantly different from those who had partial nephrectomy[11]. In the MSKCC study, none of the included subjects required renal replacement therapy, acute or chronic[2].

Recent studies have provided new insight into differences between patients with CKD caused by medical conditions and those after nephrectomy. One study found that CKD related to nephrectomy was associated with annual kidney function decline of 0.7%, which is significantly lower than the 4.7% observed in medical-related CKD[12].

Most studies have used either creatinine or eGFR to determine kidney function. Nonetheless serum creatinine alone does not reliably reflect kidney function due to variations in between days, extremes of age and people with different muscle mass[13]. More recent studies have found that using serum creatinine and eGFR have underestimated the real effect on kidney function[14]. By measuring 24-h urinary creatinine clearance, one study has shown a decline in renal function by 31.6% after radical nephrectomy[15].

PREDISPOSING FACTORS FOR CKD POST-NEPHRECTOMY

Patients with renal tumours tend to be older resulting in a higher prevalence of cardiovascular diseases. As a result, this group of patients may have a greater degree of renal disease even when their creatinine concentration is still within the reference interval.

Similar systemic comorbidities and intrinsic renal risk factors might predispose people to develop both renal malignancies and CKD[16,17]. These factors include patient characteristics (such as age, sex and ethnicity), genetic predisposition, medical comorbidities (such as hypertension, diabetes mellitus and other chronic

Table 1 The incidence or prevalence of chronic kidney disease or end-stage renal disease before and after radical or partial nephrectomy for suspected renal cancers

Population	Incidence or prevalence	Ref.
CKD in patients with T1a RCC before surgery	26%	Huang *et al*[2]
New-onset CKD after radical nephrectomy (SEER-Medicare database)	20%	Sun *et al*[10]
New-onset CKD after partial nephrectomy (SEER-Medicare database)	11%	Sun *et al*[10]
ESRD after radical nephrectomy	2%-4%	Sun *et al*[10]
		Scosyrev *et al*[11]
ESRD after partial nephrectomy	2%	Sun *et al*[10]

CKD: Chronic kidney disease; ESRD: End-stage renal disease; RCC: Renal cell carcinoma; SEER: Surveillance, Epidemiology and End Results.

Table 2 Risk factors associated with new-onset chronic kidney disease or acceleration of pre-existing chronic kidney disease after radical nephrectomy

Risk factor	Odds ratio (95%CI); *P*-value	Ref.
Diabetes mellitus	11.60 (1.39-97.04); $P = 0.024$	Brandina *et al*[24]
	2.74 (1.07-6.98); $P = 0.035$	Cho *et al*[30]
Hypertension	3.67 (1.28-10.48); $P = 0.015$	Brandina *et al*[24]
Low preoperative GFR (< 90 mL/min per 1.73 m^2)	3.30 (1.16-9.37); $P = 0.025$	Brandina *et al*[24]
Preoperative GFR (per 10 mL/min per 1.73 m^2 rise)	0.47 (0.36-0.60); $P = 0.0001$	Cho *et al*[30]
Postoperative AKI	4.24 (2.28-7.89); $P = 0.0001$	Cho *et al*[30]
Adjacent non-neoplastic kidney parenchyma abnormalities		
Arteriosclerosis > 50%	3.33 (1.03-10.79); $P = 0.045$	Brandina *et al*[24]
Interstitial fibrosis (present)	3.78 (1.32-10.76); $P = 0.013$	
Glomerulosclerosis ⩾ 5%	3.78 (1/24-11.50); $P = 0.0061$	

AKI: Acute kidney injury; GFR: Glomerular filtration rate.

or acute diseases), coexisting pathologies in adjacent non-neoplastic renal parenchyma and environmental exposures (such as nutrition and smoking status)[18,19] (Table 2).

Non-neoplastic renal parenchymal disease

Several studies have shown that arterionephrosclerosis and glomerular diseases frequently coexist with RCC[20-22]. In resected tumour specimens, up to 90% have been reported to have coexisting non-neoplastic renal disease in the adjacent parenchymal tissue[21]. Clinically significant intrinsic renal abnormalities, such as glomerular hypertrophy, diabetic nephropathy, mesangial expansion and diffuse glomerulosclerosis were evident in more than 60% of these specimens[21].

From a study of 110 neoplasm-related nephrectomy, people with significant abnormal renal parenchyma showed a higher decrease in kidney function at 6 mo after surgery in comparison to those with normal adjacent renal tissue (increase in serum creatinine by 97.24 ± 159.12 μmol/L *vs* 17.68 ± 17.68 μmol/L)[20]. Nonetheless, a limitation of this study was the small sample of serum creatinine measurement on follow-up. In another study of 156 patients after tumour nephrectomy who had follow up for 12 mo or more, findings of severe arteriosclerosis or arteriolosclerosis, tubular atrophy or interstitial fibrosis, or glomerulosclerosis in nephrectomy specimens were associated with significantly lower renal function after surgery[22].

One study with a follow-up of an average 19.7 mo found that after laparoscopic radical nephrectomy, the change in eGFR was significantly associated with the severity of glomerulosclerosis or the finding of interstitial fibrosis[23]. For every ten percent rise in the degree of glomerulosclerosis, eGFR dropped by 9% post-surgery compared with baseline.

Another study of 65 individuals who had radical nephrectomy for RCC, elevated risk of new-onset CKD (eGFR less than 60 mL/min per 1.73 m^2) was observed in association with abnormal pathology in adjacent non-neoplastic parenchyma[24]. A multivariate analysis in this study showed that arteriosclerosis of more than 50% (odds ratio, OR = 3.3), presence of interstitial fibrosis (OR = 3.8) and glomerulosclerosis of 5% or greater (OR = 3.8) were associated with significant loss in renal function after radical nephrectomy.

Findings from these studies have led the College of American Pathologists to recommend reporting of non-neoplastic renal parenchyma for examination of all tumour nephrectomy and nephroureterectomy specimens[25]. However, no study has reported any correlation between adjacent non-neoplastic renal disease and the development of ESRD or cardiovascular diseases after nephrectomy.

Co-existing morbidities

After nephrectomy, co-existing morbidities are important contributing factors to deterioration in kidney function

after nephrectomy because of their effects on remaining renal parenchyma. Diabetes mellitus, hypertension and cigarette smoking have been independently linked with the decrease in renal function after nephrectomy for kidney tumours[9,26]. These factors can lead to *de novo* development of CKD or acceleration of decline in pre-existing CKD. Studies have pointed towards a progressive increase in the risk of RCC with worsening hypertension but the pathophysiological mechanism for this relationship is still unclear[17,19,27]. Diabetes mellitus is present in 6.8%-23.0% of patients with RCC undergoing surgery[27,28]. A prior diagnosis of diabetes has been found to be a predisposing factor for development of stage Ⅲ CKD after radical nephrectomy[29].

Postoperative acute kidney injury

Acute kidney injury (AKI) after radical nephrectomy among patients diagnosed with RCC has been found to be a significant risk factor for new-onset CKD[30]. This study also found that about one-third of patients experienced post-operative AKI when they underwent radical nephrectomy. A year post-surgery, median GFR was lower in the AKI group compared to those without AKI. Advanced age, male gender, increased body mass index, low presurgical GFR and small size of RCC were identified as predisposing factors for postoperative AKI[30]. Uncertainty remains about how these factors are associated with inadequate compensation of the remaining kidney and adaptive hyperfiltration[30]. Additional research is required to identify ways of preventing AKI after radical nephrectomy as a strategy to prevent new-onset CKD after this procedure.

Characteristic of renal tumour

One study has found that larger kidney tumour diameter was independently associated with decreased preoperative estimated GFR even after adjusting for hypertension and race[31]. The findings of this study suggest that either the growth of a tumour or displacement of the non-tumour renal parenchyma affects kidney function.

On the other hand, two other studies found that small tumour size was associated with significant deterioration in renal function after radical nephrectomy[32,33]. Therefore, researchers in these studies have advocated that partial nephrectomy are more appropriate in patients with tumour size 7 cm or less.

POST-NEPHRECTOMY CKD, CARDIOVASCULAR DISEASES AND MORTALITY

Higher rates of CKD in patients who had radical nephrectomy have been associated with increased risk of cardiovascular diseases and mortality[2,34]. Using Medicare data, Huang *et al*[2] found that the risk of cardiovascular events and non-cancer mortality was increased in the group that had radical nephrectomy. This finding was corroborated by a study from Weight and colleagues[34]. In their study, they evaluated the overall and disease-specific survival in 1004 subjects with T1b RCC (tumour of 4-7 cm in diameter) who had either radical or partial nephrectomy. This study found that a significant drop in renal function was observed in those who had radical nephrectomy, over a follow-up period of 4 years. In addition, this differing rate of decline in kidney function was associated with a 25% increase in cardiovascular-related mortality and a 17% rise of all-cause mortality.

PREVENTION OF CKD AFTER RADICAL NEPHRECTOMY

In the past decade, partial nephrectomy has emerged as the standard treatment for most small kidney masses of less than 4 cm in size[35-37]. Available evidence strongly supports the notion that control of cancer and risk of cancer-associated mortality for tumours up to 7 cm are not compromised by partial nephrectomy when compared with the radical procedure[38,39].

The EORTC is the only randomized trial comparing partial and radical nephrectomy in patients with solitary kidney lesions[40]. This study randomized 541 participants with solitary renal tumours with a diameter of 5 cm or less and normal contralateral kidney to receive either radical or partial nephrectomy. After a median follow-up period of over 9 years, this trial showed an inferior outcome after partial nephrectomy in comparison with radical nephrectomy (mortality of 25.0% compared with 18.3%). However the trial closed prematurely due to low recruitment and was confounded by a large number of crossover in between the two arms of treatment.

A subsequent subgroup analysis of the EORTC study found that after a median follow-up of 6.7 years, nephron-sparing surgery was associated with a lower absolute risk (21%) of developing stage Ⅲ CKD[11]. In addition, stage Ⅳ and Ⅴ CKD (eGFR < 30 mL/min per 1.73 m^2) were observed in 10.0% of participants who had radical nephrectomy compared with 6.3% of those who had nephron-sparing surgery.

Several studies have found that partial nephrectomy can be expanded safely to patients with tumours of 4-7 cm in size (T1bN0M0)[35,41-43]. One study has extended these findings on partial nephrectomy in patients with T1b to the population level, using analyses from the SEER registry[44]. Using propensity scoring, this study found no overall survival difference between partial and radical nephrectomy in a matched cohort of patients with T1bN0M0 staging. One meta-analysis of 39 studies and 41010 individuals who had surgery for small renal neoplasms found that nephron-sparing surgery had a 19% lower all-cause mortality (hazard ratio, HR = 0.81; $P < 0.0001$)[45]. However, this finding has to be interpreted cautiously due to the heterogeneity in study population and the inclusion of retrospective studies.

In a meta-analysis of 26 studies (27845 radical nephrectomy and 8201 partial nephrectomy), nephron-

sparing surgery was associated with a 73% risk reduction of new-onset CKD (eGFR < 60 mL/min per 1.73 m^2) in all included patients (HR = 0.27; P < 0.0001) compared with radical nephrectomy[46]. In patients with tumours > 4 cm, partial nephrectomy was associated with a 65% risk reduction of new-onset CKD compared to radical nephrectomy. However this systematic review was not able to assess the incidence of ESRD (eGFR < 15 mL/min per 1.73 m^2) after surgery because of a lack of relevant data.

In one study, patients treated with nephron-sparing surgery have about half the risk of developing cardiovascular events compared with radical nephrectomy[47]. After adjusting for clinical characteristics, comorbidities, and cardiovascular risk at diagnosis, nephron-sparing surgery was independently associated with a lower risk of cardiovascular events compared to radical nephrectomy.

However, in a meta-analysis of 6 studies (16745 radical nephrectomy and 5403 partial nephrectomy), there was no significant difference between radical and partial nephrectomy in relation to post-surgery cardiovascular events (HR = 0.86; P = 0.24) and cardiovascular death (HR = 0.71; P = 0.20)[46]. However, these results are still contentious because of the limited number of studies.

The most likely mechanism of how partial nephrectomy confer the kidney function advantage is through preservation of a larger renal volume or some may refer to a functional volume. Among people with a single kidney undergoing nephron-sparing surgery, a larger preserved kidney volume is independently associated with better renal function[48,49]. An increase of 5% in the volume of preserved kidney was associated with a reduction in the risk of new-onset stage IV CKD by 17%[50].

After nephron-sparing surgery, the integrity and quality of the remaining parenchyma is predictive of CKD risk. In one study of 1169 subjects, a greater decline in kidney function was observed during open or laparoscopic partial nephrectomy with increased duration of warm ischaemia greater than 20 min[51]. This study also showed that the duration of warm ischaemia was correlated with nadir eGFR decline after surgery and the magnitude of this reduction was associated with progression to CKD[51]. Furthermore, duration of warm ischaemia of more than 25 min has been demonstrated to double the risk of severe CKD[52]. However, even with prolonged ischaemic time during partial nephrectomy (> 30 min), kidney function outcomes were still better than radical nephrectomy[53].

Cryoablation and radiofrequency ablation are emerging as other nephron-sparing therapies for localized kidney neoplasms[54-56]. However ablative procedure often precludes definitive pathological staging. Although a promising option for small lesions, the efficacy in terms of oncological and renal outcomes have not yet been established due to small study cohort and the absence of long-term data. Therefore surgical resection remains the preferred treatment modality in most cases of suspected kidney malignancy.

Active surveillance can be considered the preferred "nephron-sparing" procedure in patients with limited life expectancy due to comorbidities or advanced age. Lane *et al*[57] have demonstrated that for patients 75 years or older, the renal function deterioration after radical nephrectomy is associated with higher risk of cardiovascular death. In this older age group, neither radical nor partial nephrectomy conferred a significant survival advantage over active surveillance. In the largest prospective observational study using the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry, the 5-year overall survival was lower in the active surveillance (75% *vs* 92%) but no difference in cancer-specific survival[58].

RISK STRATIFICATION BEFORE NEPHRECTOMY

Comprehensive stratification of risk before nephrectomy is vital to ensure patients achieve the best functional renal outcomes. One of the risk stratification tool is the Screening for Occult Renal Disease (SCORED) which uses factors such as patient age, gender, anemia, proteinuria and cardiovascular comorbidities[59]. This tool has been validated in patients with small kidney masses undergoing nephrectomy and those in the high risk category (SCORED $\geqslant$ 4) were three times more likely to develop Stage Ⅲ CKD[60]. Another group has proposed an alternative instrument for risk prediction. Sorbellini *et al*[61] have devised a nomogram to predict decline in kidney function, which was defined as two or more creatinine measurements of 176 μmol/L within a month after surgery. This nomogram takes into account the change in kidney volume and pre-surgery creatinine but does not include preoperative comorbidities which can be important risk factors for CKD.

Other models of risk prediction have used information from renal parenchyma surrounding the tumour[23]. The presence and extent of glomerulosclerosis in adjacent parenchyma has been found to correlate with decline in kidney function after nephrectomy but this relationship is not observed with arteriosclerosis, interstitial fibrosis or tubular atrophy[23]. Brandina *et al*[24] have proposed a nomogram using age-adjusted Charlson comorbidity index, percentage of glomerulosclerosis in the adjacent non-neoplastic parenchyma and baseline eGFR before surgery to predict the probability of developing CKD after nephrectomy. However this nomogram has not been validated for clinical use.

KNOWLEDGE GAP AND FUTURE RESEARCH

The evidence to support nephron-sparing surgery in patients with suspected RCC has been derived mainly from single-centre cohort studies. Consequently these studies lack standardisation in the definition for renal impairment, method in assessing kidney function and varying cutoff or stages of CKD as the primary outcome.

Table 3 Questions to be addressed by future studies

How is long-term cardiovascular health affected by radical nephrectomy?
What is the incidence of end-stage renal disease and renal replacement therapy after radical or partial nephrectomy?
What reliable investigations can be used to identify patients with renal cell carcinoma prior to surgery?
How does the contralateral kidney compensate after radical nephrectomy?
How can kidney function be preserved after nephrectomy?

Furthermore there is also disparities between studies in terms of eligibility criteria and duration of follow-up after surgery.

Hitherto, none of the studies have used ESRD after nephrectomy as the primary endpoint. Future work is needed to evaluate the effects of nephrectomy on patients, particularly with ESRD as the main endpoint, and the possible two-way relationship between RCC and CKD. Further research is required to better understand how CKD develops or progresses after nephrectomy and identify effective measures to prevent CKD and associated adverse effects in this setting. While comorbidities such as hypertension and diabetes mellitus are cited as risk factors for new-onset CKD or worsening kidney function after radical nephrectomy, no study have evaluated how interventions to control these risk factors may potentially influence outcome.

Assessment of kidney function before and after nephrectomy is still largely based on serum creatinine measurement. Although serum cystatin C has been found to be a good predictor of AKI in different settings[62-64], its use has not been evaluated in those undergoing nephrectomy. Similarly, another marker, neutrophil gelatinase-associated lipocalin (NGAL), has not been studied in patients having nephrectomy.

The increased incidence of CKD after radical nephrectomy also highlights the need for more research to distinguish between high- and low-risk renal tumours before surgery to better select patients who will require surgical management. Clinical trials are currently investigating gene alterations such as chromatin remodelling and microsatellite instability as tool for such differentiation (NCT02204800 and NCT01305330). Urinary biomarkers such as aquaporin-1 and perilipin-2 have demonstrated early promise in differentiating benign tumours from malignant RCC[65]. Newer markers such as decreased expression of small non-coding RNAs known as PIWI-interacting RNAs have also been associated with poor survival in RCC[66]. However more research is required to validate the accuracy of these markers in the pre-surgical diagnosis of RCC.

Future studies are needed to address a number of important gaps in knowledge for patients who had radical nephrectomy. Table 3 summaries a few key questions about kidney function and adaptation after radical nephrectomy that warrants further research.

CONCLUSION

Consistently, patients who have undergone radical nephrectomy for a suspected kidney malignancy are at increased risk of CKD. The concern with the deterioration in kidney function after radical nephrectomy is that this group of patients are at increased risk of ESRD and adverse cardiovascular outcomes. Coexisting medical disorders including diabetes mellitus, hypertension and abnormalities in the remaining kidney parenchyma are risk factors for new-onset CKD after radical nephrectomy. A comprehensive assessment of developing CKD after radical nephrectomy should be undertaken in every patient in whom this procedure is being considered so that management decisions can be better informed.

REFERENCES

1 **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; **62**: 10-29 [PMID: 22237781 DOI: 10.3322/caac.20138]

2 **Huang WC**, Levey AS, Serio AM, Snyder M, Vickers AJ, Raj GV, Scardino PT, Russo P. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol* 2006; **7**: 735-740 [PMID: 16945768 DOI: 10.1016/S1470-2045(06)70803-8]

3 **Leibovich BC**, Blute ML. Surgical management of renal cell carcinoma. *Semin Oncol* 2006; **33**: 552-562 [PMID: 17045084 DOI: 10.1053/j.seminoncol.2006.06.007]

4 **Ibrahim HN**, Foley R, Tan L, Rogers T, Bailey RF, Guo H, Gross CR, Matas AJ. Long-term consequences of kidney donation. *N Engl J Med* 2009; **360**: 459-469 [PMID: 19179315 DOI: 10.1056/NEJMoa0804883]

5 K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**: S1-266 [PMID: 11904577 DOI: 10.1053/ajkd.2002.30940]

6 **Jewett MA**, Zuniga A. Renal tumor natural history: the rationale and role for active surveillance. *Urol Clin North Am* 2008; **35**: 627-634 [PMID: 18992616 DOI: 10.1016/j.ucl.2008.07.004]

7 **Murphy AM**, Buck AM, Benson MC, McKiernan JM. Increasing detection rate of benign renal tumors: evaluation of factors predicting for benign tumor histologic features during past two decades. *Urology* 2009; **73**: 1293-1297 [PMID: 19371933 DOI: 10.1016/j.urology.2008.12.072]

8 **Akdogan B**, Gudeloglu A, Inci K, Gunay LM, Koni A, Ozen H. Prevalence and predictors of benign lesions in renal masses smaller than 7 cm presumed to be renal cell carcinoma. *Clin Genitourin Cancer* 2012; **10**: 121-125 [PMID: 22401753 DOI: 10.1016/j.clgc.2012.01.005]

9 **Klarenbach S**, Moore RB, Chapman DW, Dong J, Braam B. Adverse renal outcomes in subjects undergoing nephrectomy for renal tumors: a population-based analysis. *Eur Urol* 2011; **59**: 333-339 [PMID: 21109345 DOI: 10.1016/j.eururo.2010.11.013]

10 **Sun M**, Bianchi M, Hansen J, Trinh QD, Abdollah F, Tian Z, Sammon J, Shariat SF, Graefen M, Montorsi F, Perrotte P, Karakiewicz PI. Chronic kidney disease after nephrectomy in patients with small renal masses: a retrospective observational analysis. *Eur Urol* 2012; **62**: 696-703 [PMID: 22483407 DOI: 10.1016/j.eururo.2012.03.051]

11 **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**: 372-377 [PMID: 23850254 DOI: 10.1016/j.eururo.2013.06.044]

12 **Lane BR**, Demirjian S, Derweesh IH, Takagi T, Zhang Z, Velet L, Ercole CE, Fergany AF, Campbell SC. Survival and functional stability in chronic kidney disease due to surgical removal of nephrons: Importance of the new baseline glomerular filtration rate. *Eur Urol* 2015; **68**: 996-1003 [PMID: 26012710 DOI: 10.1016/j.eururo.2015.04.043]

13 **Patel SS**, Molnar MZ, Tayek JA, Ix JH, Noori N, Benner D, Heymsfield S, Kopple JD, Kovesdy CP, Kalantar-Zadeh K. Serum creatinine as a marker of muscle mass in chronic kidney disease: results of a cross-sectional study and review of literature. *J Cachexia Sarcopenia Muscle* 2013; **4**: 19-29 [PMID: 22777757 DOI: 10.1007/s13539-012-0079-1]

14 **Kim HL**, Shah SK, Tan W, Shikanov SA, Zorn KC, Shalhav AL, Wilding GE. Estimation and prediction of renal function in patients with renal tumor. *J Urol* 2009; **181**: 2451-2460 [PMID: 19371883 DOI: 10.1016/j.juro.2009.01.112]

15 **McKiernan J**, Simmons R, Katz J, Russo P. Natural history of chronic renal insufficiency after partial and radical nephrectomy. *Urology* 2002; **59**: 816-820 [PMID: 12031359 DOI: 10.1016/S0090-4295(02)01501-7]

16 **Chow WH**, Gridley G, Fraumeni JF, Järvholm B. Obesity, hypertension, and the risk of kidney cancer in men. *N Engl J Med* 2000; **343**: 1305-1311 [PMID: 11058675 DOI: 10.1056/NEJM200011023431804]

17 **Chow WH**, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. *Nat Rev Urol* 2010; **7**: 245-257 [PMID: 20448658 DOI: 10.1038/nrurol.2010.46]

18 **Macleod LC**, Hotaling JM, Wright JL, Davenport MT, Gore JL, Harper J, White E. Risk factors for renal cell carcinoma in the VITAL study. *J Urol* 2013; **190**: 1657-1661 [PMID: 23665301 DOI: 10.1016/j.juro.2013.04.130]

19 **Setiawan VW**, Stram DO, Nomura AM, Kolonel LN, Henderson BE. Risk factors for renal cell cancer: the multiethnic cohort. *Am J Epidemiol* 2007; **166**: 932-940 [PMID: 17656615 DOI: 10.1093/aje/kwm170]

20 **Bijol V**, Mendez GP, Hurwitz S, Rennke HG, Nosé V. Evaluation of the nonneoplastic pathology in tumor nephrectomy specimens: predicting the risk of progressive renal failure. *Am J Surg Pathol* 2006; **30**: 575-584 [PMID: 16699311 DOI: 10.1097/01.pas.0000194296.74097.87]

21 **Henriksen KJ**, Meehan SM, Chang A. Non-neoplastic renal diseases are often unrecognized in adult tumor nephrectomy specimens: a review of 246 cases. *Am J Surg Pathol* 2007; **31**: 1703-1708 [PMID: 18059227 DOI: 10.1097/PAS.0b013e31804ca63e]

22 **Salvatore SP**, Cha EK, Rosoff JS, Seshan SV. Nonneoplastic renal cortical scarring at tumor nephrectomy predicts decline in kidney function. *Arch Pathol Lab Med* 2013; **137**: 531-540 [PMID: 23544942 DOI: 10.5858/arpa.2012-0070-OA]

23 **Gautam G**, Lifshitz D, Shikanov S, Moore JM, Eggener SE, Shalhav AL, Chang A. Histopathological predictors of renal function decrease after laparoscopic radical nephrectomy. *J Urol* 2010; **184**: 1872-1876 [PMID: 20850146 DOI: 10.1016/j.juro.2010.06.145]

24 **Brandina R**, Moreira Leite KR, Gregório EP, Fernandes KB, Srougi M. Histologic abnormalities in non-neoplastic renal parenchyma and the risk of chronic kidney disease following radical nephrectomy. *Urology* 2017; **100**: 158-162 [PMID: 27725235 DOI: 10.1016/j.urology.2016.09.041]

25 **Srigley JR**, Amin MB, Delahunt B, Campbell SC, Chang A, Grignon DJ, Humphrey PA, Leibovich BC, Montironi R, Renshaw AA, Reuter VE. Protocol for the examination of specimens from patients with invasive carcinoma of renal tubular origin. *Arch Pathol Lab Med* 2010; **134**: e25-e30 [PMID: 20367296 DOI: 10.1043/1543-2165-134.4.e25]

26 **Barlow LJ**, Korets R, Laudano M, Benson M, McKiernan J. Predicting renal functional outcomes after surgery for renal cortical tumours: a multifactorial analysis. *BJU Int* 2010; **106**: 489-492 [PMID: 20039869 DOI: 10.1111/j.1464-410X.2009.09147.x]

27 **Schlehofer B**, Pommer W, Mellemgaard A, Stewart JH, McCredie M, Niwa S, Lindblad P, Mandel JS, McLaughlin JK, Wahrendorf J. International renal-cell-cancer study. VI. the role of medical and family history. *Int J Cancer* 1996; **66**: 723-726 [PMID: 8647639 DOI: 10.1002/(SICI)1097-0215(19960611)66: 6<723: : AID-IJC2>3.0.CO; 2-1]

28 **Lindblad P**, Chow WH, Chan J, Bergström A, Wolk A, Gridley G, McLaughlin JK, Nyrén O, Adami HO. The role of diabetes mellitus in the aetiology of renal cell cancer. *Diabetologia* 1999; **42**: 107-112 [PMID: 10027588 DOI: 10.1007/s001250051122]

29 **Lane BR**, Russo P, Uzzo RG, Hernandez AV, Boorjian SA, Thompson RH, Fergany AF, Love TE, Campbell SC. Comparison of cold and warm ischemia during partial nephrectomy in 660 solitary kidneys reveals predominant role of nonmodifiable factors in determining ultimate renal function. *J Urol* 2011; **185**: 421-427 [PMID: 21167524 DOI: 10.1016/j.juro.2010.09.131]

30 **Cho A**, Lee JE, Kwon GY, Huh W, Lee HM, Kim YG, Kim DJ, Oh HY, Choi HY. Post-operative acute kidney injury in patients with renal cell carcinoma is a potent risk factor for new-onset chronic kidney disease after radical nephrectomy. *Nephrol Dial Transplant* 2011; **26**: 3496-3501 [PMID: 21406544 DOI: 10.1093/ndt/gfr094]

31 **Donin NM**, Suh LK, Barlow L, Hruby GW, Newhouse J, McKiernan J. Tumour diameter and decreased preoperative estimated glomerular filtration rate are independently correlated in patients with renal cell carcinoma. *BJU Int* 2012; **109**: 379-383 [PMID: 21851533 DOI: 10.1111/j.1464-410X.2011.10331.x]

32 **Jeon HG**, Choo SH, Sung HH, Jeong BC, Seo SI, Jeon SS, Choi HY, Lee HM. Small tumour size is associated with new-onset chronic kidney disease after radical nephrectomy in patients with renal cell carcinoma. *Eur J Cancer* 2014; **50**: 64-69 [PMID: 24060356 DOI: 10.1016/j.ejca.2013.08.018]

33 **Ohno Y**, Nakashima J, Ohori M, Hashimoto T, Iseki R, Hatano T, Tachibana M. Impact of tumor size on renal function and prediction of renal insufficiency after radical nephrectomy in patients with renal cell carcinoma. *J Urol* 2011; **186**: 1242-1246 [PMID: 21849191 DOI: 10.1016/j.juro.2011.05.087]

34 **Weight CJ**, Lieser G, Larson BT, Gao T, Lane BR, Campbell SC, Gill IS, Novick AC, Fergany AF. Partial nephrectomy is associated with improved overall survival compared to radical nephrectomy in patients with unanticipated benign renal tumours. *Eur Urol* 2010; **58**: 293-298 [PMID: 20546991 DOI: 10.1016/j.eururo.2010.04.033]

35 **Patard JJ**, Shvarts O, Lam JS, Pantuck AJ, Kim HL, Ficarra V, Cindolo L, Han KR, De La Taille A, Tostain J, Artibani W, Abbou CC, Lobel B, Chopin DK, Figlin RA, Mulders PF, Belldegrun AS. Safety and efficacy of partial nephrectomy for all T1 tumors based on an international multicenter experience. *J Urol* 2004; **171**: 2181-2185, quiz 2435 [PMID: 15126781 DOI: 10.1097/01.ju.0000124846.37299.5e]

36 **Thompson RH**, Ordonez MA, Iasonos A, Secin FP, Guillonneau B, Russo P, Touijer K. Renal cell carcinoma in young and old patients--is there a difference? *J Urol* 2008; **180**: 1262-1266; discussion 1266 [PMID: 18707708 DOI: 10.1016/j.juro.2008.06.037]

37 **Becker F**, Siemer S, Humke U, Hack M, Ziegler M, Stöckle M. Elective nephron sparing surgery should become standard treatment for small unilateral renal cell carcinoma: Long-term survival data of 216 patients. *Eur Urol* 2006; **49**: 308-313 [PMID: 16359779 DOI: 10.1016/j.eururo.2005.10.020]

38 **Dash A**, Vickers AJ, Schachter LR, Bach AM, Snyder ME, Russo P. Comparison of outcomes in elective partial vs radical nephrectomy for clear cell renal cell carcinoma of 4-7 cm. *BJU Int* 2006; **97**: 939-945 [PMID: 16643474 DOI: 10.1111/j.1464-410X.2006.06060.x]

39 **Leibovich BC**, Blute M, Cheville JC, Lohse CM, Weaver AL, Zincke H. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. *J Urol* 2004; **171**: 1066-1070 [PMID: 14767272 DOI: 10.1097/01.ju.0000113274.40885.db]

40 **Van Poppel H**, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A, Colombel M, Klotz L, Skinner E, Keane T, Marreaud S, Collette S, Sylvester R. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. *Eur Urol* 2011; **59**: 543-552 [PMID: 21186077 DOI: 10.1016/j.eururo.2010.12.013]

41 **Mitchell RE**, Gilbert SM, Murphy AM, Olsson CA, Benson MC,

McKiernan JM. Partial nephrectomy and radical nephrectomy offer similar cancer outcomes in renal cortical tumors 4 cm or larger. *Urology* 2006; **67**: 260-264 [PMID: 16461075 DOI: 10.1016/j.urology.2005.08.057]

42 **Becker F**, Siemer S, Hack M, Humke U, Ziegler M, Stöckle M. Excellent long-term cancer control with elective nephron-sparing surgery for selected renal cell carcinomas measuring more than 4 cm. *Eur Urol* 2006; **49**: 1058-1063 [PMID: 16630686 DOI: 10.1016/j.eururo.2006.03.003]

43 **Kim JM**, Song PH, Kim HT, Park TC. Comparison of partial and radical nephrectomy for pT1b renal cell carcinoma. *Korean J Urol* 2010; **51**: 596-600 [PMID: 20856643 DOI: 10.4111/kju.2010. 51.9.596]

44 **Badalato GM**, Kates M, Wisnivesky JP, Choudhury AR, McKiernan JM. Survival after partial and radical nephrectomy for the treatment of stage T1bN0M0 renal cell carcinoma (RCC) in the USA: a propensity scoring approach. *BJU Int* 2012; **109**: 1457-1462 [PMID: 21933334 DOI: 10.1111/j.1464-410X.2011.10597.x]

45 **Kim SP**, Thompson RH, Boorjian SA, Weight CJ, Han LC, Murad MH, Shippee ND, Erwin PJ, Costello BA, Chow GK, Leibovich BC. Comparative effectiveness for survival and renal function of partial and radical nephrectomy for localized renal tumors: a systematic review and meta-analysis. *J Urol* 2012; **188**: 51-57 [PMID: 22591957 DOI: 10.1016/j.juro.2012.03.006]

46 **Wang Z**, Wang G, Xia Q, Shang Z, Yu X, Wang M, Jin X. Partial nephrectomy vs. radical nephrectomy for renal tumors: A meta-analysis of renal function and cardiovascular outcomes. *Urol Oncol* 2016; **34**: 533.e11-533.e19 [PMID: 27776978 DOI: 10.1016/j.urolonc.2016.07.007]

47 **Capitanio U**, Larcher A, Terrone C, Antonelli A, Volpe A, Fiori C, Furlan M, Dehò F, Minervini A, Serni S, Porpiglia F, Trevisani F, Salonia A, Carini M, Simeone C, Montorsi F, Bertini R. End-stage renal disease after renal surgery in patients with normal preoperative kidney function: Balancing surgical strategy and individual disorders at baseline. *Eur Urol* 2016; **70**: 558-561 [PMID: 27021797 DOI: 10.1016/j.eururo.2016.03.023]

48 **Fergany AF**, Saad IR, Woo L, Novick AC. Open partial nephrectomy for tumor in a solitary kidney: experience with 400 cases. *J Urol* 2006; **175**: 1630-1633; discussion 1633 [PMID: 16600716 DOI: 10.1016/S0022-5347(05)00991-2]

49 **Sharma N**, O'Hara J, Novick AC, Lieber M, Remer EM, Herts BR. Correlation between loss of renal function and loss of renal volume after partial nephrectomy for tumor in a solitary kidney. *J Urol* 2008; **179**: 1284-1288 [PMID: 18280508 DOI: 10.1016/j.juro.2007.11.071]

50 **Thompson RH**, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, Gill IS, Blute ML, Campbell SC. Renal function after partial nephrectomy: effect of warm ischemia relative to quantity and quality of preserved kidney. *Urology* 2012; **79**: 356-360 [PMID: 22310752 DOI: 10.1016/j.urology.2011.10.031]

51 **Lane BR**, Babineau DC, Poggio ED, Weight CJ, Larson BT, Gill IS, Novick AC. Factors predicting renal functional outcome after partial nephrectomy. *J Urol* 2008; **180**: 2363-2368 [PMID: 18930264 DOI: 10.1016/j.juro.2008.08.036]

52 **Thompson RH**, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, Gill IS, Blute ML, Campbell SC. Every minute counts when the renal hilum is clamped during partial nephrectomy. *Eur Urol* 2010; **58**: 340-345 [PMID: 20825756 DOI: 10.1016/j.eururo.2010.05.047]

53 **Lane BR**, Fergany AF, Weight CJ, Campbell SC. Renal functional outcomes after partial nephrectomy with extended ischemic intervals are better than after radical nephrectomy. *J Urol* 2010; **184**: 1286-1290 [PMID: 20723936 DOI: 10.1016/j.juro.2010.06.011]

54 **Raman JD**, Raj GV, Lucas SM, Williams SK, Lauer EM, Ahrar K, Matin SF, Leveillee RJ, Cadeddu JA. Renal functional outcomes for tumours in a solitary kidney managed by ablative or extirpative techniques. *BJU Int* 2010; **105**: 496-500 [PMID: 19681900 DOI: 10.1111/j.1464-410X.2009.08776.x]

55 **Tracy CR**, Raman JD, Donnally C, Trimmer CK, Cadeddu JA. Durable oncologic outcomes after radiofrequency ablation: experience from treating 243 small renal masses over 7.5 years. *Cancer* 2010; **116**: 3135-3142 [PMID: 20564644 DOI: 10.1002/cncr.25002]

56 **Mitchell CR**, Atwell TD, Weisbrod AJ, Lohse CM, Boorjian SA, Leibovich BC, Thompson RH. Renal function outcomes in patients treated with partial nephrectomy versus percutaneous ablation for renal tumors in a solitary kidney. *J Urol* 2011; **186**: 1786-1790 [PMID: 21944103 DOI: 10.1016/j.juro.2011.07.036]

57 **Lane BR**, Abouassaly R, Gao T, Weight CJ, Hernandez AV, Larson BT, Kaouk JH, Gill IS, Campbell SC. Active treatment of localized renal tumors may not impact overall survival in patients aged 75 years or older. *Cancer* 2010; **116**: 3119-3126 [PMID: 20564627 DOI: 10.1002/cncr.25184]

58 **Pierorazio PM**, Johnson MH, Ball MW, Gorin MA, Trock BJ, Chang P, Wagner AA, McKiernan JM, Allaf ME. Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: the DISSRM registry. *Eur Urol* 2015; **68**: 408-415 [PMID: 25698065 DOI: 10.1016/j.eururo.2015.02.001]

59 **Bang H**, Vupputuri S, Shoham DA, Klemmer PJ, Falk RJ, Mazumdar M, Gipson D, Colindres RE, Kshirsagar AV. SCreening for Occult REnal Disease (SCORED): a simple prediction model for chronic kidney disease. *Arch Intern Med* 2007; **167**: 374-381 [PMID: 17325299 DOI: 10.1001/archinte.167.4.374]

60 **Lucas SM**, Nuss G, Stern J, Lotan Y, Sagalowsky AI, Cadeddu JA, Raj GV. The screening for Occult Renal Disease (SCORED) value is associated with a higher risk for having or developing chronic kidney disease in patients treated for small, unilateral renal masses. *Cancer* 2008; **113**: 2681-2686 [PMID: 18853420 DOI: 10.1002/cncr.23850]

61 **Sorbellini M**, Kattan MW, Snyder ME, Hakimi AA, Sarasohn DM, Russo P. Prognostic nomogram for renal insufficiency after radical or partial nephrectomy. *J Urol* 2006; **176**: 472-476; discussion 476 [PMID: 16813869 DOI: 10.1016/j.juro.2006.03.090]

62 **Zhang Z**, Lu B, Sheng X, Jin N. Cystatin C in prediction of acute kidney injury: a systemic review and meta-analysis. *Am J Kidney Dis* 2011; **58**: 356-365 [PMID: 21601330 DOI: 10.1053/j.ajkd.2011.02.389]

63 **Zhang Z**, Xu X, Ni H, Jin N. Serum cystatin C is associated with renal function recovery in critically ill patients undergoing continuous renal replacement therapy. *Nephron Clin Pract* 2012; **122**: 86-92 [PMID: 23594833 DOI: 10.1159/000350245]

64 **Zhang Z**. Biomarkers, diagnosis and management of sepsis-induced acute kidney injury: a narrative review. *Heart Lung Vessel* 2015; **7**: 64-73 [PMID: 25861592]

65 **Morrissey JJ**, Mellnick VM, Luo J, Siegel MJ, Figenshau RS, Bhayani S, Kharasch ED. Evaluation of urine aquaporin-1 and perilipin-2 concentrations as biomarkers to screen for renal cell carcinoma: A prospective cohort study. *JAMA Oncol* 2015; **1**: 204-212 [PMID: 26181025 DOI: 10.1001/jamaoncol.2015.0213]

66 **Iliev R**, Fedorko M, Machackova T, Mlcochova H, Svoboda M, Pacik D, Dolezel J, Stanik M, Slaby O. Expression levels of PIWI-interacting RNA, piR-823, are deregulated in tumor tissue, blood serum and urine of patients with renal cell carcinoma. *Anticancer Res* 2016; **36**: 6419-6423 [PMID: 27919963 DOI: 10.21873/antic anres.11239]

P- Reviewer: Friedman EA, Naselli A, Talas ZS, Wang F, Zhang ZH
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Clinical Urology

Submit a Manuscript: http://www.wjgnet.com/esps/

World J Clin Urol 2017 March 24; 6(1): 18-26

DOI: 10.5410/wjcu.v6.i1.18

ISSN 2219-2816 (online)

ORIGINAL ARTICLE

Observational Study

Urine chemokine levels correlate with treatment response to phosphodiesterase 4 inhibitor in prostatitis

Pradeep Tyagi, Kim Killinger, Gregory McLennan, Nirmal Jayabalan, Michael Chancellor, Kenneth M Peters

Pradeep Tyagi, Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, United States

Kim Killinger, Gregory McLennan, Michael Chancellor, Kenneth M Peters, Oakland University William Beaumont School of Medicine, Beaumont Hospital-Royal Oak, Oakland, MI 48073, United States

Nirmal Jayabalan, School of Material Science and Engineering, Nanyang Technological University, Singapore 639798, Singapore

Author contributions: All the authors contributed to the manuscript.

Institutional review board statement: The study was reviewed and approved by the Human Investigation Committed of Oakland University William Beaumont School of Medicine.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: None of the authors other than Kenneth Peters have a conflict; Dr. Kenneth M Peters was the investigator of Celgene Sponsored Clinical Trial.

Data sharing statement: No data were created no data are available.

Manuscript source: Invited manuscript

Correspondence to: Pradeep Tyagi, PhD, Associate Professor, Department of Urology, University of Pittsburgh School of Medicine, Suite 700 Kaufmann Medical Building, 3471 Fifth Avenue, Pittsburgh, PA 15213, United States. tyagip@upmc.edu

Telephone: +1-412-6924119
Fax: +1-412-6924380

Received: August 12, 2016
Peer-review started: August 16, 2016
First decision: September 28, 2016
Revised: October 27, 2016
Accepted: December 13, 2016
Article in press: December 15, 2016
Published online: March 24, 2017

Abstract

AIM

To investigate the association of urinary chemokines with the treatment response in chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) patients.

METHODS

Between 2007-2011, 18 out of 21 male CP/CPPS patients met the exclusion/inclusion criteria of the 16 wk longitudinal study on twice daily oral treatment with Phosphodiesterase 4 inhibitor called Apremilast for 12 wk. Symptom scores and urine specimen were collected at baseline and every visit at 4 wk interval from CP/CPPS patients who completed at least 8 wk of drug treatment. Urine collected at each visit was frozen and then analyzed together after thawing for chemokines and growth factors using MILLIPLEX™ MAP immunoassay. Cross sectional association of Chronic Prostatitis Symptom Index (CPSI) and visual analog scale (VAS) with chemokine levels in urine collected at baseline was assessed in 18 CP/CPPS patients relative to 10 asymptomatic male subjects. Longitudinal association between urine chemokine levels and symptom scores was assessed in 8 treatment-adherent CP/CPPS patients at baseline and at 4, 8, 12 and 16 wk.

RESULTS

Urine chemokines levels of CXCL-1 (GRO-a), CXCL-8

(IL-8), CXCL-10 (IP-10) and CCL5 (RANTES) in CP/CPPS patients at baseline were significantly elevated relative to asymptomatic subjects, whereas levels of sIL-1RA in CP/CPPS were significantly lower compared to controls (P < 0.05). Quantitatively, urine levels of CXCL-10 were higher than other chemokines in CP/CPPS, but its fold change of 5 relative to controls was lower than the 20 fold change noted for CXCL-8. The mean age of enrolled patients who completed at least 8 wk of treatment (n = 8) was 46.5 ± 9.4 years and analysis found that elevation of CXCL-8 and CCL5 increased the odds for higher score of CPSI by 54% and 25%, respectively (F test, P = 0.00007). Urine levels of CCL2 (MCP-1) and CXCL-10 together explained approximately 85% of variance in longitudinal data on multivariate analysis. Bivariate analysis of 5 patients who fully complied and completed the assigned dose regimen, showed strong linear correlation of reduced urine levels of CXCL-10, CXCL-8, CCL5, CCL2 and PDGF with improvement in clinical activity as measured by pain VAS and CPSI (Pearson r = 0.83-0.97; P < 0.05).

CONCLUSION

Urine levels of CXCL-10, CCL2 and PDGF can be sensitive, objective and non-invasive markers of response to new therapeutic intervention in CP/CPPS patients.

Key words: Chronic prostatitis; Longitudinal measurement; Phosphodiesterase 4; Urine; Chronic pelvic pain syndrome; Chemokines

Core tip: Chronic prostatitis or chronic pelvic pain syndrome is a poorly understood and prevalent male condition, which is generally described by pelvic pain in the absence of demonstrable urinary or genital tract infection. Inflammation is considered to play a critical role in the prostatitis and so we carried out a small physician initiated clinical study to investigate the potential efficacy of a new phosphodiesterase 4 inhibitor drug, Apremilast. Urine was collected from the study participants at the baseline and at each visit to assay the chemokine levels and then determine their association with the treatment response. We are the first to report that chemokine levels in urine instead of the semen or prostatic secretions have the potential to serve as non-invasive biomarkers of severity and treatment response of the prostatitis patients.

Tyagi P, Killinger K, McLennan G, Jayabalan N, Chancellor M, Peters KM. Urine chemokine levels correlate with treatment response to phosphodiesterase 4 inhibitor in prostatitis. *World J Clin Urol* 2017; 6(1): 18-26 Available from: URL: http://www.wjgnet.com/2219-2816/full/v6/i1/18.htm DOI: http://dx.doi.org/10.5410/wjcu.v6.i1.18

INTRODUCTION

Chronic prostatitis (CP) or chronic pelvic pain syndrome (CPPS) is a poorly understood and prevalent male condition that affects 10% to 14% of men of all ages and ethnic origins[1]. According to the National Institutes of Health (NIH) consensus definition, CPPS is regarded as category Ⅲ prostatitis described by genital or pelvic pain in the absence of demonstrable urinary or genital tract infection[2].

Unlike NIH category Ⅰ and Ⅱ prostatitis, the pathophysiology of category Ⅲ (CP/CPPS) is an enigma and may not be as organ (prostate) centric as categories Ⅰ and Ⅱ[2]. With progression of symptom severity, CP/CPPS may evolve into regional pain syndrome with symptoms resembling interstitial cystitis[3]. Considering the significant inflammatory component in CP/CPPS, most prior therapies have focused on targeting inflammation[4]. Leukocyte infiltration is a primary event in inflammation and because expression of chemokines temporally precede that[5] it makes the chemokines well suited to serve as biomarkers for pelvic pain disorders[6].

Interestingly, leukocytes and immune cells predominantly express a cyclic adenosine monophosphate cAMP metabolizing isoenzyme called phosphodiesterase 4 (PDE4)[7]. Consequently, selective pharmacological inhibition of PDE4 by Apremilast, a novel, orally available small molecule, can cause buildup of cAMP which affects production of cytokines including CXCL-10 (IP-10), CCL2/monocyte chemoattractant protein-1 (MCP-1), CCL5/Regulated on Activation, Normal T cell Expressed and Secreted (RANTES) and vascular endothelial growth factor (VEGF)[8]. Since mechanism of action for Apremilast is different from traditional anti-inflammatory drugs (NSAIDS), it could have potential efficacy in CP/CPPS patients refractory NSAIDS[9], which work by inhibiting COX instead of PDE4.

Previous studies have reported correlations between increased cytokines, chemokines and growth factors in the semen and prostatic secretions with symptom scores of CP/CPPS[10,11]. Instead of seminal plasma, we aimed to correlate in a longitudinal study the disease severity and treatment response to Apremilast by non-invasive measurement of chemokines in urine of CP/CPPS patients.

MATERIALS AND METHODS

Patient selection

Adult male subjects aged ≥ 18 years at time of informed consent were recruited in a prospective open-label, one arm, physician initiated study (NCT00701311)[9] that was approved by the institutional review board (HIC-2007-135). The inclusion and exclusion criteria for CP/CPPS patients enrolled in a 12 wk oral therapy of PDE4 inhibitor, Apremilast (20 mg BID; provided by Celgene), can also be found at http://clinicaltrials.gov/ct2/show/NCT00701311. The inclusion criteria were patients with clinical symptoms of CP/CPPS (pain in the pelvic area, penis, scrotum, or perineum) who were refractory to other therapies (*e.g.*, NSAIDS) for at least 3 of the 6 mo immediately before the first visit. Enrolled patients also fulfilled the NIH definition of CP/CPPS (category Ⅲ prostatitis) and had a NIH-CPSI

total score of 15 or higher. Exclusion criteria were subjects with genital infection, clinical epididymitis, documented positive urine culture (> 100000 CFU/mL) within the past three months, pelvic mass, or known active or prior genitourinary malignancies (including renal, ureteral, bladder or prostate). Urine samples from 10 age-matched males without CP/CPPS diagnosis or symptoms were also included as controls in the analysis for comparison.

Follow up protocol

Clinical and laboratory assessments were performed at baseline and then every 4 wk till the end of treatment (at 12 wk) with a final follow up at week 16. Clinical assessment for improvement in symptoms after treatment included change between week 0 and week 12 in the chronic prostatitis symptom index (CPSI), which is a validated urinary and pain measurement tool from the NIH. Pain was measured using a visual analog scale (VAS) for pain (0 = no pain and 10 = worst pain imaginable). Laboratory assays included urine culture at baseline, complete blood count, metabolic blood chemistry, urinalysis, liver and kidney function tests, and PSA.

Specimens

Urine specimens were collected from consented patients at baseline and at 4, 8, 12 and 16 wk after started treatment. Urine dipstick was done after each urine collection. After collection, all the spot-urine samples were frozen at -80 ℃ until analysis.

Assay of urinary chemokines

On the day of analysis, all the frozen urine samples were thawed quickly and nine different chemokines/cytokines in urine were measured by MILLIPLEX human cytokine/chemokine immunoassay following the procedure as previously described[6]. An automated immunoassay analyzer Bioplex Luminex 200 IS System, (Luminex, Austin, TX) purchased through Bio-Rad, was used to assay chemokines using commercially available microspheres (Millipore, Billerica, MA) following manufacturer's instructions. Microspheres of defined spectral properties conjugated to antibody directed against CXCL-1, CXCL-8, CXCL-10, IL-6, soluble interleukin-1 receptor antagonist (sIL-1RA), MCP-1 (CCL2), RANTES (CCL5), VEGF, platelet derived growth factor (PDGF) were pipetted into 96-well plate. The median fluorescence intensity of microspheres specific for each chemokine was recorded for each well to calculate chemokine concentration.

Statistical analysis

The differences in urine levels of chemokines between controls and CP/CPPS patients were measured by Mann-Whitney *U* test. The test assesses significant differences between groups without making assumptions of normality. Both bivariate and multivariate models using principal component analysis (PCA) were examined to assess the degree to which each baseline predictor was associated with the clinical outcome measures independently or in conjunction with the other variables using Unscrambler® X 10.1 software (CAMO Software Inc, NJ, United States). Assumptions of linearity were verified for each model and age, urine chemokines, and duration of CP/CPPS symptoms were included as covariates in all models. Pearson (r) and Spearman (r_s) correlation test were used to assess the correlations among reductions in urinary chemokines and clinical outcomes. All statistical tests were evaluated for statistical significance at $\alpha < 0.05$ 2-tailed, and trends at $0.05 < \alpha > 0.10$. Continuous variables are expressed as mean ± standard error of mean.

RESULTS

Baseline clinical and demographics features

Of the 21 patients recruited for the study only 18 met the exclusion/inclusion criteria and provided urine at baseline, 7 provided a urine specimen at baseline but did not complete at least 8 wk of treatment, and 3 others withdrew before completing the study. The mean age of enrolled patients who completed at least 8 wk of treatment (n = 8) was 46.5 ± 9.4 years. Among 8 CP/CPPS patients, those who fully complied and completed the assigned dose regimen are referred to as treatment adherent (n = 5) and those not completely adherent to regimen are referred to as treatment non-adherent CP/CPPS patients (n = 3).

Urine levels of chemokines in CP/CPPS and controls

Urine dipstick done after each collection ruled out presence of urinary infection. At baseline, levels of CX CL-1 (15 fold), CXCL-8 (20 fold) and CXCL-10 (5 fold) were significantly elevated in CP/CPPS ($P < 0.05$) (Figure 1A-C). Higher levels of CXCL-10 (169.8 ± 46.38 pg/mL *vs* 31.45 ± 16.83 pg/mL) relative to controls is in agreement with the intra-acinar infiltration of T-lymphocytes previously noted in prostate biopsy of CP/CPPS patients[12]. Levels of neutrophil attracting CXC chemokines CXCL-1 (32.46 ± 9.9 pg/mL) and CXCL-8 (5.3 ± 1.8 pg/mL) were comparatively lower in CP/CPPS[12] (notice scale on Y-axis Figure 1).

CCL5, which is also known to drive trafficking of lymphocytes[13] (Figure 1E), was also significantly elevated in CP/CPPS relative to controls (19.26 ± 6.8 pg/mL *vs* 0.14 ± 0.02 pg/mL). CCL2 and PDGF were detected in substantial amount in all the CP/CPPS patients, but due to high variability in the control group, results were not significant (Figure 1D and F, respectively). Levels of CXCL-1, CXCL-8 and CCL5 in the control group were uniformly below or very near the detection limit of our assay method.

Urine levels of CXCL-8 and CCL5 levels were not only quantitatively lower in CP/CPPS patients compared to other chemokines (Figure 1), but were also detected only in 7 and 8 patients, respectively, of 18 enrolled CP/CPPS patients at baseline. The urine levels of CXCL-1, CXCL-8 and CCL5 in the control group were uniformly below or very near the detection limit of our assay method.

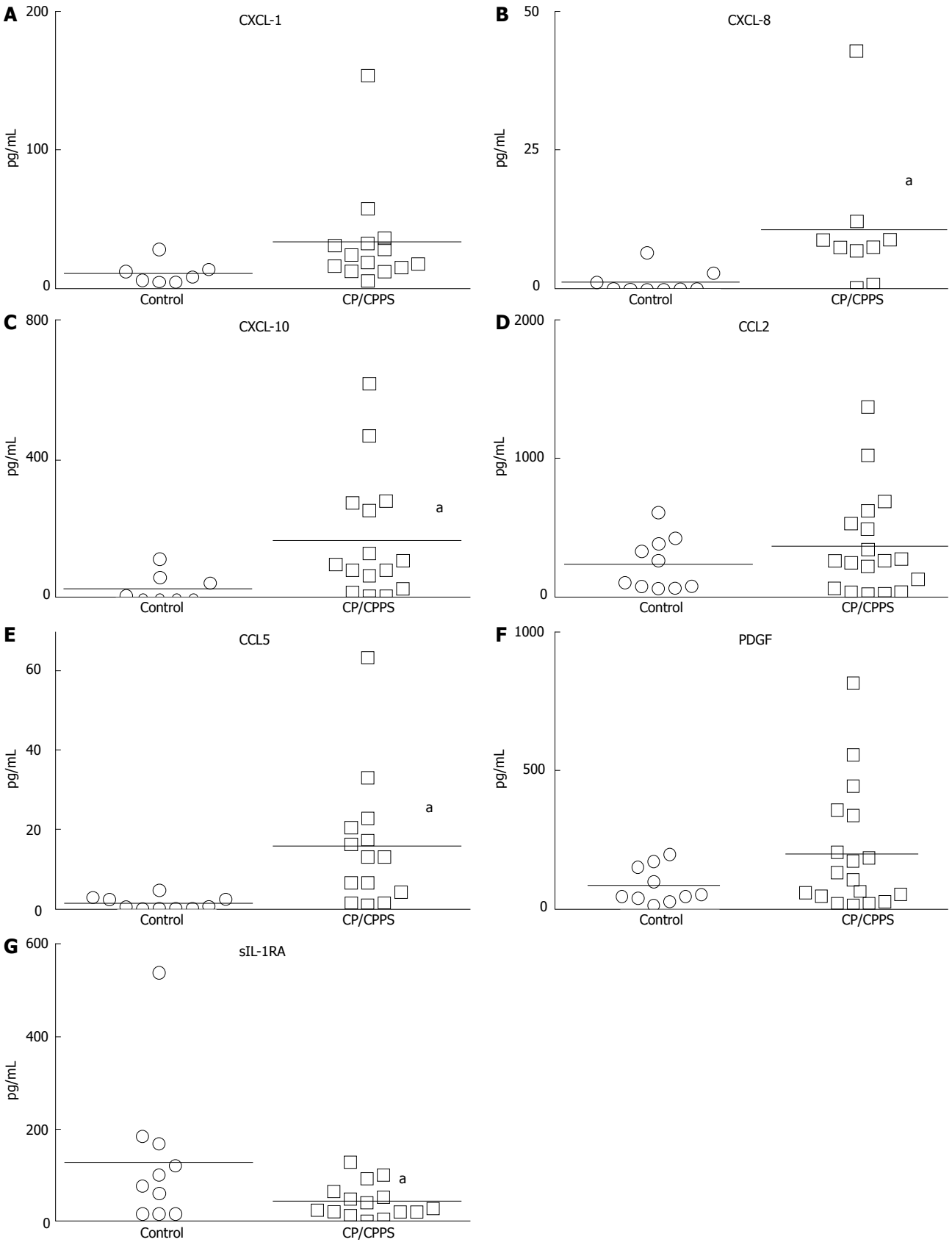

Figure 1 Comparative baseline levels of cytokines, CXC and CC chemokines and growth factors in urine obtained from asymptomatic individuals and chronic prostatitis/chronic pelvic pain syndrome patients. A-C: Urine levels of CXCL-1, CXCL-8 and CXCL-10 chemokines at baseline were significantly elevated in CP/CPPS patients ($^aP < 0.05$). Quantitatively, levels of CXCL-10 (169.8 ± 46.38 pg/mL *vs* 31.45 ± 16.83 pg/mL) that attract lymphocytes were higher relative to other CXC chemokines CXCL-1 and CXCL-8 that attract neutrophils (notice scale on y-axis). Levels of CC chemokine, CCL-5 (RANTES) also chemotactic for lymphocytes (E) were significantly elevated in CP/CPPS relative to controls ($^aP < 0.05$). Lymphocytic infiltration previously noted in biopsy of CP/CPPS patients is also consistent with significantly lower levels of sIL-1RA in CP/CPPS (G) compared to controls ($^aP < 0.05$). Due to high variability in control group, results were not significant with respect to CCL2 and PDGF (D and F, respectively). Horizontal bars represent mean of the group and Mann-Whitney *U* test was used for unpaired comparison and chemokines with significant difference appear in bold. CP/CPPS: Chronic prostatitis/ronic pelvic pain syndrome; sIL-1RA: Soluble interleukin-1 receptor antagonist.

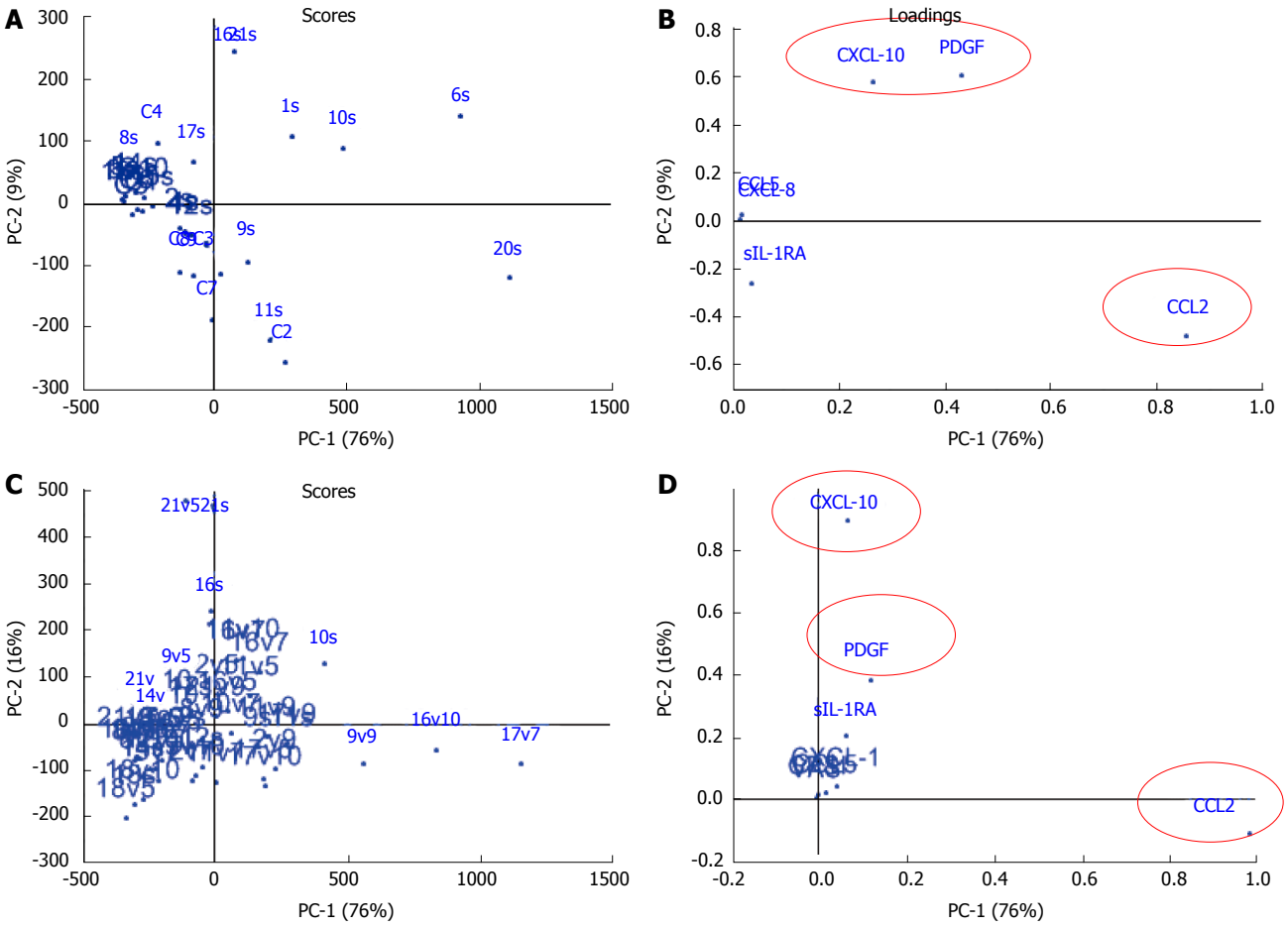

Figure 2 Visualization of principal component analysis principal component analysis for the cross sectional data of asymptomatic controls (C1-10) and chronic prostatitis/chronic pelvic pain syndrome patients (1 s-21 s). At baseline (A and B) and the longitudinal treatment response data of adherent and non-adherent CP/CPPS patients (C and D), PC1 and PC2 explained 76 % and 9% of the data characteristics at baseline (A and B), respectively which in turn was explained largely by the variation in the urine levels of CCL2, CXCL-10 and PDGF. Majority of CP/CPPS mapped separately from a close cluster for controls (A), and the spreading of CP/CPPS is explained by disease heterogeneity as revealed by the variation in the levels of different chemokines in CP/CPPS at baseline (Figure 1). PCA of longitudinal data also included VAS and CPSI scores measured at each visit as variables, where each dot represents the expression profile of an individual patient at a singular timepoint identified by baseline (s), visit 5 (v5), visit7 (v7), visit 9 (v9), and final visit (v10) (C). PCA allowed grouping of patients with overall similar cytokine expression profiles at individual time points. Compared to PCA of cross-sectional data (A and B), the contribution of CCL2 was slightly increased whereas contribution of CXCL-10 was slightly reduced in PC1 of longitudinal data (Panel D). The urine levels of CXCL-1 and CCL5 together with CPSI scores only contributed < 1% to both PC1 and PC2 scores. PC: Principal components; PDGF: Platelet derived growth factor.

Significantly higher levels of sIL-1RA in controls relative to CP/CPPS (Figure 1G) are consistent with its anti-inflammatory role ($P < 0.05$).

PCA was used to reduce the dimensionality by extracting two principal components (PCs), PC1 and PC2 from the cross-sectional data of 9 cytokines from 18 CP/CPPS patients and 10 controls at baseline (Figure 2A and B). PC1 and PC2 together explain most of the variation, 76% and 9% respectively, and are defined by a weighted sum of the individual cytokine values referred to as loadings (Figure 2B). The majority of variance at baseline was explained by CCL2, CXCL-10 and PDGF. The value of PC1 and PC2 for each patient and controls were calculated and these values are referred to as "scores". The scores are represented graphically to summarize the variation (Figure 2A). The majority of CP/CPPS mapped separately from controls, but a close cluster of CP/CPPS patients like most controls was absent which can be explained by disease heterogeneity as revealed by the variation in the levels of different chemokines in CP/CPPS at baseline (Figure 1).

Correlation of urinary chemokines with clinical outcomes

Significant improvement in clinical outcome measures (VAS and CPSI) was noted post treatment in adherent CP/CPPS patients (Figure 3). Multivariate modeling of data from treatment adherent and non-adherent patients together ($n = 8$) revealed that age and duration of CP/CPPS symptoms had no effect on the CPSI or VAS scores or on the response to treatment. The longitudinal effect of treatment was visualized by PCA (Figure 2C) after excluding the data of Patient 6 due to high variation relative to other treated CP/CPPS patients. PCA allowed grouping of patients with overall similar cytokine expression profiles at individual time points. With regard to cross-sectional data (Figure 2A and B), the contribution of CCL2 was slightly increased whereas contribution of CXCL-10 was slightly reduced in PC1. CXCL-1, CCL5 and

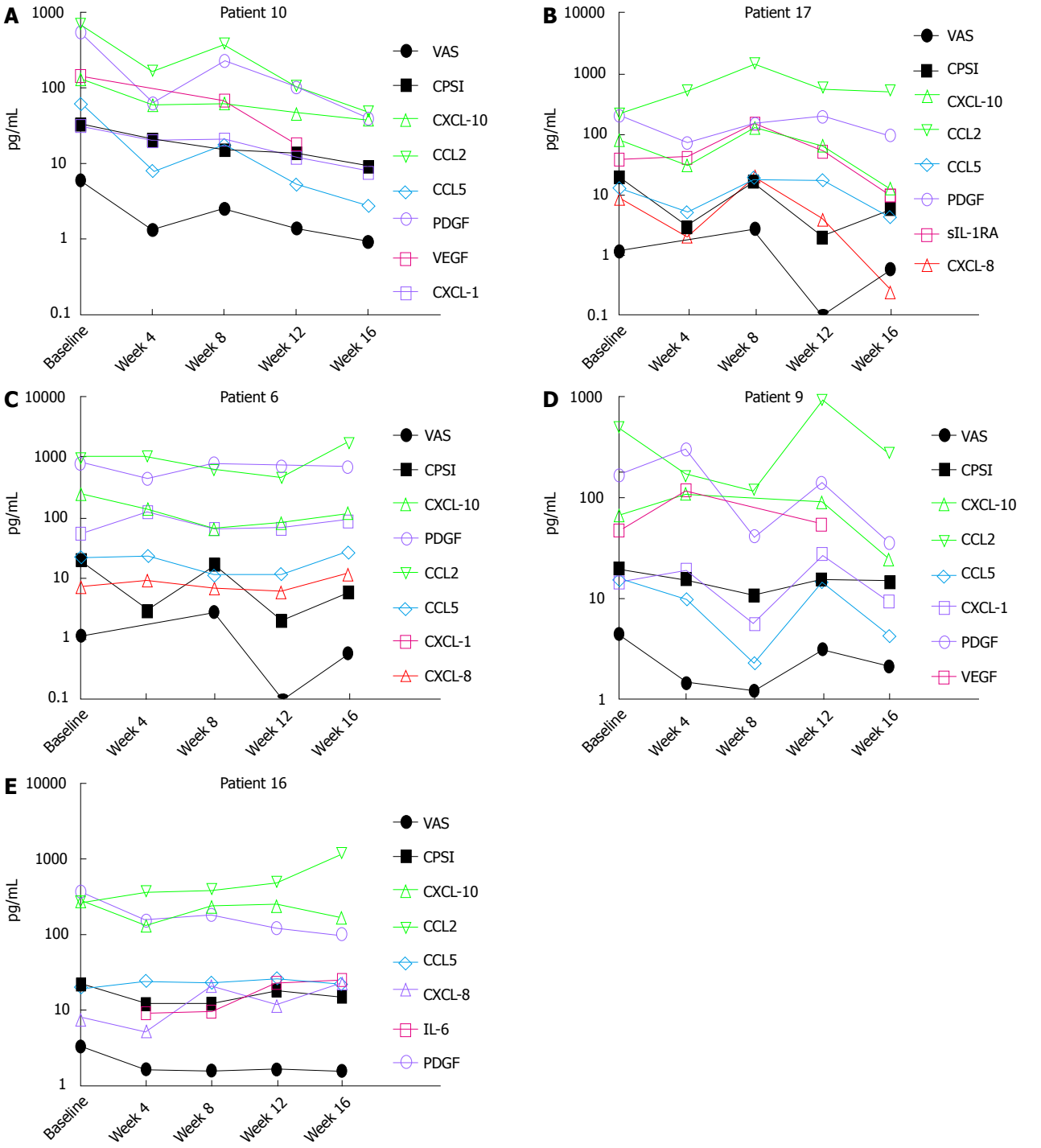

Figure 3 Significant improvement in clinical outcome measures was noted post treatment in adherent chronic prostatitis/chronic pelvic pain syndrome patients. A-E: The disease heterogeneity and variability in response to treatment in CP/CPPS patients is highlighted by different urinary chemokines correlating with the clinical outcome scores measured at each visit (VAS and CPSI) in different treatment adherent Patients 6, 9, 10, 16 and 17 at baseline and week 4, 8, 12 and 16 after starting treatment. Lower VAS in Patient 10 strongly correlated with reduced urine levels of CXCL-10 (triangle; Pearson $r = 0.97$; $P = 0.003$), CCL2 (Inverted triangle; $r = 0.97$; $P = 0.005$), CCL5 (diamond; $r = 0.99$; $P < 0.0001$), VEGF (square; $r = 0.98$; $P = 0.003$) and PDGF (circular; $r = 0.99$; $P < 0.0001$) at various time points and CPSI scores correlated with CXCL-10 (triangle; Pearson $r = 0.96$; $P = 0.009$), CCL2 (Inverted triangle; $r = 0.86$; $P = 0.05$), CCL 5 (diamond; $r = 0.91$; $P = 0.03$), VEGF (square; $r = 0.80$; $P = 0.1$), PDGF (circular; $r = 0.86$; $P = 0.06$) and CXCL-1 ($r_s = 0.9$; $P = 0.08$) (A). In contrast, in Patient 17, only VAS scores showed strong correlation with CXCL-10 (triangle) (Pearson $r = 0.84$; $P = 0.07$), IL-8 (triangle) ($r = 0.94$; $P = 0.01$) and sIL-1RA (square) ($r = 82$; $P = 0.08$) (B) and CPSI showed Spearman r_s coefficient of 0.4-0.5 for PDGF, CXCL-10 and CXCL-8 without any significance. In Patient 6 (C), reduced CXCL-10 (triangle) strongly correlated with lower VAS ($r = 0.89$; $P = 0.04$) and CPSI ($r = 0.82$; $P = 0.08$) and PDGF (circular) correlated with VAS (rs = 0.89; P = 0.08) and CPSI ($r_s = 0.9$; $P = 0.08$). In Patient 9 (D), lower CCL5 (diamond) strongly correlated VAS ($r = 0.80$; $P = 0.09$) and CPSI ($r = 0.86$; $P = 0.05$) whereas CCL2 (Inverted triangle) correlated only with VAS ($r_s = 0.9$; $P = 0.08$). In Patient 16 (E), PDGF (circular) correlated with VAS ($r = 0.95$; $P = 0.01$) and CPSI correlated with CXCL-10 (triangle) ($r_s = 0.82$; $P = 0.13$) Notice the log-scale on the y-axis in all the panels. The units of pg/mL only apply to chemokines and not to VAS and CPSI scores. PDGF: Platelet derived growth factor; VAS: Visual analog scale; CPSI: Chronic Prostatitis Symptom Index; IL: Interleukin; VEGF: Vascular endothelial growth factor.

CPSI scores together contributed < 1% to both PC1 and PC2 scores. Furthermore, the elevated CXCL-8 and CCL5 raised the odds ratio for higher CPSI scores by 54% and 25%, respectively (*F* test, $P = 0.00007$).

Considering the variability of treatment response, we used both parametric and non-parametric bivariate correlation analysis for clinical outcome scores measured at each visit with the respective urine levels of chemokines individually for each of the 5 treatment adherent patients (Figure 3). Analysis of longitudinal data from treatment adherent Patient 10 (Figure 3A) demonstrated that lower VAS strongly correlated with reduced levels of CXCL-10 (Pearson $r = 0.97$; $P = 0.003$), CCL2 ($r = 0.97$; $P = 0.005$), CCL5 ($r = 0.99$; $P < 0.0001$), VEGF ($r = 0.98$; $P = 0.003$) and PDGF ($r = 0.99$; $P < 0.0001$). Lower CPSI also correlated with reduced levels of CXCL-10 ($r = 0.96$; $P = 0.009$), CCL2 ($r = 0.86$; $P = 0.05$), CCL5 ($r = 0.91$; $P = 0.03$), VEGF ($r = 0.80$; $P = 0.1$), PDGF ($r = 0.86$; $P = 0.06$) and CXCL-1 ($r_s = 0.9$; $P = 0.08$). In contrast, only the VAS of Patient 17 (Figure 3B) strongly correlated with CXCL-10 ($r = 0.84$; $P = 0.07$), CXCL-8 ($r = 0.94$; $P = 0.01$) and sIL-1RA ($r = 82$; $P = 0.08$) and CPSI showed r_s coefficient of 0.4-0.5 for PDGF, CXCL-10 and CXCL-8 without achieving statistical significance.

In Patient 6 (Figure 3C), reduced CXCL-10 strongly correlated with VAS ($r = 0.89$; $P = 0.04$) and CPSI ($r = 0.82$; $P = 0.08$) and PDGF correlated with VAS ($r_s = 0.89$; $P = 0.08$) and CPSI ($r_s = 0.9$; $P = 0.08$). For Patient 9 (Figure 3D), lower CCL5 strongly correlated with VAS ($r = 0.80$; $P = 0.09$) and CPSI ($r = 0.86$; $P = 0.05$), and CCL2 correlated only with VAS ($r_s = 0.9$; $P = 0.08$). In Patient 16 (Figure 3E) PDGF correlated with VAS ($r = 0.95$; $P = 0.01$) and CPSI correlated with CXCL-10 ($r_s = 0.82$; $P = 0.13$).

DISCUSSION

In our study, we focused on chemokines, which are mainly subdivided into 2 families (CXC and CC) based on the position and number of conserved cysteine as well as the presence of intervening amino acid(s) between the first two conserved cysteine residues[14]. The CXC chemokines (CXCL-1, CXCL-8, CXCL-10) mainly act on neutrophils and lymphocytes, while the CC chemokines (CCL2/MCP-1 and CCL5/RANTES) act on monocytes and lymphocytes without affecting neutrophils[14]. Chemokines not only induce chemotaxis but also activation of these target cells in affected tissue[15] through their influence on the expression and/or affinity of leukocyte integrins to cause inflammatory cell adhesion and infiltration.

A major finding of our clinical study is the successful measurement of chemokines in urine of CP/CPPS patients, which have been previously detected only in seminal plasma (CXCL-8 and CCL2)[16,17]. Previous longitudinal studies on CP/CPPS only reported subjective symptom scores[18], but we were able to correlate the subjective scores with objective urine biomarker data. CP/CPPS, being a chronic disease with substantial variation in symptoms across patients[18], probably contributes to the variable levels of different chemokines at baseline (Figure 1) and different chemokines correlating with treatment induced reduction in VAS and CPSI scores in different patients (Figure 3). The disease heterogeneity and variability in treatment response of CP/CPPS patients justify the need for personalized treatment guided by urinary biomarkers.

CCL2 previously detected in seminal plasma[17] can also be non-invasively measured in urine (Figure 1D). Loading plots of cross-sectional and longitudinal data identified CCL2 as the key variable explaining the variance in data (Figure 2). CCL2, together with significant elevation of another CC chemokine (CCL5) in CP/CPPS (Figure 1E), agrees with previous suggestions of a dominant T-helper Th1-mediated inflammation in CP/CPPS[19]. Previously observed activated T-lymphocytes in prostate biopsy of CP/CPPS patients[12] also supports Th1-mediated inflammation and concurs with the results of our study that showed higher urine levels of CXCL-10 (Figure 1C) that chemoattracts activated T-lymphocytes[14] relative to CXCL-1 and CXCL-8 (Figure 1A and B) that attract neutrophils[20]. CXCL-10 is induced by pro-inflammatory interferfon-γ (IFN-γ) or TNF-α directly or through activation of nuclear factor-κB (NF-κB)[20] and it chemoattracts T cells, which inhibit the proliferation of endothelial cells and inflammatory angiogenesis[21]. Since sIL-1RA is known to block T lymphocyte activation[22], the significantly lower levels of sIL-1RA (Figure 1G) in urine of CP/CPPS relative to controls ($P < 0.05$) also supports predominance of T-lymphocytes in the pathophysiology of CP/CPPS.

Interestingly, the same CCR5 receptor acted on by CCL2 and CCL5 for recruitment of macrophages, monocytes and lymphocytes to inflammatory foci highlight the inbuilt redundancy in chemokines signaling[23]. Because chemokines operate in integrated networks[24], a more complete understanding of their role can be gained by measuring multiple chemokines for examining patterns associated with symptoms and prognosis of CP/CPPS. The results of our study and the statistical logic lend impetus to the assertion that a multiple panel of chemokines instead of single protein like PSA[25] will be able to better serve as a "proteomic signature" to predict treatment response and stratify CP/CPPS patients according to disease severity.

The predictive association of CXCL-8 and CCL5 with CPSI scores is corroborated by previous studies with regard to CXCL-8 (IL-8)[16] where CXCL-8 is known to act as a secretagogue for histamine from basophils[26]. Reduced levels of CXCL-8, CXCL-10, CCL2, CCL5, and PDGF measured individually in treatment adherent patients strongly correlated with coincident lower VAS and CPSI scores (Figure 3). PCA analysis of longitudinal data agree (Figure 2D) with regard to CXCL-10, and CCL2 is in agreement with the bivariate correlation of lower CXCL-10 and CCL2 with lower VAS in Patients 6, 9, 10 and 17 (Figure 3).

The negative association of lower CXCL-10 and CCL2 with pain scores of CP/CPPS is presumably linked to the concentration dependent suppression of opioid receptors[27] and augmentation of TRPV1 receptor responses[28,29] caused by elevated chemokines. Drug related lowering

of chemokines will unmask the endogenous pain killing effect of opioid receptors and block the adverse effect of afferents sensitization on pain to explain the lower pain scores. The lower VAS and CPSI scores in Patients 6, 9, 10, 16, 17 may also be related to reduced inflammatory angiogenesis in prostate as a consequence of reduced expression of PDGF[30], CXCL-10[21] and CCL5[31] caused by Apremilast.

The dose of Apremilast 20 mg BID was selected based on pre-clinical studies to maintain the serum level above the IC_{50} of 77 nM for TNF-α inhibition in serum for the duration of therapy. As predicted by pre-clinical studies[8], steady PDE4 inhibition by Apremilast reduced chemokines in urine collected without any prostatic massage from treatment adherent CP/CPPS patients (Figure 3). Considering that CP/CPPS may not be as organ (prostate) centric as categories Ⅰ and Ⅱ[2], the ability to track disease severity and treatment response by non-invasive measurement of chemokines in urine is a significant improvement. The urine levels probably reflect the inflammation not only localized in prostate but in pelvic floor muscle as well.

These results demonstrate that chemokines are better biomarker candidates than the cytokines TNF-α or IL-1β that have been previously measured only in seminal plasma[10]. Chemokines are the downstream member of the inflammation cascade[20,24] and are therefore produced in copious amounts[6] which explains their substantial presence in urine of CP/CPPS patients (Figure 1). Very small amounts of TNF-α have been detected previously in urine[22] and very low levels of IL-6 and VEGF (Figure 3) were detected in one or two patients of our study. Possibly the secretion of IL-6 and VEGF is just enough from the inflamed site to bind with receptors in nearby tissue and not available for release into urine of other patients. Unlike PDGF, VEGF was only detected in urine of 3 patients at various time points, which is probably related to the differences in expression of cognate receptors of two growth factors at inflamed site leading to trapping of secreted VEGF within the tissue.

These findings show the promise of urinary chemokines for monitoring disease activity of CP/CPPS and objectively evaluate the response to therapeutic intervention. The present study was limited by small size of the cohort and incomplete adherence to treatment in some patients; nevertheless these results can build the framework for a larger prospective longitudinal study to investigate the causal relationship of these chemokines with patient symptoms. Perhaps, urine may be able to serve as a non-surgical diagnostic tool for prostate disease in the future.

In conclusion, a major finding of our study is the successful longitudinal measurement of chemokines in urine of CP/CPPS patients instead of seminal plasma and objective urine chemokines data strongly correlated with subjective symptom scores in treatment adherent patients. Urine levels of chemokines such as CXCL-10, CCL2 and PDGF can be sensitive, objective and non-invasive biomarkers for monitoring patient response to novel therapy in CP/CPPS. The study also offers insight into the mechanisms underlying the benefit from Apremilast in CP/CPPS.

COMMENTS

Background

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a poorly understood and prevalent male condition that is described by genital or pelvic pain in the absence of demonstrable urinary or genital tract infection.

Research frontiers

Unlike NIH category Ⅰ and Ⅱ prostatitis, the pathophysiology of category Ⅲ (CP/CPPS) is an enigma and may not be as organ (prostate) centric as categories Ⅰ and Ⅱ. With progression of symptom severity, CP/CPPS may evolve into regional pain syndrome with symptoms resembling interstitial cystitis, which necessitates the search for objective tools to assist in differential diagnosis and treatment.

Innovations and breakthroughs

The significant inflammatory component in CP/CPPS can be leveraged as a target for symptomatic drug treatment and paracrine messengers mediating inflammation can be tracked in non-invasive bio-fluids as objective surrogate markers.

Applications

Data described here can be the basis of a large scale clinical study to assess the potential of identified chemokines as treatment surrogates and for basic research to understand the biological significance of identified chemokines.

Terminology

CP/CCPS is chronic prostatitis or chronic pelvic pain syndrome also called NIH category III prostatitis.

Peer-review

Available papers on urine analysis of CP/CPPS patients without prostate massage are scarce. Authors are first analyze the urine from a longitudinal study uncover their potential as non-invasive biomarkers for CP/CPPS.

REFERENCES

1 **Nickel JC**, Tripp DA, Chuai S, Litwin MS, McNaughton-Collins M, Landis JR, Alexander RB, Schaeffer AJ, O'Leary MP, Pontari MA, White P, Mullins C, Nyberg L, Kusek J. Psychosocial variables affect the quality of life of men diagnosed with chronic prostatitis/chronic pelvic pain syndrome. *BJU Int* 2008; **101**: 59-64 [PMID: 17924985 DOI: 10.1111/j.1464-410X.2007.07196.x]

2 **Nickel JC**, Alexander RB, Anderson R, Berger R, Comiter CV, Datta NS, Fowler JE, Krieger JN, Landis JR, Litwin MS, McNaughton-Collins M, O'Leary MP, Pontari MA, Schaeffer AJ, Shoskes DA, White P, Kusek J, Nyberg L. Category III chronic prostatitis/chronic pelvic pain syndrome: insights from the National Institutes of Health Chronic Prostatitis Collaborative Research Network studies. *Curr Urol Rep* 2008; **9**: 320-327 [PMID: 18765132 DOI: 10.1007/s11934-008-0055-7]

3 **Pontari MA**. Chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: are they related? *Curr Urol Rep* 2006; **7**: 329-334 [PMID: 16930505]

4 **Anothaisintawee T**, Attia J, Nickel JC, Thammakraisorn S, Numthavaj P, McEvoy M, Thakkinstian A. Management of chronic prostatitis/chronic pelvic pain syndrome: a systematic review and network meta-analysis. *JAMA* 2011; **305**: 78-86 [PMID: 21205969 DOI: 10.1001/jama.2010.1913]

5 **Pérez de Lema G**, Maier H, Nieto E, Vielhauer V, Luckow B, Mampaso F, Schlöndorff D. Chemokine expression precedes inflammatory cell infiltration and chemokine receptor and cytokine expression during the initiation of murine lupus nephritis. *J Am Soc Nephrol* 2001; **12**: 1369-1382 [PMID: 11423566]

6 **Tyagi P**, Killinger K, Tyagi V, Nirmal J, Chancellor M, Peters K. Urinary chemokines as Non-Invasive predictors of Ulcerative interstitial cystitis. *J Urol* 2012; **187**: 2

7 **Lagente V**, Martin-Chouly C, Boichot E, Martins MA, Silva PM. Selective PDE4 inhibitors as potent anti-inflammatory drugs for the treatment of airway diseases. *Mem Inst Oswaldo Cruz* 2005; **100** Suppl 1: 131-136 [PMID: 15962112]

8 **Buenestado A**, Grassin-Delyle S, Guitard F, Naline E, Faisy C, Israël-Biet D, Sage E, Bellamy JF, Tenor H, Devillier P. Roflumilast inhibits the release of chemokines and TNF-α from human lung macrophages stimulated with lipopolysaccharide. *Br J Pharmacol* 2012; **165**: 1877-1890 [PMID: 21913898 DOI: 10.1111/j.1476-5381.2011.01667.x]

9 **McLennan GP**, Khourdaji I, Killinger KA, Boura JA, Peters KM. Apremilast in the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Pilot Study. *Low Urin Tract Symptoms* 2012; **4**: 140-143 [PMID: 26676621 DOI: 10.1111/j.1757-5672.2012.00150.x]

10 **Miller LJ**, Fischer KA, Goralnick SJ, Litt M, Burleson JA, Albertsen P, Kreutzer DL. Nerve growth factor and chronic prostatitis/chronic pelvic pain syndrome. *Urology* 2002; **59**: 603-608 [PMID: 11927336]

11 **Watanabe T**, Inoue M, Sasaki K, Araki M, Uehara S, Monden K, Saika T, Nasu Y, Kumon H, Chancellor MB. Nerve growth factor level in the prostatic fluid of patients with chronic prostatitis/chronic pelvic pain syndrome is correlated with symptom severity and response to treatment. *BJU Int* 2011; **108**: 248-251 [PMID: 20883485 DOI: 10.1111/j.1464-410X.2010.09716.x]

12 **John H**, Barghorn A, Funke G, Sulser T, Hailemariam S, Hauri D, Joller-Jemelka H. Noninflammatory chronic pelvic pain syndrome: immunological study in blood, ejaculate and prostate tissue. *Eur Urol* 2001; **39**: 72-78 [PMID: 11173942]

13 **Kabelitz D**, Wesch D. Features and functions of gamma delta T lymphocytes: focus on chemokines and their receptors. *Crit Rev Immunol* 2003; **23**: 339-370 [PMID: 15030305]

14 **Luster AD**. Chemokines--chemotactic cytokines that mediate inflammation. *N Engl J Med* 1998; **338**: 436-445 [PMID: 9459648 DOI: 10.1056/NEJM199802123380706]

15 **Qin S**, Rottman JB, Myers P, Kassam N, Weinblatt M, Loetscher M, Koch AE, Moser B, Mackay CR. The chemokine receptors CXCR3 and CCR5 mark subsets of T cells associated with certain inflammatory reactions. *J Clin Invest* 1998; **101**: 746-754 [PMID: 9466968 DOI: 10.1172/JCI1422]

16 **Penna G**, Mondaini N, Amuchastegui S, Degli Innocenti S, Carini M, Giubilei G, Fibbi B, Colli E, Maggi M, Adorini L. Seminal plasma cytokines and chemokines in prostate inflammation: interleukin 8 as a predictive biomarker in chronic prostatitis/chronic pelvic pain syndrome and benign prostatic hyperplasia. *Eur Urol* 2007; **51**: 524-533; discussion 533 [PMID: 16905241]

17 **Thumbikat P**, Shahrara S, Sobkoviak R, Done J, Pope RM, Schaeffer AJ. Prostate secretions from men with chronic pelvic pain syndrome inhibit proinflammatory mediators. *J Urol* 2010; **184**: 1536-1542 [PMID: 20723928 DOI: 10.1016/j.juro.2010.05.086]

18 **Propert KJ**, McNaughton-Collins M, Leiby BE, O'Leary MP, Kusek JW, Litwin MS. A prospective study of symptoms and quality of life in men with chronic prostatitis/chronic pelvic pain syndrome: the National Institutes of Health Chronic Prostatitis Cohort study. *J Urol* 2006; **175**: 619-623; discussion 623 [PMID: 16407009]

19 **Motrich RD**, Maccioni M, Riera CM, Rivero VE. Autoimmune prostatitis: state of the art. *Scand J Immunol* 2007; **66**: 217-227 [PMID: 17635799 DOI: 10.1111/j.1365-3083.2007.01971.x]

20 **Antoniou KM**, Tzanakis N, Tzortzaki EG, Malagari K, Koutsopoulos AV, Alexandrakis M, Wells AU, Siafakas NM. Different angiogenic CXC chemokine levels in bronchoalveolar lavage fluid after interferon gamma-1b therapy in idiopathic pulmonary fibrosis patients. *Pulm Pharmacol Ther* 2008; **21**: 840-844 [PMID: 18644457 DOI: 10.1016/j.pupt.2008.06.005]

21 **Luster AD**, Cardiff RD, MacLean JA, Crowe K, Granstein RD. Delayed wound healing and disorganized neovascularization in transgenic mice expressing the IP-10 chemokine. *Proc Assoc Am Physicians* 1998; **110**: 183-196 [PMID: 9625525]

22 **Sadeghi M**, Daniel V, Naujokat C, Weimer R, Opelz G. Strikingly higher interleukin (IL)-1alpha, IL-1beta and soluble interleukin-1 receptor antagonist (sIL-1RA) but similar IL-2, sIL-2R, IL-3, IL-4, IL-6, sIL-6R, IL-10, tumour necrosis factor (TNF)-alpha, transforming growth factor (TGF)-beta and interferon IFN-gamma urine levels in healthy females compared to healthy males: protection against urinary tract injury? *Clin Exp Immunol* 2005; **142**: 312-317 [PMID: 16232218]

23 **Burke SM**, Issekutz TB, Mohan K, Lee PW, Shmulevitz M, Marshall JS. Human mast cell activation with virus-associated stimuli leads to the selective chemotaxis of natural killer cells by a CXCL8-dependent mechanism. *Blood* 2008; **111**: 5467-5476 [PMID: 18424663 DOI: 10.1182/blood-2007-10-118547]

24 **Tessier PA**, Naccache PH, Clark-Lewis I, Gladue RP, Neote KS, McColl SR. Chemokine networks in vivo: involvement of C-X-C and C-C chemokines in neutrophil extravasation in vivo in response to TNF-alpha. *J Immunol* 1997; **159**: 3595-3602 [PMID: 9317159]

25 **Nadler RB**, Collins MM, Propert KJ, Mikolajczyk SD, Knauss JS, Landis JR, Fowler JE, Schaeffer AJ, Alexander RB. Prostate-specific antigen test in diagnostic evaluation of chronic prostatitis/chronic pelvic pain syndrome. *Urology* 2006; **67**: 337-342 [PMID: 16442595]

26 **Ley K**. Arrest chemokines. *Microcirculation* 2003; **10**: 289-295 [PMID: 12851646]

27 **Zhang N**, Rogers TJ, Caterina M, Oppenheim JJ. Proinflammatory chemokines, such as C-C chemokine ligand 3, desensitize mu-opioid receptors on dorsal root ganglia neurons. *J Immunol* 2004; **173**: 594-599 [PMID: 15210821]

28 **Jung H**, Toth PT, White FA, Miller RJ. Monocyte chemoattractant protein-1 functions as a neuromodulator in dorsal root ganglia neurons. *J Neurochem* 2008; **104**: 254-263 [PMID: 17944871 DOI: 10.1111/j.1471-4159.2007.04969.x]

29 **Bhangoo S**, Ren D, Miller RJ, Henry KJ, Lineswala J, Hamdouchi C, Li B, Monahan PE, Chan DM, Ripsch MS, White FA. Delayed functional expression of neuronal chemokine receptors following focal nerve demyelination in the rat: a mechanism for the development of chronic sensitization of peripheral nociceptors. *Mol Pain* 2007; **3**: 38 [PMID: 18076762 DOI: 10.1186/1744-8069-3-38]

30 **Krzystek-Korpacka M**, Neubauer K, Matusiewicz M. Platelet-derived growth factor-BB reflects clinical, inflammatory and angiogenic disease activity and oxidative stress in inflammatory bowel disease. *Clin Biochem* 2009; **42**: 1602-1609 [PMID: 19679116 DOI: 10.1016/j.clinbiochem.2009.08.002]

31 **Barcelos LS**, Coelho AM, Russo RC, Guabiraba R, Souza AL, Bruno-Lima G, Proudfoot AE, Andrade SP, Teixeira MM. Role of the chemokines CCL3/MIP-1 alpha and CCL5/RANTES in sponge-induced inflammatory angiogenesis in mice. *Microvasc Res* 2009; **78**: 148-154 [PMID: 19427874 DOI: 10.1016/j.mvr.2009.04.009]

P- Reviewer: Cai T, Schatz F, Slobedman B **S- Editor**: Qiu S
L- Editor: A **E- Editor**: Lu YJ

World Journal of Clinical Urology

Submit a Manuscript: http://www.wjgnet.com/esps/ *World J Clin Urol* 2017 March 24; 6(1): 27-29

DOI: 10.5410/wjcu.v6.i1.27 ISSN 2219-2816 (online)

CASE REPORT

Classical seminoma in a 92-year-old patient

Catharine Denning, Li June Tay, James Carton, Kaka Hama Attar

Catharine Denning, Li June Tay, James Carton, Kaka Hama Attar, Department of Urology, Chelsea and Westminster Hospital, London SW10 9NH, United Kingdom

Author contributions: The manuscript is original work of all authors; all authors made a significant contribution to this study; all authors have read and approved the final version of the manuscript; the principal author of this report is Denning C; Denning C also collected the majority of patient information and data; Tay LJ helped collect data and reviewed the writing of this case report; Carton J provided his expert histopathological opinion on this case and provided specimen histopathology slide pictures; Attar KH was the consultant in charge of this patient's case; he provided his expert opinion and was the over-all reviewer and consultant in the writing of this report.

Institutional review board statement: Chelsea and Westminster Review Board.

Informed consent statement: N/A, patient deceased with no next of kin.

Conflict-of-interest statement: The manuscript is being submitted by me, Dr. Catharine Denning on behalf of all the authors. This manuscript has not been submitted for publication; it has not been accepted for publication and has not been published in any other journal. There is no conflict of interest from any author, including but not limited to commercial, personal, political, intellectual, or religious interests.

Manuscript source: Invited manuscript

Correspondence to: Dr. Catharine Denning, Department of Urology, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, United Kingdom. drcdenning@gmail.com
Telephone: +44-7795-387870

Received: August 17, 2016
Peer-review started: August 18, 2016
First decision: September 6, 2016
Revised: December 8, 2016
Accepted: December 27, 2016
Article in press: December 29, 2016
Published online: March 24, 2017

Abstract

Seminoma is a germ cell tumour which primarily affects the testes. Seminomas are treated by orchidectomy with usually excellent outcomes. We report the occurrence of a classical seminoma in a 92-year-old man, who is currently the oldest patient with this histology reported in literature. He presented with a painful, swollen testis. Scrotal ultrasound scan revealed a testicular mass. A left inguinal orchidectomy was carried out and histological examination confirmed the diagnosis of a classical seminoma. Further staging by computerised tomography revealed pulmonary lesions suspicious of metastases. The patient declined further treatment in view of his age and co-morbidities.

Key words: Urology; Geriatrics; Seminoma; Medical oncology

Core tip: This is the first case in the literature which describes the occurrence of such a tumour in patients over the age of 90 and should raise the index of suspicion for malignant testicular tumours in elderly patients where infectious causes of testicular swellings are by far the most common.

Denning C, Tay LJ, Carton J, Attar KH. Classical seminoma in a 92-year-old patient. *World J Clin Urol* 2017; 6(1): 27-29 Available from: URL: http://www.wjgnet.com/2219-2816/full/v6/i1/27.htm DOI: http://dx.doi.org/10.5410/wjcu.v6.i1.27

INTRODUCTION

We would like to introduce the first case in the literature which describes the occurrence of a testicular seminoma in patients over the age of 90 and we hope that this presentation will educate the future doctors to raise the index of suspicion for malignant testicular tumours in elderly patients where infectious causes of testicular swellings are by far the most common.

CASE REPORT

A 92-year-old man presented with a 4 wk history of a left painful swollen scrotal mass, initially to his General Practitioner (GP), and subsequently to the emergency department. His medical history included alcoholic liver disease, oesophageal varices, chronic obstructive airway disease, and a cardiac pacemaker. Scrotal ultrasound scan showed a 4cm heterogeneous vascular testicular mass. Laboratory tests revealed normal levels of serum alpha feta protein (AFP) (2 kU/L) βhCG (< 2 iU/L) and lactate dehydrodgense (LDH) (59 iU/L). Left inguinal orchidectomy was performed in view of the suspicious findings. Macroscopic histopathological examination revealed a well-circumscribed pale grey mass measuring 6.5 cm with central necrosis. Histological sectioning showed sheets of large polygonal cells (Figure 1) which stained positively for Oct-3/4 (Figure 2) and placental alkaline phosphatase (PLAP). These findings were consistent with a diagnosis of classical seminoma with no evidence of intratubular germ cell neoplasia. The tumour had not breached the tunica vaginalis nor involved the spermatic cord. A staging computerised tomography (CT) scan revealed diffuse pulmonary metastases, a collapse fracture of the 12th thoracic vertebra and severe ascites (secondary to chronic liver disease). The patient declined further intervention including oncological input in view of his age and co-morbidities. He died 6 wk later but a post mortem was not carried out.

DISCUSSION

Testicular cancer is the 16th most common cancer in men in the United Kingdom. It accounts for 1% of all new cases of male cancer. Between 2009 and 2011, 84% of testicular cancer cases were diagnosed in men aged 15-49 years in the United Kingdom; only 6% occurred in patients aged over 60[1]. The incidence of testicular cancer in patients older than 85 is only 2.4 per 100000. Ninety-five percent of testicular tumours are germ cell tumours (GCTs), which includes seminomas (40%-45%) and non-seminomas (55%-60%). GCTs develop from a non-invasive lesion called carcinoma *in situ* (CIS) of the testis (ITGCN), whose malignant transformation is likely to be influenced by hormones at or after puberty[2]. Seminoma rarely occurs in the adolescent or infant population and the peak age of incidence is between aged 35-39 years with less than 10% being diagnosed after the age of 50[3]. A large study in 2008 revealed an 86-year-old patient with spermatocytic seminoma[4] while a recent case report describes spermatocytic seminoma in a 92-year-old.

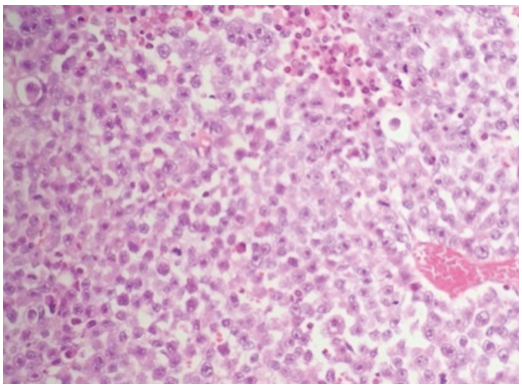

Figure 1 Sheets of seminoma cells with vesicular nuclei containing prominent nucleoli (H and E × 100).

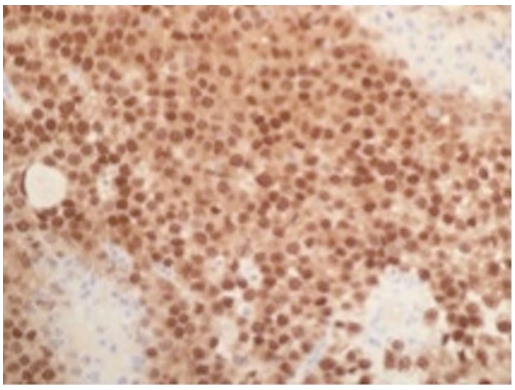

Figure 2 Oct-4 immunohistochemistry showing positive nuclear expression in tumour cells.

Malignant testicular lumps are usually painless, and hence the presentation of seminoma as a painful, swollen testis is unusual[5]. Differential diagnosis in a 92-year-old patient with a painful lump in the testicle would include orchitis, epididymitis, or an abscess, especially if accompanied by symptoms of systemic infection. Testicular torsion is also possible, but this is most common in the second and third decades of life and presents acutely. A persistent processus vaginalis may lead to a hydrocele or an indirect inguinal hernia, and a painful strangulated hernia or hydrocele can present at any age[6]. This is often accompanied by abdominal pain, nausea, and vomiting all of which were absent in this patient.

Serum tumour markers may detect the presence of a testicular seminoma. Serum AFP is not raised in classical seminoma and serum β human Chorionic Gonadotrophin is elevated in only 10%-20%. PLAP is positive in 50% of cases, but has a low sensitivity in smokers, and on its own, has a limited use in the diagnosis of testicular cancer[7]. LDH may be elevated in seminomas and usually has some prognostic value in later stages[8].

It remains uncertain as to why this gentleman only

presented to his GP after four weeks. Perhaps a limited awareness of sinister causes of testicular lumps or apprehension to accessing care may have led to this delay. Patient education is of key importance, not only to highlight symptoms to be aware of but also to reiterate the importance of early presentation.

This is a rare case of classical seminoma in a 92-year-old, which we believe is the oldest patient in the literature. Testicular cancer should remain within the differential diagnoses of an elderly patient presenting with a testicular swelling, even if their symptoms are atypical. Education of the general public should highlight the importance of urgent access to medical care when faced with symptoms of a testicular swelling.

COMMENTS

Case characteristics

Elderly gentleman with a painful, swelling in his left testicle.

Clinical diagnosis

Four centimeter tender, scrotal mass in left testicle.

Differential diagnosis

A combination of ultrasound, blood markers and histopathology following orchidectomy allowed us to exclude orchitis, epididymitis, abscess testicular torsion persistent and processus vaginalis to conclude that the cause of these symptoms was a seminoma.

Laboratory diagnosis

Laboratory tests revealed normal levels of serum alpha feta protein (2 kU/L) βhCG (< 2 iU/L) and lactate dehydrodgense (59 iU/L).

Imaging diagnosis

Scrotal ultrasound scan showed a 4 cm heterogeneous vascular testicular mass alongside a staging computerised tomography scan which revealed diffuse pulmonary metastases, a collapse fracture of the 12th thoracic vertebra and severe.

Pathological diagnosis

Histological sectioning of the mass showed sheets of large polygonal cells which stained positively for Oct-3/4 and placental alkaline phosphatase which was consistent with seminoma.

Treatment

The patient declined treatment following orchidectomy.

Related reports

Please provide other contents related to the case report to help readers better understand the present case.

Experiences and lessons

Testicular cancer should remain within the differential diagnoses of an elderly patient presenting with a testicular swelling, even if their symptoms are atypical. Education of the general public should highlight the importance of urgent access to medical care when faced with symptoms of a testicular swelling.

Peer-review

This is a well written case report on a seminoma in a 92-year-old patient. It is an interesting report, since the vast majority of seminomas occur at a much earlier age.

REFERENCES

1 **Office for National Statistics**. Testicular incidence by age. [accessed 2014 Oct 10]. Available from: URL: http://www.ons.gov.uk/ons/search/index.html?newquery=cancer registrations

2 **Rajpert-De Meyts E**, Bartkova J, Samson M, Hoei-Hansen CE, Frydelund-Larsen L, Bartek J, Skakkebaek NE. The emerging phenotype of the testicular carcinoma in situ germ cell. *APMIS* 2003; **111**: 267-278; discussion 278-279 [PMID: 12752272 DOI: 10.1034/j.1600-0463.2003.11101301.x]

3 **Townsend JS**, Richardson LC, German RR. Incidence of testicular cancer in the United States, 1999-2004. *Am J Mens Health* 2010; **4**: 353-360 [PMID: 20031937 DOI: 10.1177/1557988309356101]

4 **Berney DM**, Warren AY, Verma M, Kudahetti S, Robson JM, Williams MW, Neal DE, Powles T, Shamash J, Oliver RT. Malignant germ cell tumours in the elderly: a histopathological review of 50 cases in men aged 60 years or over. *Mod Pathol* 2008; **21**: 54-59 [PMID: 17975539 DOI: 10.1038/modpathol.3800978]

5 **Horwich A**, Shipley J, Huddart R. Testicular germ-cell cancer. *Lancet* 2006; **367**: 754-765 [PMID: 16517276 DOI: 10.1016/S0140-6736(06)68305-0]

6 **Kraft BM**, Kolb H, Kuckuk B, Haaga S, Leibl BJ, Kraft K, Bittner R. Diagnosis and classification of inguinal hernias. *Surg Endosc* 2003; **17**: 2021-2024 [PMID: 14577028 DOI: 10.1007/s00464-002-9283-y]

7 **Doherty AP**, Bower M, Christmas TJ. The role of tumour markers in the diagnosis and treatment of testicular germ cell cancers. *Br J Urol* 1997; **79**: 247-252 [PMID: 9052477 DOI: 10.1046/j.1464-410X.1997.27517.x]

8 **Mencel PJ**, Motzer RJ, Mazumdar M, Vlamis V, Bajorin DF, Bosl GJ. Advanced seminoma: treatment results, survival, and prognostic factors in 142 patients. *J Clin Oncol* 1994; **12**: 120-126 [PMID: 7505805]

P- Reviewer: Crea F, Mehdi I, Romani A **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Clinical Urology

Submit a Manuscript: http://www.wjgnet.com/esps/

World J Clin Urol 2017 March 24; 6(1): 30-33

DOI: 10.5410/wjcu.v6.i1.30

ISSN 2219-2816 (online)

CASE REPORT

Radical cystectomy and *en-bloc* resection of enterovesical fistula from bladder cancer

Zi Qin Ng, Willy KW Low, Sathiyananthan Jr, Pradeep Subramanian, Joel Stein

Zi Qin Ng, Willy KW Low, Pradeep Subramanian, Joel Stein, Department of General Surgery, Royal Perth Hospital, Perth 6000, Australia

Sathiyananthan Jr, Department of Urology, Royal Perth Hospital, Perth 6000, Australia

Author contributions: Ng ZQ designed the study, analyzed the data and drafted the article; Low WKW, Jr S and Subramanian P critically reviewed the article; Stein J co-designed the study, critically revised the article; Ng ZQ, Low WKW, Jr S, Subramanian P and Stein J approved final version of the article to be published.

Institutional review board statement: This study does not require an approval from the institutional review board.

Informed consent statement: Written consent was obtained from the patient prior to submission of the article.

Conflict-of-interest statement: Nil.

Manuscript source: Unsolicited manuscript

Correspondence to: Zi Qin Ng, MBBS (Hons), Department of General Surgery, Royal Perth Hospital, Wellington Street, Perth 6000, Australia. kentng@hotmail.co.uk
Telephone: +61-8-92242244
Fax: +61-8-92243511

Received: December 23, 2016
Peer-review started: December 28, 2016
First decision: January 16, 2017
Revised: January 21, 2017
Accepted: February 20, 2017
Article in press: February 21, 2017

Published online: March 24, 2017

Abstract

Enterovesical fistulae secondary to benign or malignant bowel disease are not uncommonly reported in the literature. However, bladder malignancy as the primary pathology is exceedingly rare. We report a case of muscle invasive urothelial carcinoma of bladder with an enterovesical fistula to a loop of small bowel. The patient first presented with signs and symptoms of per rectal bleeding, haematuria, pneumaturia, faecaluria and rectal micturition. Her initial biochemistry test revealed significant metabolic acidosis with normal anion gap and hypokalemia. A computed tomography abdomen/pelvis with rectal contrast demonstrated an enterovesical fistula from the dome of bladder to a loop of small bowel. The patient underwent radical cystectomy with *en-bloc* resection of a loop of involved ileum and sigmoid colon due to the intraoperative findings of the sigmoid colon adherent to the tumour. The published literature is reviewed, focusing on the incidence, diagnostic modality and treatment strategies available for this rare condition.

Key words: Bladder cancer; Enterovesical fistula; *En-bloc* resection; Malignant fistula; Urothelial carcinoma

Core tip: A 68-year-old lady presented with per rectal bleeding and haematuria. Other important history includes her reporting diarrhea with associated weight loss over the last 3 mo and faecaluria, pneumaturia and rectal micturition. On presentation, she was found to be in severe metabolic acidosis with hypokalemia. A computed tomography scan with rectal contrast showed an enterovesical fistula from bladder to a loop of small bowel. She underwent radical cystectomy, *en-bloc* resection of a

loop of the involved small bowel and sigmoid colon with formation of ileal conduit and end-colostomy.

Ng ZQ, Low WKW, Jr S, Subramanian P, Stein J. Radical cystectomy and *en-bloc* resection of enterovesical fistula from bladder cancer. *World J Clin Urol* 2017; 6(1): 30-33 Available from: URL: http://www.wjgnet.com/2219-2816/full/v6/i1/30.htm DOI: http://dx.doi.org/10.5410/wjcu.v6.i1.30

INTRODUCTION

Enterovesical fistulae (EVF) are not uncommon in the setting of colonic diseases such as inflammation and malignancy. Nevertheless, EVF secondary to a primary urological malignancy is extremely rare with an estimated incidence of 0.5 per 100000[1]. We herein report a patient who presented initially with per rectal bleeding and haematuria and metabolic acidosis with normal anion gap. During the work-up, an EVF was found caused by a urothelial carcinoma of the bladder.

CASE REPORT

A 68-year-old female presented with per rectal (PR) bleeding and haematuria. She had been suffering from diarrhea and with associated 10 kg of weight loss within the last three months, and was profoundly hypokalaemic on presentation (potassium 2.4 mmol/L). She had also reported faecaluria, pneumaturia and recently noticed that she had been passing urine through the rectum. However, she denied any symptoms of recurrent urinary tract infections. A cystoscopy done 4 years previously for investigation of haematuria found an erythematous and velvety patch on the posterior bladder wall which was biopsied at the time and only showed chronic inflammation with no evidence of malignancy. Urine cytology was also negative for malignancy.

On examination, her vital signs were stable and she was afebrile. Her abdomen was soft with mild generalized tenderness. PR examination was unremarkable. Biochemical tests revealed metabolic acidosis with normal anion gap (pH 7.13, bicarbonate 10 mmol/L, hypokalemia and iron deficiency anaemia. The initial unenhanced computed tomography (CT) scan revealed a bladder fistula with possible communication to large bowel. She underwent a colonoscopy which did not show any colonic pathology or evidence of a colovesical fistula. A subsequent CT abdomen/pelvis with rectal contrast showed an EVF from dome of bladder to mid-to-distal ileum (Figure 1). At cystoscopy, the EVF was confirmed to be involving the posterior wall of the bladder within close proximity of the trigone and the right ureteric orifice.

Total parenteral nutrition was initiated to optimize her pre-operatively. A midline laparotomy was performed. Intraoperatively, an EVF was found 15 cm from terminal ileum with the sigmoid colon adherent to bladder

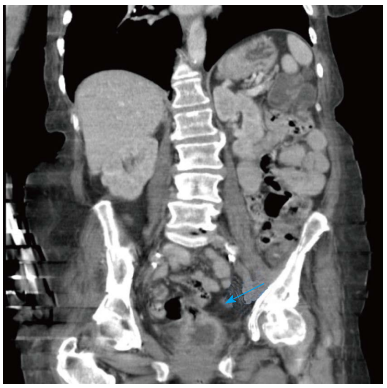

Figure 1 Computed tomography abdomen/pelvis demonstrating the enterovesical fistula from dome of bladder to terminal ileum (arrow).

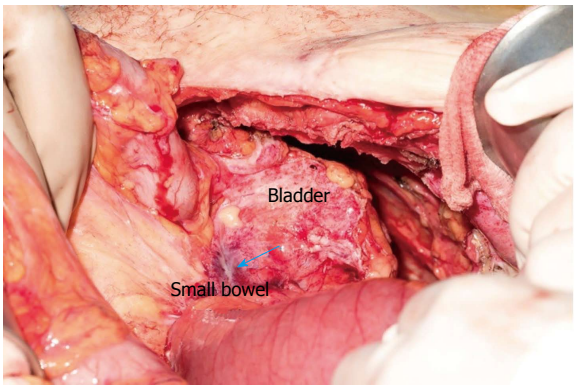

Figure 2 An enterovesical fistula is demonstrated (arrow) intraoperatively.

(Figure 2). Decision was made to perform an *en-bloc* radical cystectomy, small bowel resection and sigmoid colectomy with formation of both an ileal conduit and end colostomy (Figure 3). Histopathology confirmed a high-grade urothelial carcinoma with extensive squamous differentiation. There was significant tumour infiltration to the sigmoid colon but there was no evidence of a colovesical fistula.

DISCUSSION

An enterovesical fistula is an abnormal tract between the epithelialized surface of bowel and the bladder. They are considered a difficult complication of various causes such as inflammation (52%), malignancy (35%) and trauma (16%)[2]. Only a few cases of primary urological EVF have been described in the literature[3-6]. In a series of 100 cases of EVFs, the majority of cases were secondary to an inflammatory bowel condition (61%) and bowel cancer (16%); only 5% were due to bladder carcinoma[6]. The classical symptoms and signs described in the literature include pneumaturia, faecaluria and haematuria as shown in our case[7]. Refractory urinary tract infections[7] were not present in our case. The low intravesical bladder pressure favours unidirectional flow of bowel contents into the bladder. Infrequently, rectal micturition can occur and is reported to be approximately

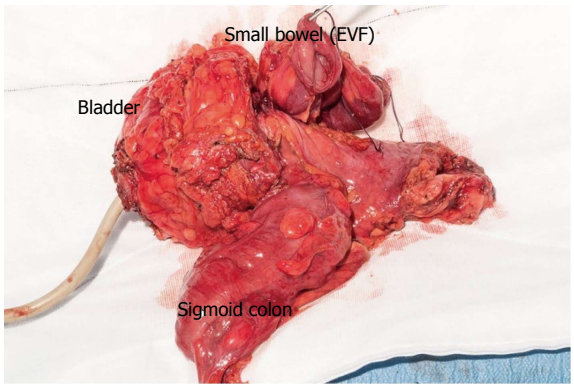

Figure 3 *En-bloc* resection including radical cystectomy, small bowel resection and sigmoid colectomy. EVF: Enterovesical fistulae.

19% of cases[7]. They may also have a constellation of symptoms such as suprapubic pain, frequency, dysuria and tenesmus, known as Gouverneur syndrome.

The diagnosis of EVF usually relies on a high index of suspicion. Metabolic acidosis with normal anion gap could be indicative of this condition due to loss of bicarbonate or a reduction of renal acid excretion as shown in our case. Typically, this occurs in patients with chronic diarrhea or prolonged exposure of urine to colonic/ileal mucosa[8]. There is no consensus for a diagnostic algorithm. Various diagnostic studies can be considered such as CT scan, MRI, barium enema, cystogram, cystoscopy and colonoscopy. CT and MRI have the advantages of helping in pre-operative planning by clearly defining the fistulous tract and its anatomic relationship with adjacent structures. The distinguishing features on CT scan are air or contrast within the bladder, thickening of bladder wall, or an extraluminal gas-containing mass adjacent to the bladder[9]. A cystoscopy has a diagnostic sensitivity that ranges from 77% to 79%[4] and is usually performed to obtain biopsies from the fistulous tract for histological evaluation. The initial signs under cystoscopy examination maybe subtle, with only a hyperemic area noted in the early stage, and with cystic mucosal hyperplasia or localized granulation tissue at the late stage. Hence, in retrospect, our patient may have had early dysplastic changes on her initial cystoscopy four years ago. Alternatively, cystogram or barium enema will be able to demonstrate the presence of fistulous tract with a sensitivity of 66.6% and 20%-35% respectively[5]. Given that some of the symptoms such as pneumaturia, faecaluria and rectal micturition are not uncommon in cases of colovesical fistula caused by inflammatory or malignant bowel disease, colonoscopy is essential to rule out a synchronous colovesical fistula.

EVF due to malignancy carries a very poor prognosis as by definition the tumour is considered a T4 tumour under the TNM classification due to extravesical spread. The optimal treatment remains an area of debate. Surgical treatment is usually offered to patients. *En-bloc* resection of surrounding structures that are adherent to it may be necessary to provide an R0 resection and a multidisciplinary approach thereafter for a combination of adjuvant chemo-radiotherapy to improve progression free survival. In patients with intractable symptoms who are poor surgical candidates, octreotide can be considered as a viable therapeutic option in the palliative setting[10].

EVF from a primary urological malignancy remains rare and a high degree of clinical suspicion is required. Pre-operative optimization of nutrition status is paramount for successful reconstruction. The ideal management is surgical intervention and may involve *en-bloc* resections. A multidisciplinary approach may be required for the best clinical outcome.

COMMENTS

Case characteristics

A 68-year-old lady who presented initially with per rectal bleeding and haematuria was found that she has been suffering from a 3-mo history of diarrhea and more recently she has been troubled by pneumaturia, faecaluria and rectal micturition.

Clinical diagnosis

Pneumaturia, faecaluria and rectal micturition were suggestive of enterovesical fistula.

Differential diagnosis

Colorectal malignancy or inflammatory bowel disease forming a colovesical fistula, inflammatory bowel disease forming an enterovesical fistula.

Laboratory diagnosis

Metabolic acidosis with normal anion gap.

Imaging diagnosis

An enterovesical fistula is seen from the dome of bladder to the terminal ileum.

Pathological diagnosis

A high-grade urothelial carcinoma with extensive squamous differentiation.

Treatment

Radical cystectomy with *en-bloc* resection of a loop of involved ileum and sigmoid colon with ileal conduit and end colostomy formation.

Related reports

Enterovesical fistula due to malignancy carries a very poor prognosis as the tumour is considered a T4 tumour. *En-bloc* resection is usually required to achieve RO resection. If the patient is not a surgical candidate, medical management with octreotide is an alternative palliative option for intractable symptoms.

Term explanation

Enterovesical fistula is an abnormal tract between the epithelialized surface of bowel and the bladder. Enterovesical fistula arising from a primary urological malignancy is extremely rare.

Experiences and lessons

Enterovesical fistula from a primary urological malignancy remains a rare entity and usually requires a high degree of clinical suspicion. Optimization of pre-operative nutritional status is often helpful to achieve good post-operative healing. Often, a multidisciplinary approach involving various subspecialties may need required for the best outcome for the patient.

Peer-review

The case report is well written, clear and concise.

REFERENCES

1 **Karamchandani MC**, West CF. Vesicoenteric fistulas. *Am J Surg* 1984; **147**: 681-683 [PMID: 6721047]
2 **Couris GD**, Block MA. Intestinovesical fistula. *Surgery* 1963; **54**: 736-742 [PMID: 14083579]
3 **Sellers W**, Fiorelli R. Enterovesical Fistula Secondary to Squamous Cell Carcinoma of the Bladder. *Urol Case Rep* 2015; **3**: 201-203 [PMID: 26793552 DOI: 10.1016/j.eucr.2015.06.004]
4 **Dawam D**, Patel S, Kouriefs C, Masood S, Khan O, Sheriff MK. A "urological" enterovesical fistula. *J Urol* 2004; **172**: 943-944 [PMID: 15311004 DOI: 10.1097/01.ju.0000135119.81501.5a]
5 **Yang CH**, Liu KH, Chen TC, Chang PL, Yeh TS. Enterovesical fistula caused by a bladder squamous cell carcinoma. *World J Gastroenterol* 2009; **15**: 4215-4217 [PMID: 19725163 DOI: 10.3748/wjg.15.4215]
6 **Carson CC**, Malek RS, Remine WH. Urologic aspects of vesicoenteric fistulas. *J Urol* 1978; **119**: 744-746 [PMID: 660758]
7 **Vidal Sans J**, Pradell Teigell J, Palou Redorta J, Villagrasa Serrano M, Banús Gassol JM. Review of 31 vesicointestinal fistulas: diagnosis and management. *Eur Urol* 1986; **12**: 21-27 [PMID: 3948896]
8 **Coelho R**, Rodrigues-Pinto E, Cardoso H, Santos-Antunes J, Marques M, Horta e Vale A, Malheiro L, Macedo G. Severe metabolic acidosis: the presenting sign of an enterovesical fistula. *Int J Colorectal Dis* 2016; **31**: 785-786 [PMID: 26105744 DOI: 10.1007/s00384-015-2287-6]
9 **Golabek T**, Szymanska A, Szopinski T, Bukowczan J, Furmanek M, Powroznik J, Chlosta P. Enterovesical fistulae: aetiology, imaging, and management. *Gastroenterol Res Pract* 2013; **2013**: 617967 [PMID: 24348538 DOI: 10.1155/2013/617967]
10 **Shinjo T**, Kondo Y, Harada K, Yamazaki J, Okada M. Treatment of malignant enterovesical fistula with octreotide. *J Palliat Med* 2009; **12**: 965-967 [PMID: 19807246 DOI: 10.1089/jpm.2009.0086]

P- Reviewer: Naselli A, Rais-Bahrami S **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 2219-2816 (online)

World Journal of *Clinical Urology*

World J Clin Urol 2017 July 24; 6(2): 34-50

Published by Baishideng Publishing Group Inc

WJCU

World Journal of Clinical Urology

A peer-reviewed, online, open-access journal of clinical urology

Editorial Board

2016-2019

The *World Journal of Clinical Urology* Editorial Board consists of 201 members, representing a team of worldwide experts in urology. They are from 32 countries, including Australia (2), Austria (1), Belgium (2), Brazil (4), Canada (2), Chile (1), China (19) , Czech Republic (1), Egypt (7), France (3), Germany (7), Greece (7), Hungary (1), India (3), Iran (1), Israel (4), Italy (20), Japan (8), Malaysia (1), Mexico (1), Netherlands (2), Pakistan (3), Portugal (1), Romania (1), Saudi Arabia (3), South Korea (4), Spain (2), Switzerland (1), Thailand (2), Turkey (12), United Kingdom (7), and United States (68).

WJCU

World Journal of Clinical Urology

Contents

Four-monthly Volume 6 Number 2 July 24, 2017

NAME OF JOURNAL
World Journal of Clinical Urology

ISSN
ISSN 2219-2816 (online)

LAUNCH DATE
December 28, 2011

FREQUENCY
Four-monthly

EDITOR-IN-CHIEF
Makoto Ohori, MD, Professor, Department of Urology, Tokyo Medical University, Shinjuku-ku, Tokyo 160-0023, Japan

EDITORIAL BOARD MEMBERS
All editorial board members resources online at http://www.wjgnet.com/2219-2816/editorialboard.htm

EDITORIAL OFFICE
Fang-Fang Ji, Director

World Journal of Clinical Urology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
July 24, 2017

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Clinical Urology

Submit a Manuscript: http://www.f6publishing.com

World J Clin Urol 2017 July 24; 6(2): 34-39

DOI: 10.5410/wjcu.v6.i2.34

ISSN 2219-2816 (online)

MINIREVIEWS

Recirculating chemohyperthermia as a treatment for non-muscle invasive bladder cancer: Current and future perspectives

Javier Flores-Carbajal, Alejandro Sousa-Escandón, Daniel Sousa-Gonzalez, Silvia Rodriguez Gomez, Manuel Lopez Saavedra, M Elia Fernandez Martinez

Javier Flores-Carbajal, Alejandro Sousa-Escandón, Daniel Sousa-Gonzalez, Silvia Rodriguez Gomez, Manuel Lopez Saavedra, M Elia Fernandez Martinez, Comarcal Hospital of Monforte, 27400 Monforte-Lugo, Spain

Author contributions: All authors contributed to the treatment with CHT and follow up of patients assisted in our Hospital; Flores-Carbajal J, Sousa-Escandón A and Sousa-Gonzalez D was involved in writing the manuscript.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Manuscript source: Invited manuscript

Correspondence to: Alejandro Sousa-Escandón, Chief of Service, Comarcal Hospital of Monforte, Curros Enriquez St. 41, 27400 Monforte-Lugo, Spain. sousa-alejandro@hotmail.com
Telephone: +34-607-856407

Received: August 28, 2016
Peer-review started: September 1, 2016
First decision: December 13, 2016
Revised: December 19, 2016
Accepted: March 13, 2017
Article in press: March 15, 2017
Published online: July 24, 2017

Abstract

About 75% of all bladder cancer diagnosed are non-muscle invasive bladder cancer (NMIBC), recurring over 50% of them after transurethral resection of the bladder tumor. In order to prevent recurrences, adjuvant intravesical chemotherapy with mitomycin C and immunotherapy with bacillus Calmette-Guérin (BCG) is traditionally used. Unfortunately, many patients relapse after receiving these treatments and a significant proportion of them require surgery. After a one-to-three years BCG maintenance, the risk for progression at 5 years was 19.3% for T1G3 tumors. Many new treatment approaches are being investigated to increase the effectiveness of adjuvant intravesical therapy. One of the developing treatments for intermediate and high-risk NMIBC is the combination of intravesical chemotherapy and hyperthermia, called chemohyperthermia. This article provides a review of the mechanism of action, current status and indications, results and future perspectives.

Key words: Bladder cancer; Thermotherapy; Non-muscle invasive; Chemohyperthermia; Recirculating; Intravesical chemotherapy; Treatment; Mechanism of action

Core tip: Chemohyperthermia has demonstrated a selective cytotoxicity on tumoral cells without affecting the remaining healthy cells and it significantly increases the penetration of MMC during intravesical instillations. Moreover, hyperthermia and many chemotherapeutic agents have a synergistic effect, significantly reducing the relative risk of tumoral recurrence in patients non-muscle invasive bladder cancer. Recirculative systems are a novel way to apply endovesical chemohyperthermia, which achieves excellent clinical results with a better side effects profile and a lower price than the one of other chemohyperthermia technologies.

Flores-Carbajal J, Sousa-Escandón A, Sousa-Gonzalez D, Rodriguez Gomez S, Lopez Saavedra M, Fernandez Martinez ME. Recirculating chemohyperthermia as a treatment for non-muscle invasive bladder cancer: Current and future perspectives. *World J Clin Urol* 2017; 6(2): 34-39 Available from: URL: http://www.wjgnet.com/2219-2816/full/6/i2/34.htm DOI: http://dx.doi.org/10.5410/wjcu.v6.i2.34

INTRODUCTION

Bladder cancer is the fourth tumor with the highest incidence in men, after lung, prostate and colorectal cancers. About 75% of all bladder cancer diagnosed are non-muscle invasive bladder cancer (NMIBC), recurring over 50% of them after TURBT[1].

In order to prevent recurrences, adjuvant intravesical chemotherapy with MMC and immunotherapy with bacillus Calmette-Guérin (BCG) is traditionally used. Intravesical chemotherapy, with single postoperative or with maintenance protocols, is the common treatment for patients with low and intermediate NMIBC risk[2]. Immunotherapy with BCG is the gold standard treatment for high-risk patients. However, BCG is associated with important side effects as systemic tuberculosis and bladder retraction[3]. Unfortunately, many patients relapse after receiving these treatments and a significant proportion of patients require surgery, therefore, 19% of those patients with T1G bladder cancer, after adjuvant treatment with BCG (1-3 years), progressed after 5 years[4].

Considering the high relapse and progression after the adjuvant treatment, treatment alternatives have been investigated in order to improve the intravesical treatment outcomes. For those patients with intermediate and high NMIBC risk, the combination of intravesical therapy with hypertemia (CHT) has been developed.

To write this paper, we reviewed all major database available on internet (MEDLINE, EMBASE, Cochrane Library, Web of science and ClinicalTrials.gov) including both clinical trials as general reviews.

HYPERTHERMIA

Also called thermotherapy, is a type of therapy for tumors in which the whole body, or part thereof, is subjected to high temperatures (up to 45 ℃). Numerous studies have shown that high temperatures damage and kill cancer cells by preventing the denaturing of their proteins and the DNA repair. However, hyperthermia causes little damage to normal tissue[5,6]. The first clinical experiences in the use of hyperthermia as a treatment for cancer were performed by Coley[7] more than a century ago. Hyperthermia may be applied in different ways, such as a whole body, regional, intracavitary, local, or interstitial hyperthermia. Similarly, sources of heat vary and include microwaves, ultrasound, radiofrequency and recirculating liquid systems.

In bladder tumors, there are two types. One is used in infiltrating cancers and involves the application of external heat on the entire pelvis associating radio or chemotherapy[8] while the other is used in NMIBC, consisting in the intravesical application of heat (through microwaves or recirculation of heated liquids). In this type of treatment, a chemotherapeutic agent is associated to the heat in order to achieve a synergistic effect by using both treatments together which are known as CHT[9].

MECHANISM OF ACTION OF HYPERTHERMIA

The human body has several autonomic mechanisms of regulating body temperature to ranges suitable for normal functioning[10].

Cellular necrosis and apoptosis occurs at a temperature above 40.5 ℃ and cell, molecular and metabolic disorders, also known as HT effect, contribute to this fact[11].

The effect of heat on both normal body cell function and on cancerous cells varies based on the degree of hyperthermia with different cytotoxic, vascular and immune effects (Table 1).

MMC AND HEAT

MMC absorption increases with high temperatures. The absorption thereof is significantly affected by dilution, urinary pH and exposure time. They observed that, with passive instillations, the absorption of the administered dose is less than 30%[12].

In 2001, Paroni *et al*[13] showed that microwave-induced hyperthermia increased considerably the MMC absorption, after 30, 45 and 60 min ($P < 0.008$). It is important to understand that the MMC absorption increase is not only due to increased permeability of the bladder urothelium, but also to a noteworthy increase in solubility. Therefore, while at 25 ℃, the maximum concentration that can get by dissolving 1 g of MMC is 0.8 mg/mL, this value is doubled at 40 ℃ since concentrations are up to 1.7 mg/mL (Data from Kyowa Hakko Kirin Co Ltd.).

It stems from the above that the chemohyperthermia (CHT) is the combination of intravesical chemotherapy and hyperthermia in order to increase efficiency. In summary, the increased cell permeability, the changes in the blood perfusion, and the direct cytotoxic effect, are the reasons why the MMC efficacy increases when it is combined with heat[13,14].

CHEMOHYPERTHERMIA

There are two types of treatment: Adjuvant (intermediate and high-risk NMIBC) and neoadjuvant. To improve the effectivity of intravesical chemotherapy are

Table 1 Mechanisms of action of hyperthermia

	39-41	41-43	43-45
Direct Cytotoxic Effects	Slight growth arrest	Reversible growth arrest Mainly in phase M and S Brief RNA synthesis impaired Prolonged DNA synthesis impaired	Irreversible growth arrest Permanent protein denaturalization DNA repair impaired Activation of both ways of apoptosis
Immune effects	Initial increase of intracellular HSP followed by increase of extracellular HSP Signals to immune cells Cross-priming of $CD8^+$ T cells Dendritic cell activation Natural Killer activation Increase cytosine release (IL-6, IL-10)	As above	Altered cytosine production Inactivation of immune cells Reduced expression of extracellular HSP
Vascular effects	Vasodilatation which means: Improved tumor blood flow Improve tissue O_2 Reduce acidosis Improve drug absorption	Improved tumor blood flow: Improve tumor oxygenation Improve drug delivery	Reduced tumor blood flow due to vascular collapse Microthrombosis Endothelial cell damage Vessel permeation Increased acidosis and reduce tissue O_2

Adapted from Rampersaud *et al*[11]. IL: Interleukin.

used "device assisted", these are fundamentally two: Electromotive drug administration (EMDA) that enhance the absorption of MMC by using iontophoresis. On the other hand, it is the chemohyperthermia (CHT) the one that is based on heating the bladder with the instilled chemotherapeutic drug.

EMDA, CHT and device assisted

EMDA uses an electric current to enhance transepithelial drug penetration. EMDA is administered *via* a battery-powered generator delivering an electric current of 0-30 mA DC at 0-55 V, which is passed between two electrodes: An active electrode is placed into the bladder as part of a transurethral catheter and the dispersive ground electrode pads are placed on the skin of the lower abdomen. EMDA takes advantage of three phenomena: Iontophoresis, electro-osmosis and electroporation. Iontophoresis involves propelling a substance into tissues by passing an electrical current through a solution containing the charged active ingredient[15].

The first CHT system approved for human use was the Synergo™ System. This system has been used for 15 years and has conclusive studies in both neoadjuvant and adjuvant settings. It has proved clinical efficacy in high-risk patients (including BCG failures and CIS). It has demonstrated a 60% reduction of tumoral recurrences when comparing to standard MMC. Moreover, its better results were maintained during time periods up to 10 years.

An alternative way to apply heat to the bladder are those systems based on recirculation of a solution of chemoterapeutic drugs heated externally and reintroduced to the bladder through a triple lumen catheter. Two different devices using this technology are currently available: Combat BRS™ and BWT™ systems, which are based on simple technology, and use cheap disposables that make it attractive for performing CHT in a sustainable public medicine. They both use a triple lumen modified Foley catheter, which are soft and flexible, avoiding most problems related to the urethral catheterization, which appear with other technologies. They both enable the removal of the MMC from the patient in safe disposals without contact to the sanitary staff. They both try to maintain the chemotherapeutic solution at a fixed temperature but there are some differences between them. Main differences about all three devices may be seen in Table 2.

Adjuvant CHT treatment

As described above, most patients with high-risk bladder cancer recur one year after the TURBT[16]. This justifies the study of adjuvant treatment strategies. Colombo *et al*[17] performed a multicenter, prospective and randomized study comparing CHT with MMC and MMC alone, in 42 and 41 patients respectively, as adjuvant treatment after the TURBT. The recurrence rate in the CHT and MMC group was 17.1% *vs* 57% in the other group. The meta-analysis performed by Lammers *et al*[18] found a 59% decrease in recurrences after combined therapy (CHT with MMC) and only 10.6% of patients ended up on radical cystectomy.

In our center[19], there was a recurrence free disease rate of 87.5% in high-risk patients treated with Combat recirculant CHT and to whom a 2-year follow-up was performed. However, Ekin *et al*[20] showed that the recurrence rates of high-risk patients treated with BWT recirculant CHT were 82% and 61% after 1 and 2 years of follow-up.

The first randomized trial comparing CHT *vs* BCG was published by Arends *et al*[16]. They observed a recurrence-free survival after 2 years of follow-up of 78% in the CHT group *vs* 64.8% with BCG ($P < 0.0082$). Progressions were lower than 2% in both groups (P = NS). In another study, the therapy has not been shown to be as effective as the BCG, although this is a

Table 2 Characteristic of devices for intravesical chemohyperthermia treatment

Device	Synergo™	BWT system™	Combat™
Heat Source	Intravesical 915 MHz microwave antenna (Recirculating cooling system)	External heating plates (Recirculating heating system)	External flat, low volume heat exchanger (Recirculating heating system)
Temperature and fluctuation	40 ℃-44 ℃ ± 3 ℃	45 ℃	43.5 ℃ ± 1 ℃
Priming volume	± 100 mL	± 50 mL	± 30 mL
Catheter characteristics	20 Fr. Rigid (Radiofrequency emitter + cooling system inside)	18 Fr Flexible	16 Fr Flexible
Advantages	Strong supporting evidence (*neoadjuvant and adjuvant*) Long term follow up Proved superior to BCG Proved effectiveness against CIS	Simple and Cheap	Lower dilution of MMC Proved effectiveness in sequential schedules Proved neoadjuvant effectiveness Medium term follow up Simple and Cheap
Disadvantages	Higher side effects Lower patient tolerance Intravesical Hot and cold spots Expensive device and disposables Continuous machine control required while working	Limited evidence Quick and Turbulent flow + higher temperature (increase hematuria and reduce patient tolerance)	Limited evidence (multicentric studies ongoing)

BCG: Bacillus Calmette-Guérin.

retrospective study[21,22].

Some comparative studies between patients who have not responded to treatment with BCG *vs* non-previously-treated patients showed better results in the former group. The interim analysis of Lombardia project (unpublished data from R. Colombo, Milan-Italy) showed that, after two years of follow-up, the recurrence-free rates of patients treated with *de novo* CHT were significantly better than those who had previous failed intravesical treatment (91% and 62%, respectively $P < 0.006$). In the same vein, van der Heijden *et al*[23] followed 76 patients treated with CHT during 2 years, observing a 42% recurrence in the group with a previous failed BCG treatment compared to a 24% of recurrences in *de novo* treatment group.

A sequential treatment study by using intravesical BCG and CHT was performed in Leicester United Kingdom to treat 33 high-risk NMIBC patients (including a 40% with Cis) which were followed during a median of 16 mo[24]. Three of them (9%) did not respond and were proposed for radical cystectomy. Two (6%) showed tumoral progression and were treated with radiotherapy. The other 85% of them were disease-free after follow up.

Neodjuvant CHT treatment

Colombo *et al*[25] evaluated the ablative efficacy of neoadjuvant hyperthermia in bladder cancer for the first time in 1998. In that study, 19 patients with NMIBC tumors which were unresectable in a one-stage TURBT in which a cystectomy was indicated, were instead treated with neoadjuvant CHT. After eight doses of hyperthermic MMC per week, a complete TURBT was possible in 16 patients (84%). A histological examination of the specimen showed a tumor absence in 47% (complete response) of the patients and > 50% tumor reduction (partial response) in the other 37%. A cystectomy was performed on the remaining three patients. After an average follow-up of 33 mo, eight superficial recurrences were resected without having to remove the bladder.

Our group published in 2014 a small series of 15 patients treated with eight weekly doses of recirculating neoadjuvant MMC achieving a 66.6% CR and 33% PR. As in the previous case, the beneficial effect of CHT remained in time and, after 3 years of follow-up, only two patients showed recurrences (15%) which were treated with TUR-B and intravesical adjuvant MMC[26]. Lüdecke *et al*[27] reported after TUR-B, 76.1% complete response and 7.6% partial response.

Safety

The CHT Side effects may occur during and after treatment. Arends *et al*[16] analysed the side effects; during the treatment, the most frequent side effects were bladder spasm in 14%, and bladder pain in 11.4%. After the treatment, the most frequent were the dysuria (11.7%) and the increase of the voiding frequency (9.9%).

With the microwave technology, the most common adverse events during treatment were spasms of the bladder (21.6%) and bladder pain (17.5%). Bladder Spasms tend to occur more frequently with neoadjuvant treatment (17.8% *vs* 10.7%, $P = 0.398$)[18]. Similar results were seen with BWT™[20,21] and Combat™[26,28] recirculant systems. Side effects are frequent but almost all cases were stages 1 and 2.

In our experience, with almost 800 recirculant instillations, only 3.1% of doses were delayed and less than 1% were definitely not performed. The main reasons for delaying were infection, hematuria and irritative chemical cystitis. The only reasons for the anticipated end of the treatment were allergy or intolerance to catheterization. Approximately 6% of the doses were interrupted before the 60 min, usually by bladder spasms or pelvic

discomfort[26,28]. Those patients who did not tolerate well the first dose, were orally premedicated with 600 mg of Ibuprofen or antispasmodic treatment depending on whether they had complained of pain or spasms. In selected cases spasmolytic IV were administered during treatment. Both oral medications and IV proved to be effective to achieve a good tolerance in subsequent doses of CHT.

FUTURE PERSPECTIVES

The growing interest in magnetic nanoparticles for biomedical applications stems, in part, from their ability to respond to applied magnetic fields through translation, physical particle rotation or internal dipole rotation. As a result, there is local conversion of magnetic field energy into either mechanical forces and/or thermal energy. Then, if magnetic nanoparticles are placed in contact with the desired tumoral tissue, either by intravesical instillation or systemically, and an alternating magnetic field is applied, the heat dissipation due to the nanoparticles will apply a high thermal dose, which will cause the tumoral cell death.

Magnetic fluid hyperthermia is attractive because of the possibility of developing particles whose physicochemical properties are able to attach selectively tumoral tissues through a combination of the enhanced permeation and retention effect[29-33] and, even better, through the activation through surface ligands[34]. This could result in the localization of nanoparticles in the extracellular matrix surrounding cancer cells, or in the cellular uptake and accumulation in intracellular structures, such as vesicles, endosomes and lysosomes. But these nanoparticles are not only able to deliver heat near the tumor but also chemoterapics which will develop a synergic effect over tumoral cells[35,36].

Moreover, nanoparticles joined to chemotherapics are not the only way to increase synergistic effect of CHT. Experimental work performed by Dr. Inman at Duke University, showed that by delivering intravenous novel heat-activated drugs and heating up the bladder, the activated form of the drug could allow the administration of a dose that is 10 to 30 times higher and free-floating drug, while reducing toxicity from other parts of the body (not published data).

Also of growing interest is the use of hyperthermia in combination with immunotherapy treatments. Heating the body activates the immune system, increasing interactions between immune cells designed to alert the body when it is under attack and mobilizing immune cells such as T and B cells to tissues where they are needed[37,38].

CHT is a concept and a developing technology, which comes to remain, and many of the future strategies against cancer will include this promising therapy.

CONCLUSION

CHT published results in neoadjuvant and adjuvant therapy are encouraging. It is likely that in the future the CHT is an alternative to BCG and MMC therapy.

Current CHT is an option in BCG refractory tumors. Those who are intolerant to BCG are unsuitable for radical cystectomy or in the context of the international BCG shortage. Their uses instead of MMC, both in adjuvant or neoadjuvant protocols, are promising options pending further evaluation.

REFERENCES

1 **Burger M**, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, Kassouf W, Kiemeney LA, La Vecchia C, Shariat S, Lotan Y. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol* 2013; **63**: 234-241 [PMID: 22877502 DOI: 10.1016/j.eururo.2012.07.033]

2 **Tomaszewski JJ**, Smaldone MC. Emerging intravesical therapies for management of nonmuscle invasive bladder cancer. *Open Access J Urol* 2010; **2**: 67-84 [PMID: 24198616]

3 **Meyer JP**, Persad R, Gillatt DA. Use of bacille Calmette-Guérin in superficial bladder cancer. *Postgrad Med J* 2002; **78**: 449-454 [PMID: 12185215 DOI: 10.1136/pmj.78.922.449]

4 **Cambier S**, Sylvester RJ, Collette L, Gontero P, Brausi MA, van Andel G, Kirkels WJ, Silva FC, Oosterlinck W, Prescott S, Kirkali Z, Powell PH, de Reijke TM, Turkeri L, Collette S, Oddens J. EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guérin. *Eur Urol* 2016; **69**: 60-69 [PMID: 26210894 DOI: 10.1016/j.eururo.2015.06.045]

5 **van der Zee J**. Heating the patient: a promising approach? *Ann Oncol* 2002; **13**: 1173-1184 [PMID: 12181239 DOI: 10.1093/annonc/mdf280]

6 **Hildebrandt B**, Wust P, Ahlers O, Dieing A, Sreenivasa G, Kerner T, Felix R, Riess H. The cellular and molecular basis of hyperthermia. *Crit Rev Oncol Hematol* 2002; **43**: 33-56 [PMID: 12098606 DOI: 10.1016/S1040-8428(01)00179-2]

7 **Coley WB**. The Treatment of Inoperable Sarcoma by Bacterial Toxins (the Mixed Toxins of the Streptococcus erysipelas and the Bacillus prodigiosus). *Proc R Soc Med* 1910; **3**: 1-48 [PMID: 19974799]

8 **Dietzel F**. Basic principles in hyperthermic tumor therapy. *Recent Results Cancer Res* 1983; **86**: 177-190 [PMID: 6647999 DOI: 10.1007/978-3-642-82025-0_31]

9 **Falk MH**, Issels RD. Hyperthermia in oncology. *Int J Hyperthermia* 2001; **17**: 1-18 [PMID: 11212876 DOI: 10.1080/02656730150201552]

10 **Sessler DI**. "Thermoregulatory defense mechanisms". *Critical Care Med* 2009; **Supple 37**: 203-210 [PMID: 19535948 DOI: 10.1097/CCM.0b013e3181aa5568]

11 **Rampersaud EN**, Vujaskovic Z, Inman BA. Hyperthermia as a treatment for bladder cancer. *Oncology* (Williston Park) 2010; **24**: 1149-1155 [PMID: 21141697]

12 **Dalton JT**, Wientjes MG, Badalament RA, Drago JR, Au JL. Pharmacokinetics of intravesical mitomycin C in superficial bladder cancer patients. *Cancer Res* 1991; **51**: 5144-5152 [PMID: 1913640]

13 **Paroni R**, Salonia A, Lev A, Da Pozzo LF, Cighetti G, Montorsi F, Rigatti P, Colombo R. Effect of local hyperthermia of the bladder on mitomycin C pharmacokinetics during intravesical chemotherapy for the treatment of superficial transitional cell carcinoma. *Br J Clin Pharmacol* 2001; **52**: 273-278 [PMID: 11560559 DOI: 10.1046/j.0306-5251.2001.01449.x]

14 **van der Heijden AG**, Verhaegh G, Jansen CF, Schalken JA, Witjes JA. Effect of hyperthermia on the cytotoxicity of 4 chemotherapeutic agents currently used for the treatment of transitional cell carcinoma of the bladder: an in vitro study. *J Urol* 2005; **173**: 1375-1380 [PMID: 15758808 DOI: 10.1097/01.ju.0000146274.85012.e1]

15 **Di Stasi SM**, Giannantoni A, Massoud R, Dolci S, Navarra P, Vespasiani G, Stephen RL. Electromotive versus passive diffusion of mitomycin C into human bladder wall: concentration-depth profiles studies. *Cancer Res* 1999; **59**: 4912-4918 [PMID: 10519404]

16 **Arends TJ**, Nativ O, Maffezzini M, de Cobelli O, Canepa G, Verweij F, Moskovitz B, van der Heijden AG, Witjes JA. Results of a Randomised Controlled Trial Comparing Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Guérin for Adjuvant Treatment of Patients with Intermediate- and High-risk Non-Muscle-invasive Bladder Cancer. *Eur Urol* 2016; **69**: 1046-1052 [PMID: 26803476 DOI: 10.1016/j.eururo.2016.01.006]

17 **Colombo R**, Da Pozzo LF, Salonia A, Rigatti P, Leib Z, Baniel J, Caldarera E, Pavone-Macaluso M. Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. *J Clin Oncol* 2003; **21**: 4270-4276 [PMID: 14581436 DOI: 10.1200/JCO.2003.01.089]

18 **Lammers RJ**, Witjes JA, Inman BA, Leibovitch I, Laufer M, Nativ O, Colombo R. The role of a combined regimen with intravesical chemotherapy and hyperthermia in the management of non-muscle-invasive bladder cancer: a systematic review. *Eur Urol* 2011; **60**: 81-93 [PMID: 21531502 DOI: 10.1016/j.eururo.2011.04.023]

19 **Sousa A**, Piñeiro I, Aparici V, Neira P, Monserrat V, Uribarri C. [Analysis of budgetary impact of moderate and high risk non muscle-invasive bladder cancer by means of neoadjuvant hyperthermia chemotherapy compared to the standard adjuvant treatment with BCG]. *Arch Esp Urol* 2015; **68**: 482-492 [PMID: 26102052]

20 **Ekin RG**, Akarken I, Zorlu F, Tarhan H, Kucuk U, Yildirim Z, Divrik RT. Intravesical bacillus Calmette-Guérin versus chemohyperthermia for high-risk non-muscle-invasive bladder cancer. *Can Urol Assoc J* 2015; **9**: E278-E283 [PMID: 26029295 DOI: 10.5489/cuaj.2708]

21 **Ekin RG**, Akarken I, Cakmak O, Tarhan H, Celik O, Ilbey YO, Divrik RT, Zorlu F. Results of Intravesical Chemo-Hyperthermia in High-risk Non-muscle Invasive Bladder Cancer. *Asian Pac J Cancer Prev* 2015; **16**: 3241-3245 [PMID: 25921126 DOI: 10.7314/APJCP.2015.16.8.3241]

22 **Ayres B**, Connor A, Corbishley C, Bailey MJ. 3-year single-centre UK experience of radiofrequency hyperthermia and mitomycin C in BCG failures. *BJU Int Supplement June* 2010: 106 [DOI: 10.1111/j.1464-410X.2010.09373.x]

23 **van der Heijden AG**, Kiemeney LA, Gofrit ON, Nativ O, Sidi A, Leib Z, Colombo R, Naspro R, Pavone M, Baniel J, Hasner F, Witjes JA. Preliminary European results of local microwave hyperthermia and chemotherapy treatment in intermediate or high risk superficial transitional cell carcinoma of the bladder. *Eur Urol* 2004; 46: 65-71; discussion 71-72 [PMID: 15183549 DOI: 10.1016/j.eururo.2004.01.019]

24 **Griffits TR**. Plenary session conference at the annual national congress of the Spanish Urological Association. Secuential chemo-hyperthermia plus BCG in high risk NMIBC. Plenary session conference at the annual national congress of the Spanish Urological Association Toledo; June 16, 2016; Spain

25 **Colombo R**, Da Pozzo LF, Lev A, Salonia A, Rigatti P, Leib Z, Servadio C, Caldarera E, Pavone-Macaluso M. Local microwave hyperthermia and intravesical chemotherapy as bladder sparing treatment for select multifocal and unresectable superficial bladder tumors. *J Urol* 1998; **159**: 783-787 [PMID: 9474148 DOI: 10.1016/S0022-5347(01)63728-5]

26 **Sousa A**, Inman BA, Piñeiro I, Monserrat V, Pérez A, Aparici V, Gómez I, Neira P, Uribarri C. A clinical trial of neoadjuvant hyperthermic intravesical chemotherapy (HIVEC) for treating intermediate and high-risk non-muscle invasive bladder cancer. *Int J Hyperthermia* 2014; **30**: 166-170 [PMID: 24697672 DOI: 10.3109/02656736.2014.900194]

27 **Lüdecke GSL**, Nativ O, Witzsch U, Hanitzsch H, Hasner F, Issa R, Witjes F, Weidner W. Radiofrequence induced hyperthermia chemotherapy in high-risk NMIBC: Multiinstitutional, international outcome analysis of 271 treated patients with a follow-up time of more than 2 years. *Eur Urol* 2015; **Suppl**: 949 [DOI: 10.1016/S1569-9056(15)60937-X]

28 **Sousa A**, Piñeiro I, Rodríguez S, Aparici V, Monserrat V, Neira P, Carro E, Murias C, Uribarri C. Recirculant hyperthermic IntraVEsical chemotherapy (HIVEC) in intermediate-high-risk non-muscle-invasive bladder cancer. *Int J Hyperthermia* 2016; **32**: 374-380 [PMID: 26915466 DOI: 10.3109/02656736.2016.1142618]

29 **Fang J**, Nakamura H, Maeda H. The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. *Adv Drug Deliv Rev* 2011; **63**: 136-151 [PMID: 20441782 DOI: 10.1016/j.addr.2010.04.009]

30 **Kwon IK**, Lee SC, Han B, Park K. Analysis on the current status of targeted drug delivery to tumors. *J Control Release* 2012; **164**: 108-114 [PMID: 22800574 DOI: 10.1016/j.jconrel.2012.07.010]

31 **Lammers T**, Kiessling F, Hennink WE, Storm G. Drug targeting to tumors: principles, pitfalls and (pre-) clinical progress. *J Control Release* 2012; **161**: 175-187 [PMID: 21945285 DOI: 10.1016/j.jconrel.2011.09.063]

32 **Maeda H**. Macromolecular therapeutics in cancer treatment: the EPR effect and beyond. *J Control Release* 2012; **164**: 138-144 [PMID: 22595146 DOI: 10.1016/j.jconrel.2012.04.038]

33 **Taurin S**, Nehoff H, Greish K. Anticancer nanomedicine and tumor vascular permeability; Where is the missing link? *J Control Release* 2012; **164**: 265-275 [PMID: 22800576 DOI: 10.1016/j.jconrel.2012.07.013]

34 **Alexis F**, Rhee JW, Richie JP, Radovic-Moreno AF, Langer R, Farokhzad OC. New frontiers in nanotechnology for cancer treatment. *Urol Oncol* 2008; **26**: 74-85 [PMID: 18190835 DOI: 10.1016/j.urolonc.2007.03.017]

35 **Ferreira RV**, Martins TM, Goes AM, Fabris JD, Cavalcante LC, Outon LE, Domingues RZ. Thermosensitive gemcitabine-magnetoliposomes for combined hyperthermia and chemotherapy. *Nanotechnology* 2016; **27**: 085105-820520 [PMID: 26820520 DOI: 10.1088/0957-4484/27/8/085105]

36 **Thakor AS**, Gambhir SS. Nanooncology: the future of cancer diagnosis and therapy. *CA Cancer J Clin* 2013; **63**: 395-418 [PMID: 24114523 DOI: 10.3322/caac.21199]

37 **Evans SS**, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: the immune system feels the heat. *Nat Rev Immunol* 2015; **15**: 335-349 [PMID: 25976513 DOI: 10.1038/nri3843]

38 **Frey B**, Weiss EM, Rubner Y, Wunderlich R, Ott OJ, Sauer R, Fietkau R, Gaipl US. Old and new facts about hyperthermia-induced modulations of the immune system. *Int J Hyperthermia* 2012; **28**: 528-542 [PMID: 22690925 DOI: 10.3109/02656736.2012.677933]

P- Reviewer: Pellucchi F, Rais-Bahrami S **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Lu YJ

World Journal of Clinical Urology

Submit a Manuscript: http://www.f6publishing.com

World J Clin Urol 2017 July 24; 6(2): 40-43

DOI: 10.5410/wjcu.v6.i2.40

ISSN 2219-2816 (online)

ORIGINAL ARTICLE

Basic Study

Urinary supersaturation as a diagnostic measure in urolithiasis

Otakar Söhnel, Felix Grases

Otakar Söhnel, Faculty of Environmental Studies, University of J.E. Purkyně, 40096 Ústí n.L., Czech Republic

Felix Grases, Laboratory of Renal Lithiasis Research, University Institute of Health Sciences Research, University of Balearic Islands, 07122 Palma of Mallorca, Spain

Author contributions: Söhnel O and Grases F contributed to the conception and development of the theoretical aspects that have led to the conclusions reached; both authors approved the final version of the article to be published.

Institutional review board statement: Not applicable.

Institutional animal care and use committee statement: Not applicable.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: Not applicable.

Manuscript source: Unsolicited manuscript

Correspondence to: Felix Grases, PhD, Professor, Director of the Laboratory of Renal Lithiasis Research, Director of the University Institute of Health Sciences Research, Laboratory of Renal Lithiasis Research, University Institute of Health Sciences Research, University of Balearic Islands, Carretera Valldemossa Km 7.5, 07122 Palma of Mallorca, Spain. fgrases@uib.es
Telephone: +34-971-173257
Fax: +34-971-259935

Received: November 9, 2016
Peer-review started: November 10, 2016
First decision: February 16, 2017
Revised: February 26, 2017
Accepted: March 13, 2017
Article in press: March 13, 2017
Published online: July 24, 2017

Abstract

AIM

To demonstrate that urinary supersaturation *per se* is not a reliable diagnostic measure of the risk for stone formation.

METHODS

Available physical and chemical data for calcium oxalate monohydrate (COM) and calcium hydrogen phosphate dihydrate (brushite, BRU), and urinary supersaturations with respect to COM and BRU in healthy individuals and stone formers, were obtained from the literature. Classical theory of nucleation was used for calculations.

RESULTS

It was found that the rate of homogeneous nucleation (unaided by substrates) of COM and BRU is nil at all conceivable supersaturations of urine. Consequently spontaneous formation of crystals in urine requires the presence of nucleation substrates for (heteronuclei).

CONCLUSION

Urinary supersaturation with respect to lithiatic compounds is a necessary, but not a sufficient condition for nephrolithiasis. The absence of crystallization inhibitors and the presence of efficient nucleation promoters (heteronuclei) in urine are further necessary conditions of urolithiasis occurrence. Urinary supersaturation per se is not a reliable diagnostic measure of the risk of kidney stone formation.

Key words: Urinary supersaturation; Heterogeneous

nucleation; Urolithiasis

Core tip: The supersaturation of urinary compounds has been considered during long time as a key risk factor for renal lithiasis. Nevertheless, theoretical studies demonstrate that the rate of spontaneous (homogeneous) nucleation of calcium oxalate monohydrate and brushite only occurs at urinary supersaturations much higher than conceivable in any individual. This demonstrates the necessity of presence of efficient substances or foreign solid particles for induced nucleation (heterogeneous) of lithiatic compounds. Consequently, urinary supersaturation per se is necessary but not sufficient condition for stone development. Fundamental condition of renal stone formation and development is presence of heteronuclei and significantly reduced content of crystal growth inhibitors. Identification of nucleation promoters and absence of crystal growth inhibitors is very important as a diagnostic aspect to avoid urolithiasis.

Söhnel O, Grases F. Urinary supersaturation as a diagnostic measure in urolithiasis. *World J Clin Urol* 2017; 6(2): 40-43 Available from: URL: http://www.wjgnet.com/2219-2816/full/6/i2/40.htm DOI: http://dx.doi.org/10.5410/wjcu.v6.i2.40

INTRODUCTION

The supersaturation of urine with respect to lithogenic compounds as a key risk factor for urolithiasis has been introduced by Robertson *et al*[1]. Rodgers recently showed that urinary supersaturation of calcium oxalate monohydrate (COM) and calcium hydrogen phosphate dihydrate (BRU) varied widely among healthy individuals and stone formers and that it was impossible to discriminate between these two groups based on urinary supersaturation levels. Rodgers therefore concluded that urinary supersaturation *per se* is not useful as a diagnostic measure of the risk of stone formation[2].

The aim of this contribution is to demonstrate that the conclusion of Rodgers is fully substantiated based on the theory of precipitation.

MATERIALS AND METHODS

The driving force for the transfer of one "molecule" of a solute (electrolyte) composed of v ions from solution into the solid phase, ϕ, is the difference of the chemical potentials of the solute in solution and in a macroscopic crystal, $\Delta\mu$, expressed as a positive quantity[3].

$$\phi = -\Delta\mu = k\,T\,\ln(a_{soln}/a_{cryst}) \quad (1).$$

where k is the Boltzmann constant (1.38×10^{-23} J/K), T is the absolute temperature (K), a_{soln} is the activity of a solute in solution and a_{cryst} is the activity of a solute in a macroscopic solid. The activity of a ionic solute $A^{vA}B^{vB}$ (electrolyte) is[2]: $a_{soln,cryst} = a_{\pm}{}^{v} = a_A{}^{vA}a_B{}^{vB}$ (2).

where a_A and a_B are the activities of ions A and B, v_A and v_B are the stoichiometric coefficients and $v = (v_A + v_B)$ is the number of ions that form "molecule" of solute. The driving force for mass transfer can be expressed as: $\phi = v\,k\,T\,\ln S$ (3).

The supersaturation S is a measure of the thermodynamic driving force for crystallization at a constant temperature (our case) defined as: $S = a_{\pm,soln}/a_{\pm,cryst}$ (4).

where $a_{\pm}$ is the mean activity of an electrolyte. The activity of a solute in a macroscopic crystal is equal to the activity of solute in a saturated solution. No mass transfer of solute to solid phase, *i.e.*, crystallization, can proceed if S = 1.

The supersaturation of COM) and BRU is defined as: $S = [(a_A a_B)/K_{a,sp}]^{1/2}$ (5).

where $K_{a,sp}$ is the respective thermodynamic solubility product. The supersaturation SS used by Rodgers[2] and the supersaturation S defined by eq. (5) are related by $S = (SS)^{1/2}$.

The classical model of nucleation assumes the formation of a solid phase nucleus in a supersaturated solution by gradual attachment of building units (ions) to the already formed crystalline "cluster" of these units. The rate of homogeneous nucleation, *i.e.*, spontaneous formation of crystalline nuclei in the bulk solution by accretion of ions that is not facilitated by a solid substrate, in 1 m^3 per second can b expressed as[3]: $J_{hom} = (2\,D/d^5)\exp(-\Delta G^*/kT)$ (6).

where D is the diffusion coefficient of the solute (10^{-9} m^2/s), d is the molecular diameter, ΔG^* is the change of Gibbs energy accompanying formation of the critical nucleus and k and T are as defined above.

The rate of heterogeneous nucleation, *i.e.*, spontaneous formation of crystalline nuclei facilitated by a solid substrate, in 1 m^3 per second is[4]: $J_{het} = (2D/d^5)\exp[-\Delta G^* f(\Theta)/Kt]$ (7).

The correction factor $f(\Theta)$ is smaller than 1 and can be best considered as a measure of the nucleation enhancement by the foreign substrate without ascribing to it any precise physical interpretation. Heterogeneous nucleation occurs at a lower supersaturation then homogeneous nucleation.

The energetic barrier for formation of a nucleus is[3]: $\Delta G^*/kT = (\beta\,v^2\,\sigma^3)/[(kT)^3(v\ln S)^2]$ (8).

where β is the geometrical factor (32 for a cube), v is the molecular volume, σ is the interfacial tension.

Nuclei smaller than the critical size are unstable and disintegrate, whereas nuclei of the critical size or larger further grow to macroscopic sizes. The number of molecules, N^*, forming the critical nucleus is[3]: $N^* = 2\beta\,v^2\,\sigma^3/\phi^3$ (9).

RESULTS

COM has a molecular weight of 0.1461 kg/mol, density of 2120 kg/m^3, surface tension of 0.123 J/m^2[5], $K_{a,sp}$ =

2.24×10^{-9} $mol^2 L^{-2}$ at 37 ℃[6], molecular volume of 1.14×10^{-28} m^3, molecular diameter of 4.85×10^{-10} m. BRU has a molecular weight of 0.1721 kg/mol, density of 2310 kg/m^3, surface tension of 0.068 J/m^2[7], $K_{a,sp} = 2.74 \times 10^{-7}$ mol^2L^{-2} at 37.5 ℃[8], molecular volume of 1.24×10^{-28} m^3 and molecular diameter of 5.0×10^{-10} m.

The rate of homogeneous nucleation of COM for $S = \sqrt{12} = 3.5$ (maximum S reported in[2]) at 37 ℃ according to eq. (6) is: $J_{hom} = 3.7 \times 10^{37} \exp(-4722) \sim 0$.

The rate of homogeneous nucleation of BRU for $S = \sqrt{2.5} = 1.6$ (maximum S reported in[2]) at 37 ℃ is: $J_{hom} = 3.2 \times 10^{37} \exp(-2178) \sim 0$.

A nucleation rate of 1 nucleus in 1 cm^3 per second, *i.e.*, $J = 10^6$ $m^{-3}s^{-1}$, can be considered as the threshold for the onset of homogeneous nucleation. This rate is achieved when the supersaturation S with respect to COM and BRU is 35.9 and 13.6, respectively.

The critical nucleus of COM at S = 3.5 according to eq. (9) consists of 1257 "molecules" (ion pairs) and has a diameter of 6×10^{-9} m. The critical nucleus of BRU at S = 1.6 consists of 4757 "molecules" (ion pairs) and has a diameter of 11×10^{-9} m.

DISCUSSION

The urine of most people is supersaturated with respect to COM and BRU, the predominant constituents of kidney stones. However, only small fraction of people suffer from urolithiasis.

The first step in stone formation is the establishment of a tiny stable nucleus of a solid compound either in the liquid volume inside the kidney or on an inner wall of the kidney. A nucleus formed in the liquid volume must be retained within the kidney and grow to a macroscopic size.

Spontaneous unaided formation of a stable nucleus of COM or BRU in a liquid volume, this is by the mechanism of the homogeneous nucleation, only occurs at urinary supersaturations much higher than conceivable in any individual. Therefore the present analysis based on the theory of precipitation indicates that kidney stones cannot originate by homogeneous nucleation.

A necessary condition for the formation of solid phase nuclei in bulk urine is the presence of efficient substrates for nucleation. Spontaneous formation of crystals in urine can occur when value of the factor $f(\Theta)$ in eq. (7) is equal or lower than 0.015 for COM and 0.033 for BRU. Such low values of the factor $f(\Theta)$ indicate that substrates which are highly efficient in promoting nucleation must be present for the solid crystalline phase to appear. The phenomenon of crystalluria demonstrates that under special conditions macroscopic crystals with size up to 35×10^{-8} m and concentration of about 2×10^5 m^{-3} can originate in bulk urine[9]. This concentration of crystals is typical for heterogeneous nucleation.

The critical nucleus is very small and can be retained in the kidney after formation directly on the kidney wall or after attachment to the wall following formation in the liquid phase. However, some renal stones do not attach to the kidney wall. The nuclei of these stones must have originated in a cavity with poor urodynamics, and as they grew they formed an agglomerate that was large enough not to be washed from the kidney.

Nuclei formed in urine and retained in the kidney reach a macroscopic size by the accretion of additional building units (ions or ion pairs) and by subsequent agglomeration. The development of nuclei is strongly influenced by crystal growth modifiers naturally present in the urine that impede or completely stop solute attachment to the nucleus. Inhibitors, such as citrate, chondroitin sulphate, serum albumin, transferrin, osteopontin and Tamm-Horsfall protein[10,11], interact with COM crystal surfaces and impede growth. Protein lysozyme and lactoferrin, which occur in the organic matrix of renal stones, promote the growth of COM crystals[12]. Citrate, phytate, pyrophosphate and polyphosphates are effective inhibitors of BRU crystallization[13,14].

Nuclei that are formed and retained in the kidney can reach macroscopic size only in the absence of growth inhibitors and/or the presence of growth promoters.

Renal stones composed of COM and/or BRU are formed only in the case that: (1) urine is supersaturated with respect to these compounds; (2) efficient substrates for solid phase nucleation (heteronuclei) are present; and (3) inhibitors of crystallization are absent and/or promoters of crystallization are present. In the presence of suitable nucleation substrates and a deficiency of inhibitors, higher urinary supersaturation enhances formation and the development of stones. Urinary supersaturation *per se* is a necessary but not a sufficient condition for urolithiasis and is therefore not a reliable diagnostic measure of the risk of stone formation. If conditions of stone formation (2) and (3) are fulfilled the magnitude of supersaturation indicates the probability of nephrolithiasis.

COMMENTS

Background

The supersaturation of urinary compounds has been considered during long time as a key risk factor for renal lithiasis. Recently it has been demonstrated that urinary supersaturation of calcium oxalate monohydrate (COM) and calcium hydrogen phosphate dihydrate varied widely among healthy individuals and stone formers.

Research frontiers

The previously presented studies have been developed exclusively using information related to urinary biochemical parameters of patients and healthy individuals and checking that the values of supersaturation do not allow a good discrimination between both groups.

Innovations and breakthroughs

This study analyzes, using the classical theory of crystalline nucleation, the possibility of formation of crystals of COM or brushite (BRU) in human urine, as

a function of supersaturation.

Applications

This study demonstrates that the formation of COM and/or BRU renal calculi in urine supersaturated with these substances can only take place in the presence of efficient substrates for the nucleation of the corresponding solid phases (heteronuclei) and in the absence or deficit of crystallization inhibitors. Therefore, supersaturation is a necessary but not sufficient condition for the development of these stones. Supersaturation is therefore not a reliable diagnostic measure of the risk of stone formation. Nevertheless, in the presence of heteronuclei and crystallization inhibitory deficit, the magnitude of supersaturation may indicate the probability of nephrolithiasis. Identification of nucleation promoters and deficit of crystallization inhibitors is therefore very important as a diagnostic aspect to avoid urolithiasis.

Peer-review

The paper deals with theory of renal stones development; the paper is well written, clear and concise.

REFERENCES

1 **Robertson WG**, Peacock M, Nordin BE. Activity products in stone-forming and non-stone-forming urine. *Clin Sci* 1968; **34**: 579-594 [PMID: 5666884]

2 **Rodgers AL**. Urinary saturation: casual or causal risk factor in urolithiasis? *BJU Int* 2014; **114**: 104-110 [PMID: 24119074 DOI: 10.1111/bju.12481]

3 **Nielsen AE**. Kinetics of precipitation. Oxford: Pergamon Press Ltd., 1984: 3 and 5

4 **Ihli J**, Wang Y-W, Cantaert B, Kim Y-Y, Green DC, Bomans PHH, Sommerdijk NAJM, Meldrum FC. Precipitation of Amorphous Calcium Oxalate in Aqueous Solution. *Chem Mater* 2015; **27**: 3999-4007 [DOI: 10.1021/acs.chemmater.5b01642]

5 **Streit J**, Tran-Ho L-C, Königsberger E. Solubility of the Three Calcium Oxalate Hydrates in Sodium Chloride Solutions and Urine-Like Liquors. *Monatshefte Chem* 1998; **129**: 1225-1236 [DOI: 10.1007/PL00010134]

6 **Dey A**, Bomans PH, Müller FA, Will J, Frederik PM, de With G, Sommerdijk NA. The role of prenucleation clusters in surface-induced calcium phosphate crystallization. *Nat Mater* 2010; **9**: 1010-1014 [PMID: 21076415 DOI: 10.1038/nmat2900]

7 **Bennema P**, Söhnel O. Interfacial surface tension for crystallization and precipitation from aqueous solutions. *J Cryst Growth* 1990; **102**: 547-556 [DOI: 10.1016/0022-0248(90)90412-E]

8 **Gregory TM**, Moreno EC, Brown WE. Solubility of CaHPO4.2H2O in the system Ca(OH)2 – H3PO4 – H2O at 5, 15, 25 and 37.5 °C. J Res Nat Bureau Stand - A. *Chem Phys* 1970; **74A**: 461-475 [DOI: 10.6028/jres.074A.036]

9 **Daudon M**, Jungers P. Clinical value of crystalluria and quantitative morphoconstitutional analysis of urinary calculi. *Nephron Physiol* 2004; **98**: p31-p36 [PMID: 15499212 DOI: 10.1159/000080261]

10 **Farmanesh S**, Ramamoorthy S, Chung J, Asplin JR, Karande P, Rimer JD. Specificity of growth inhibitors and their cooperative effects in calcium oxalate monohydrate crystallization. *J Am Chem Soc* 2014; **136**: 367-376 [PMID: 24313314 DOI: 10.1021/ja410623q]

11 **Qiu SR**, Wierzbicki A, Orme CA, Cody AM, Hoyer JR, Nancollas GH, Zepeda S, De Yoreo JJ. Molecular modulation of calcium oxalate crystallization by osteopontin and citrate. *Proc Natl Acad Sci USA* 2004; **101**: 1811-1815 [PMID: 14766970 DOI: 10.1073/pnas.0307900100]

12 **Farmanesh S**, Chung J, Sosa RD, Kwak JH, Karande P, Rimer JD. Natural promoters of calcium oxalate monohydrate crystallization. *J Am Chem Soc* 2014; **136**: 12648-12657 [PMID: 25119124 DOI: 10.1021/ja505402r]

13 **Parekh BB**, Joshi MJ. Crystal growth and dissolution of brushite crystals by different concentration of citric acid solution. *Ind J Pure Appl Phys* 2005; **43**: 675-678

14 **Grases F**, Ramis M, Costa-Bauzá A. Effects of phytate and pyrophosphate on brushite and hydroxyapatite crystallization. Comparison with the action of other polyphosphates. *Urol Res* 2000; **28**: 136-140 [PMID: 10850638 DOI: 10.1007/s002400050152]

P- Reviewer: Naselli A **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Lu YJ

World Journal of Clinical Urology

Submit a Manuscript: http://www.f6publishing.com

World J Clin Urol 2017 July 24; 6(2): 44-50

DOI: 10.5410/wjcu.v6.i2.44

ISSN 2219-2816 (online)

ORIGINAL ARTICLE

Randomized Clinical Trial

Combined urethral and suprapubic catheter drainage improves post operative management after open simple prostatectomy without bladder irrigation

Anselm Okwudili Obi

Anselm Okwudili Obi, Department of Surgery, Federal Teaching Hospital, Abakaliki 48000, Ebonyi State, Nigeria

Anselm Okwudili Obi, Department of Surgery, Ebonyi State University, Abakaliki 48001, Ebonyi State, Nigeria

Author contributions: This is a sole authorship.

Institutional review board statement: The study design was reviewed and approved by the Ebonyi state university Research Ethics Committee.

Informed consent statement: All participants gave their written informed consent before inclusion in the study.

Conflict-of-interest statement: I have no conflicts of interest to declare.

Data sharing statement: The author on request will provide the raw data on which the study results were derived.

Manuscript source: Invited manuscript

Correspondence to: Dr. Anselm Okwudili Obi, FWACS, FICS, Department of Surgery, Federal Teaching Hospital, PMB 102, Abakaliki 48000, Ebonyi State, Nigeria. draoobi@yahoo.com
Telephone: +234-80-33464195

Received: December 29, 2016
Peer-review started: December 31, 2016
First decision: January 26, 2017
Revised: March 9, 2017
Accepted: April 16, 2017

Article in press: April 17, 2017
Published online: July 24, 2017

Abstract

AIM

To compare outcomes after open simple prostatectomy without bladder irrigation, in subjects drained by combined 2-way urethral catheter and suprapubic catheter (SPC) *vs* those drained by 2-way urethral catheter only.

METHODS

A total of 84 participants undergoing Freyer's simple prostatectomy over an 18-mo period were randomized into 2 groups (n = 42). Subjects in group 1 were managed with 2-way urethral catheter and *in situ* 2-way SPC while subjects in group 2 had a 2-way urethral catheter drainage only. In group 1 subjects, the SPC was spigotted and only used for drainage if there was clot retention. The primary outcomes were number of clot retention episodes, and number of clot retention episodes requiring bladder syringe evacuation. Other secondary outcomes evaluated were blood loss, requirement of extra analgesics, duration of surgery, hospital stay and presence or absence of post-op complications.

RESULTS

The mean age in the groups was 65.7 (± 7.6) in group 1 *vs* 64.8 (± 6.8) in group 2. The groups were similar with respect to age, prostate specific antigen, prostate volume, blood loss, duration of surgery, blood transfusion and overall complication rate. However statistically significant differences were observed in clot retention episodes between group 1 and 2: 0.8 (± 1.5) *vs* 3.5 (± 4.4), P < 0.000, clot retention episodes requiring evacuation with bladder syringe 0.4 (± 0.9) *vs* 2.6 (± 3.8), P = 0.001, requirement of extra analgesics 0.4 (± 0.5) *vs* 4.0 (± 1.5), P < 0.000 and duration of admission 8.6 d (± 1.2) *vs* 7.3

d (± 0.6), $P < 0.000$.

CONCLUSION

Subjects drained with a combination of urethral and SPCs have fewer clot retention episodes and reduced requirement of extra analgesics but slightly longer hospital stay.

Key words: Open suprapubic prostatectomy; Catheter drainage; Clot retention; Post operative outcome; Benign prostatic hyperplasia

Core tip: Most urologists will agree that the most worrisome post operative challenge after open suprapubic prostatectomy (OSP) is post operative haemorrhage and the attendant clot retention. This paper seeks to show that the use of a combination of suprapubic and urethral catheters as opposed to using only a urethral catheter to drain the bladder after OSP is associated with reduced clot retention episodes, reduced clot retention episodes requiring bladder syringe evacuation and therefore less post operative morbidity.

Obi AO. Combined urethral and suprapubic catheter drainage improves post operative management after open simple prostatectomy without bladder irrigation. *World J Clin Urol* 2017; 6(2): 44-50 Available from: URL: http://www.wjgnet.com/2219-2816/full/6/i2/44.htm DOI: http://dx.doi.org/10.5410/wjcu.v6.i2.44

INTRODUCTION

Despite the advent of transurethral resection of the prostate (TURP)[1], holmium laser enucleation of the prostate (HOLEP)[2] and other minimally invasive procedures, open simple prostatectomy (OSP) still remains a common treatment option for bladder outlet obstruction due to benign prostatic hypertrophy (BPH)[3-5], especially in the developing world. OSP is usually indicated in patients with large prostates above 80-100 g, patients with diverticular, large cystoliths, where the facilities and skills for less invasive procedures are not available or due to patient preference[3,4,6]. In developed countries TURP and Laser prostatectomy account for most procedures[3,4,6] but in the developing world OSP either in the form of Freyer's transvesical or Millin's retropubic prostatectomy is the commonest treatment modality[3-5,7].

The most worrisome post operative challenge after OSP is post operative haemorrhage and the attendant clot retention. Tinckler[8] has pointed out that, apart from general patient management, patient care following OSP is mainly concerned with ensuring uninterrupted drainage of urine and blood from the lower urinary tract until normal haemostasis is attained, avoiding accumulation of blood and clot retention. The urethral drainage catheter is frequently blocked by blood clots in the immediate post operative period leading to painful clot retention episodes requiring repeated clot evacuation and occasionally a return to the operating room for either cystoscopic evacuation or re-exploration with its attendant risks. Clot retention rates as low as 4.3%-8%[4,9,10] and as high as 47%[5] have been documented. Also re exploration rates as high as 4.3%[4] have been reported for recalcitrant clot-retention in patients undergoing OSP. Byrne[11] observed that a significant percentage of deaths that occur secondary to haemorrhage after OSP can be attributed to inadequate catheter drainage of the bladder.

Therefore effective drainage of the bladder after OSP is key to a smooth post operative course and successful outcome. Measures to drain the bladder and deal with the problem of clot retention in the post operative period after OSP have included such things as the suprapubic double glass tube of Cabot[12], the use of various types of wide bore catheters such as the perineal tube of Fuller[13], the rusch red rubber rectal catheter used by Plawker *et al*[14], and special suction devices[15]. In contemporary practice however most urologists use continuous bladder irrigation(CBI) through a 3 way catheter[16-18] or *via* a combination of 2 way urethral catheter and a suprapubic catheter (SPC)[4,6,19]. Some however practice non irrigation and use only a 2 way urethral catheter to drain the bladder[10,20,21]. Open simple prostatectomy without continuous bladder irrigation has been shown to be safe[7,10,20,21] and is our current practice. Manual evacuation of clots with the 60cc catheter tip syringe (bladder syringe) may be an adjunct to any of the above measures. In difficult cases there might be need to return to the theatre for cystoscopic evacuation or outright re exploration.

We hypothesized that on a policy of non irrigation, the addition of an in situ SPC acting as a safety valve against clot retention will greatly simplify post operative management after OSP and that the outcome will be better than using only a 2-way urethral catheter. We therefore conducted a prospective 2-arm open label randomized trial comparing patients managed post operatively on combined urethral and *in situ* SPC *vs* patients managed on 2 way urethral catheter drainage only. To the best of our knowledge there is no randomized study comparing these two modalities in patients managed without bladder irrigation.

MATERIALS AND METHODS

Following institutional research ethical board review and approval, 84 participants undergoing Freyer's simple prostatectomy at Federal Teaching Hospital Abakaliki, Ebonyi State, Nigeria and Alpha Specialist Hospital (Urology Centre), Enugu Nigeria over an 18 mo period, January 2014 to June 2015 were randomized using

prelabelled sealed envelopes into 2 groups. This was a prospective 2-arm parallel, open-label randomized trial conducted in compliance with the principles enunciated in the Helsinki declaration. The statistical review of the study was done by a biomedical statistician.

The study power was set at 95%, *i.e.*, (1 - β) = 0.95 and at a level of significance, α, of 0.01% to sufficiently detect a difference of 8%[4,9,10] *vs* 47%[5] in the proportion of those developing clot retention after open simple prostatectomy without bladder irrigation, in subjects drained by combined 2-way urethral catheter and SPC *vs* those drained by 2-way urethral catheter only.

The sample size required to detect the above effect size was determined using the following formula[22]; $n = \{f(\alpha,\beta)[P_0(100 - P_0) + P_1(100 - P_1)]\}/(P_0 - P_1)2$.

Where P_0 = proportion of participants in Group 2 expected to develop clot retention = 47%; P_1 = proportion of participants in Group 1 expected to develop clot retention = 8%. $f(\alpha, \beta) = 17.8$.

This returned a sample size of approximately 40 participants per arm of the study and 80 participants in both arms.

Group 1 patients were managed post operatively with combined 2 way urethral catheter drainage and *in situ* 2 way SPC while group 2 patients were managed post operatively with only 2 way urethral catheter drainage. Informed consent was obtained from all patients before surgery. Prior to surgery detailed clinical history of all patients was documented. Indications for surgery were severe lower urinary tract symptoms; IPSS (International Prostate Symptom Score > 19) and acute urinary retention necessitating urethral catheterization. Preoperative laboratory work up included urinalysis, urine microscopy culture and sensitivity, complete blood count, platelet count, prostate specific antigen (PSA), serum electrolyte urea and creatinine (S/E/U/Cr) estimation, abdominopelvic ultrasound scan, chest X-ray and electrocardiogram. Patients with PSA above 4 ng/mL were subjected to transrectal prostate biopsy and operated on only, if the result showed BPH. Sterile urine was ensured as well as normal platelet count and S/E/U/Cr. Pre-operative hemoglobin levels were optimized to at least 11.5 g/dL.

Operative technique

All patients had Freyer's transvesical prostatectomy done in standard fashion. All the surgeries were done by the author who had 12 years post fellowship experience at the commencement of the study. Patients were administered *I.V.* ceftriaxone 1 g and *I.V.* metronidazole 500 mg 15 min prior to surgery. These antibiotics were continued till the 4th post operative day following which, patients were converted to oral ciprofloxacin 500 mg bid till post operative day 10.

All surgeries were done under regional anesthesia (spinal or epidural). The bladder was assessed *via* a pfannenstiel incision and opened transversely in its lower half between two stay sutures. After finger enucleation of the prostatic adenoma haemostasis was secured by running 2/0 polyglactin suture of the bladder neck between the 5 and 7 o'clock positions. Additional bleeding points were either electro fulgurated or suture ligated. The prostatic fossa was not packed. A size 22F, 2 way silicone Foley urethral catheter was introduced into the bladder. Its balloon was inflated to 40 mL within the bladder and used to apply traction against the bladder neck by means of gauze bandage tied to the catheter and pushed snuggly against the penile tip. This traction was maintained at the end of surgery by strapping the catheter to the patients thigh with plaster. The decision on whether or not to add a SPC was taken at the point of closing the bladder by an independent investigator, using prelabelled sealed envelopes. The SPC (size 22F) was sited at the dome of the bladder in group 1 patients and brought out through a separate stab incision of the skin in the midline about two finger breaths above the pfannenstiel incision. The SPC was retained with 15 mL sterile water for injection and spigotted. The bladder was closed in 3 layers and the wound washed with normal saline. A perivesical wound drain of size 22F Foley catheter was placed in the perivesical space and the abdominal wound was closed in layers. The skin was closed with subcuticular 2/0 polyglactin suture. Traction on the bladder neck was released fully by 24 to 36 h. None of the patients had continuous bladder irrigation. Post operatively patients received, alternately 8 hourly intramuscular tramadol and pentazocine for analgesia.

Data collected and analyzed include demographic and clinical data such as age, prostate volume, PSA, pre and post operative hemoglobin, duration of surgery, clot retention episodes, clot retention episodes requiring evacuation with the 60 cc bladder syringe, requirement for extra analgesics, blood transfusion, hospital stay and complications. The primary outcomes were number of participants with clot retention episodes, and number of clot retention episodes requiring bladder syringe evacuation. Secondary outcomes evaluated were blood loss, requirement of extra analgesics, duration of surgery, hospital stay and presence or absence of post-op complications. Post operative hemoglobin was estimated on post operative day 2. Hospital stay was calculated from the day of operation to the day of discharge. For group 1 patients the SPC was left in situ as a safety valve. It was deployed for drainage of the bladder only when the urethral catheter was blocked by clots. The SPC was removed when the urine became consistently clear, usually by post operative day 2 or 3. The suprapubic cystostomy site was dressed and allowed to close naturally. The urethral catheters were spigotted by post operative day 5 or 6 and removed 24 h later. Patients in group 1 required an additional day or two to ensure closure of the SPC site. All enucleated prostates were sent for histology.

Statistical analysis

Data were analyzed using SPSS Version 16, Chicago IL,

Table 1 Demographic and clinic characteristics of groups 1 and 2 patients

Reps	Group 1 (mean ± SD)	Group 2 (mean ± SD)	*P* value
Patients (*n*)	42	42	
Age (yr)	65.7 (± 7.6)	64.8 (± 6.8)	0.598
Prostate volume (mL)	85.6 (± 49.1)	89.3 (± 42.1)	0.715
PSA (ng/mL)	15.3 (± 15.0)	12.6 (± 15.3)	0.417
Duration of surgery (min)	102.9 (± 18.8)	100.7 (± 14.9)	0.555
Blood transfusion (pints)	0.4 (± 0.6)	0.6 (± 0.9)	0.277
Clot retention episodes	0.8 (± 1.5)	3.5 (± 4.4)	0
Clot retention episodes requiring bladder syringing	0.4 (± 0.9)	2.6 (± 3.8)	0.001
Requirement for extra analgaesic	0.4 (± 0.5)	4.0 (± 1.5)	0
Change in haemoglobin (g/dL)	1.9 (± 1.2)	2.1 (± 1.1)	0.408
Duration of admission (d)	8.6 (± 1.2)	7.3 (± 0.6)	0

PSA: Prostate specific antigen.

United States. Student's *t* test was used to determine whether the observed differences in means was significant. Categorical variables were analyzed with the χ^2 test. $P < 0.01$ was taken as significant.

RESULTS

There were 42 patients in each group. The mean age of the groups was 65.7 (± 7.6) in group 1 *vs* 64.8 (± 6.8) in group 2. The groups were similar with respect to age, PSA, prostate volume, change in hemoglobin level, duration of surgery, blood transfusion and overall complication rate. However statistically significant differences were observed in clot retention episodes, clot retention episodes requiring evacuation with the 60 mL bladder syringe, requirement of extra analgesics and duration of admission (Table 1). Abnormally high PSA values were observed in some patients. However these patients had negative prostate biopsies prior to surgery and the resected specimens also had negative histology.

Overall complication rate showed that 33.3% of patients in group 1 and 35.7% of patients in group 2 had complications. The difference was not statistically significant. Detailed evaluation of complications showed a total of 39 complications; 24 (61.5%) in group 1 and 15 (38.5%) in group 2 (Table 2). Many patients in group 1 had more than one complication thus explaining the disparity in overall and actual complication rates. Post prostatectomy lower urinary tract symptoms (frequency, urgency, urge incontinence and dribbling) was the commonest complication accounting for 12 (30.8%), followed by urinary tract infection 10 (25.6%) and secondary haemorrhage 5 (5.1%). Details of complications are shown in Table 2. Persistent suprapubic urinary fistula was observed in 3 patients (8.1%) in group 1. No patient in group 2 had a urinary fistula. Urinary fistulas were managed by continuous bladder drainage and treatment of urinary tract infection (UTI). Additional measure was to close the fistula with 2/0 nylon suture after freshening the edges. These 3 patients were discharged home on catheter. There was no mortality. There were no incidental prostate carcinomas. Follow up period is currently 7.13 (± 1.91) mo.

DISCUSSION

There has been a paradigm shift in the management of BPH in the last four decades towards less invasive procedures such as TURP[1] and Laser prostatectomy[2], especially for prostates less than 80-100 g. In the developed world these minimally invasive transurethral procedures account for most of the procedures, while open suprapubic prostatectomy (OSP) accounts for only 3%-40% of procedures[3,23]. The reverse is the case in the developing world largely because of absence of skilled manpower and technology for minimally invasive transurethral procedures[7]. It has also been noted that more and more patients are presenting these days with prostates in the 80 to 100 g range because of the increasing use of medical treatment or watchful waiting[2,23]. Thus there will always be a place for OSP whether in the developed or developing world. While OSP is more invasive and requires an abdominal incision with subsequently longer hospitalization and convalescence than transurethral techniques, it results in an excellent functional outcome and low reoperation rates[3,18,24].

Morbidity and mortality after OSP is closely tied to the problem of clot retention and adequacy of bladder drainage[8,11]. Clot retention if left untreated, can lead to severe pain, tachycardia, azotemia, hypertension and bladder rupture[14,25].

Traditionally effective drainage of the bladder and prevention of clot retention after OSP has been by means of continuous bladder irrigation (CBI) with normal saline through a 3 way urethral catheter[16-18] or *via* a combination of 2 way urethral catheter and a SPC[4,19] with or without manual evacuation of clots with the 60 cc catheter tip syringe. There might be a resort to cystoscopic evacuation or outright re-exploration if the latter fails. Some studies[20,21] have queried the need for CBI pointing out, that clot retention still frequently occurs even under CBI and that there is a risk of bladder rupture with unregulated inflow of irrigant. CBI is also associated with increased workload on the staff and increased financial burden to the patient. OSP without CBI has been shown to be safe[7,10,20,21] and is our current practice. Under this non irrigation protocol two options exist for draining the bladder; One is the use of a 2 way urethral catheter alone and the other is the use of a combination of 2 way urethral catheter with addition of a SPC as a safety valve against clot retention. This study compares post operative outcomes in patients managed with combined SPC and 2 way urethral catheter and those drained by 2 way urethral catheter only. All patients were managed without CBI.

Table 2 Overall complication rate and details of complications by Clavien Dindo grade observed in both groups *n* (%)

Complications	Clavien Dindo grade	Group 1	Group 2	Total	*P* value
Overall complications		14 (33.3)	15 (35.7)	29 (34.5)	0.5
Post prostatectomy (LUTS)	II	5 (12.8)	7 (17.9)	12 (30.8)	0.378
Post prostatectomy UTI	II	8 (20.5)	2 (5.1)	10 (25.6)	0.044
Secondary hemorrhage	II	4 (10.3)	1 (2.6)	5 (12.8)	0.18
Surgical site infection	IIIa	3 (7.7)	1 (2.6)	4 (10.3)	0.308
Persistent suprapubic fistula	IIIa	3 (7.7)	-	3 (7.7)	0.12
Delirium	II	-	2 (5.1)	2 (5.1)	0.247
Left ventricular failure	IVa	-	1 (2.6)	1 (2.6)	0.5
Cardiac arrhythmia	IVa	-	1 (2.6)	1 (2.6)	0.5
Septicemia	II	1 (2.6)	-	1 (2.6)	0.5
Total		24 (61.5)	15 (38.5)	39 (100)	

LUTS: Lower urinary tract symptoms; UTI: Urinary tract infection.

The mean age of the groups was respectively, 65.7 (± 7.6) in group 1 *vs* 64.8 (± 6.8) in group 2. These means are similar to the mean age of patients undergoing OSP[4,20]. The age difference between the two groups was not statistically significant, *P* = 0.598. The difference between the two groups with respect to prostate volume, PSA and duration of surgery was also not statistically significant (Table 1). However statistically significant differences were observed in the mean clot retention episodes (CREs), clot retention episodes requiring evacuation with the 60 mL bladder syringe, requirement of extra analgesics and duration of admission.

The mean CREs in group 1 was much lower than that of group 2; 0.8 (± 1.5) (range 0-6) *vs* 3.5 (± 4.4) (range 0-16), *P* = 0.000. CREs of between 0.9% to 47% have been reported by various authors[1,5,9,10]. The difference in CREs between the groups is not surprising because group 1 patients had an alternative route for bladder drainage in the event of clot retention. In this group the spigotted SPC was opened and connected to a urine bag once the first clot retention episode occurred. The SPC was then left open to drain the bladder alongside the 2 way urethral catheter until the urine became clear enough for the SPC to be removed. Formed clots naturally gravitate to a dependent position in the bladder and block the urethral draining catheter leaving the SPC which is sited at the dome of the bladder free to drain the bladder, while clot lysis is ongoing.

In the presence of clot retention, some clots may pass spontaneously or pass following milking of the urethral catheter. When these fail the next option is to evacuate the clots using the 60 cc bladder syringe. Evaluation of CREs requiring evacuation with the bladder syringe between the two groups showed that mean CREs requiring bladder syringe evacuation was 0.4 (± 0.9) (range 0-4) in group 1 compared to a mean of 2.6 (± 3.8) (range 0-14) in group 2. This difference was statistically significant, *P* = 0.001. Patients are better off with fewer CREs requiring evacuation with the bladder syringe. For one, clot evacuation can be tasking, time consuming and sometimes inefficient, because the catheter walls tend to collapse under the negative pressure of the bladder syringe[14]. There is also the risk of introducing infection into the bladder by too frequent flushing out of clots. None of the groups required reoperation for clot retention or cystoscopic evacuation and there was no mortality.

Clot retention is not just associated with increased demand on the time and resources of the staff but is also associated with increased patient discomfort, post operative pain and requirement of extra analgesic. The mean demand for extra analgesic between the two groups varied considerably. While it was 0.4 (± 0.5) (range 0-2) for group 1, it was 4.0 (± 1.5) (range 0-7) for group 2. This difference was statistically significant, *P* = 0.000. The reduced demand for extra analgesic in group 1 is in keeping with the fewer CREs and CREs requiring evacuation with the bladder syringe in this group. A cost analysis reveals an extra cost of approximately 42USD per patient for dealing with the burden of extra clot retention episodes and clot retention episodes requiring evacuation with the 60 cc bladder syringe observed in group 2. This is broken down into; cost of SPC-1.2USD, urine bag-0.5USD, 60 cc bladder syringe(average of 3/patient)-4.5USD, Normal saline for flushing the catheters(average, 4L/patient)-3.6USD, extra analgesic (average 8 ampoules of tramadol/patient)-3.0USD, extra demand on nursing services-20USD, change of soiled beddings and dressings-9USD. In a resource poor environment this extra 42USD can be a significant economic burden to the patient.

Mean blood transfusion was lower in group 1 compared to group 2; 0.4 (± 0.6) *vs* 0.6 (± 0.9) respectively. Also the mean change in hemoglobin was lower in group 1 compared to group 2; 1.9 (± 1.2) g/dL *vs* 2.1 (± 1.1) g/dL. These differences approached but did not reach statistical significance. *P* values, 0.277 and 0.408 respectively. Blood transfusion rates after OSP can vary greatly. While some authors claim zero transfusion[10,21]. Most large series report blood transfusion in the range of 1% to 57.1%[3,6,7]. Bleeding

after OSP occurs not just because of inadequate haemostasis but also because clots and clot retention cause over distension of the bladder. Over distention provokes further bleeding because the bladder and prostatic fossa are prevented from contracting down on the bleeding points. Therefore any measure that can reduce clot retention will reduce post operative bleeding. In this study the mean blood transfusion and change in hemoglobin concentration was lower in group 1 in keeping with the reduced CREs and CREs requiring evacuation observed in this group.

Overall complication rate in this study was 34.5%. This is similar to the 30% and 31.3% rates reported in some other series[18,24]. Both groups were similar in terms of overall complication rate with 33.3% of patients in group 1 and 35.7% of patients in group 2 having complications P = 0.500 (Table 2). However detailed analysis of actual complications showed that there were more complications in group 1 than group 2 because some patients in this group had more than one complication (Table 2). Post prostatectomy lower urinary tract symptoms (LUTS) namely frequency, urgency, urge incontinence and dribbling was the commonest complication in both groups accounting for 30.8% of the overall complications. It was slighter commoner in group 2 than group 1; 7 (17.9%) *vs* 5 (12.8%). Others have also observed worrisome post prostatectomy LUTS to be a common complication after OSP[1,9]. A range of 6.7% to 11.1% has been reported[1,9] which is slightly lower than observed in this study. The condition usually resolves with keggel exercises over a short period of time with or without antimuscarinics. UTI has to be ruled out as a cause and treated. In this series all cases resolved within one month after discharge. The next most common complication was post prostatectomy urinary tract infection which accounted for 25.6% of complications. This is lower than the 40% figure reported by Bapat *et al*[9] after Freyer's prostatectomy. It was seen more in group 1 than group 2; 8 (20.5%) *vs* 2 (5.1%). Post prostatectomy haematuria (secondary hemorrhage) was also commoner in group 1 than group 2; 4 (10.3%) *vs* 1 (2.6%). Haematuria may be a complication of UTI. The higher incidence of these two complications in group 1 may be related to the presence of the SPC. The suprapubic ostium may have been a source of bacterial entry into the urinary tract. Persistent suprapubic urinary fistula was observed in 3 patients (7.7%) in group 1. No patient in group 2 had a suprapubic urinary fistula. The urinary fistulas were managed by continuous bladder drainage and treatment of UTI if present. These three patients had UTI. In these three patients the suprapubic ostium was sutured and the patients discharged home on catheter. Mean duration of admission was 8.6 d (± 1.2) in group 1 and 7.3 d (± 0.6) in group 2, P = 0.000. This statistically significant difference in duration of admission between the two groups can be attributed to the extra time it took for the suprapubic fistulae to close in group 1 patients. There was no mortality in this series.

Draining the bladder with a combination of urethral and SPC is associated with a smoother post operative course because of fewer clot retention episodes and clot retention episodes requiring bladder syringe evacuation. It is also associated with reduced requirement of extra analgesic. These advantages have to be weighed against the disadvantage of an occasional persistent suprapubic fistula resulting in slightly longer hospital stay.

COMMENTS

Background

Despite the advent of newer technologies for treating benign prostatic hypertrophy (BPH), open simple prostatectomy (OSP) still remains a common treatment option for bladder outlet obstruction due to BPH. Currently some urologists advocate non bladder irrigation after OSP and they site several disadvantages of bladder irrigation such as cost, increased staff workload, patient discomfort, risk of bladder rupture, prolonged immobilization, and perhaps more importantly that it does not prevent clot retention. Two options exist for draining the bladder after non irrigated OSP; one is the use of a urethral catheter only and the other is to use a combination of urethral and suprapubic catheters (SPCs) so that the SPC acts as a safety valve should there be recalcitrant clot retention. It is expected that this latter method will guarantee uninterrupted drainage of urine and blood from the lower urinary tract until normal haemostasis is attained, avoiding accumulation of blood and clot retention.

Research frontiers

This study is important because it helps to support the advocacy for OSP without bladder irrigation. The disadvantages of bladder irrigation after OSP have already been clearly spelt out.

Innovations and breakthroughs

To the best of the knowledge this is the only study evaluating in a randomized fashion, bladder drainage after OSP.

Applications

The practical applications of using a combination of urethral and SPCs to drain the bladder after OSP is that because it is associated with fewer clot retention episodes, it requires less monitoring. It is therefore useful in settings where there is less manpower such as private hospitals and in developing countries. It is also cheaper because it is associated with less requirement of extra analgesic, need to evacuate clots and blood transfusion.

Peer-review

The subject of the study is original and the manuscript is well written.

REFERENCES

1 **Mebust WK**. Transurethral prostatectomy. *Urol Clin North Am* 1990; **17**: 575-585 [PMID: 2197768]

2 **Elzayat EA**, Elhilali MM. Holmium laser enucleation of the prostate (HoLEP): the endourologic alternative to open prostatectomy. *Eur Urol* 2006; **49**: 87-91 [PMID: 16314033 DOI: 10.1016/j.eururo.2005.08.015]

3 **Varkarakis I**, Kyriakakis Z, Delis A, Protogerou V, Deliveliotis C. Long-term results of open transvesical prostatectomy from a contemporary series of patients. *Urology* 2004; **64**: 306-310 [PMID: 15302484 DOI: 10.1016/j.urology.2004.03.033]

4 **Mgbakor AC**. Problematics of open prostatectomy in an Ivorian District Hospital setting. *Arch Ital Urol Androl* 2012; **84**: 123-128 [PMID: 23210403]

5 **Umunna JI**. Prostatic fossa gauze-packing in the prevention of blood clot obstruction of the bladder after transvesical prostatectomy. *West Afr J Med* 2010; **29**: 184-186 [PMID: 20665463]

6 **Luttwak Z**, Lask D, Abarbanel J, Manes A, Paz A, Mukamel E.

Transvesical prostatectomy in elderly patients. *J Urol* 1997; **157**: 2210-2211 [PMID: 9146617 DOI: 10.1016/S0022-5347(01)64720-7]
7 **Condie JD Jr**, Cutherell L, Mian A. Suprapubic prostatectomy for benign prostatic hyperplasia in rural Asia: 200 consecutive cases. *Urology* 1999; **54**: 1012-1016 [PMID: 10604700 DOI: 10.1016/S0090-4295(99)00307-6]
8 **Tinckler LF**. Post-prostatectomy management--a new catheter system. *Br J Urol* 1972; **44**: 165-168 [PMID: 4557439 DOI: 10.1111/j.1464-410X.1972.tb10061.x]
9 **Bapat RD**, Relekar RG, Pandit SR, Dandekar NP. Comparative study between modified Freyer's prostatectomy, classical Freyer's prostatectomy and Millin's prostatectomy. *J Postgrad Med* 1991; **37**: 144-147 [PMID: 1723756]
10 **Okorie CO**, Pisters LL. Effect of modified suprapubic prostatectomy for benign prostatic hyperplasia on postoperative hemoglobin levels. *Can J Urol* 2010; **17**: 5255-5258 [PMID: 20735903]
11 **Byrne JE**. Continuous bladder irrigation following prostatectomy. *Med Bull St Louis Univ* 1952; **4**: 77-79 [PMID: 12992066]
12 **Cabot F**. Value of sight in suprapubic prostatectomy. *Tr Am Urol* 1909; **3**: 449
13 **Fuller E**. Diseases of the genito-urinary system. New York: MacMillan, 1900
14 **Plawker MW**, Hashmat AI. The rectal tube: an excellent catheter for severe clot retention. *J Urol* 1997; **157**: 1781-1782 [PMID: 9112527 DOI: 10.1016/S0022-5347(01)64863-8]
15 **Yu HS**, Ham WS, Hah YS, Lee CK, Jang WS, Cho KS. Simple, safe, and successful evacuation of severe organized clot retention using a catheter connected with wall suction: suction and fishing method. *Urology* 2011; **78**: 1199-1202 [PMID: 21940043 DOI: 10.1016/j.urology.2011.07.1390]
16 **Han M,** Partin AW. Retrograde and suprapubic open prostatectomy. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell - Walsh Urology. Philadelphia: Saunders Elsevier, 2012: 2695-2703 [DOI: 10.1016/B978-1-4160-6911-9.00094-3]
17 **Scholtes S**. Management of clot retention following urological surgery. *Nurs Times* 2002; **98**: 48-50 [PMID: 12168380]
18 **Tubaro A**, Carter S, Hind A, Vicentini C, Miano L. A prospective study of the safety and efficacy of suprapubic transvesical prostatectomy in patients with benign prostatic hyperplasia. *J Urol* 2001; **166**: 172-176 [PMID: 11435849 DOI: 10.1016/S0022-5347(05)66102-2]
19 **Adams AW**. A third ureter in prostatectomy. *Br Med J* 1949; **1**: 809 [PMID: 18120853 DOI: 10.1136/bmj.1.4609.809]
20 **Okorie CO**, Salia M, Liu P, Pisters LL. Modified suprapubic prostatectomy without irrigation is safe. *Urology* 2010; **75**: 701-705 [PMID: 19914705 DOI: 10.1016/j.urology.2009.06.109]
21 **Okorie CO**. Is continuous bladder irrigation after prostate surgery still needed? *World J Clin Urol* 2015; **4**: 108-114 [DOI: 10.5410/wjcu.v4.i3.108]
22 **Altman DG**. Practical statistics for Medical Research. London: Chapman and Hall, 1991; Chapter 10, section 10.3: p232-235
23 **Mozes B**, Cohen YC, Olmer L, Shabtai E. Factors affecting change in quality of life after prostatectomy for benign prostatic hypertrophy: the impact of surgical techniques. *J Urol* 1996; **155**: 191-196 [PMID: 7490831 DOI: 10.1097/00005392-199601000-00070]
24 **Baumert H**, Ballaro A, Dugardin F, Kaisary AV. Laparoscopic versus open simple prostatectomy: a comparative study. *J Urol* 2006; **175**: 1691-1694 [PMID: 16600732 DOI: 10.1016/S0022-5347(05)00986-9]
25 **Ritch CR**, Ordonez MA, Okhunov Z, Araujo J, Walsh R, Baudin V, Lee D, Badani KK, Gupta M, Landman J. Pilot study of Alteplase (tissue plasminogen activator) for treatment of urinary clot retention in an in vitro model. *J Endourol* 2009; **23**: 1353-1357 [PMID: 19594375 DOI: 10.1089/end.2008.0513]

P- Reviewer: Creta M, Naselli A, Naspro R **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com