University of Southampton

Faculty of Medicine

Minimally invasive surgical (MIS) techniques in the management of benign and malignant kidney conditions

Bhaskar Kumar Somani MRCS, FEBU, FRCS (Urol)

Thesis for the degree of Doctor of Medicine (DM)

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Abstract

My thesis underlines the role and current evidence of minimally invasive surgical (MIS) technique for benign and malignant renal conditions.

Evidence is presented for the use of laparoscopic and robotic partial nephrectomy along with expanding indications for ureteroscopy. Systematic reviews of ureteroscopy for large stones, obese patients, patients with bleeding diathesis and children is presented. Use of ureteroscopy for endoscopic diagnosis and management of upper urinary tract tumours is also presented.

The work is comprised of 12 peer-reviewed published papers including 8 systematic reviews and 4 original research papers using retrospective or prospective case series on the subject.

Based on the evidence, new insight into MIS for renal conditions will help clinicians and patients in informed decision-making. Minimally invasive surgery is a step in the right direction for management of various benign and malignant renal conditions. My work demonstrates evidence-based outcomes, which will ensure widespread adoption of these techniques in future.

DM (Alt Rt) Doctor of Medicine

Declaration of Originality

The work described in this thesis was performed by myself and the relative contribution has been mentioned. All 12 papers have been published in peer review journals. It has not been submitted anywhere else for a degree. All sources of information have been acknowledged.

Bhaskar Kumar Somani

December 2016

Acknowledgements

I would like to thank my colleagues with whom I have collaborated for these papers. I am extremely grateful for their cooperation, corrections and constant improvement with the content of the published papers.

I would also thank Dr Simon Crabb and Mr Brian Birch for agreeing to be my advisor for the thesis.

A special thanks to my wife Sweta, who constantly reassured and supported me through this period.

List of Abbreviations

A		
5-ALA	-	5-Aminolevulinic acid
B		
BAUS	-	British Association of Urological Surgeons
BMI	-	Body Mass Index
C		
CT	-	Computerised Tomography scan
C-FURS	-	Conventional flexible ureteroscopes
D		
D-FURS	-	Digital ureteroscopes
F		
FURSL	-	Flexible ureteroscopy and laser stone fragmentation
FURSs	-	Flexible ureterorenoscopes
L		
LPN	-	Laparoscopic Partial Nephrectomy
LNU	-	Laparoscopic Nephroureterectomy
M		
MIS	-	Minimally Invasive Surgery
MMC	-	Mitomycin C
N		
NICE	-	National Institute of Clinical Excellence

NHS	-	National Health Service
O		
ONU	-	Open Nephroureterectomy
P		
PDD	-	Photodynamic Diagnosis
PCNL	-	Percutaneous Nephrolithotomy
R		
RCT	-	Randomised Controlled Trial
RPN	-	Robotic Partial Nephrectomy
RNU	-	Radical Nephroureterectomy
S		
SFR	-	Stone Free Rate
SIU	-	Société Internationale d'Urologie
SWL	-	Shockwave Lithotripsy
U		
UK	-	United Kingdom
USA	-	United States of America
URS	-	Ureteroscopy
URSL	-	Ureteroscopy and laser fragmentation
UUT	-	Upper Urinary Tract
UUT-TCC	-	Upper Urinary Tract Transitional Cell Carcinoma

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Minimally invasive surgical (MIS) techniques in the management of benign and malignant kidney conditions

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DM Supporting statement

Aims:

Over the last 2 decades there have been a lot of surgical innovations in minimally invasive urological techniques. While it started with the advent of percutaneous renal stone surgery and lithotripsy, laparoscopy came of age and became well established for renal conditions. The aims of my thesis were to establish the current role and evidence for minimally invasive surgical (MIS) techniques in modern urological surgery for benign and malignant kidney conditions. The two most innovative urological techniques in recent times include the use of laparoscopy and ureteroscopy.

While laparoscopic nephrectomy is well established (1-3), laparoscopic partial nephrectomy (LPN) for management of malignant renal tumours is comparatively recent but has been increasing over the last decade (4-6). Although LPN has been deemed a relatively safe procedure, its outcomes in obese patients and when compared to robotic surgery have been largely unclear. We conducted a systematic review of literature to find the current evidence and outcomes for LPN in these two settings.

Ureteroscopy for management of stone disease and for diagnosis and treatment of upper urinary tract tumours has become increasingly common (7-10). Although its use for stone disease management is fairly standard, there remain unanswered questions for its use in special situations such as in obesity, pregnancy, very large stones (>2cm in size), children and patients with bleeding diathesis. We conducted a systematic review of literature to look at the outcomes of ureteroscopy and stone treatment in these patient groups. We also compared the treatment outcomes of stone disease using traditional fibreoptic ureteroscopes with new generation digital ureteroscopes and discuss the 'tips and tricks' of performing flexible ureteroscopy.

Ureteroscopy for diagnosing and endoscopically managing upper urinary tract (UUT) tumours is also on the rise (11-13). We reviewed all available literature on surgical management of upper urinary tract (UUT) tumours. An audit of outcomes for a new technology for diagnosing these tumours using oral 5-aminolevulinic acid (5-ALA) and photodynamic diagnosis technique (PDD) is also presented. Finally the use of mitomycin C chemotherapy instillation following ureteroscopic laser ablation to look at the recurrences of these UUT tumours is also covered.

Nature of research: Primary research and systematic reviews

My thesis involves systematic reviews on a wide range of topics covering benign and malignant renal disease conditions using laparoscopy and ureteroscopy. In addition to this, original research using retrospective or prospective case series on management of these conditions is also presented. This work includes 12 peer-reviewed papers previously published, including 8 systematic review papers and 4 original research papers.

Statement in the share of the work: The contribution of my share for these 12 papers varies from 25%-80% and has been detailed at the end of every paper.

1. Laparoscopic partial nephrectomy (LPN) in obese patients: A Systematic review and Meta-Analysis

With rise in levels of obesity worldwide and the lack of data on LPN for this patient group, we wanted to compare the safety and efficacy of laparoscopic partial nephrectomy (LPN) in obese and non-obese patients. A systematic review was performed for relevant studies from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials – CENTRAL, CINAHL, Clinicaltrials.gov, Google Scholar and Individual urological journals. The search was conducted in October 2011 and obesity was defined as having a body mass index (BMI) of $\geq$30 kg/m^2.

Of the146 titles reviewed, 140 were excluded due to irrelevance from the title or abstract. Four of the remaining 6 were included (659 patients). There was no difference in the operative duration, warm ischaemia time, blood loss or hospital stays between the obese and non-obese group. The obese group had significantly (p=0.03) higher Clavien Grade III complications (4.3%, 11/256) compared to the non-obese group (1.5%, 6/403), although the overall complications were equivalent. Our meta-analysis showed that LPN could be safely done in obese patients but with a slightly higher risk of major complication compared to the non-obese group.

(Contribution 40%, doing the systematic review, proofreading/correcting the paper and helping with subsequent revisions).

BJUI
BJU INTERNATIONAL

Laparoscopic partial nephrectomy in obese patients: a systematic review and meta-analysis

Omar M. Aboumarzouk, Robert J. Stein*, Georges-Pascal Haber*, Jihad Kaouk*, Piotr L. Chlosta† and Bhaskar K. Somani‡

*The Royal Bournemouth and Christchurch Hospitals NHS Trust, Urology Department, Bournemouth, UK, *Cleveland Clinic, Glickman Urologic and Kidney Institute, Cleveland, Ohio, USA, †Faculty of Health, Jan Kochanowski University, Holy Cross Cancer Centre, Department of Urology Institute of Oncology, Kielce, Poland, and ‡Southampton University Hospitals NHS Trust, Southampton, UK*

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• To compare the safety and efficacy of laparoscopic partial nephrectomy (LPN) in obese and non-obese patients.
• We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966 to November 2011), EMBASE (1980 to November 2011), CINAHL, Clinicaltrials.gov, Google Scholar, reference lists of articles and abstracts from conference proceedings without language restriction for studies comparing LPN in obese and non-obese patients.
• Four observational cohort studies were included for 256 obese patients compared with 403 non-obese patients who underwent LPN.
• There was no difference in operative duration (mean difference [MD] 5.64, 95% confidence interval [CI] −3.80 to 15.09), warm ischaemic time (MD −1.04, 95% CI −2.68 to 0.59), estimated blood loss (MD 53.73, 95% CI 0.72–106.74) or hospital stay (MD −0.04, 95% CI −0.30 to 0.22).
• There was no difference in complications in total (odds ratio [OR] 1.02, 95% CI 0.70–1.49), intraoperative complications (OR 0.68, 95% CI 0.30–1.53), or postoperative complications (OR 1.15, 95% CI 0.75–1.77).
• The obese group had significantly more Clavien grade III complications (OR 3.95, 95% CI 1.36–11.42), despite the low absolute incidence, with 4.3% (11/256) in the obese group vs 1.5% (6/403) in the non-obese group.
• Experienced laparoscopic surgeons can safely and efficiently perform PN for obese patients with comparable results to those of non-obese patients.
• The likelihood of major (Clavien Classification ≥ III) complications is higher for the obese patient.

What's known on the subject? and What does the study add?
The literature yielded only four studies on the subject; however, no clear outcome can be taken from individual studies.

This review adds a meta-analysis of these four studies to make the patient cohort larger and to allow for a greater understanding of the procedure in this select group of patients.

KEYWORDS

laparoscopy, partial nephrectomy, renal cell carcinoma, obesity, systematic review, meta-analysis

INTRODUCTION

Worldwide, obesity is on the rise and is now considered an epidemic with >300 million people afflicted [1]. About 25–34% of the adult population of the USA are considered obese [2–7]. Evidence suggests that the incidence of RCC increases with obesity, but that obese patients might have a better prognosis compared with non-obese patients [3,4,6]. With advances in imaging technology the detection of smaller RCCs has increased, leading to current figures of up to 60% of RCC being <4 cm [8,9]. The identification of smaller renal tumours has led to an increase in the number of patients who are candidates for partial nephrectomy (PN) resulting in decreased renal insufficiency [8,10].

With advances in laparoscopic techniques, equipment, and operator skill, laparoscopic PN (LPN) has emerged as a viable alternative to open PN with comparable oncological outcomes, less morbidity, and faster recovery [8,9,11]. However, there are certain circumstances that may make LPN more challenging, e.g. operating on obese patients [6]. These patients not only tend to have a prolonged procedure but also often have multiple co-morbidities with a higher risk of intra and postoperative complications [3–6].

With the rising incidence of obesity in society, laparoscopy has been increasingly used for PN in obese patients [2–6]. Nevertheless, controversy still remains about the safety of the laparoscopic approach despite evidence of more rapid recovery and equivalent oncological results with laparoscopy [5].

Therefore, we aimed to conduct a Cochrane level, systematic review of the literature with a meta-analysis of the results to

evaluate the safety and efficacy of LPN compared with the standard open PN.

The primary aim was to compare the efficacy of LPN in obese and non-obese patients; specific outcomes include the operative duration, the warm ischaemic time (WIT), estimated blood loss (EBL), and hospital stay. Our secondary objectives were to compare the safety of LPN between the two groups, with outcomes such as complications, conversion rates, and transfusion rates.

MATERIALS AND METHODS

SEARCH STRATEGY AND STUDY SELECTION

The systematic review was performed according to the Cochrane reviews guidelines and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [12].

The search strategy was conducted to find relevant studies from MEDLINE (1966 to October 2011), EMBASE (1980 to October 2011), Cochrane Central Register of Controlled Trials – CENTRAL (in The Cochrane Library Issue 1, 2011), CINAHL (1982 to October 2011), Clinicaltrials.gov, Google Scholar and Individual urological journals. The search was conducted in October 2011.

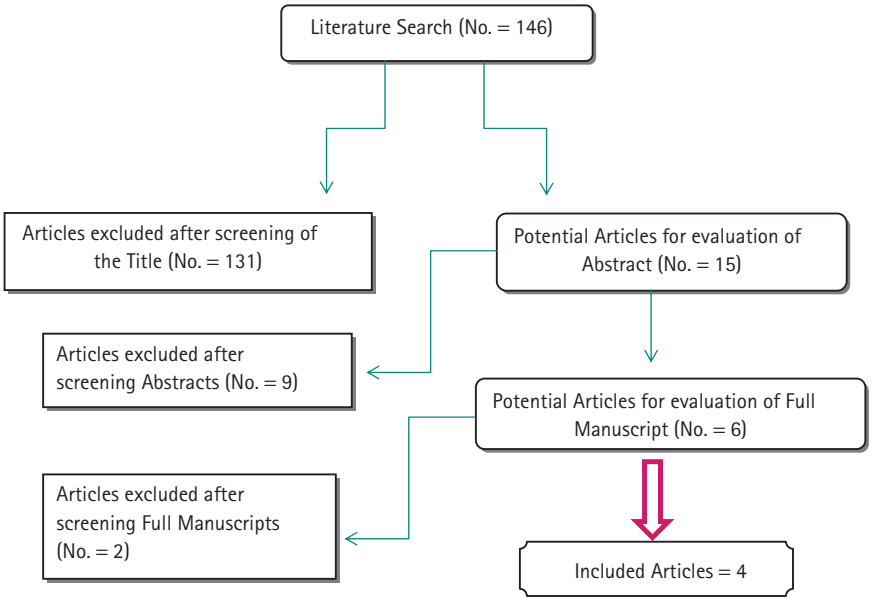
Terms used included: 'Laparoscopic', 'Laparoscopy', 'Partial', and 'Nephrectomy', and 'Obesity'.

Medical Subject Headings (MeSH) phrases included:
(('Laparoscopy'[MeSH]) AND 'Obesity'[MeSH]) AND 'Nephrectomy'[MeSH])
(('Obesity'[MeSH]) AND 'Nephrectomy'[MeSH])

Papers in languages other than English were included if data was extractable, also references of searched papers were evaluated for potential inclusion. Authors of the included studies were contacted wherever the data was not available or not clear.

Three reviewers (O.A., B.S., and R.S.) identified all studies that appeared to fit the inclusion criteria for full review. Each reviewer independently selected studies for inclusion in the review. Disagreement between the extracting authors was resolved by consensus or referred to a third author (G.H.).

FIG. 1. Flowchart for article selection process of the review.



DATA EXTRACTION AND ANALYSIS

The objectives were to evaluate the efficacy and safety of LPN for obese compared with non-obese patients. Obesity was defined as having a body mass index (BMI) of ≥30 kg/m^2.

The following variables were extracted from each study: patient demographics, tumour size, laterality, BMI, operating duration, ischaemic time, blood loss, transfusion rates, hospital stay, conversion rates, RCC rate, positive margins, and complications which were classified according the Clavien postoperative classification [13]. The data of each study was grouped into a meta-analysis, in an intention-to-treat basis, to allow a numerical representation of the results. Only similar results that were pooled from the included studies were meta-analysed [14]. For dichotomous data a Mantel-Haenszel chi-square test was used and expressed as odds ratios (ORs) with 95% CIs and for continuous data an inverse variance was used and the mean difference (MD) used, or the standardised mean difference (SMD), if different scales have been used [14].

There was no heterogeneity between the studies that were analysed using a chi-square test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test [14,15]. I^2 values of 25%, 50% and 75% correspond to low, medium and high (significant) levels of heterogeneity [14]. Data was pooled using the fixed-effect model as there was no statistically significant heterogeneity (I^2 > 50% was considered as significant heterogeneity) existing between studies [14]. We used Review Manager (RevMan 5.0.23) to calculate the comparisons and plot the quality assessment tables.

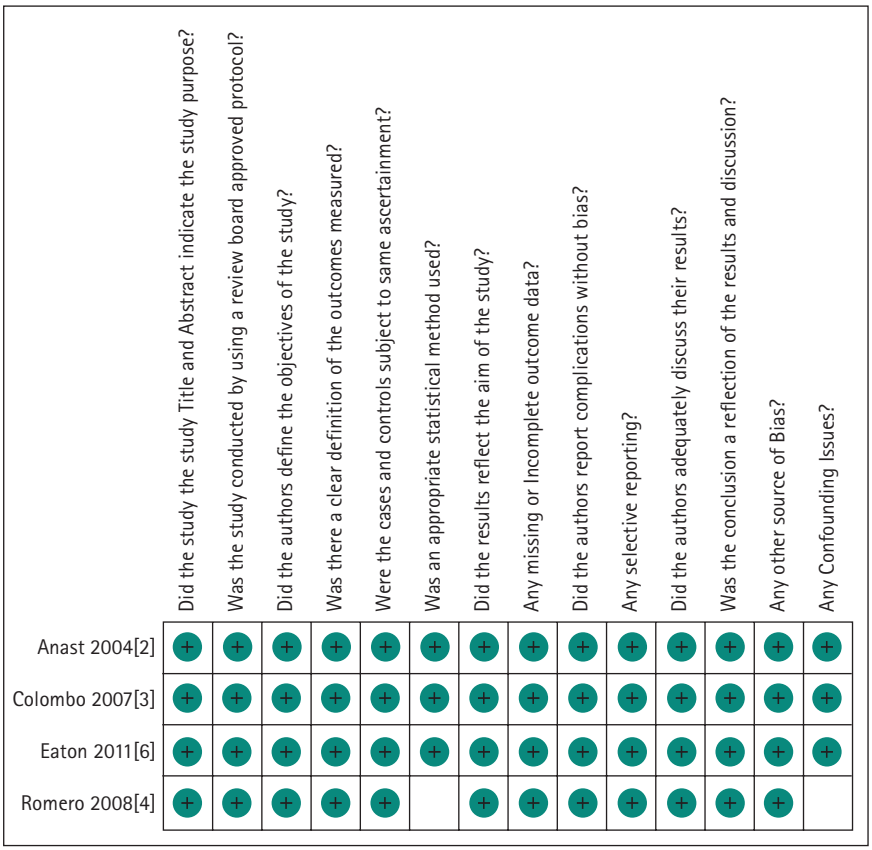
QUALITY ASSESSMENT

We intended to assess the methodological quality of the included studies by using the National Health Service's Critical Appraisal Skills Programme (CASP) amalgamated with Newcastle-Ottawa scale checklist for methodology quality assessment [16].

RESULTS

The study selection process depicted in Fig. 1 shows that 146 titles were reviewed for potential inclusion. Of which, 140 were excluded due to irrelevance from the title or abstract. Of the remaining six, four were included, the remaining two were excluded

FIG. 2. Quality assessment (risk of bias summary: review authors' judgements about each risk of bias item for each included study).



[2–7]. The Naeem *et al.* [7] study was on robot-assisted PN in obese patients rather than laparoscopy. While the Gong *et al.* [5] article was a review of the impact BMI has on the outcomes of laparoscopic surgery in general rather than focusing on just PN.

CHARACTERISTICS OF THE INCLUDED STUDIES

Four studies were included with 659 patients of which 256 were obese and were compared with 403 non-obese patients [2,4,6,7]. All the studies were retrospective studies in English language publications and conducted between 1998 and 2010. All the studies compared LPN between obese and non-obese patients.

Three of the studies were included in the meta-analysis of the patients' age and tumour size [3,4,6]. All the studies reported on the laterality of the tumours. Only two studies reported on the means of the BMI of the patients and the RCC rate [3,4]. Anast *et al.* [2] conducted a comparison of laparoscopic radical, partial, and simple nephrectomies in obese and non-obese patients and had not differentiated between the three procedures in numerous outcomes of this review and therefore their data was not included in those sections.

All the studies reported on the operative duration, WIT, EBL, and hospital stay. Although, one study did not report the WIT and therefore no data available for the meta-analysis [2]. Furthermore, only one study reported positive margins [6].

All the studies reported on complication rates. However, two of the studies divided their complications into intra and postoperative [3,4]. Eaton *et al.* [6] classified the complications accord to the Clavien system, while Anast *et al.* [2] classified the complications as minor and major. Minor complications are those classified as Clavien I or II while, major complications are Clavien ≥ III.

All the studies reported on conversion rates [2–4], while three reported on transfusion rates [2,3,6].

QUALITY ASSESSMENT

In the absence of randomised controlled trials dealing with the issue, a meta-analysis of observational studies can be considered vital to fill the void [17]. Assessment of quality of observational studies is more difficult than that of randomised controlled trials and there is a lack of validated assessment tools available [17]. Despite this, the Cochrane Non-Randomized Studies Methods Working group recommend the use of the Newcastle-Ottawa Scale checklist to assess these types of studies [17,18]. Therefore, we have made a checklist that depicts all the important points that observational studies need to address (Fig. 2 [2–4,6]).

Although all the studies are limited by being retrospective and have a potential risk of selection bias, we found no other potential sources of bias in any of the studies. However, one study had a confounding issue, which was not made clear by the corresponding author despite attempts to contact him. Romero *et al.* [4] presented their data in both median (range) in the results section and again as mean ± SD in the tables. There was no mention of which data set was used for the statistical comparison between the two groups and to why both data sets were used. However, this did not alter the meta-analysis of this review.

EFFECTS OF INTERVENTION

There was no difference between the two groups for tumour size, laterality, and RCC rate ($P = 0.86$, 0.75, 0.63, and 0.18). There was of course significantly higher BMI within the obese group ($P < 0.001$). The obese group additionally had a younger cohort of patients compared with the non-obese group ($P = 0.01$; Table 1).

Concerning the primary objective of the present review, the efficacy, there was no statistically significant difference between obese and non-obese patients in any of the parameters considered. Both groups were statistically similar for operative duration ($P = 0.24$; MD 5.64, 95% CI −3.80 to 15.09), WIT ($P = 0.21$; MD −1.04, 95% CI −2.68 to

0.59), EBL ($P = 0.05$; MD 53.73, 95% CI 0.72–106.74) or hospital stay ($P = 0.76$; MD −0.04, 95% CI −0.30 to 0.22) (Table 1 and Fig. 3 [2–4,6]). Furthermore, two of 48 patients in the obese group vs two of 77 in the non-obese group had positive margins; however, this was not statistically significant ($P = 0.63$).

The secondary objective was to compare the safety of LPN between the groups. There was no statistically significant difference between obese and non-obese patients for complications in total ($P = 0.9$; OR 1.02, 95% CI 0.70–1.49), intraoperative complications ($P = 0.36$; OR 0.68, 95% CI 0.30–1.53), or postoperative complications ($P = 0.51$; OR 1.15, 95% CI 0.75–1.77). Furthermore, there was no significant difference for procedure conversions ($P = 0.05$; OR 4.13, 95% CI 1.00 to 16.97) or blood transfusion rates ($P = 0.28$; OR 1.60, 95% CI 0.68–3.74) (Fig. 4 [2–4,6]).

Interestingly, when we group the complications according to the Clavien classification of postoperative complications, we found that for Clavien I and II there was no significant difference between the groups with 52/403 complications in the non-obese group and 38/256 in the obese ($P = 0.03$; OR 1.10, 95% CI 0.69–1.73). However, the obese group had significantly more complications classified as Clavien III with 11/256 complications compared with six of 403 in the non-obese group ($P = 0.01$; OR 3.95, 95% CI 1.36–11.42).

DISCUSSION

The present review found no difference between the obese and non-obese groups for tumour size, laterality, or cancer incidence (Table 1). However, evidence suggests that obesity is a risk factor for RCC due to the elevated concentration of insulin-like growth factor-I, free oestrogens and lipid peroxidation [3,6]. However, a quantitative review by Bergstrom *et al.* [19] reported that 27% and 29% of RCC among women and men respectively was related to excess weight or obesity. Despite the increased incidence of RCC in the obese group, studies have suggested a better prognosis in the obese group [3,4,6].

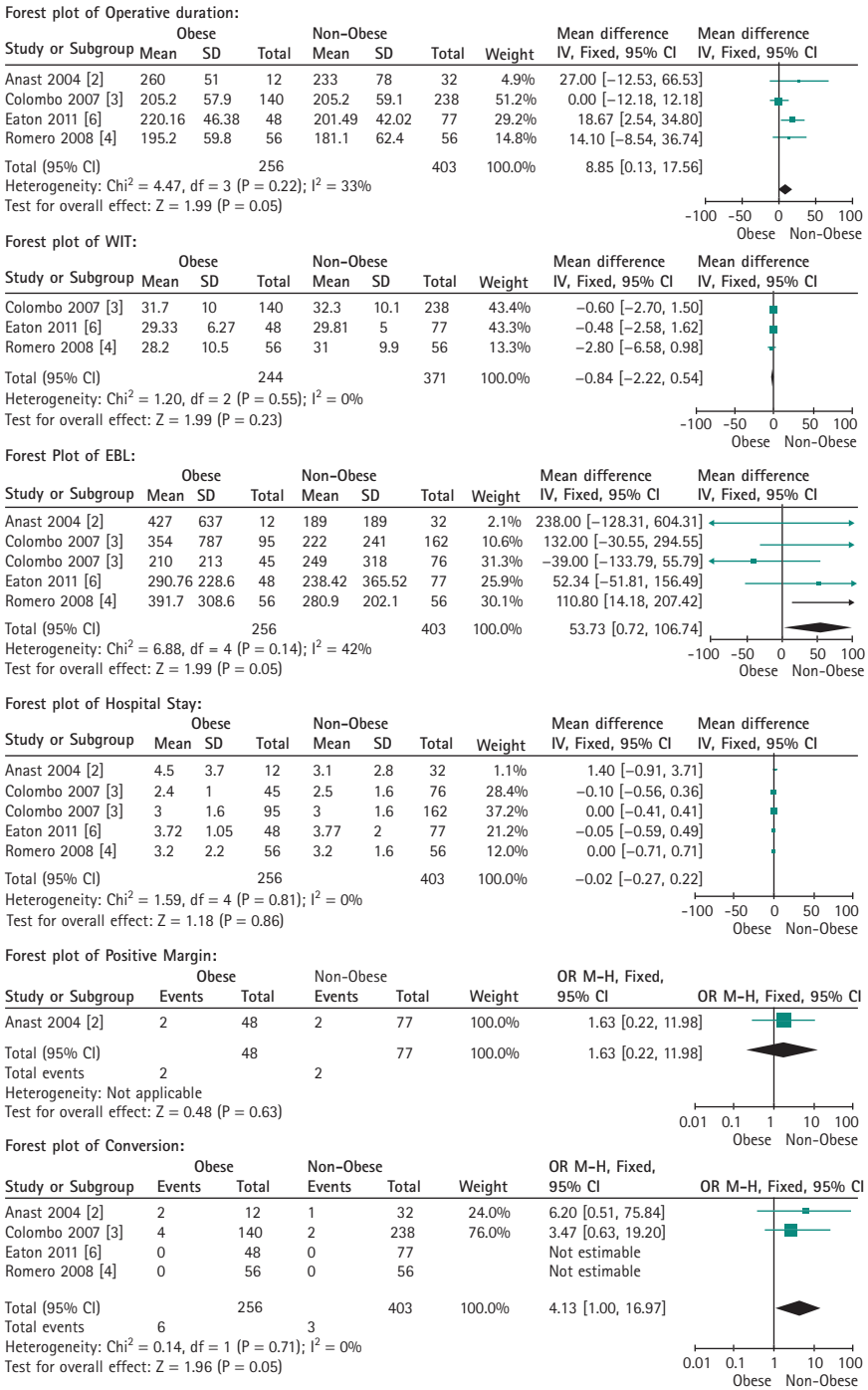
The better prognosis encourages the aggressive management of obese patients

TABLE 1 Table showing study results non-obese vs obese

Reference	No. of patients	Mean (SD) age, years	Mean (SD) tumour size, cm	Right:left, n	Mean (SD) BMI, kg/m^2	Malignant, n	Mean (SD) operating time, min	Mean (SD) WIT, min	Mean (SD) EBL, mL	Positive margins, n	Mean (SD) hospital stay, days
Anast *et al.* 2004 [2]	32 vs 12	NA	NA	21:11 vs 8:4	NA	NA	233 (78) vs 260 (51)	NA	189 (189) vs 427 (637)	2/77 vs 2/48	3.1 (2.8) vs 4.5 (3.7)
Colombo *et al.* 2007 [3]	238 vs 140	60.2 (13.5) vs 57.6 (11.2)	2.8 (1.3) vs 2.8 (1.1)	131:107 vs 76:64	25.7 (2.6) vs 35.7 (6.4)	139 vs 92	205.2 (59.1) vs 205.2 (57.9)	32.3 (10.1) vs 31.7 (10)	76:249 (318) vs 45:210 (213) 162:222 (241) vs 95:354 (787)	NA	76:2.5 (1.6) vs 45:2.4 (1) 162:3 (1.6) vs 95:3 (1.6)
Romero *et al.* 2008 [4]	56 vs 56	58 (11) vs 55.4 (10.8)	3.1 (0.9) vs 3.1 (1.2)	28:28 vs 30:26	25.5 (2.5) vs 36.6 (7.2)	42 vs 45	181.1 (62.4) vs 195.2 (59.8)	31 (9.9) vs 28.2 (10.5)	280.9 (202.1) vs 391.7 (308.6)	NA	3.2 (1.6) vs 3.2 (2.2)
Eaton *et al.* 2011 [6]	77 vs 48	55.61 (12.26) vs 54.02 (12.16)	2.64 (2) vs 2.74 (1.37)	27:50 vs 21:27	NA	64 vs 39	201.49 (42.02) vs 220.16 (46.38)	29.81 (5) vs 29.33 (6.27)	238.42 (365.52) vs 290.76 (228.6)	NA	3.77 (2) vs 3.72 (1.05)

NA, not available.

FIG. 3. Forest plots of outcomes.



with RCC. However, due to the accompanying co-morbidities and difficulty in anaesthetising these patients, risks of major complications have to be considered.

Matin *et al.* [20] conducted a study to evaluate age and comorbidities as risk factors after laparoscopic procedures. They reported that laparoscopy is well tolerated with no increased risk of complications in patients aged ≥ 65 years; however, is associated with a prolonged hospital stay in this population. The present review found that the non-obese patients were older; however, no difference was found between the groups for hospital stay (Fig. 3).

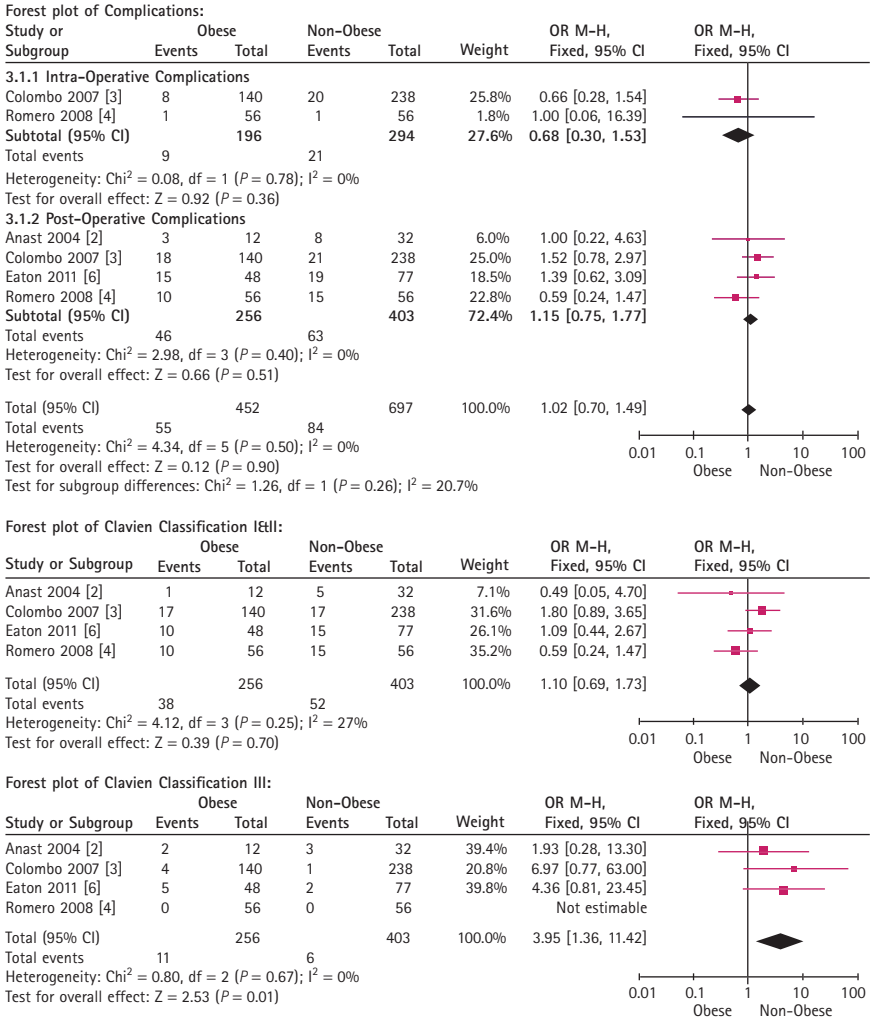
While Gong *et al.* reported that obesity is associated with increased operative difficulty and prolonged operative durations with increased intraoperative complications, we found no difference between the two groups for operative duration (Fig. 3) [5]. We also found no evidence to suggest that obese patients are more likely to develop intraoperative complications (Fig. 4). However, when a sub-group analysis was conducted to classify the complications according to the Clavien classification; we found that obese patients were significantly more likely to develop Clavien III complications compared to the non-obese patients (Fig. 4). There was no difference between obese and non-obese for Clavien I and CII complications (Fig. 4).

Furthermore, there was no difference in conversion rates, but there was a higher trend in the obese group for conversions (six of 256 vs three of 403). There was also no difference in the intraoperative EBL (Fig. 3). By contrast, to Jacobs *et al.* [21] reported that obese patients had longer operative durations and increased blood loss.

Numerous comparative studies comparing obese and non-obese patients have shown a variety of results, but no conclusive report has been published in this regard [2–6]. The present review, meta-analysed four studies that met the inclusion criteria and the only significant difference found between the obese and non-obese patient undergoing LPN was the greater risk of developing a major complication class Clavien ≥ III (Fig. 4). This in itself should alert surgeons to be especially vigilant when managing obese patients intra- or postoperatively. However, the incidence of Clavien III complications was still low at 4.3% (11/256).

Limitations of the present review are that the studies meta-analysed are observational control studies. However, due to the nature of the procedure in question, LPN, and looking at two distinct groups of patients, the obese and non-obese, randomisation and 'blinding' are not feasible options. To this end, the present review is an accurate depiction of the comparison between these two cohorts for LPN. The studies also did

FIG. 4. Forest plots of complications and Clavien classifications.



not detail nephrometry scoring of renal tumours and therefore comparison corrected for similar tumour characteristics is not possible. A further limitation is the differing experience of the surgeons conducting the procedures, although none of the studies mention the level of expertise, all the studies were conducted in high-volume centres.

As more centres conduct these procedures, a prospective multi-centred, protocol-driven study would be useful. Including various centres with different levels of operator experience would be more representative of the standard Urological cross-section of practice. Furthermore, sub-group analysis comparing different levels of obesity to normal-weighted patients will allow a more robust comparison.

CONCLUSION

Based on the findings of the present meta-analysis, LPN can be safely and efficiently performed for obese patients with comparable results to those for non-obese patients. Nevertheless, although still uncommon, the likelihood of major complications is higher for obese patients.

CONFLICT OF INTEREST

None declared.

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Correspondence: Omar M. Aboumarzouk, The Royal Bournemouth and Christchurch Hospitals NHS Trust, Urology Department, Castle Lane East, Bournemouth, BH7 7DW, UK.
e-mail: aboumarzouk@gmail.com

Abbreviations: **(L)PN**, (laparoscopic) partial nephrectomy; **WIT**, warm ischaemic time; **EBL**, estimated blood loss; **BMI**, body mass index; **OR**, odds ratio; **(S)MD**, (standardised) mean difference.

2. Robotic versus laparoscopic partial nephrectomy: a systematic review and meta-analysis

Many centers have now reported their early experience in doing robotic partial nephrectomy (RPN). The perceived advantage of this technique with laparoscopic partial nephrectomy (LPN) is getting an optically magnified three-dimensional imaging and a greater range of fully articulated wristed-instrument motion. We wanted to review outcomes comparing RPN with LPN. A systematic review was performed for relevant studies in February 2012 from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials – CENTRAL, CINAHL, Clinicaltrials.gov, Google Scholar and Individual urological journals.

Of the 521 studies, 447 were excluded due to non-relevance based on the titles and 51 excluded due to non-relevance based on the abstracts. After evaluating the full manuscripts, 12 studies were included in the systematic review and 7 studies (717 patients) in the meta-analysis. Although, there were no significant differences in patient age, tumour size and location and final pathology result between RPN and LPN groups the RPN group had a significantly less warm ischaemia time but there were no differences in hospital stay or complication rates. Our results showed that RPN is a safe and feasible alternative to LPN with a shorter warm ischaemia time.

(Contribution 35%, doing the systematic review, proofreading/correcting the paper and helping with subsequent revisions).

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Editorials by Alexandre Mottrie, Marco Borghesi and Vincenzo Ficarra on pp. 1034–1036 and by Anthony T. Corcoran, Alexander Kutikov and Robert G. Uzzo on pp. 1037–1038 of this issue

Robotic Versus Laparoscopic Partial Nephrectomy: A Systematic Review and Meta-Analysis

Omar M. Aboumarzouk [a,b,], Robert J. Stein [c], Remi Eyraud [c], Georges-Pascal Haber [c], Piotr L. Chlosta [d], Bhaskar K. Somani [e], Jihad H. Kaouk [c]*

[a] *Wales Deanery, Urology Department, Cardiff, Wales, UK;* [b] *Islamic University of Gaza, College of Medicine, Gaza, Palestine;* [c] *Cleveland Clinic, Glickman Urologic and Kidney Institute, Cleveland, OH, USA;* [d] *Department of Urology, Institute of Oncology, UJK University, Kielce, Poland and Department of Urology, the Medical Centre of Postgraduate Education, Warsaw, Poland;* [e] *University Hospitals Southampton NHS Trust, Southampton, UK*

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Abstract

Context: Centres worldwide have been performing partial nephrectomies laparoscopically for greater than a decade. With the increasing use of robotics, many centres have reported their early experiences using it for nephron-sparing surgery.
Objective: To review published literature comparing robotic partial nephrectomy (RPN) with laparoscopic partial nephrectomy (LPN).
Evidence acquisition: An online systematic review of the literature according to Cochrane guidelines was conducted from 2000 to 2012 including studies comparing RPN and LPN. All studies comparing RPN with LPN were included. The outcome measures were the patient demographics, tumour size, operating time, warm ischaemic time, blood loss, transfusion rates, length of hospital stay, conversion rates, and complications. A meta-analysis of the results was conducted. For continuous data, a Mantel-Haenszel chi-square test was used; for dichotomous data, an inverse variance was used. Each was expressed as a risk ratio with a 95% confidence interval $p < 0.05$ considered significant.
Evidence synthesis: A total of 717 patients were included, 313 patients in the robotic group and 404 patients in the laparoscopic group (seven studies). There was no significant difference between the two groups in any of the demographic parameters except for age (age: $p = 0.006$; sex: $p = 0.54$; laterality: $p = 0.05$; tumour size: $p = 0.62$, tumour location: $p = 57$; or confirmed malignant final pathology: $p = 0.79$). There was no difference between the two groups regarding operative times ($p = 0.58$), estimated blood loss ($p = 0.76$), or conversion rates ($p = 0.84$). The RPN group had significantly less warm ischaemic time than the LPN group ($p = 0.0008$). There was no difference regarding postoperative length of hospital stay ($p = 0.37$), complications ($p = 0.86$), or positive margins ($p = 0.93$).
Conclusions: In early experience, RPN appears to be a feasible and safe alternative to its laparoscopic counterpart with decreased warm ischaemia times noted.

* Corresponding author. Wales Deanery, Urology Department, Cardiff, Wales, UK and Islamic University of Gaza, College of Medicine, Gaza, Palestine. Tel. +44 7886 885677.
E-mail address: aboumarzouk@gmail.com (O.M. Aboumarzouk).

1. Introduction

Partial nephrectomy (PN) is the gold standard for treatment of small renal masses, with laparoscopy becoming a more commonly used approach [1]. With advancements in laparoscopic techniques, equipment, and operator skills, laparoscopic PN (LPN) has emerged as a viable alternative to open PN with comparable oncologic outcomes, less

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morbidity, and faster postoperative recovery [1–4]. However, LPN is technically challenging and has a steeper learning curve because it requires not only precise tumour margin resection but complex and time-dependent renal reconstruction [5–9]. This led the European Association of Urology to propose that these techniques be performed only in experienced centres [1].

Current robotic surgical systems provide not only optically magnified three-dimensional imaging but also a greater range of fully articulated wristed-instrument motion. This provides precision control with scaling of the surgeons' movements [1,2].

Numerous centres have published their experiences with robotic PN (RPN) [1–3,6,7,9–11]. RPN outcomes have been reported to be similar to laparoscopic or open procedures in terms of oncologic and functional outcomes [6–9]. Enhanced precision robotic handling has reduced the technical challenges posed by LPN, helped reduce the surgical learning curve needed, and shortened operative and ischaemic times with less blood loss compared with LPN [1,2,4]. Several studies have emerged recently comparing experience with outcomes of RPN and LPN [2,8,11,12].

We conducted a systematic review of the literature with a meta-analysis of the results to compare RPN and LPN in terms of operative and ischaemic times, blood loss, hospital stay, conversion rates, positive surgical margin rates, and perioperative complications.

2. Evidence acquisition

2.1. Search strategy and study selection

The systematic review was performed according to the Cochrane review guidelines. The search strategy was conducted to find relevant studies from Medline (2000–2012), Embase (2000–2011), Cochrane Central Register of Controlled Trials—CENTRAL (in the Cochrane Library, Issue 1, 2011), CINAHL (2000–2012), Clinicaltrials.gov, Google Scholar, and individual urologic journals. The search was conducted on February 6, 2012.

Search terms used included *robot, robotic, robotics, laparoscopic, laparoscopy, partial, nephron sparing*, and *nephrectomy*. Medical Subject Heading (MeSH) phrases included ("Robotics"[MeSH]) AND "Nephrectomy"[MeSH]); (("Robotics"[MeSH]) AND "Nephrectomy"[MeSH]) AND "Laparoscopy"[MeSH]); (("Robotics"[MeSH]) AND "Laparoscopy"[MeSH]) AND "Nephrectomy"[MeSH]) AND Partial).

Papers in languages other than English were included if data were extractable. References of searched papers were also evaluated for potential inclusion. Authors of the included studies were contacted wherever the data were not available or not clear. If data were not provided or clarified, the study was excluded.

Two reviewers (O.A. and R.S.) identified all studies that appeared to fit the inclusion criteria for full review. Four reviewers (O.A., R.S., R.E., and B.S.) independently selected studies for inclusion in the review. Disagreement between the extracting authors was resolved by consensus by all authors.

2.2. Data extraction and analysis

Studies comparing RPN with LPN were included. The main outcome was to assess the pre-, peri-, and postoperative results between the two procedures. The secondary outcome will be to assess the learning curve required and a cost analysis. The following variables were extracted from each study: patient demographics, tumour size, operating time, warm ischaemic time, blood loss, transfusion rates, length of hospital stay, conversion rates, and complications. The data of each study were grouped into a meta-analysis, in an intention-to-treat basis, to allow a numerical representation of the results. Only similar results that were pooled from the included studies were meta-analysed. A subgroup analysis was conducted to evaluate whether or not the tumour location or the complication classification varied between the two procedures. For continuous data, a Mantel-Haenszel chi-square test was used and expressed as the mean difference with 95% confidence interval (CI). For dichotomous data, an inverse variance was used and expressed as risk ratio with 95% CI. In both cases $p < 0.05$ was considered significant.

Taking into consideration that the first 25 procedures can be attributed to the learning curve for the procedures, we conducted a subgroup analysis to compare the two procedures regarding operative times, estimated ischaemic times, blood loss, length of hospital stay, and complication rates.

Heterogeneity will be analysed using a chi-square test on n-of-1 degree of freedom, with an α of 0.05 used for statistical significance and with the I^2 test [13]. I^2 values of 25%, 50%, and 90% correspond to low, medium, and high levels of heterogeneity. A fixed-effect model was used unless statistically significant high heterogeneity (ie, $I^2 > 90\%$) existed between studies. A random-effects model was used if heterogeneity existed. Although not included in the meta-analysis, studies of relevance were included in the systematic review for a general overview.

An assessment of the methodological quality of the included studies in the meta-analysis was conducted in line with the Cochrane handbook [13,14]. For quality assessment, the selection bias, performance bias, detection bias, attrition bias, and reporting bias were assessed in each of the included studies. We used Review Manager (RevMan v.5.0.23) to plot the quality assessment.

3. Evidence synthesis

3.1. Literature search

The literature search yielded 521 studies, of which 447 were excluded due to nonrelevance based on the titles and 51 excluded due to nonrelevance based on the abstracts (Fig. 1). Full manuscripts were evaluated in 25 studies, of which 12 were included in the systematic review [4,8,12,15–23]. Of the 12 initially included studies, 7 were included in a pooled meta-analysis [4,12,19–23]. Most of the studies were published within the last 5 yr, reflecting the increased use of this procedure.

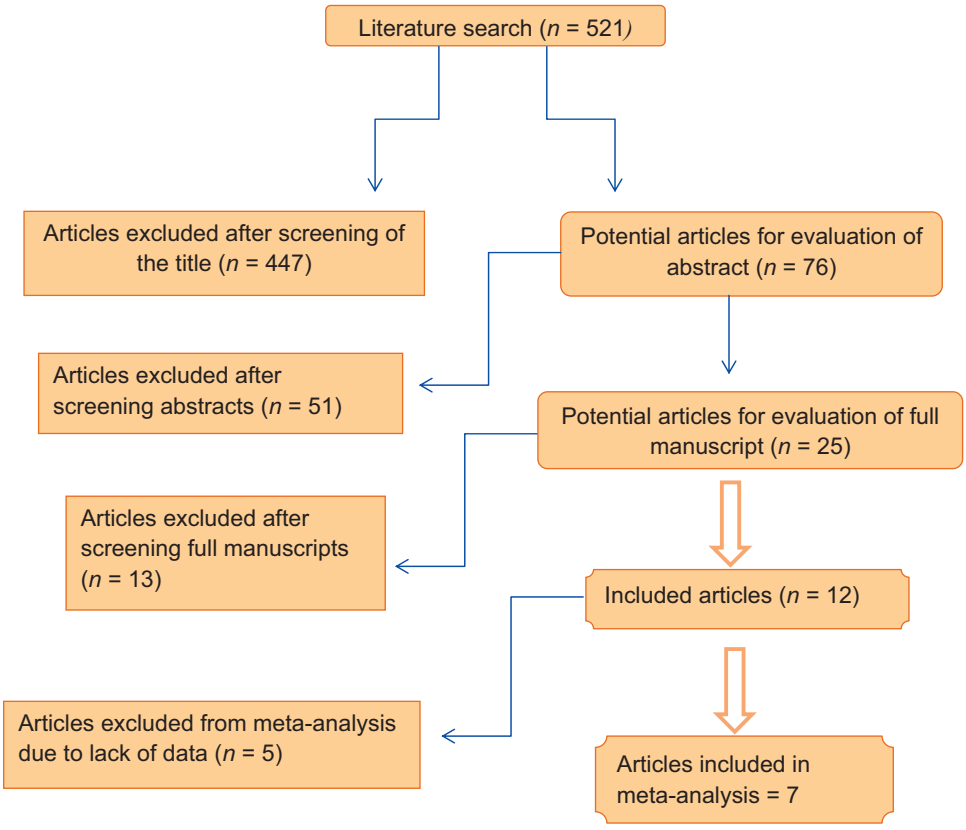


Fig. 1 – Flowchart for article selection process of the review.

After reading the full manuscripts, we excluded 13 studies for various reasons [1–3,7,10,11,24–30]. Laydner and Kaouk was a systematic review of RPN [24]. Lee et al. compared RPN with the open procedure rather than LPN [25]. Yu et al. assessed the use, costs, and outcomes of laparoscopic surgery in urology with no specific comparison of RPN versus LPN [26]. Aron et al. was excluded because the authors provided data of their larger cohort of patients over a longer period of time published more recently [11,12]. The study by Spana et al. only looked at complications of RPN [7]. Gupta et al. reported on RPN for large tumours with no comparison with LPN (27). Long et al. compared the outcomes of LPN and RPN of just complex renal tumours and therefore was excluded; however, a previously published study comparing LPN and RPN for the same group was included [12,30]. Although the remaining excluded studies were on RPN, no comparison with LPN was made [1–3,6,10,28,29].

All the included studies were cohort observational studies with no randomisation, and all reported on their centres' experience with RPN compared with LPN. All the studies reported on the patient demographics, tumour size, operating time, warm ischaemic time, blood loss, transfusion rates, length of hospital stay, conversion rates, and complications (plotted into Table 1, Fig. 2, and Fig. 3). Table 2 depicts the data of the five studies that were excluded from the meta-analysis due to lack of data [8,15–18]. All corresponding authors of the studies were contacted for data

Table 1 – Study results of robotic versus laparoscopic partial nephrectomy

Study	Patients, RPN vs LPN, no.	Age, RPN vs LPN, yr	Male:female, RPN vs LPN	Right:left, RPN vs LPN	Pathology, malignant:benign, RPN vs LPN
Ellison et al. [23]	108 vs 108	59.4 ± 12.1 vs 55.9 ± 10.6	66:42 vs 62:42	52:56 vs 57:51	92:16 vs 84:24
Haber et al. [12]	75 vs 75	62.6 ± 11.3 vs 60 ± 12.05	44:31 vs 40:35	36:39 vs 43:32	59:16 vs 59:16
Jeong et al. [19]	31 vs 26	53.4 ± 14 vs 58.7 ± 8.4	0.94:1 vs 1:1	NA	22:9 vs 18:8
Kural et al. [20]	11 vs 20	50.81 ± 13.15 vs 58.9 ± 15.4	8:3 vs 14:6	3:8 vs 8:12	11:0 vs 16:4
Pierorazio et al. [4]	48 vs 102	60.15 ± 9.13 vs 54.8 ± 11.59	27:21 vs 63:39	22:26 vs 55:47	36:12 vs 84:18
Seo et al. [21]	13 vs 14	54.2 ± 12.4 (33–72) vs 53.9 ± 11.6 (34–72)	10:3 vs 8:6	4:9 vs 10:4	11:2 vs 9:5
Williams et al. [22]	27 vs 59	55.74 ± 11.23 vs 54.6 ± 11.69	17:10 vs 41:18	13:14 vs 28:31	22:4 vs 58:2

LPN = laparoscopic partial nephrectomy; RPN = robotic partial nephrectomy; NA = not available.

or clarification either by e-mail or by postal address. The corresponding authors of the seven studies in the meta-analysis replied with the missing or unclear data where appropriate [4,12,19–23]. After numerous attempts at contacting the authors of the five remaining studies, no reply was received. Hence they were excluded because their data could not be pooled for analysis [8,15–18]. The authors failed to report the standard deviation of their results that are needed for meta-analysis of the data. The emphasis of this review is on the seven studies included in the meta-analysis.

3.2. Characteristics of the included studies

Although a literature search was conducted between 2000 and 2012, comparison studies were published between 2009 and 2012, four conducted in the United States, two in

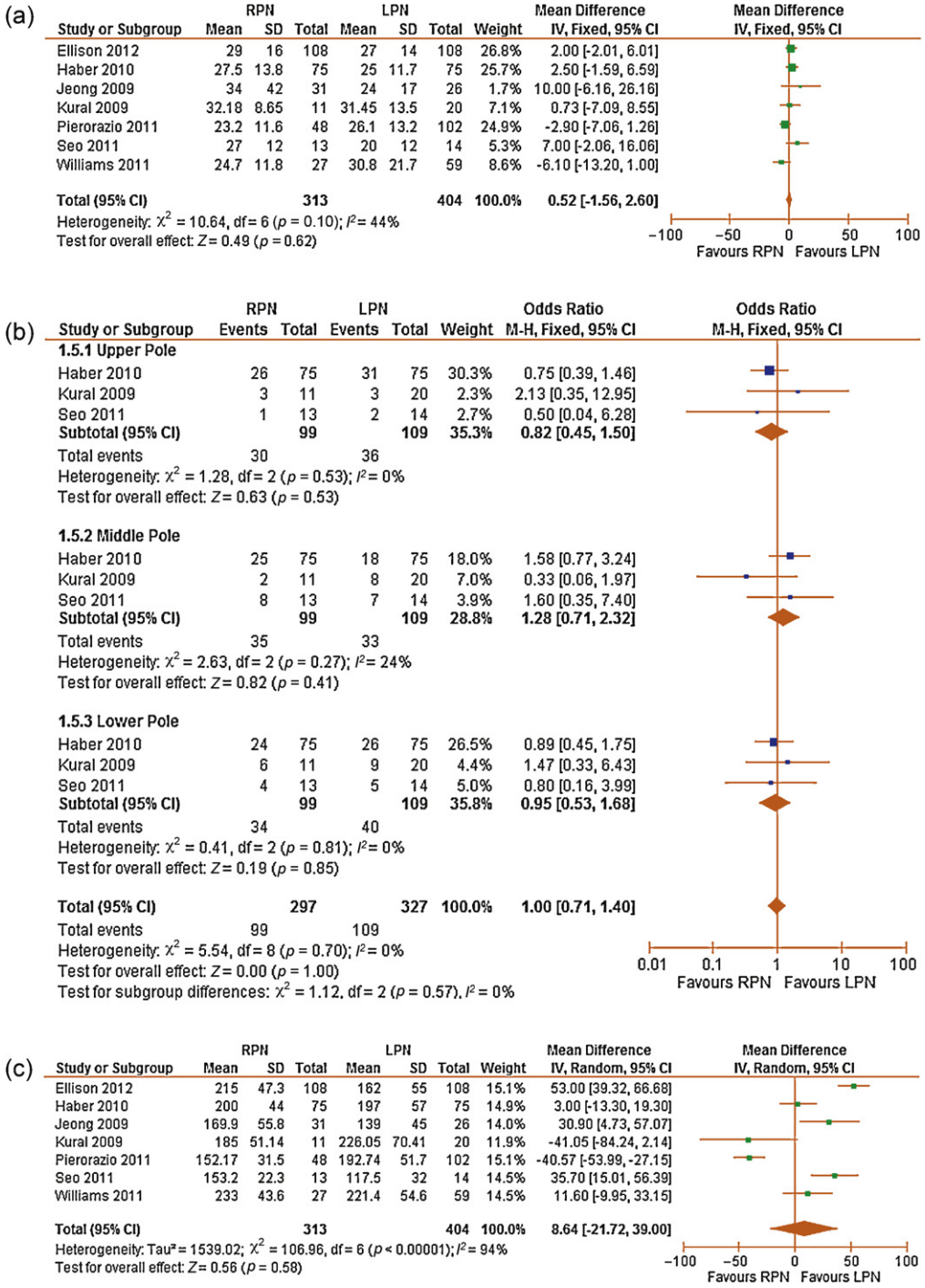
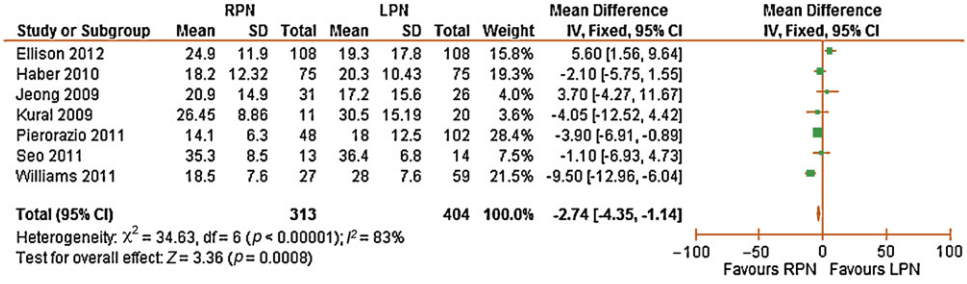


Fig. 2 – Forest plots of outcomes: (a) tumour size in millimetres; (b) tumour location; (c) operative time; (d) warm ischaemic time; (e) estimated blood loss; (f) length of hospital stay; (g) positive margin; (h) conversion. The following studies are cited: Ellison [23], Haber [12], Jeong [19], Kural [20], Pierazio [4], Seo [21], and Williams [22]. CI = confidence interval; IV = inverse variance; LPN = laparoscopic partial nephrectomy; M-H = Mantel-Haenszel; RPN = robotic partial nephrectomy; SD = standard deviation.

(d)



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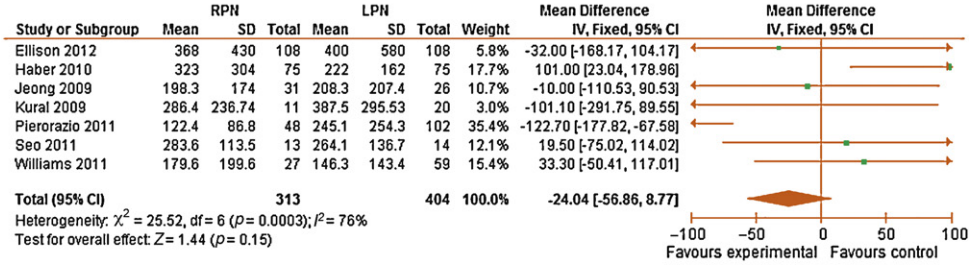

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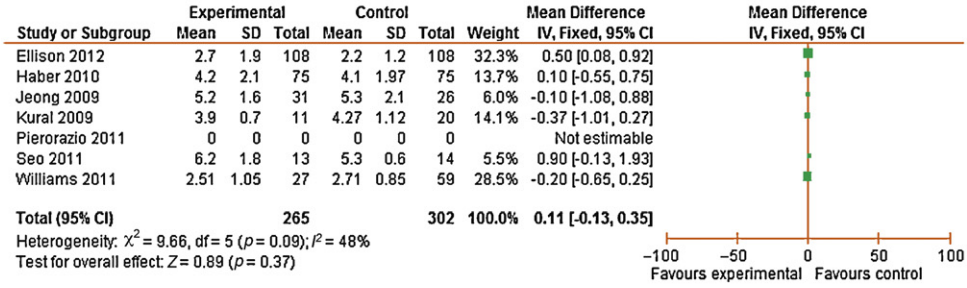

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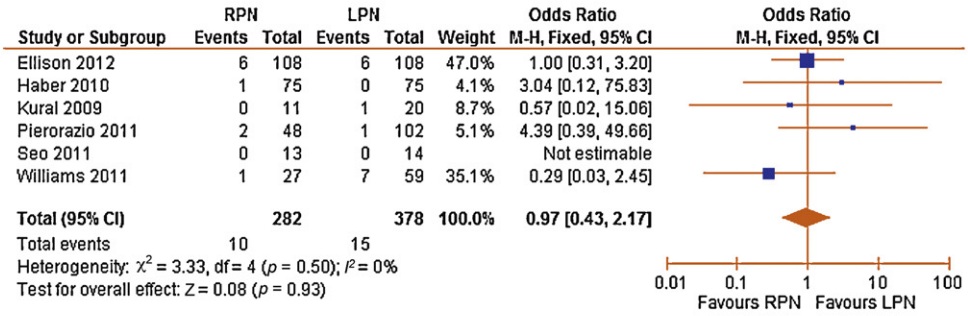

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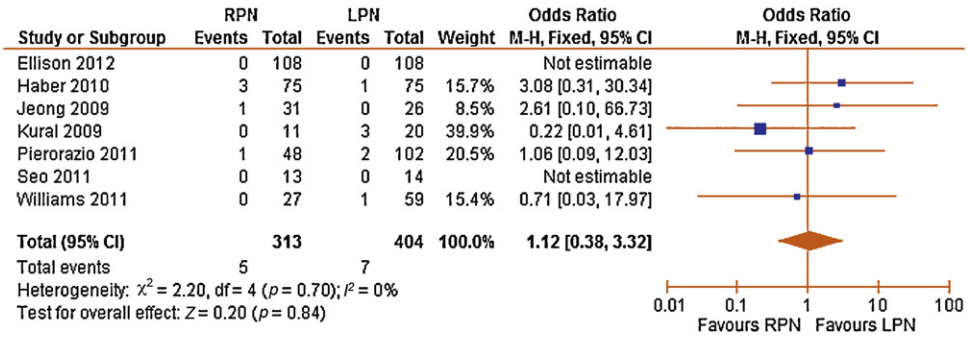

Fig. 2. (*Continued*).

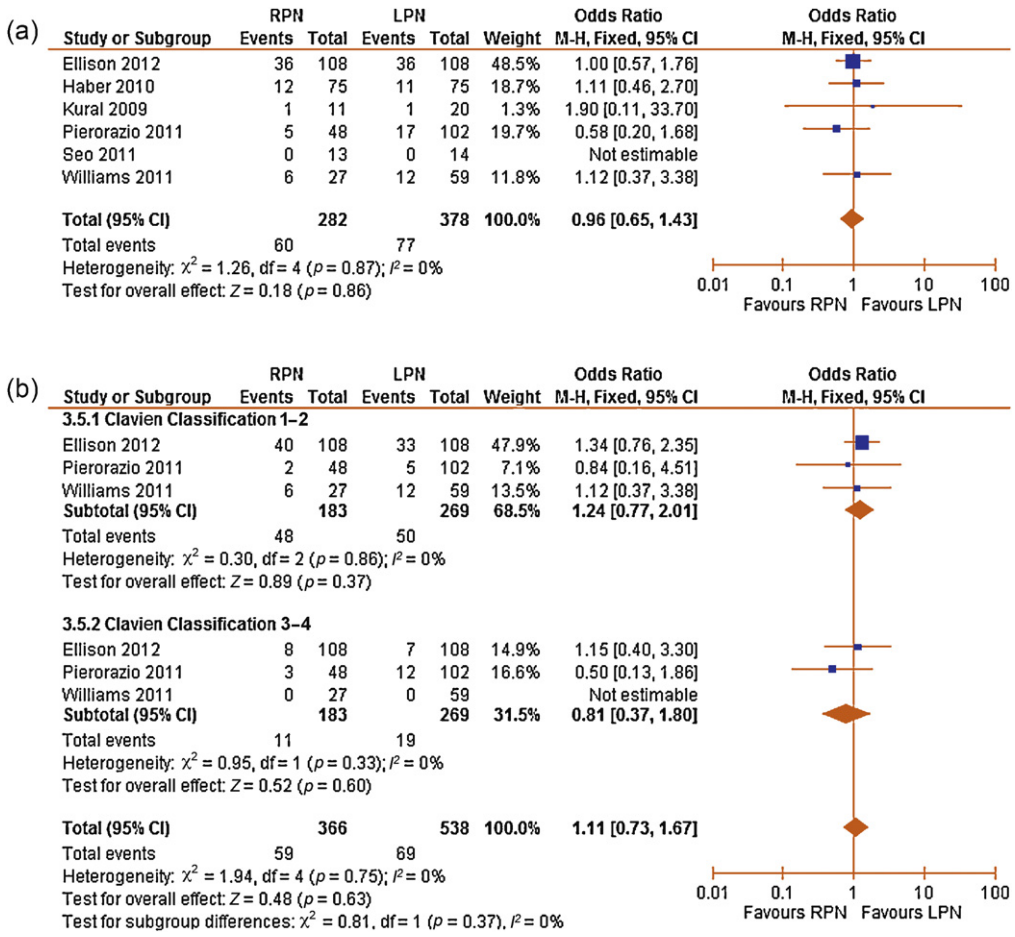

Fig. 3 – Forest plots of complications and Clavien classifications: (a) complications; (b) Clavien classifications 1–2 and 3–4. The following studies are cited: Ellison [23], Haber [12], Kural [20], Pierazio [4], Seo [21], and Williams [22].

Korea, and one in Turkey. Among the 717 patients, the ages of 313 patients (the robotic group) ranged from 37 to 73 yr; the ages of 404 patients (the laparoscopic group) ranged from 42 to 73 yr. In the RPN group there were 188 men; 130 procedures were right sided. In the LPN group there were 241 men; 201 procedures were right sided. Jeong et al. did not report on the laterality of their procedure [19].

All seven studies reported on the tumour size, operative times, warm ischaemic times, estimated blood loss, transfusion requirement, length of hospital stay, conversion rates, and malignant and benign rates [4,12,19,23]. Three studies reported on tumour location [12,20,21]. Six studies reported surgical margins and complications [4,12,20–23]; however, only three studies classified their complications using the Clavien scheme [4,22,23]. The data of all the studies were given as means plus or minus the standard deviation, which allowed for a meta-analysis of the pooled data.

3.3. *Meta-analysis results*

Table 1 depicts the demographics of the studies including number of patients, age, sex, laterality, and pathology. There was no significant difference between the two groups for any of the demographic parameters except for age (age: $p = 0.006$, MD: 2.38, 95% CI, 0.69–4.06; sex: $p = 0.54$, odds ratio [OR]: 1.00, 95% CI, 0.81–1.24; laterality: $p = 0.05$, OR: 1.00; 95% CI, 0.80–1.25; malignant pathology: $p = 0.79$, OR: 1.05, 95% CI, 0.72–1.54).

There was no statistical difference found between RPN and LPN regarding tumour size ($p = 0.62$; MD: 0.52; 95% CI, −1.56 to 2.60), tumour location ($p = 1$; OR: 1.0; 95% CI, 0.71–1.4), or positive margins ($p = 0.93$; OR: 0.97; 95% CI, 0.43–2.17) (Fig. 2).

There was no perioperative difference between the two groups regarding operative times ($p = 0.58$; MD: 8.64; 95% CI, −21.72 to 39.00), estimated blood loss ($p = 0.15$; MD: −24.04; 95% CI, −56.86 to 8.77), or conversion rates ($p = 0.84$; OR: 1.12; 95% CI, 0.38–3.32). However, the RPN group had significantly less warm ischaemic time than the LPN group ($p = 0.0008$; MD: −2.74; 95% CI, −4.35 to −1.14) (Fig. 2). There was no difference regarding postoperative length of hospital stay ($p = 0.37$; MD: 0.11; 95% CI, −0.13 to 0.35) (Fig. 2).

There was no statistical difference between the two groups regarding complications ($p = 0.86$; OR: 0.96; 95% CI, 0.65–1.43). There was no difference between the two groups regarding the Clavien classification (CC) of complications

Table 2 – Study results of robotic versus laparoscopic partial nephrectomy of studies excluded

Study	Tumour size, RPN vs LPN. mm (mean)	Patients, RPN vs LPN, no.	Age, RPN vs LPN, yr	Male: female, RPN vs LPN	Right: left, RPN vs LPN	Operating time, RPN vs LPN, min (mean)	Warm ischaemia time, RPN vs LPN, min (mean)	Blood loss, RPN vs LPN, ml (mean)	Length of stay, RPN vs LPN, d (mean)	Location U/M/L pole, RPN vs LPN	Positive surgical margins, RPN vs LPN	Pathology, malignant: benign, RPN vs LPN
Benway and Bhayani [6]	28 vs 25	129 vs 118	59.2 vs 59.2	NA	NA	189 vs 174	19.7 vs 28.4	155 vs 196	2.4 vs 2.7	NA	5 vs 1	87:42 vs 89:29
Deane et al. [17]	31 (25–40) vs 23 (17–62)	11 vs 11	53.2 vs 54	10:1 vs 7:4	4:7 vs 4:7	228.7 (98–375) vs 289.5 (145–369)	32.1 (30–45) vs 35.3 (15–49)	115 (75–500) vs 198 (25–300)	2 vs 3.1	8/0/3 vs 3/3/5	0 vs 0	11:0 vs 8:3
Caruso et al. [15]	19.5 vs 21.8	10 vs 10	58 vs 61	NA	NA	279 vs 253	26.4 vs 29.3	240 vs 200	2.6 vs 2.65	3/3/4 vs 4/1/5	0 vs 1	8:2 vs 5:5
DeLong et al. [18]	26 vs 28	13 vs 15	59.7 vs 53.6	8:5 vs 8:7	7:6 vs 8:7	344 vs 254	29.7 (21–45) vs 39.9 (24–51)	Median: 100 vs 150	Not clear	NA	NA	13:0 vs 9:6
Cho et al. [16]	27 (9–35) vs 28 (15–35)	10 vs 10	63 (36–78) vs 56 (31–79)	8:2 vs 5:5	3:7 vs 5:5	376 (179–470) vs 361 (197–477)	31 (26–36) vs 40 (27–50)	329 (50–700) vs 328 (200–550)	7 (5–12) vs 14 (6–51)	3/4/3 vs 5/5/0	0 vs 0	9:1 vs 8:2

LPN = laparoscopic partial nephrectomy; RPN = robotic partial nephrectomy; U = upper; M = middle; L = lower; NA = not available.

CC 1 and 2 ($p = 0.89$; OR: 1.24; 95% CI, 0.77–2.01) and CC 3 and 4 ($p = 0.6$; OR: 0.81; 95% CI, 0.37–1.80) (Fig. 3).

3.3.1. *Subgroup analysis*

Removing the studies with <25 procedures, there was no difference found between the two groups regarding operative times ($p = 0.55$; MD: 11.32; 95% CI, −25.90 to 48.55), estimated blood loss ($p = 0.13$; MD: −27.53; 95% CI, −63.13 to 8.07), or postoperative length of hospital stay ($p = 0.31$; MD: 0.14; 95% CI, −0.13 to 0.41), Fig. 4. Furthermore, there was no difference regarding the complication rates ($p = 0.81$; OR: 0.95; 95% CI, 0.64–1.42). However, similar to the general analysis, the RPN group had significantly less warm ischaemic time than the LPN group ($p = 0.001$; MD: −2.83; 95% CI, −4.53 to −1.13) (Figs. 2 and 4).

3.4. *Methodological quality assessment*

All the studies were observational controlled studies. Figure 5 depicts the summary of the quality assessment based on the reviewing author's judgement of risks of bias for each included study. Only Pierorazio et al. had a high risk of selection bias due to the difference noted between the demographics of the LPN and RPN groups (the RPN group tended to be older) [4]. Otherwise the studies had a low risk of bias in all the categories. None of the studies were randomised or blinded, and the LPN groups were considered the control group.

3.5. *Discussion*

3.5.1. *Summary of the main results*

This review found no significant difference between RPN and LPN, except that the RPN group had significantly less warm ischaemic time (Fig. 2). With the exception of Pierorazio et al. and Ellison et al, there was no difference between the two groups regarding age, sex, tumour size, laterality, or location. However, a pooled analysis did show that the RPN group had older patients, implying the procedure can safely accommodate a wider age range than its laparoscopic counterpart.

Regarding the operative parameters, no significant difference was found pertaining to the operative time, blood loss, or conversion rate (Fig. 2). No statistical significance was found regarding the postoperative and oncologic parameters such as hospital stay, surgical margins, or complications (Fig. 2 and 3).

Four studies reported less warm ischaemia time in the RPN group [4,20,22,23]. One study had less blood loss in the LPN group [12]; another had less blood loss in the RPN group [4]. Seo et al. reported that the overall operative time in the LPN group was shorter; however, they further subdivided the operative time into laparoscopic time, defined as the insertion of the ports to their removal, which did not show any difference between the two groups [21]. Ellison et al. also found that the LPN group had shorter operative times, overall ischaemic time, and shorter length of hospital stay [23]. Pierorazio et al. reported that the RPN group had less operative time [4]. Despite the subtle variations between the

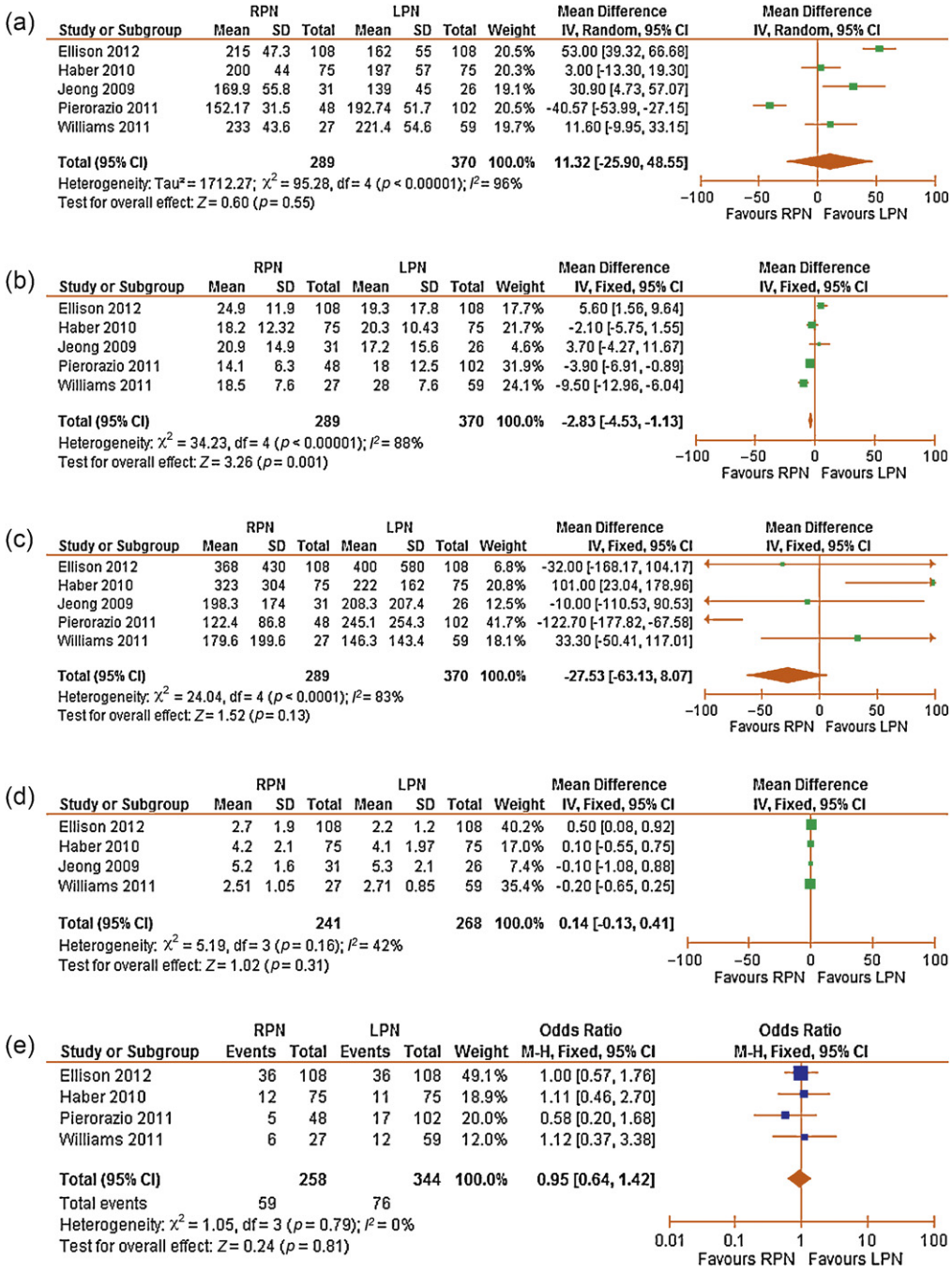

Fig. 4 – Forest plots of subgroup analysis: (a) subgroup analysis of operative times; (b) subgroup analysis of estimated ischaemic times; (c) subgroup analysis of blood loss; (d) subgroup analysis of length of hospital stay; (e) subgroup analysis of complications. The following studies are cited: Ellison [23], Haber [12], Jeong [19], Pierazio [4], Seo [21], and Williams [22].

groups, the pooled meta-analysis found no statistical difference between the two groups regarding most of the outcome parameters, except for warm ischaemic time favouring the RPN group with less time needed [4,12,19–23].

Although the only significant parameter favouring RPN, it is of vital importance because return of renal function depends on the duration of ischaemic time [31]. In fact, it is recommended that the pedicle clamping necessary during PN should be limited to 20 min of warm ischaemia [31,32]. Although the kidney can tolerate longer cold ischaemic times, up to 2 h, an international collaborative review suggested it should not go beyond 35 min [32]. Nevertheless, controversy exists regarding the importance of warm ischaemia time compared with other modifiable risk factors such as the amount of benign renal parenchyma preserved. Warm ischaemia was used in all studies in this review when hilar clamping was performed (Fig. 2 and Table 2). Because PN is essentially nephron-sparing surgery, every minute is vital for preservation of renal function. Therefore, it can be deduced that RPN is superior

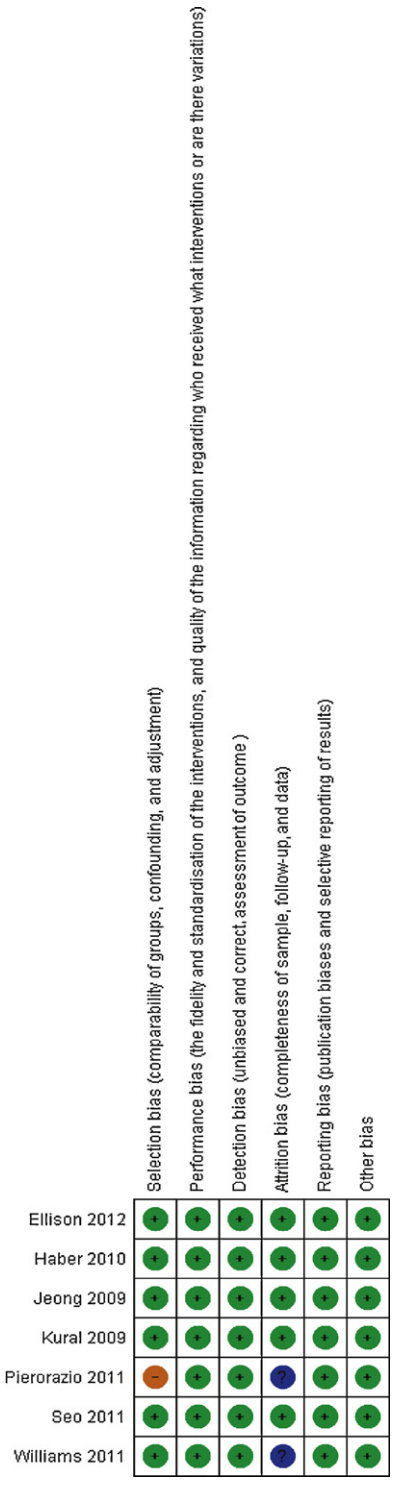

Fig. 5 – Quality assessment (risk of bias summary: review authors' judgements about each risk of bias item for each included study). The following studies are cited: Ellison [23], Haber [12], Jeong [19], Kural [20], Pierazio [4], Seo [21], and Williams [22].

to LPN in preserving nephrons and ultimately renal function.

The meta-analysis for one of the outcome parameters had significant heterogeneity, two other parameters had medium-level heterogeneity, and the remaining comparisons were considered as having low heterogeneity (Fig. 2). No cause for the heterogeneity was found because no difference regarding the risk of bias, timing and length of the studies, inclusion criteria, or country was isolated. Subgroup analysis conducted based on isolating small and large numbered cohort studies had no effect on the heterogeneity; however, no statistical significance between the two groups remained. Heterogeneity also applied to the warm ischaemia time. However, when small and large numbered cohorts were isolated, the heterogeneity did not change, and no change was found regarding the statistical difference, which favoured the RPN with less time. The discrepancy between the patient cohorts in the studies could explain the significant heterogeneity; however, no difference was found with the end result.

Regarding the five studies not included in the meta-analysis due to lack of data, three studies found no significant difference in any of the outcome parameters measured [15–17]. DeLong et al. reported that the LPN had significantly less operative time but significantly longer warm ischaemic time [18]. Benway et al. reported significantly less blood loss, shorter warm ischaemic time, and shorter hospital stay in the RPN group; otherwise no difference was noted regarding the other outcome parameters [8].

3.5.2. *Learning curve*

Pierorazio et al. conducted a further analysis to determine whether or not a learning curve has an effect on the end result. Comparing their first 25 patients to their most recent patients, they found a significant improvement in the operative time, warm ischaemic time, and estimated blood loss in the LPN group [4]. However, similar differences were not found in the RPN group when comparing the earlier and later patient data. Ellison et al. also found that the ischaemic time, blood loss, and operative times improved after the first 33 cases, suggesting the learning curve does improve with time and more familiarity with the procedure by both the surgeon and the operating team [23]. Mottrie et al. also found that the impact of surgeons' learning curve improved with time [1]. They showed that with more experience, the operative time, warm ischaemia time, and the need for pelvicaliceal repairs due to injury were reduced; however, no impact was found regarding blood loss or complications. In the largest reported series comparing early and later experiences of RPN, they showed that once the learning curve was past, there was a significantly decreased blood loss, transfusion rate, conversion rate, rate of postoperative complications, mean operative time, and length of hospital stay [33]. With further experience with RPN, lower complication rates and better results, especially with more complex tumours, compared with LPN may be noted. Nevertheless, further study is needed for verification, especially at a multi-institutional level.

3.5.3. *Cost analysis*

None of the studies conducted a cost analysis comparison between the laparoscopic and robotic groups. Nonetheless, Yu et al. compared the costs of various urologic procedures

carried out open, laparoscopically, or using robots [26]. They found that robotic surgery was significantly more expensive than both laparoscopic and open procedures. But it was associated with a significantly shorter hospital stay with fewer complications and transfusion rates compared with laparoscopic and open procedures. Despite this, no social cost analysis was found in the literature that factors in the implications of a quicker recovery and shorter convalescence. It is estimated that RPN costs about $1600 more per person or an additional 6% per case [26].

Despite the increase in costs, numerous reports have suggested that RPN is feasible for tumours >4 cm, complex tumours, in patients with prior abdominal surgery, in children, and even as single-port surgery [27,34–38]. A systematic review that included >700 patients who underwent RPN showed that RPN was feasible and had similar results to laparoscopic and open techniques [24].

3.5.4. Strengths and limitations of the review

The main limitation of this review is the inclusion of studies with small patient cohorts in the meta-analysis. Three of the seven studies included had ≥150 patients; the remaining studies had fewer numbers [4,12,23]. This can skew the results because these studies might be reporting on their initial experiences. However, with more experience reported beyond the initial learning curve, results of such comparative analysis may differ. Removing studies with <25 procedures in either group, we found no difference in the end results in any of the parameters.

This review was impartial and conducted systematically and methodically in keeping with Cochrane standards. This represents the evidence available in the literature comparing early experiences of RPN with LPN.

It is evident that a large multicentre trial comparing the two procedures in addition to open PN is required once the learning curve for RPN has been overcome. This study needs to include a cost analysis between the procedures, including postdischarge convalescence and return to work analysis, in addition to patient and surgeon perspectives regarding pain and overall satisfaction with the procedure.

4. Conclusions

Meta-analysis of the literature reveals that RPN is a feasible and safe alternative to LPN with similar outcomes and low complication rates. RPN was found to have significantly less ischaemic time. Further studies are needed to evaluate the benefits of RPN and its cost effectiveness compared with LPN.

Author contributions: Omar M. Aboumarzouk had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Aboumarzouk
Acquisition of data: Aboumarzouk, Stein, Eyraud, Haber.
Analysis and interpretation of data: Aboumarzouk.
Drafting of the manuscript: Aboumarzouk, Stein, Somani.
Critical revision of the manuscript for important intellectual content: Aboumarzouk, Stein, Haber, Chlosta, Somani, Kaouk.
Statistical analysis: Aboumarzouk.
Obtaining funding: None.
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Supervision: Aboumarzouk, Kaouk.
Other (specify): Bhaskar Somani and Jihad Kaouk have equal senior authorship.

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3. Flexible ureteroscopy and laser lithotripsy for stones >2 cm: a systematic review and meta-analysis

Flexible ureteroscopy and laser lithotripsy (FURSL) is now an established minimally invasive procedure for small renal stones. However larger stones (>2cm) are still preferably treated with percutaneous nephrolithotomy (PCNL), which carries a risk of significant morbidity. We wanted to assess the efficacy and safety of FURSL in renal stones >2cm in size. A systematic review was performed in August 2011 for relevant studies from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials – CENTRAL, CINAHL, Clinicaltrials.gov, Google Scholar and Individual urological journals. A subgroup analysis to evaluate the stone free rate (SFR) was also done in patients with stones between 2-3cm and above 3cm in size.

Of the 296 titles reviewed, 273 were excluded due to irrelevance from the title (252) or abstract (21). Nine of the remaining 23 studies were included after evaluating the full manuscripts (445 patients). Our results showed that for a mean stone size of 2.5 cm, the mean operative time was 82.5 minutes with a stone free rate (SFR) of 94% and an overall complication rate of 10%. The sub-group analysis showed a significantly better SFR for stones between 2-3 (96%) compared to stones >3cm (85%). Our results showed that FURSL could be safely used to treat stones larger than 2cm with good outcomes.

(Contribution 40%, doing the systematic review, writing up, proofreading/correcting the paper and helping with subsequent revisions).

(In top 10 most downloaded articles for *J Endourology* 2014).

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Flexible Ureteroscopy and Laser Lithotripsy for Stones >2 cm: A Systematic Review and Meta-Analysis

Omar M. Aboumarzouk, MBChB, MRCS (Glasg),[1,2,3] Manoj Monga, M.D.,[4] Slawomir G. Kata, M.D., FEBU,[5] Olivier Traxer, M.D.,[6] and Bhaskar K. Somani, MRCS, FEBU, FECS(Urol)[7]

Abstract

Background and Purpose: Urinary stones >2 cm are traditionally managed with percutaneous nephrolithotomy (PCNL). Recently, flexible ureteroscopy and laser lithotripsy (FURSL) has been used to manage them with comparable results. In a comparative study of renal stones between 2 and 3 cm, FURSL was reported to need less second-stage procedures and be just as effective as PCNL. Our purpose was to review the literature for renal stones >2 cm managed by ureteroscopy and holmium lasertripsy.

Materials and Methods: A systematic review and quantitative meta-analysis was performed using studies identified by a literature search from 1990s (the first reported large renal stones treated ureteroscopically) to August 2011. All English language articles reporting on a minimum of 10 patients treated with FURSL for renal stones >2 cm were included. Two reviewers independently extracted the data from each study. The data of studies with comparable results were included into a meta-analysis.

Results: In nine studies, 445 patients (460 renal units) were reportedly treated with FURSL. The mean operative time was 82.5 minutes (28–215 min). The mean stone-free rate was 93.7% (77%–96.7%), with an average of 1.6 procedures per patient. The mean stone size was 2.5 cm. An overall complication rate was 10.1%. Major complications developed in 21 (5.3%) patients and minor complications developed in 19 (4.8%) patients. A subgroup analysis shows that FURSL has a 95.7% stone-free rate with stones 2–3 cm and 84.6% in those >3 cm ($P = 0.01$), with a minor complication rate of 14.3% and 15.4%, respectively, and a major complication rate of 0% and 11.5%, respectively.

Conclusion: In experienced hands, FURSL can successfully treat patients with stones >2 cm with a high stone-free rate and a low complication rate. Although the studies are from high-volume experienced centers and may not be sufficient to alter everyday routine practice, this review has shown that the efficacy of FURSL allows an alternative to PCNL.

Introduction

Historically, renal stones larger than 2 cm were managed with percutaneous nephrolithotomy (PCNL), shockwave lithotripsy (SWL), or a combination of both and, in rare instances, an open procedure.[1–3] PCNL is considered the gold standard treatment for large stones with a clearance rate of 77% to 95%.[1–5] SWL has an overall stone-free rate (SFR) of 23% to 57%, and the rate decreases with increasing stone size.[2,4] Combined therapy, PCNL + SWL, only slightly increases the SFR to 66%, but necessitates, on average, 3.3 procedures per patient; therefore, it is not an ideal management strategy.[2] Open surgery has been relatively abandoned for the management of stones, with only a selective indication, such as patients with complex collecting systems, excessive morbid obesity, or extremely poor function of the affected renal unit.[2]

The last decade has witnessed not only technical advancements in endoscopic procedures and equipment, but also an increase in surgical skills using them.[3,6,7] The development of smaller diameter scopes, increased scope flexibility, improvement of accessories, and holmium laser technology has led more urologists to attempt management of large renal stones with flexible ureteroscopy and laser lithotripsy (FURSL). The resulting SFRs were comparable to those of PCNL.[3,4,8] Indeed, studies report a SFR of 88% to 92% in patients with large stones.[3,4]

[1]Department of Urology, Royal Bournemouth Hospital, Bournemouth, United Kingdom.
[2]Wales Deanery, Urology Department, Cardiff, Wales, United Kingdom.
[3]Islamic University of Gaza, College of Medicine, Gaza, Palestine.
[4]Department of Urology, Glickman Urological & Kidney Institute, Cleveland, Ohio.
[5]Department of Urology, Ninewells Hospital and Medical School, Dundee, Dundee, United Kingdom.
[6]Urology Department, Tenon University Hospital, Pierre and Marie Curie University, Paris, France.
[7]University Hospitals Southampton NHS Trust, Southampton, United Kingdom.

To this end, we aimed to conduct a systematic review and a meta-analysis to assess the efficacy and safety of FURSL in the treatment of patients with renal stones larger than 2 cm. Our secondary aim was to assess the operative times, number of procedures per patient needed to achieve a SFR, average stone size, and the use of ureteral access sheaths.

Materials and Methods

Search strategy and study selection

The systematic review was performed according to the Cochrane reviews guidelines. The search strategy was conducted to find relevant studies from MEDLINE (1990–August 2011), EMBASE (1990–August 2011), Cochrane Central Register of Controlled Trials-CENTRAL (in The Cochrane Library-Issue 1, 2011), CINAHL (1990–August 2011), Clinicaltrials.gov, Google Scholar, and individual urologic journals.

Terms used included: "ureteroscopy," "flexible ureteroscopy," "large stones," "stones >2 cm," "urolithiasis," "renal," "calculi," "laser," and "lasertripsy."

Mesh phrases included: ("Ureteroscopy"[Mesh]) AND "Urinary Calculi"[Mesh] and ("Ureteroscopy"[Mesh]) AND "Urinary Calculi"[Mesh]) AND "Lasers, Solid-State"[Mesh].

Articles in languages other than English were included if data were extractable and references of searched papers were evaluated for potential inclusion. Authors of the included studies were contacted wherever the data were not available or not clear.

Two reviewers (OA and BS) identified all studies that appeared to fit the inclusion criteria for full review. Each reviewer independently selected studies for inclusion in the review. Disagreement between the two extracting authors was resolved by consensus by all authors.

Data extraction and analysis

Studies relevant to ureteroscopic management of patients with stones larger than 2 cm were included. The following variables were extracted from each study: Period of the study, country of origin of the study, number of patients included, operative time, SFRs after completion of management, number of procedures per patient, stone sizes, and complications. The data of each study were grouped into a meta-analysis, in an intention to treat basis, to allow a numerical representation of the results. Data that were similar were pooled and included for the meta-analysis. Furthermore, a subgroup analysis was conducted to evaluate the SFR, mean number of procedures, and complications in patients with stones 2 to 3 cm and in those with stones >3. For continuous data a Mantel-Haenszel chi-square test was used and for dichotomous data an inverse variance was used.

A quality assessment of harms using the McHarm scale, was conducted for each included study.[9] This was deemed appropriate by all reviewers because we were analyzing safety as well as efficacy of ureteroscopic treatment of large stones. We used Review Manager (RevMan 5.0.23) to plot the quality assessment of harms tables.

Results

The literature search yielded 296 studies, of which 273 were excluded because of nonrelevance based on titles (252) and abstracts (21) (Fig. 1). These titles and abstracts of the studies did not focus on FURSL or large stones; hence, the exclusion. Full manuscripts were evaluated in 23 studies, of which, 9 were included into the review.[4–8,10–13] The majority of the studies were published within the last 3 years, reflecting the increased use of FURSL for fragmentation of large stones.[4–6,10,11,13]

All included studies were cohort observational studies, with no randomization or control groups and reported on FURSL for renal stones larger than 2 cm. All studies reported on the variables indicated in the data extraction section and are plotted in Tables 1 and 2. Tables 3 and 4 delineate patients grouped into stone size 2 to 3 cm and >3 cm.

After reading the full manuscripts, we excluded 14 studies. Eight of these studies were not related to FURSL of large stones. Three looked at combined electrohydraulic and holmium laser treatment of stones where the electrohydraulic treatment was the main procedure.[1,14,15] Two other studies had patients with stones larger than 1 cm.[3,16,17] The last study overlapped with a similar included study from the same authors.[13,18] While the included study was more focused on the

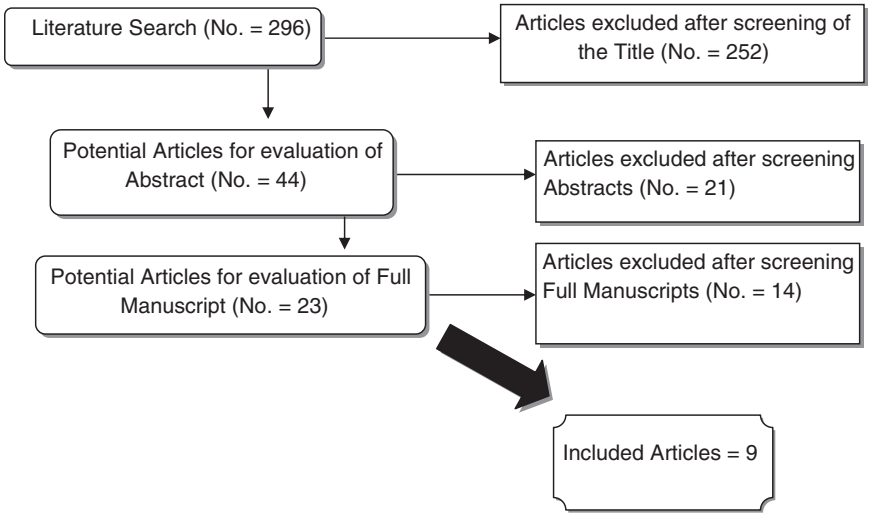

FIG. 1. Flowchart for article selection of the review.

Table 1. Study and Patient Demographics

Author	*Journal*	*Center, Country*	*Year*	*Number of patients (renal units)*	*Mean age (average)*	*Male: female*
Grasso[8]	J Urol	New York University, USA	1998	51 (63)	No mentioned (10–77)	33:18
El-Anany[12]	BJU Int	Assiut University Hospital, Egypt	2001	30	43 (18–62)	22:8
Breda[7]	J Urol	David Geffen School of Medicine, UCLA, USA	2008	15	56.4 (39–70)	10:5
Riley[6]	J Endourol	University of Missouri, USA	2009	22	52.1 (25–78)	16:6
Breda 2009[11]	Eur Urol	David Geffen School of Medicine, UCLA, USA	2009	27	Not clear	Not clear
Bader[10]	Urol Res	University Hospital Großhadern, Germany	2010	24	55.8 (20–78)	11:13
Hyams[13]	J Endourol	New York University School of Medicine, USA	2010	120	55.7 ± 12.8	72:48
Al-Qahtani[4]	Adv in Urol	Tenon University Hospital, Pierre and Marie Curie University, France	2011	120 (123)	48 ± 15.3	59:64
Hussain[5]	J Endourol	Maidstone Hospital, UK	2011	36	Not clear	Not clear
Total				445 (460)	10–78	223:162

USA = United States of America; UCLA = University of California, Los Angeles; UK = United Kingdom.

FURSL treatment of large stones, the excluded study was aimed at comparing PCNL with FURSL.[18]

Characteristics of the included studies

The studies were published between 1998 and 2011, with majority conducted in the United States (5/9), three conducted in Europe, and one in Africa. There were 460 renal units in 445 patients with an age range between 10 and 78 years. There were 1.4 times as many men as there were women (Table 1). All the studies reported on FURSL of stones >2 cm.

With regard to the main outcome of efficacy, all nine studies reported on SFRs, and eight studies reported on complications; however, Breda and associates (2009) was not clear on whether complications occurred in patients with stones larger or smaller than 2 cm and therefore this information was left out of the meta-analysis.[4,6–8,10–13] Two studies were from the same institute, but were on different cohorts of patients; therefore both studies were included.[7,11] Hussain and colleagues[5] only reported on SFRs of varying sized stones with no mention of any other outcome that could be included. Six studies reported on the average number of procedures performed,[4,6–8,10,11] with seven studies reporting on the average operative time.[4,6,7,10–13] A further five studies reported their use of ureteral access sheath.[4,6,7,10,11,13] All studies reported on stone size. One article had included one child with a large renal stone, while the remaining cohort were adults; therefore, the study was included because the authors did not think one patient's results can skew the final outcome.[8] Furthermore, two of studies just mentioned that the stones were larger than 2 cm rather than the average and therefore this information was excluded from the meta-analysis.

In five studies, the data for the subgroup analysis were performed; however, only SFR data were available for all five of the studies.[4,6,7,10,12] Mean procedure number and minor complications were analyzed in three studies in the 2 to 3 cm group and two in the 3 cm group (Tables 3 and 4), while major complications were analyzed in four studies in the 2 to 3 cm group and two in the 3 cm group (Tables 3 and 4).

Meta-analysis results

The combined data of the included studies showed that FURSL had an average SFR of around 93.7% (77%–97.5%) with an average of 1.6 procedures per patient.

Concerning complications, the combined data had an overall complication rate of 10.1%, with minor complications developing in 19 (4.8%) patients, major complications developing in 21 (5.3%) patients, and a 0% mortality rate.

Of the 19 minor complications, self-limiting hematuria occurred in six patients, postoperative pyrexia or pain in three patients, urinary tract infection treated with simple oral antibiotics in five patients, and minor intraoperative bleeding and postoperative urinary retention in one patient each.

Of the 21 major complications, Steinstrasse occurred in five patients, subcapsular hematoma in four patients, and obstructive pyelonephritis in four patients of which one went to the intensive care unit. The remaining three major complications were cerebrovascular accident, acute prostatitis, and hematuria causing clot retention in one patient each.

The average operative time was 82.5 minutes with a range of 28 to 215 minutes. The average stone size of the combined data was 2.5 cm. The combined use of ureteral access sheaths came to 86%. A subgroup analysis grouped into stones 2 to 3 cm and >3cm was also performed (Tables 3 and 4). There were 162 patients in the 2 to 3 cm stone group and 52 in the >3 cm group. It was evident that the success rate for FURSL for stones 2 to 3 cm was higher than for stones >3 cm with 95.7% *vs* 84.6% ($P = 0.01$; odds ratio: 4.03; 95% confidence interval [CI]: 1.38–11.72) SFR, respectively. Furthermore, the 2 to 3 cm stone group had fewer procedures per patient (mean 1.46 ± 0.2 *vs* 1.85 ± 0.02 ($P < 0.0001$; 95% CI: −0.42–0.36)). There were also fewer minor and major complications than the >3 cm group (14.3% *vs* 15.4%, and 0% *vs* 11.5%).

Methodologic quality assessment

Overall, the quality of the reported studies was poor, because six of the studies were reported as retrospective while

Table 2. Review of All Literature for Renal Stones >2 cm Managed with Flexible Ureteroscopy and Laser Lithotripsy

Author	*Mean operative time (min)*	*SFR after treatment completion*	*Mean number of procedures*	*Mean stone size (cm)*	*Use of access sheath*	*Minor complications*	*Major complications*	*Total complications*
Grasso[8]	Not mentioned	93%	1.3	2.4	Not mentioned	0	3 (CVA: 1; hematuria and clot retention needing transfusion: 1; pyelonephritis: 1)	3
El-Anany[12]	85 (55–160)	77%	Not mentioned	>2 cm	Not mentioned	2 (fever: 1; hematuria: 1)	0	2
Breda[7]	83.3 (45–140)	93%	1.4	2.2	15/15	3 (fever/pain: 1; hematuria: 2)	0	3
Riley[6]	72 (28–138)	91%	1.82	3	22/22	3 postoperative pain	2 (ITU admission with bacteremia: 1; subcapsular hematoma: 1)	5
Breda 2009[11]	66	85%	1.6	>2 cm	27/27	Not clear	Not clear	Not clear
Bader[10]	114.1 (50–215)	92%	1.7	3	24/24	3 UTI	1 (Steinstrasse: 1)	4
Hyams[13]	Operating room time: 102.7 ± 20.6 Surgical time: 74.3 ± 20	97.5%[a]	Not mentioned	2.4	80/120	3 (acute retention: 1; fever: 1; UTI: 1)	5 (perforation: 1; obstructive pyelonephritis: 1; Steinstrasse: 2; subcapsular hematoma: 1)	8
Al-Qahtani[4]	89.1 (60–140)	96.7%	1.6	2.6	117/123	5 (hematuria: 3; UTI: 1; intraoperative bleeding: 1)	10 (perforation: 1; fornix rupture: 3; prostatitis: 1; obstructive pyelonephritis: 1; Steinstrasse: 2; subcapsular hematoma: 2)	15
Hussain[5]	Not mentioned	94.4%	Not clear	2.8	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Total (mean)	82.5[b]	93.7%	1.6	2.5	86% (285/331)	4.8% (19/397)	5.3% (21/397)	10.1% (40/397)

SFR = stone-free rate; CVA = cerebrovascular accident; UTI = urinary tract infection.
[a]Study mentions that after 18-month follow-up, 3/120 patients needed reoperation for residual stones.
[b]The surgical time was what was counted into the meta-analysis.

Table 3. Subgroup Analysis Stratified to Stones 2 to 3 cm

Author	Number of patients	SFR after treatment completion	Mean number of procedures	Minor complications	Major complications
El-Anany[12]	23	86.95%	Not mentioned	Not mentioned	0
Breda[7]	15	93%	1.4	3 (fever/pain: 1; hematuria: 2)	0
Riley[6]	10	90%	1.6	1 postoperative pain	0
Bader[10]	10	90%	1.4	1 UTI	0
Al-Qahtani[4]	104	98%	Not mentioned	Not mentioned	Not mentioned
Total (mean)	162	95.7%	1.46	5 (14.3%)	0%

SFR = stone-free rates; UTI = urinary tract infection.

two were unclear, although they seemed to be retrospective from the methodology. All the included studies may be subject to bias because they recruited patients from databases retrospectively; this could lead to selection as well as reporting bias. Some of the studies did not prospectively define the selection of patients for FURSL as opposed to PCNL.[5,7,12,13] The majority of the studies, however, mentioned that FURSL was attempted because of previous PCNL or SWL failure, patient preference after counseling, or if PCNL was contraindicated.[4,6,8,10,11] None of the studies was randomized or had a control group. Blinding was not an issue, because this is a surgical procedure and all groups will know the modality of treatment eventually. All the studies had clearly focused aims and used appropriate methodology to address those aims. There seemed to be no or little risk of classification bias because all the studies had the numbers accounted for, and all the patients had similar treatments.

The quality assessment of harms indicates that the studies generally have a low risk of bias concerning reporting the harms that could potentially be caused by the procedure (Table 5). The harms quality assessment could not be performed on one study because that study had not reported on any complications and did not mention an intention to do so.[5]

Discussion

Principal findings

In this review, FURSL had an average SFR of around 93.7% (77%–97.5%) for a mean stone size of 2.5 cm, with an average of 1.6 procedures per patient and a mean operative time of 82.5 minutes. On a subgroup analysis, the SFR for stones between 2 and 3 cm was statistically significantly better than for stones >3 cm (95.7% *vs* 84.6%; $P = 0.01$). Minor and major complications were seen in 4.8% and 5.3%, respectively.

Meaning of the study and comparison of FURSL in various studies (possible mechanism and implications for policy and practices)

Ureteroscopy and laser fragmentation of stone in the upper urinary tract has undergone development and refinement.[4,19–22] Rigid ureteroscopy (URS) has been proven to be as efficient in stone clearance as SWL for proximal ureteral stones and superior in treating distal ureteral stones.[19,20]

Harmon and coworkers[23] reported that because of the decrease in size of the ureteroscope, their complication rates for URS dropped from 6.6% to 1.5%. With advancements in ureteroscopic technology, the overall complication rates have decreased with major complication rates reported to be <1% to 1.5%. At the same time, the overall complication rates in PCNL have been reported to be as high as 83% with a 15% to 20% major complication rate.[1,13,24–26] FURSL has become the procedure of choice in patients in whom other modalities have failed and is a viable alternative for patients with obesity, anatomic deformity such as kyphoscoliosis, and in pregnancy.[4,7,10,22]

The use of a ureteral access sheath facilitates easy passing of the ureteroscope, allows the removal of stone fragments, allows additive benefit of protecting the ureter from repeated insertion and removal of the scope, in addition to decreasing the intrarenal pressures during prolonged procedures by maintaining continuous drainage.[6,11] This review found that 86% of the FURSL procedures were ureteral sheath-assisted. It is worth noting that the two studies that did not use a ureteral access sheath were Grasso and associates[8] and El-Anany and coworkers,[12] published in 1998 and in 2001 respectively, while the first article published on assessing ureteral access sheath use was in 2001.[28] Therefore, it is safe to say this technology was not readily available at the time these two studies were conducted.

None of the studies predefined the meaning of minor or major complications. The reviewing authors, however,

Table 4. Subgroup Analysis Stratified to Stones >3 cm

Author	Number of patients	SFR after treatment completion	Mean number of procedures	Minor complications	Major complications
El-Anany[12]	7	42.9 %	Not mentioned	Not mentioned	0
Riley[6]	12	91.7%	1.83	2 postoperative pain	2 (ITU admission with bacteremia: 1; subcapsular hematoma: 1)
Bader[10]	14	92.9%	1.86	2 UTI	1 Steinstrasse
Al-Qahtani[4]	19	89.5%	Not mentioned	Not mentioned	Not mentioned
Total (mean)	52	84.6%	1.85	4 (15.4%)	3 (11.5%)

SFR = stone-free rates; ITU = intensive treatment unit; UTI = urinary tract infection.

Table 5. Quality Assessment of Harms

Author	Were the harms pre-defined using standardized or precise definitions?	Were serious events precisely defined?	Were severe events precisely defined?	Were the number of Deaths in the study group specified or were the reasons (s) for not specifying them given?	Was the mode of harms collection specified as active?	Was the mode of harms collection specified as passive?	Did the study specify Who collected the harms?	Did the study specify the training or background of who ascertained the harms?	Did the study specify the timing and frequency of who ascertained the harms?	Did the author(s) use standard scale(s) or checklist(s) for harms collection?	Did the authors specify if the harms reported encompass all the events collected or a selected sample?	Was the number of participants who withdrew or were lost to follow-up specified for each study group?	Did the authors specify the number for each type of harmful event?	Did the authors specify the type of analyses undertaken for harms data?
Grasso[8]	+	+	+	+	+	+	+	–	+	–	+	+	+	+
El-Anany[12]	+	+	–	+	+	–	+	–	+	–	+	+	+	+
Breda[7]	+	+	–	+	+	+	–	–	+	–	+	+	+	+
Riley[6]	+	+	–	+	+	+	–	–	+	–	+	+	+	+
Breda 2009[11]	+	+	–	+	+	+	+	–	+	–	+	+	+	+
Bader[10]	+	+	–	+	+	+	+	+	+	–	+	+	+	+
Hyams[13]	+	+	–	+	+	+	+	+	+	–	+	+	+	+
Al-Qahtani[4]	+	+	–	+	+	+	+	+	+	–	+	+	+	+
Hussain[5]	+	+	–	+	+	+	+	–	+	–	+	+	+	+

considered minor complications as those that would settle on their own or with minimal support or a grade I of the Clavien-Dindo classification—ie, self-limiting hematuria or urinary tract infection necessitating antibiotics or analgesic[27]—while major complications are those that needed either further procedures or close monitoring, classified as grade II or above of the Clavien-Dindo classification—ie, perforation, obstructive pyelonephritis, steinstrasse, or subcapsular hematoma.

Furthermore, a major discrepancy between the studies was the definition of the SFR. Two studies defined it as fragments <1 mm; however, the same lead author conducted both these studies.[7,11] The majority of the studies considered stone free as those 2 mm and below.[4–6,8,10,12] In addition, Hyams and associates[13] subdivided the stone-free groups into those who are truly stone free, those who had a 0 to 2 mm retained fragment, and those with <4 mm retained fragment.

With regard to the subgroup analysis, although not all the studies were grouped for a meta-analysis, it is evident from the studies that FURSL has a high SFR in stones 2 to 3 cm compared with stones >3 cm. The SFR, however, decreased with the increase in stone size; furthermore, higher numbers of procedures were needed to achieve stone clearance with a rising risk of major complications.

Strengths and weaknesses of the study

The strength of the study remains the systematic approach taken to review the last 21 years of literature reporting on patients undergoing FURSL for large renal stones. The quality of the evidence was assessed using a validated instrument. Two independent researchers (not involved in any of the studies) performed data extraction to minimize potential for bias. Outcome parameters were predetermined and data were extracted using standard forms. An obvious weakness of all systematic reviews is that they depend on and reflect the evidence from the available primary studies and may not always be in a position to provide specific guidance on interventions as a result. The weaknesses of our conclusions are therefore closely linked to the weaknesses in the individual studies. These nonrandomized studies were potentially prone to large bias in patient selection, outcome assessment, and reporting.

Limitations and future areas of research

One of the limitations of this review was that all the included studies were retrospectively conducted. Full description of the methodology, however, was delineated in all the studies, which might be construed as lowering the risk of bias. Despite these limitations, all the studies had similar comparative parameters, which allowed for a meta-analysis of the data to formulate a more figurative result as well as a subgroup analysis. Another limitation is that the SFR was defined differently in studies. All the studies were from high-volume centers of excellence with procedures performed by trained experienced endourologists, and such high SFR may not be achievable in centers in which there is less experience.

Further research is vital to evaluate the role of URS and laser fragmentation of large urinary stones. Furthermore, a multicentric randomized trial comparing FURSL with PCNL for treatment of stones larger than 2 cm needs to be conducted. The parameters should ideally encompass operative times, number of procedures per patient, length of hospital stay, number of clinic or emergency department visits, SFRs, and complication

rates. These parameters need to be explicitly defined. In addition to this, a cost analysis comparison between the two groups should also be performed. The complications should be classified into a known system, such as the Clavien-Dindo classification for surgical complications.[27]

Conclusion

Although PCNL remains the gold standard, FURSL can successfully treat patients with stones larger than 2 cm with a high SFR and a low complication rate. The results of observational cohort studies, however, are from high-volume experienced centers and may not be sufficient to alter everyday routine practice; this review has shown that the efficacy of FURSL allows an alternative to PCNL. Because this high SFR may not be reproducible, an informed treatment decision should be made with the patients based on the outcomes for FURSL of the surgeons/centers.

Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Omar M. Aboumarzouk, M.B.Ch.B.
Department of Urology
Royal Bournemouth Hospital
Bournemouth
United Kingdom

E-mail: aboumarzouk@gmail.com

Abbreviations Used

CI = confidence interval
FURSL = flexible ureteroscopy and laser lithotripsy
PCNL = percutaneous nephrolithotomy
SFR = stone-free rate
SWL = shockwave lithotripsy
URS = ureteroscopy

4. Safety and efficacy of ureteroscopic lithotripsy for stone disease in obese patients: a systematic review of the literature

Renal stone treatment in obese patients is challenging. Worldwide there is an increasing trend of both renal stones and obesity. Treatment with lithotripsy is not always successful and percutaneous stone surgery carries a high morbidity. We wanted to review the literature to meta-analyze the evidence for safety and efficacy of URS in these patients. We conducted a systematic review in March 2011 for relevant studies from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials – CENTRAL, CINAHL, Clinicaltrials.gov, Google Scholar and Individual urological journals.

Of the 497 titles reviewed, 486 were excluded due to irrelevance from the title or abstracts. Seven of the remaining 11 studies were included after evaluating the full manuscripts (131 patients). The mean age of the patients was 53 years with a mean BMI of 42 and the mean stone size of 1.4 cm. With a mean operating time of 97 minutes (30-275 minutes), the stone free rate (SFR) was 87.5% and an overall complication rate of 11%. Patients with stone size of <2cm and patients with ureteric stones had a significantly higher SFR.

Our results showed that ureteroscopy for stone disease in obese patients is a relatively safe procedure with a high SFR especially for stones <2cm in size.

(*Contribution 45%, doing the systematic review, writing up, proofreading/correcting the paper).*

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Safety and efficacy of ureteroscopic lithotripsy for stone disease in obese patients: a systematic review of the literature

Omar M. Aboumarzouk, Bhaskar Somani* and Manoj Monga†

*The Royal Bournemouth and Christchurch Hospitals NHS Trust, Urology Department, Bournemouth, UK, *Southampton University Hospitals NHS Trust, Southampton, UK, †Stevan B. Streem Center for Endourology and Stone Disease, Glickman Urological and Kidney Institute, The Cleveland Clinic, Cleveland, OH, USA*

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Study Type – Prognosis (systematic review)
Level of Evidence 1a

What's known on the subject? and What does the study add?
Case series on ureteroscopy for obese patients have been published in the literature, but as yet no decisive conclusion has been published because of the small patient numbers included the study cohorts.

This review provides an overview of the literature discussing ureteroscopy for obese patients. In addition, it provides a meta-analysis of the case series and published literature on the topic, which focuses on the safety and efficacy of ureteroscopy for obese patients.

OBJECTIVE

- To look at the role and safety of ureteroscopy for stone management in obese patients.

METHODS

- We searched MEDLINE, PubMed and the Cochrane Library from January 1990 to June 2011 for results of ureteroscopy and stone treatment in obese patients.
- Inclusion criteria were all English language articles reporting on ureteroscopy in patients with morbid obesity.
- Data on the outcomes and complications was extracted and a meta-analysis of the results conducted.

RESULTS

- Seven studies with 131 patients (136 renal units) were included.
- All the studies included obese patients (mean BMI 42.2) treated with flexible URS for urinary calculi. The mode of fragmentation was pulse dye laser, holmium laser, and combined modality including electrohydraulic lithotripsy and basket retrieval in others.
- The average stone size was (1.37). The stone free rate was 87.5% after completion of treatment with a ranged follow up between 3 months and 3.5 years. The mean operative time was 97.1 minutes (30-275).
- There was an overall 11.4% complication rate, however, none of the patients needed further monitoring and were treated conservatively.
- A sub-group analysis of the stones depending on size found the URS has a higher stone free rate in stones <2 cm in size ($P = 0.0003$). Furthermore, URS has a higher stone free rate when treating ureteric stones compared to renal stones ($P = 0.04$).

CONCLUSION

- Retrograde stone treatment using ureteroscopy is a safe and efficient modality for treating obese patients with urinary tract calculi with an increased efficiency with smaller stones less than 2 cm in size.

KEYWORDS
obesity, ureteroscopy, flexible ureterorenoscopy, urinary stones, laser, systematic review

INTRODUCTION

Nephrolithiasis is a common condition with a lifetime risk in the general population of ≈13% in men and 7% in women. Its peak incidence is in the third to fourth decades of life [1,2]. With obesity now considered a worldwide epidemic, affecting >300 million people, more obese patients are presenting with urinary calculi [3,4]. Numerous studies have shown that obesity increases the risk of nephrolithiasis; specifically, the risk of uric acid and calcium oxalate stones increases in obese people because the defect in ammonia excretion leads to low pH [3–5].

Obesity poses a management dilemma with regard to diagnostic imaging, anaesthetic risk and surgical approach [3]. Normally, stone disease is diagnosed by CT scans and treated with either ESWL, ureteroscopy (URS), or percutaneous nephrolithotripsy (PCNL) but, in the case of an obese patient, excessive weight or girth (abdominal circumference) might prevent their entry through the CT scanner [3]. Furthermore, intubation and high pressure ventilating might be required during surgical procedures which might also be complicated by carbon dioxide retention or difficulty

with weaning the patient off of the ventilator after surgery [3]. Obesity also increases the risk of cardiovascular, respiratory, thromboembolic and wound complications after surgery [6] and, because of the increased distance from the skin to the stone, ESWL might not be successful [3]. With regard to PCNL, the positioning of the patient in the prone position increases the respiratory compromise and impedes venous return [3]. This can leave URS as the only potentially viable treatment method, but treating larger stones requires longer and possibly repeat procedures [3] and this, in itself, puts the patient at risk of anaesthesia.

To address these issues, we aimed to conduct a systematic review to assess the safety and efficacy of ureteroscopic lithotripsy in obese patients.

METHODS

SEARCH STRATEGY AND STUDY SELECTION

The systematic review was performed according to the Cochrane reviews guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. The search strategy was aimed at finding relevant studies from MEDLINE (1966 to March 2011), EMBASE (1980 to March 2011), the Cochrane Central Register of Controlled Trials: CENTRAL (in *The Cochrane Library* – Issue 1, 2011), CINAHL (1872 to March 2011), Clinicaltrials.gov, Google Scholar and individual urological journals. The search terms used were 'ureteroscopy', 'obese', 'obesity', 'endoscopy', 'urolithiasis' and 'calculi'. Mesh phrases included: ('Ureteroscopy'[Mesh]) AND 'Obesity'[Mesh]; (('Obesity'[Mesh]) AND 'Ureteroscopy'[Mesh]) AND 'Urolithiasis'[Mesh]); and (('Obesity'[Mesh])) AND 'Urolithiasis'[Mesh]). Papers in languages other than English were excluded and the references of searched papers were evaluated for potential inclusion.

Two reviewers (O.A. and B.S.) identified all studies that appeared to fit the inclusion criteria for full review. Each reviewer independently selected studies for inclusion in the review. Disagreement between the two extracting authors was resolved by consensus. If consensus between the two reviewers could not be reached, the third author (M.M.) was deferred to for arbitration.

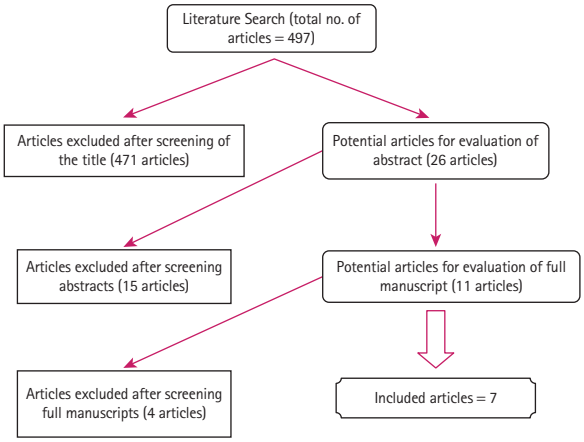


FIG. 1.
Flowchart showing article selection process.

DATA EXTRACTION AND ANALYSIS

Studies relevant to the ureteroscopic management of obese patients were included. The following variables were extracted from each study: population demographics, period of the study; country of origin of the study; body mass index (BMI); stone size and location; stone-free rates; follow-up; and complications. For complications the Clavien classification for surgical complications was used [8]. The data from each study were grouped into a meta-analysis, on an intention-to-treat basis, to allow a numerical representation of the results.

A sub-group analysis was conducted to determine whether or not the safety and efficacy of URS was affected by stone size. A Mantel–Haenszel chi-squared test was used for calculating the absolute risk difference with 95% CI, to be able to identify the absolute change in risk that was attributed to the intervention [9].

A quality assessment of harms, using the McHarm scale, was conducted for each included study [10]. We used Review Manager (RevMan 5.0.23) to plot the quality assessment of harms tables.

RESULTS

The literature search yielded 497 studies, of which 486 were excluded owing to non-relevance, based on titles and abstracts (Fig. 1). Eleven studies were then retrieved for further assessment, seven of which were included in the review [11–17]. All the included studies were published between 1998 and 2010. All seven studies were retrospective and all reported on the variables indicated in the 'data extraction section' and are shown in Table 1 [11–17].

Four articles were excluded after reading the full manuscript [3,4,18,19] because none of them looked at URS for stones in obese patients.

CHARACTERISTICS AND META-ANALYSIS OF THE INCLUDED STUDIES

Six of the studies were from the USA, and the remaining studies were from the UK (Table 1). A total of 131 obese patients in 136 renal units were included in the present review and a total of 68 renal stones and 68 ureteric stones were treated. All the patients were treated with flexible URS for urinary stones. The mean (range) age of the present review population was 53.3 (19–67) years. The mean (range) BMI was 42.2 (30.13–65.2) kg/m^2. The mean (range) stone size was 1.37 (0.4–7.2) cm.

There was a discrepancy between the studies with regard to investigative method; two of the studies used CT scans [11,17], one used only plain x-rays [16] and two used either plain x-rays, i.v. urogram, ultrasonography or CT [14,15]. One study used x-rays, CT and ultrasonography [12].

The majority of the studies used URS with holmium laser to treat the stones [11–15,17], while Nguyen and Belis [16] used pulsed dye laser. Dash *et al.* [14] also used electrohydraulic lithotripsy if the stone was too large for laser treatment. Andreoni *et al.*

TABLE 1 Characteristics of the studies included in the review

Study	Year	Place	Patients (renal units)	Sex M : F	Mean age, years	Mean (range) BMI, kg/m^2	Mean stone size, cm	Mean stone-free rate, %	Mean (range) operating time, min	Complication
Nguyen and Belis [16]	1998	USA	30	11:19	55.8 (29–68)	mean weight 288 lb*	1.48	97	131 (80–275)	One ureteric perforation; two fever
Andreoni *et al.* [11]	2001	USA	8 (10)	3:7	46.7 (33–68)	54 (45–65.2)	1.14	70	101 (45–160)	None
Dash *et al.* [14]	2002	USA	16 (18)	NM	NM	45.7	1.14 (0.4–1.8)	83	74.1	One urosepsis; One pyelonephritis; two not mentioned
Bultitude *et al.* [13]	2004	UK	12 (13)	ND	49.1 (19–66)	46.8 (41.3–56.2)	1.4 (0.6–3)	100	NM	Three postoperative sepsis
Natalin *et al.* [15]	2009	USA	34	21:13	53.32	33.6 (30.13–45.55)	<1 cm:1.8 >1 cm:1.6	94	78.23 (30–156)	None
Wheat *et al.* [17]	2009	USA	9	6:3	58 (45–67)	47.8 (35–57.5)	3.8 (2–7.2)	33	Not clear	Two fever; one pain
Best *et al.* [12]	2010	USA	22	ND	ND	>30	0.86	91	ND	ND
Total			131 (136)	41: 42	53.3 (19–67)	42.2 (30.13–65.2)	1.58 (0.4–7.2)	87.5	97.1 (30–275)	13/114 or 11.4%

**Mean weight given rather than BMI. NM, no mention; ND, No differentiation.*

[11] used all three intracorporeal lithotripters: holmium and pulsed dye laser and electrohydraulic lithotripsy.

Only two of the studies mentioned if their patients had stents inserted before surgery. The number of patients who had stent insertions before surgery was not clear in one of these studies [12], while Dash *et al.* [14] mention that 9/18 patients had this procedure. A further two studies reported they routinely stented all their patients after surgery [11,16].

None of the studies reported whether or not preoperative urine analysis was done and only one study reported giving antibiotics prophylactically on induction [13].

Three of the studies routinely used ureteric access sheaths in their patients [11,15,17]. Dash *et al.* [14] state these were not routinely used, but were used in selected patients where access was difficult [14].

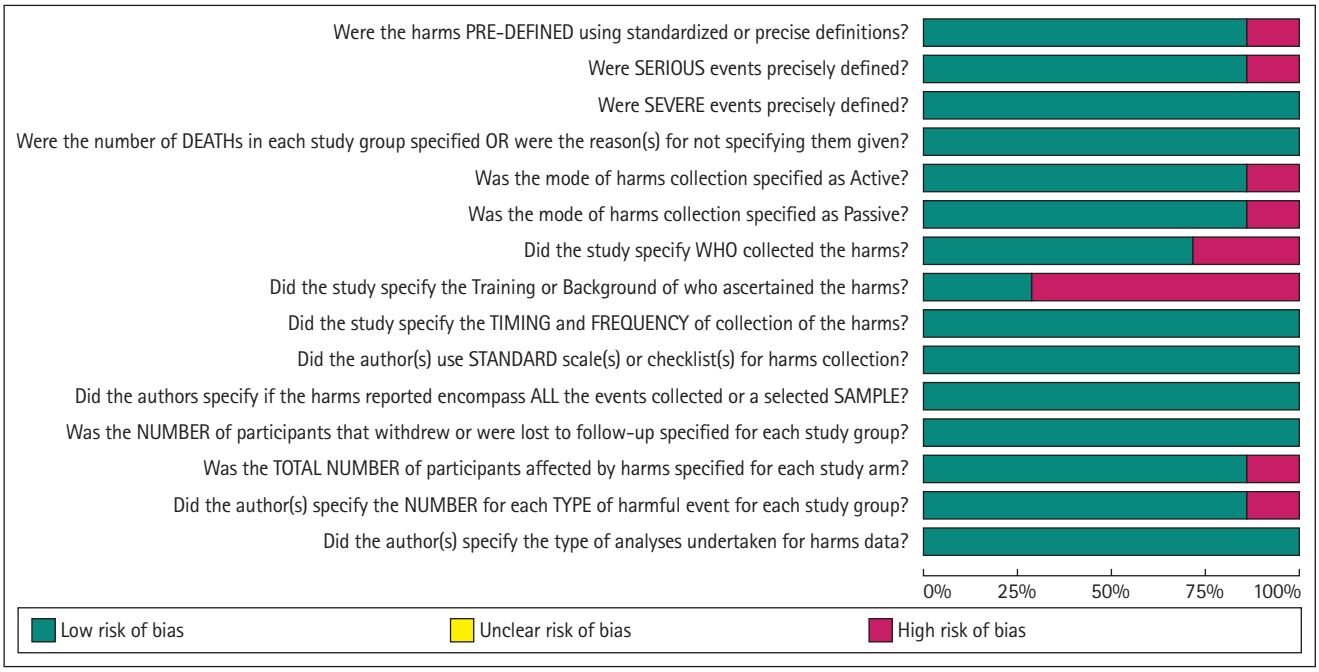
With regard to stone-free rates, 87.5% (119/136) of the patients were stone-free. Three studies defined the stone-free rate as having no residual stones [11,16,17], while a further three studies defined it as having stones <2 mm in size [12,13,15]. Dash *et al.* [14] did not define what they meant by stone-free.

The mean (range) operating time was 97.1 (30–275) min and the overall complication rate in the included studies was 11.4%. Most of the complications were Grade II, requiring antibiotics or strong analgesics, with only one Grade III complication, a ureteric perforation (Table 1). There were no Grade IV or V complications.

A sub-group analysis of the studies reporting on stones with a mean size <2 cm was conducted [11–16]. Six studies of 122 patients in 127 renal units were analysed. The mean BMI of these patients was 41.5 kg/m^2. The mean (range) stone size was 1.37 (0.4–1.8) cm with a mean stone-free rate of 91.3% ($P < 0.001$; RD (Risk Difference) [M-H (Mantel-Haenszel), 95% CI]: 0.58 [0.27–0.89]) and an overall complication rate of 9.5%.

A sub-group analysis based on stone location was also conducted, but only five of the studies had data available on stone-free rates according to location

FIG. 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



[11–14,17]. There were 48 renal stones and 24 ureteric stones, with stone-free rates of 75% and 91.7%, respectively ($P = 0.04$; RD [M-H, 95% CI]: –0.17 [–0.33––0.0016]). A further subanalysis was done on the same group, in which stones >2 cm were excluded. This raised the renal stone-free rate to 84.6%.

Only two studies mentioned the number of URS procedures conducted per stone, The study by Bultitude *et al.* [13] had a mean of 2.6 procedures while that of Wheat *et al.* [17] had a mean of 2.3. Furthermore, only two studies mentioned if additional procedures were done: in the study by Bultitude *et al.* [13] two patients required open pyelolithotomy owing to stag horn calculi, while no patients required any further procedures in the study by Best *et al.* [12].

METHODOLOGICAL QUALITY ASSESSMENT OF THE INCLUDED STUDIES

The quality of the reported studies was modest to high in standard, although all of the studies were retrospective. All the included studies might be subject to risk of bias as they all recruited patients from databases, which could lead to selection as well as reporting bias; however, the data reported seemed to be complete. All the studies had a clear definition of their objectives with a clear methodological approach to how the patients were recruited and to the conduction of the study. Furthermore, all the studies discussed their findings and compared them with the literature for analysis. The quality assessment of harms indicates that the studies have a low risk of bias concerning reporting the harms that could potentially be caused by the procedure (Figs 2 and 3).

The present review includes all the topics and completes the checklist required by the PRISMA guidelines.

DISCUSSION

Obesity has always been a challenge to surgeons of all specialties. It is widely recognised that with obesity comes a higher risk of stone formation owing to the increased secretion of calcium, oxalate and uric acid in obese patients [17]. With the increasing prevalence of obesity, more and more urologists will be faced with the dilemma of how to treat these patients. Interestingly, a search of the literature yielded only a few endo-urological papers that discuss the risks when it comes to stone treatment and these were retrospective small patient studies [11–17].

Traditionally, the first-line treatment for small stones was ESWL [12,14], but with obese patients this poses a few issues, the first being the weight restrictions of the operating table [13,17]. The second, a logistic problem, is the shockwave focal length. The skin to stone distance increases because of the girth of obese patients, which leads to difficulties with focusing the shockwave to the stone [3,13,17]. Ultimately, with this reduction in focusing power, stone fragmentation rates are reduced, leading to increasing failure rates or repeat procedures [17].

A thorough search of the literature found no study that compared the various treatment methods in obese patients (ESWL, URS and PCNL); however, previous studies have shown that stone-free rates after ESWL were significantly better in non-obese patients [20]. Furthermore, de la Rosette *et al.* [21], in their review, looked at the outcomes of prone vs supine PCNL and found that, for obese patients, the stone-free rate was slightly higher and operating time was significantly shorter in the prone position. This was in contrast to the non-obese patients where the mean

FIG. 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

operating time was significantly shorter in the supine position, with similar success in both positions.

Carson *et al.* [22] were the first to publish on the endoscopic treatment of obese patients and reported that they successfully treated 44 obese patients by PCNL with few complications. Nonetheless, risks of open surgery in obese patients do exist [11,13,17]. Putting the risk of anaesthesia and surgery itself aside, further issues with the surgical approach include the positioning of the patients and the instruments used [14,15,17]. Numerous studies published their techniques and modified instruments in dealing with these issues, but the results were variable [13–15]. Despite these studies, there are still conflicting data on how best to manage stones in obese patients [17]; in fact, a few studies reported an increased complication rate, transfusion rate, and secondary procedure rate in obese patients after PCNL [17].

Advances in endoscopic instruments have led to the development of smaller-diameter scopes with increased flexibility, coupled with a greater angle of deflection of the tip of the scope and improved optics, which in turn has led to the ability to visualize and treat stones in the whole upper urinary system [12,23–25]. Advances in laser technology led to the development of the holmium laser, which provides effective and efficient intracorporeal lithotripsy for even hard stones such as cysteine and calcium oxalate monohydrate stones, and can also be used to ablate upper urinary tract tumours [25,26]. Furthermore, holmium lasers offer haemostatic capabilities during the procedure, which give an additive benefit to patients with bleeding diathesis [25]. All these have led to the increased use of URS in the management of urinary stones. Furthermore, as the scope is passed through the ureter, the patients' size and girth do not affect the procedure itself [12].

The present review found that the use of URS on obese patients is not only safe but also efficient, with an overall stone-free rate of 87.5%, a minor complication rate (Grade I, II, or III) of 11.4% and a major complication rate (Grade IV) or mortality (Grade V) rate of 0%. Furthermore, the stone-free rate was significantly higher for ureteric stones compared with renal stones ($P = 0.04$).

When taking into consideration stone size, we found that URS has a significantly higher stone-free rate (91.3%, $P < 0.001$) as well as a lower complication rate (9.5%) if we only calculate the stones <2 cm in size.

Limitations of the present review include the fact that all the studies included small cohorts and were retrospective; however, there were no missing data, which allowed for an accurate meta-analysis of the results. Another limitation was that we were unable to analyse the stone-free rate according to the stones' location in the ureter, however, we were able to analyse the rate of ureteric stones in general. Furthermore, we were

unable to sub-categorize the findings according the types of obesity, i.e. obese, morbidly obese, or super obese.

Future research efforts should be concentrated on higher quality, more rigorous evaluation of URS in obese patients. Studies should be multi-institutional and protocol-driven, and preferably peer-reviewed before the start. Studies should be prospectively evaluated and include a control group of patients who have a normal BMI for comparison, in addition to comparing the different positioning of the patient during the procedure, i.e. supine or prone. These studies should specifically look at how the stones were investigated, patients should, if possible, be randomized to ESWL, PCNL, or URS depending on the size and site of the stone, and the studies should include the operating time, stone-free rate, complication rate and length of follow-up. Furthermore, health economic outcome measures should be analysed. More precise definitions should be used, such as the definition of stone-free, and the complications should be categorized into classifications using a known complication classification system.

In conclusion, URS is a safe and efficient treatment method for obese patients with urinary tract stones, and has an increased efficiency with smaller stones, i.e. those <2 cm. URS also has a high ureteric stone-free rate and a renal stone-free rate similar to other treatment methods and the relatively short duration of the procedure reduces the anaesthetic risks.

CONFLICT OF INTEREST

None declared.

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Correspondence: Omar M. Aboumarzouk, The Royal Bournemouth and Christchurch Hospitals NHS Trust, Urology Department, Castle Lane East, Bournemouth, BH7 7DW, UK.
e-mail: aboumarzouk@gmail.com

Abbreviations: **URS**, ureteroscopy; **PCNL**, percutaneous nephrolithotripsy; **PRISMA**, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

5. Flexible ureteroscopy and Holmium:YAG laser lithotripsy for stone disease in patients with bleeding diathesis: A systematic review of literature

Managing urolithiasis in patients with anticoagulants or with an underlying bleeding diathesis is challenging. Lithotripsy and percutaneous stone surgery is contraindicated unless the bleeding risk is reversed which may not always be possible. Ureteroscopic stone management is the only comparative safe option in this scenario. We did a systematic review in March 2011 for relevant studies from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials – CENTRAL, CINAHL, Clinicaltrials.gov, Google Scholar and Individual urological journals to assess the safety and efficacy of URS stone management in patients with bleeding diathesis.

Of the 199 titles reviewed, 191 were excluded due to irrelevance from the title or abstracts. Three of the remaining 8 studies were included after evaluating the full manuscripts (70 patients). Coagulopathies included warfarin (n=36), thrombocytopenia (n=6), von Willebrand disease (n=2), liver dysfunction (n=3), clopidogrel (n=5), low dose aspirin (n=13) and high dose aspirin (n=5). For a mean stone size of 13mm, the SFR was 88% (64/73 patients) and a complication rate of 11% (8/73 patients) of which three patients (4%) had minor bleeding.

Our results showed that ureteroscopy and laser stone treatment is safe and effective for patients who have bleeding diathesis or are anticoagulated and these patients do not need their coagulopathy reversed.

(Contribution 45%, doing the systematic review, proofreading/correcting the paper).

REVIEW ARTICLE

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Flexible Ureteroscopy and Holmium:YAG Laser Lithotripsy for Stone Disease in Patients with Bleeding Diathesis: a Systematic Review of the Literature

Omar M Aboumarzouk, Bhaskar K. Somani, Manoj Monga

Department of Urology, Wales Deanery, Cardiff, Wales (OMA), University Hospitals Southampton NHS Trust, Southampton (BKS), United Kingdom and Glickman Urological & Kidney Institute, Cleveland Clinic, Department of Urology (MM), Cleveland, Ohio, USA

ABSTRACT

Introduction and Objectives: The management of urolithiasis in patients on anticoagulants presents a challenge to the endourologist. Due to multiple comorbidities, it may be impossible to safely discontinue the anticoagulant treatment. Other modalities such as shock wave lithotripsy and PCNL are contraindicated in these patients, so ureteroscopic treatment may be the only option. We conducted a systematic review of the literature to look at the safety and efficacy of ureteroscopic management in these patients.

Methods: Systematic review and quantitative meta-analysis was performed using studies identified by a systematic electronic literature search from January 1990 to August 2011. All articles reporting on treatment for stones in patients with a bleeding diathesis using ureteroscopy and a Holmium:YAG laser were included. Two reviewers independently extracted the data from each study. The data was included into a meta-analysis and discussed.

Results: Three studies were identified reporting on 70 patients (73 procedures). All patients had stone fragmentation using Holmium laser. The mean stone size was 13.2mm with a range of 5-35mm. The quality of the included studies was modest. Stone free status was achieved in sixty-four patients (87.7%). There were no major complications and only 11% of the patients developed minor complications with only 4% rate of minor bleeding.

Conclusions: Retrograde stone treatment using ureteroscopy and holmium laser lithotripsy can be safely performed in patients with bleeding diathesis with a low complication rate.

ARTICLE INFO

Key words:
Ureteroscopy; Laser Therapy; Lithotripsy; Bleeding time; Blood Coagulation Disorders; Urinary Calculi

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INTRODUCTION

Nephrolithiasis is a common condition affecting the population with a peak incidence around the third to fourth decade of life (1). The lifetime risk of urolithiasis in the general population is 13% in men and 7% in women (2).

The preferred treatment modalities for ureteric calculi include shock wave lithotripsy (SWL) or ureteroscopy (URS) (3,4). With the advancement in technology of fibre optics and the production of smaller calibre ureteroscopes, ureteroscopic extraction has led to a higher stone free rate than SWL and is recommended as first line management for ureteric calculi (5-8).

However, despite the advancements made in the instrumentation, urologists have always opted to correct coagulopathy before undertak-

ing endourological procedures (7). This poses a controversial question concerning the management of patients who are anticoagulated or have a coagulopathy (9). SWL and percutaneous nephrolithotomy are contraindicated in these patients and correction of coagulopathy is recommended before endoscopic procedures (9,10). However, despite the use of low molecular weight heparin for thromboembolic protection, patients can still develop organ or life threatening clots (10). Conversely, if coagulopathy was not reversed, the procedures run the risk of causing continual bleeding or haematoma formation (10).

In view of all these facts, we aimed to conduct a systematic review to assess the safety and efficacy of ureteroscopic procedures in patients with bleeding diathesis.

MATERIALS AND METHODS

Search strategy and study selection

The systematic review was performed according to the Cochrane diagnostic accuracy reviews guidelines. The search strategy was conducted to find relevant studies from MEDLINE (1990- March 2011), EMBASE (1990- March 2011), Cochrane Central Register of Controlled Trials - CENTRAL (in The Cochrane Library - Issue 1, 2011), CINAHL (1990- March 2011), Clinicaltrials.gov, Google Scholar and Individual urological journals.

Terms used included: 'ureteroscopy', 'coagulopathy', 'anticoagulant', 'warfarin', 'bleeding', 'urolithiasis', 'aspirin', 'coumarin', 'clopidogrel', 'thrombocytopenia', and 'calculi'.

Mesh phrases included: ("Ureteroscopy"[Mesh]) AND "Blood Coagulation Disorders"[Mesh], ("Anticoagulants"[Mesh]) AND "Ureteroscopy"[Mesh], ("Ureteroscopy"[Mesh]) AND "Hemorrhage"[Mesh], ("Anticoagulants"[Mesh]) AND ("Lasers"[Mesh] OR "Laser Therapy"[Mesh]), ("Lasers"[Mesh]) AND "Calculi"[Mesh]) AND "Anticoagulants"[Mesh], ("Anticoagulants"[Mesh]) AND "Calculi"[Mesh], ("Ureteroscopy"[Mesh]) AND "Aspirin"[Mesh], ("Ureteroscopy"[Mesh]) AND "clopidogrel" [Supplementary Concept], ("Ureteroscopy"[Mesh]) AND "Coumarins"[Mesh], and ("Ureteroscopy"[Mesh]) AND "Thrombocytopenia"[Mesh], ("Kidney Calculi"[Mesh] OR "Ureteral Calculi"[Mesh]) AND "Aspirin"[Mesh], ("Coumarins"[Mesh]) AND ("Kidney Calculi"[Mesh] OR "Ureteral Calculi"[Mesh]), ("Kidney Calculi"[Mesh] AND "Ureteral Calculi"[Mesh]) AND "Coumarins"[Mesh], and ("Thrombocytopenia"[Mesh]) AND ("Kidney Calculi"[Mesh] OR "Ureteral Calculi"[Mesh]).

Reference lists of previous reviews and previous trials were included; papers in languages other than English were included, references of searched papers were evaluated for potential inclusion, and recently published versions were included if the publication was duplicated. Authors of the included studies were contacted whenever the data was not available or not clear.

Two reviewers (OA and BS) identified all studies that appeared to fit the inclusion criteria for full review. Each reviewer independently selected studies for inclusion in the review. Disagreement between the two extracting authors was resolved by consensus. If consensus between the two reviewers could not be reached, a third author (MM) was deferred to for arbitration and consensus.

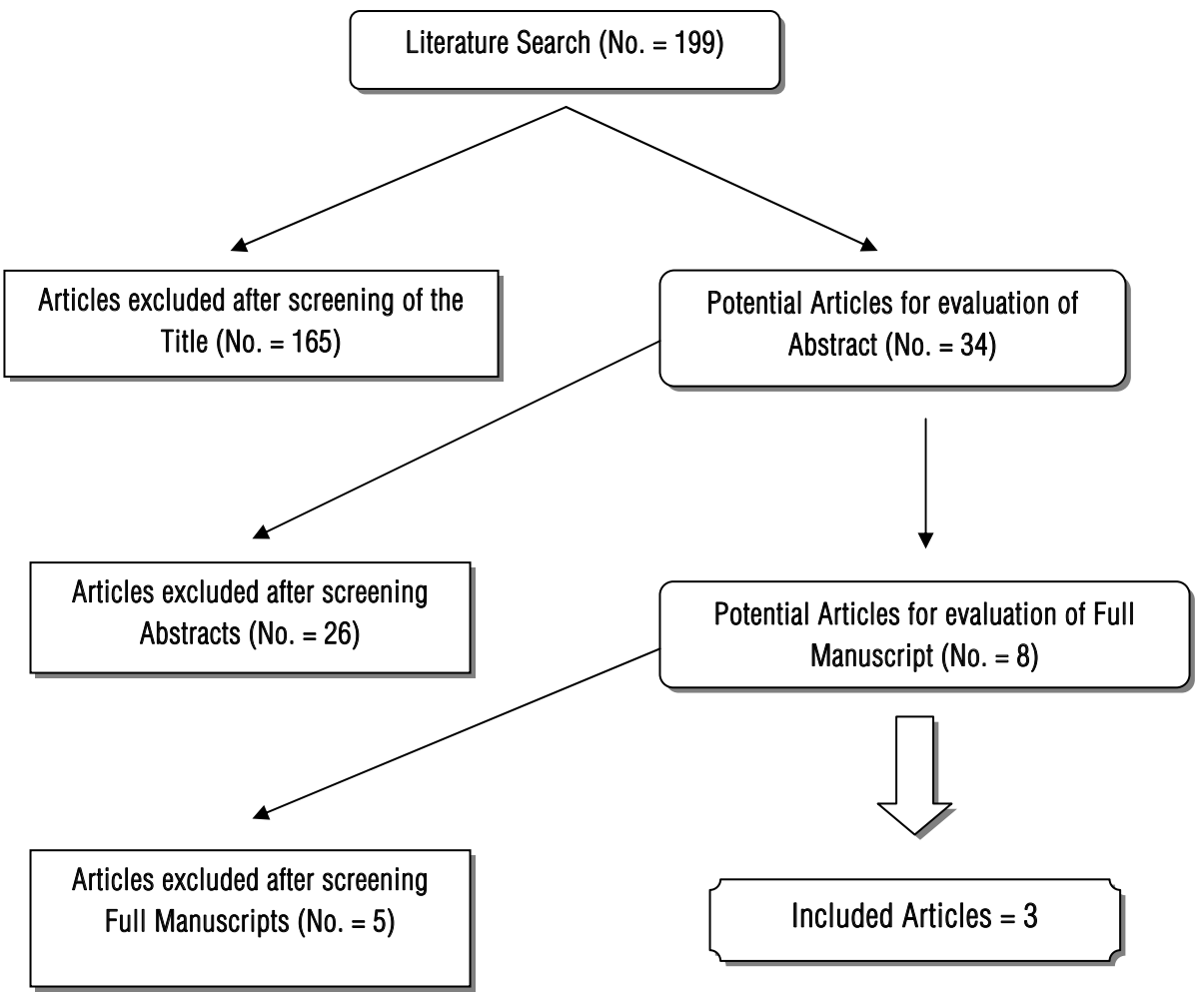
Data extraction and analysis

Studies reporting on the treatment of patients with a bleeding diathesis with flexible ureteroscopy and laser lithotripsy were included. Patients included were adults with a bleeding diathesis who had urinary stones. The following variables were extracted from each study: period of the study; country of origin of the study; study population demographics; type of anticoagulant used or coagulopathy; stent insertion; stone free rates; follow up; and complications. The data of each study was grouped into a meta-analysis to allow a numerical representation of the results. A quality assessment of harms using the McHarm scale was conducted for each included study (11). We used Review Manager (RevMan 5.0.23) to plot the quality assessment of harms tables.

RESULTS

The literature search yielded 199 studies, of which 165 were excluded by title or abstract for non-relevance to the aims of this review or not reporting on ureteroscopy treatment of patients with a bleeding diathesis (Figure-1). Eight

Figure 1 - Flowchart for article selection process of the review.



studies were then retrieved for further assessment, of which three were included in the review (7,8,12). All the included studies were published between 1998 and as recent as 2008, reflecting the continued debate of how to treat stones in patients with bleeding diathesis.

All 3 studies were retrospective studies; however, Turna et al. also compared the anticoagulated group to a similar group of patients as a control group. All the studies reported on the variables indicated in the 'data extraction section' and were plotted into Table-1. Wherever data was not available in the reports or there was not enough clarification, lead authors were contacted to get the raw data.

Five articles were excluded after reading the full manuscript. One study was not included since the authors looked at all treatment modalities for urinary stones and though mentioned that 8 patients were ureteroscopically treated only 2 were holmium laser treated (10). Furthermore, the authors had not provided demographic, coagulopathy, or stone details separately for these patients and therefore could not be extracted. Attempts at contacting the author were unsuccessful. The remaining four studies did not look

Table 1 - Table of included studies.

Name	Journal	Year	Period	Pla-ce	No.	Age mean (range)	Bleeding Diathesis mean (range)	Mode	Stone Size/ Location (mm) mean (range)	Stent	Stone Free Rate	Complications
Kuo	Urology	1998	1997-1998	USA	8	58.3 (42-74)	Coumadin (INR: 2.1 (1.6-2.9)): 5 Thrombocytopaenia: 2 vWd: 1	Flexi Hol	(3-15) Ureteric (proxi-mal: 1; middle: 1; distal: 1) Renal: 5	All	6/7 (one 2mm residual frag (1 patient had no stone on URS)	2 – (epistaxis: 1; post-op urinary retention: 1)
Watterson	Journal of Urology	2002	1996-2001	USA	25 (28)	(42-84)	Warfarin (INR 2.3): 17 Thrombocytopaenia: 4 vWd: 1 Liver dysfunction: 3	Flexi Hol	11.9 (6-25) Ureteric (proxi-mal: 9; middle: 3; distal: 7) Renal: 9	87% (26/30)	96% (27/28) 2 patients had electrohydrau-lic lithotripsy treatment	2 – (renal colic: 1; AF: 1)
Turna	Journal of Urology	2008	2001-2007	USA	37	58.2 (35-86)	Coumadin (INR 1.8 (1.1-3.3)): 14 Clopidogrel: 5 Low dose (81mg) Aspirin: 13 High dose (325 mg) Aspirin: 5	Flexi Hol	13.2 (5-35) Ureteric: 8 Renal: 29	All	81.1% (30/37)	4 – (transient macroscopic haematuria: 3; UTI: 1)

AF: Atrial Fibrillation; Flexi: Flexible Ureteroscopy; Hol: Holmium Laser; INR: International Normalisation Ratio; mm: millimetre; URS: Ureteroscopy; vWd: von Willebrand disease

at patients with bleeding diathesis and therefore were excluded (2,4,9,13).

Characteristics of the included studies

All the studies were conducted in the USA (Table-1). Seventy patients who underwent 73 procedures were included in this review. The study population was composed of patients with 35 to 86 years old. All patients had some sort of coagulopathy including 36 patients on warfarin, 6 patients with thrombocytopaenia, 2 with von Willebrand disease, 3 had liver dysfunction, 5 on clopidogrel, 13 on low dose aspirin, and 5 patients on a high dose aspirin. None of the patients had their coagulopathy reversed, except for 2 patients who had thrombocytopaenia and had recently had chemotherapy; both were given 2 units of platelets for fear of the platelet count dropping further (7,12). The mean international normalization ratio (INR) for the patients on warfarin was 2.1 with a range of 1.1-3.3. Turna et al. had included patients on coumadin; however, their INR was 1.1, and there was no mention of how many patients with subtherapeutic INR levels were included. All patients were treated with a flexible ureteroscopy and a holmium:YAG laser. The stone sizes ranged from 3-35mm with 43 renal stones and 30 ureteric, of which 10 were proximal, 4 middle and 8 distal ureteric. Turna et al. had not mentioned the location of the ureteric stones.

Two studies routinely stented their patients after ureteroscopy and holmium:YAG laser fragmentation. However, the third study (by Watterson et al.) did not differentiate between the patients who had holmium treatment and those that had electrohydraulic lithotripsy and stent insertion, therefore their data was not included.

With regards to stone free rate, 87.7% (64/73) of the patients were stone free. In this review, none of the patients developed any major complications and 11% (8/73) of the patients developed minor complications; however, five of the patients had complications unrelated to their coagulopathy. This brought the complication rate that could be attributed to an anticoagulated state, i.e. bleeding, to 4.1% (3/73). These three patients developed transient macroscopic haematuria for at least 3 days but did not require continuous bladder irrigations, secondary procedures or blood transfusions (8). The five other complications included one patient who developed a post-operative urinary retention, one patient developed worsening renal colic attributed to stone passage, another developed atrial fibrillation, another developed a urinary tract infection and the last developed an epistaxis. The epistaxis was attributed to ketorolac; however, there was no mention of how they were certain that ketorolac was the cause rather than the coagulopathy. All patients were routinely followed up, however each study varied in the length of follow up. Kuo et al. followed up their patients for 4-6 weeks, while Turna et al. followed up for 4 weeks, and Watterson et al. for 1-2 weeks only. All the patients were stone free and complication free after follow up discharge.

Methodological quality assessment of the included studies

Overall, the quality of the reported studies was modest as two of the studies were reported as retrospective while one was unclear; however it seemed to be retrospective from the methodology. All the included studies might have been subjected to bias as their method of recruitment of patients consisted of recruiting patients from databases; this could lead to selection as well as reporting bias. None of the studies were randomized, blinded (7,12), and only one study had a control group (8). However, the study group (coagulopathy patients) was significantly older than the control group, which poses the question to whether or not these groups could be compared. Furthermore, there was no mention on how the control group patients were selected from the authors' database of 692 patients. This again could be construed as selection bias.

The quality assessment of harms indicates that the studies generally have a low risk of bias concerning reporting the harms that could potentially be caused by the procedure (Figures 2 and 3).

DISCUSSION

Normalizing coagulopathy pre-operatively is the mainstay of patients' management before surgical procedures. This usually leads to the combined consult and co-ordinated efforts of the sur-

Figure 2 - Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

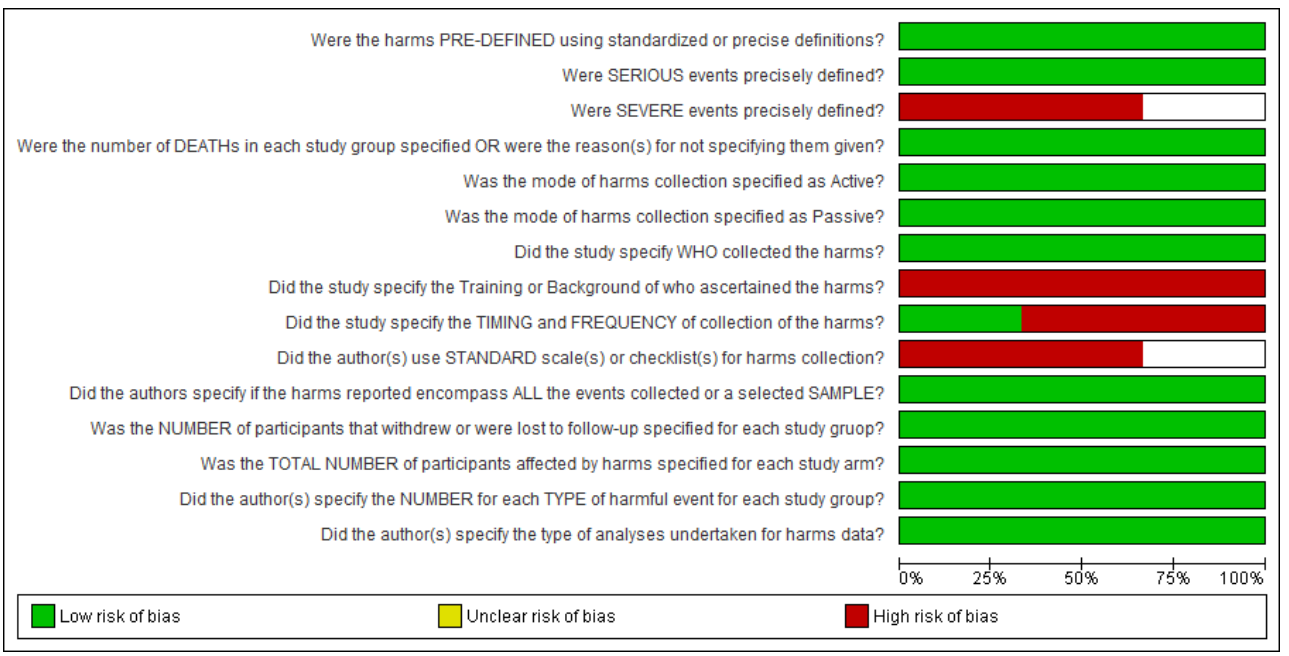
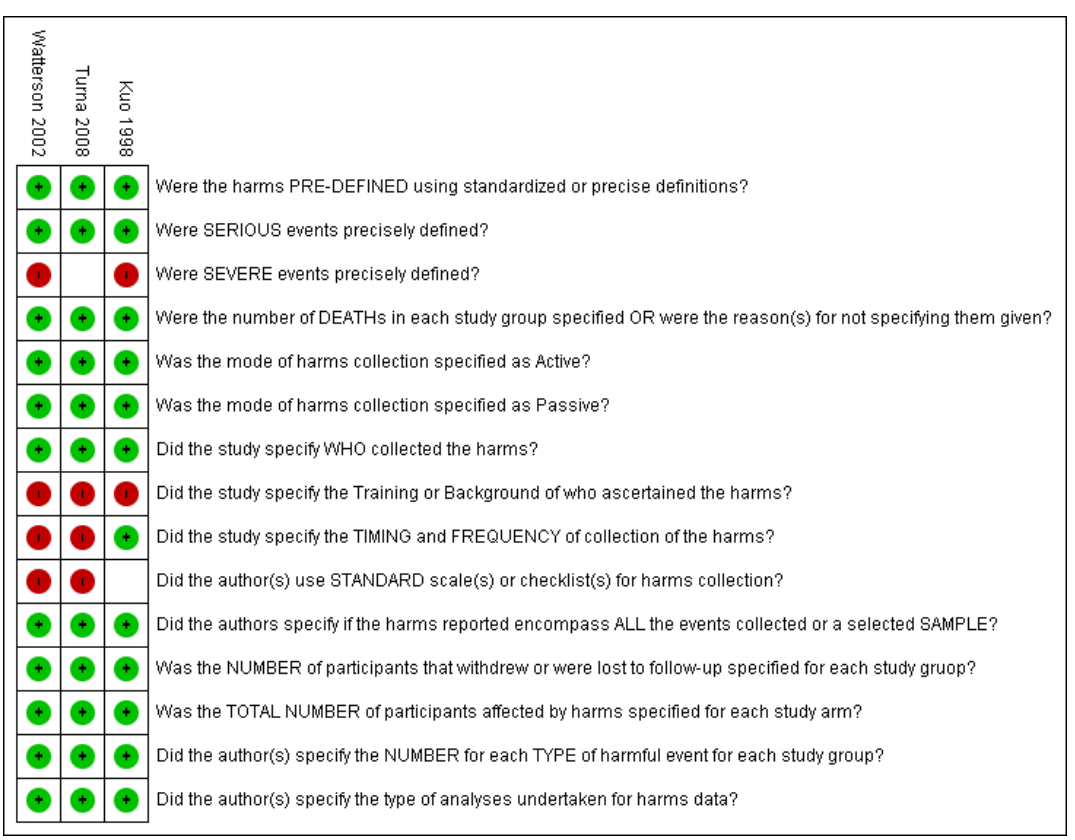


Figure 3 - Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



geons with the haematologists and anaesthetists (12). However, the risk of thromboembolic events during perioperative bridging with heparin is 1-2% (14). Furthermore, treating the coagulopathy is significantly more costly when compared to patients without coagulopathy undergoing similar procedures (10).

Though other modalities exist for the treatment of large urinary stones, such as SWL, PCNL, and open or laparoscopic surgery, these are contraindicated if the bleeding diathesis is not corrected (8,10). This only leaves ureteroscopic management for these patients (8).

Advancements in endoscope engineering and laser technologies allow an operator to visualise and treat stones in the whole upper urinary system, including the renal calyxes with a reported long-term complication rate of less than 1% (12,15,16). Holmium lasers provides effective and efficient intracorporeal lithotripsy for even hard stones such as cysteine and calcium oxalate monohydrate stones, and can also be used to ablate upper urinary tract tumours (7,12). Furthermore, holmium lasers offer haemostatic capabilities during the procedure, which gives an additive benefit to patients with bleeding diathesis (12). Lastly, holmium laser energy is rapidly absorbed by water, leading to a minimal risk of ureteric injury if the laser fibre is at least 0.5mm away from the ureter and no risk of ureteric perforation if the distance is more than 1mm (12).

This review found that the use of flexible ureteroscopes and holmium lasers on patients with bleeding diathesis is not only safe but also efficient, with an overall stone free rate of 87.7%, a minor complication rate of 11%, but only a 4% rate of minor bleeding, and a major complication rate of 0%.

The validity of the results of systematic review depends on the quality of included studies including selection of participants and inclusion criteria. The studies included seemed to all be retrospective reports of a larger database. Therefore at most this review has a level 2a Levels of Evidence according to CEBM (17). No study evaluated cost analyses.

The other limitation of this review is related to the patient population; the majority of patients were on warfarin. However, the remaining had various other causes for coagulopathy, whether the heterogeneity of the study sample would impact outcomes is not known. However, we aimed at reviewing all patients with coagulopathy and did not target one group. Furthermore, due to the limited number of patients, we did not see a need of conducting sub-groups analysis which would have reduced the cohort even further.

Furthermore, though the level of evidence is considered a 2a, this review has a small cohort of patients (70) from case series basing this evidence on. In addition, no trial or study was found in the literature. This reflects the need for further larger participant studies to further explore the safety and efficacy of ureteroscopy in these patients.

Despite the limitation, grouping of the data was possible and revealed the safety and efficacy of the combined studies. Furthermore, this review opens possibility for further research into the question.

This review has shown that it is not only safe but also efficient to treat patients suffering with urinary stones and afflicted with a bleeding diathesis with ureteroscopy and holmium laser. This can have cost benefits in practice as patients on anticoagulants need not undergo reversal and most patients with coagulopathy need further management to support their coagulation system.

Future research efforts should be concentrated on higher quality, more rigorous evaluation of ureteroscopic treatment in these groups of patients. Studies should be multi-institutional and protocol driven, preferably peer reviewed before the start. Studies should be prospectively evaluated and include a control group of patients who are not anticoagulated for comparison. A detailed evaluation of the different types of bleeding diathesis such as patients on warfarin, clopidogrel, thrombocytopenia or haemophilia should be analyzed individually rather than as a whole. Furthermore, health economic outcome measures should be analyzed.

CONCLUSIONS

The use of ureteroscopy with the holmium laser is a safe and efficient modality for treating patients with urinary tract calculi who also have a bleeding diathesis or are anticoagulated. Further-

more, these patients do not need their coagulopathy reversed, which leads to reduction the risk of thromboembolism with very minimal short-term complications and no long term consequence.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Manoj Monga
Glickman Urological & Kidney Institute, Cleveland Clinic,
Department of Urology, Desk Q10-1, 9500 Euclid Ave,
Cleveland, Ohio, USA
Fax: +1 216 636-0770
E-mail: endourol@yahoo.com

EDITORIAL COMMENT

It has been recently published that urolithiasis is an entity associated with metabolic syndrome, which is characterized by hypertension, obesity, diabetes and abnormal lipid levels (1).

As the world drags its way towards obesity, urologists of all around the globe have noticed that, not only kidney stones have become more frequent, but also those patients who present them have more often other co-morbidities. One particular instance is the drug-induced blood diathesis, which is characterized by the use of "blood thinners" for cardiovascular protection.

These phenomena (obesity, metabolic syndrome, kidney stones, blood thinners) have brought upon the endourologist a current and challenging topic that every kidney stone specialist needs to be up-to-date on: Stone treatment versus bleeding diathesis.

The present study reports on what has been published in the literature that could serve as foundation to our decision making process while counseling a stone patient with any kind of bleeding diathesis. Surprisingly, the authors very well presented the lack of prospective (high evidence levels) studies on this matter; however, based on what has been judiciously selected in the literature, stone free and complication rates of flexible ureteroscopy with holmium: YAG laser lithotripsy for patients with blood diathesis are similar to healthy individuals.

It is important to emphasize that if one considers doing a retrograde endoscopic stone treatment in a patient with bleeding diathesis, it is strongly advised, based on evidence level 2a, following analogous surgical technique to what has been described in the selected studies of this systematic review:

A) Energy/lithotripsy - there is no scientific support for using other energy than holmium:YAG laser;

B) Scopes - flexible ureteroscopes were used in all cases;

C) Double J - stenting seems to be a wise routine.

D) General anesthesia might be safer (routine in USA), given the obvious risks of spinal puncture in such patients.

In conclusion, due to a pandemy of obesity and its metabolic consequences, kidney stone patients will more often present co-morbidities and also some kind of bleeding diathesis (aspirin, warfarin, clopidogrel), thus, they must be informed that flexible ureteroscopy and holmium:YAG laser lithotripsy is safe and efficient for treating their ureteral/renal stones.

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Dr. Renato Nardi Pedro
Emphasis on Kidney stone Treatment
Clínica Padre Almeida, Campinas
SWL Center Coordinator
Ambulatory Surgical Unit Santa Barbara D'Oeste/ UNICAMP
E-mail: rnpedro@gmail.com

6. Outcomes of ureteroscopy for stone disease in pregnancy: Results from a systematic review of the literature

Stone disease in pregnancy is difficult to diagnose and manage. Although the management is usually conservative, infection and obstruction associated with renal stone is associated with significant morbidity for both mother and child. With improvement in endoscopic technology, ureteroscopy has become less invasive and has been increasingly used as a first-line treatment for stones in pregnancy. We conducted a systematic review in June 2011 for relevant studies reporting on at least 3 patients, from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials – CENTRAL, CINAHL, Clinicaltrials.gov, Google Scholar and Individual urological journals to assess the merits and harms of ureteroscopy in treatment of stone disease in pregnancy.

Of the 239 titles reviewed, 200 were excluded due to irrelevance from the title or abstracts. Fifteen of the remaining 39 studies were included after evaluating the full manuscripts (116 patients). The mean age of patients was 28 years and a stone free rate of 86% was achieved with 2 major and 7 minor complications and with no cases of maternal or fetal deaths. While the major complications included premature uterine contraction and ureteric perforation, the minor complications were urinary tract infection in 5 patients and prolonged post-operative hospital stay from ongoing pain in two patients. Our results showed that stone clearance using ureteroscopy is a relatively safe option in pregnancy with a high success rate.

(Contribution 40%, doing the systematic review, writing up, analyzing the data and proofreading/correcting the paper and subsequent revisions).

Review

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K.A. Laing[a] **T.B.L. Lam**[a]
S. McClinton[a] **N.P. Cohen**[a]
O. Traxer[c] **B.K. Somani**[b]

[a]Department of Urology, Aberdeen Royal Infirmary, Aberdeen, and [b]Department of Urology, University Hospitals Southampton NHS Trust, Southampton, UK; [c]Department of Urology, Tenon University Hospital, Paris, France

Outcomes of Ureteroscopy for Stone Disease in Pregnancy: Results from a Systematic Review of the Literature

Key Words
Pregnancy · Stones · Lithotripsy · Laser · Urolithiasis

Abstract

Introduction: Our aim was to evaluate the clinical efficacy and safety of ureteroscopy as a primary treatment for pregnant women with symptomatic ureteric stones who have failed conservative management. ***Materials and Methods:*** A systematic review of the literature from January 1990 to June 2011 was performed, including all English language articles. Outcome measures were clinical efficacy, in terms of stone clearance and need for additional procedures, and safety in terms of complications. ***Results:*** A total of 239 abstracts were screened and 15 studies were identified reporting on 116 procedures. The surgical methods of stone management employed were stone extraction with basket only (n = 55, 47%), laser fragmentation (n = 27, 23%; holmium, n = 20, pulse dye, n = 7), impact lithotripsy (n = 21, 18%), ureteroscopic lithotripsy (n = 6, 5%) and a combination of methods (n = 6, 5%). A post-operative stent was inserted in 64 of 116 procedures (55%). Complete stone clearance was seen in 100 of the 116 procedures (86%). There were 2 major complications (1 ureteral perforation and 1 case of premature uterine contraction) and 7 minor complications (5 urinary tract infections and 2 cases of post-operative pain). ***Conclusion:*** This review suggests that stone clearance using ureteroscopy is a relatively safe option in pregnancy with a high success rate.

Introduction

Urolithiasis can complicate up to 1 in 200 pregnancies [1–3]. It is the second most common cause of abdominal pain in pregnant women after urinary tract infection (UTI) [1–3] and is the commonest non-obstetric reason for admission to hospital during pregnancy. Within this group, 80–90% of pregnant women are in the 2nd or 3rd trimester of their pregnancy. Multiparous women are also more commonly affected [4–7].

During pregnancy, there is physiologic dilatation of the collecting systems, allowing for migration of renal stones into the ureter, leading to obstruction and/or pain. This could explain the reason for the observation that during pregnancy, stones are twice as likely to be found in the ureter than in the renal pelvis or calyxes. Physiological hydronephrosis caused by the enlarging uterus is present in 90% of pregnancies by the 3rd trimester [8–11]. This can make it more difficult to diagnose intramural obstruction during pregnancy. However, hydronephrosis due to pregnancy does not usually extend below the pelvic brim, and hence dilatation below this level is more likely to be due to an intraluminal cause such as ureteric stones.

Renal colic, infection and obstruction are a source of significant morbidity and potentially mortality to mother and child. The main risks are pre-term labour, which can occur in up to 40% of women [8], pre-term delivery and premature rupture of membranes.

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Bhaskar K. Somani
University Hospitals Southampton NHS Trust
Southampton SO16 6YD (UK)
E-Mail bhaskarsomani@yahoo.com

The management of urolithiasis in pregnancy is mainly conservative in the first instance, with spontaneous stone passage in approximately 70–80% of patients [9]. Expectant management includes hydration and analgesia. The use of oral calcium channel blockers, α-blockers and corticosteroids remains unproven in pregnant women, predominately due to safety concerns within this population. Approximately 20–30% of pregnant women will require therapeutic intervention. Indications for operative intervention are renal colic refractory to conservative treatment, sepsis and renal tract obstruction in a solitary kidney [3, 10–14].

The European Association of Urology guidelines [15] state that pregnant women with renal colic who have failed conservative management should be treated with temporising measures such as a stent or nephrostomy. Ureteroscopy (URS) can be considered, but only in specialist centres.

Temporising measures such as ureteric stenting or nephrostomy insertion can be performed under local anaesthetic with ultrasound scanning or minimal radiographic screening; however, during pregnancy there is accelerated encrustation and plugging which may result in frequent replacement of stents or nephrostomy tubes. With continued advancements in endoscopic technology and endourological techniques, URS has become less invasive and less traumatic such that it may be considered as first-line treatment in the management of ureteric stones in pregnancy.

We conducted a systematic review to assess the relative merits and harms of URS in the treatment of urolithiasis in pregnancy.

Materials and Methods

Search Strategy

This systematic review was performed according to the Cochrane diagnostic accuracy review guidelines. The search strategy was conducted to find relevant studies from MEDLINE (1966 to June 2011), EMBASE (1980 to June 2011), the Cochrane Central Register of Controlled Trials (in *The Cochrane Library,* Issue 1, 2011), CINAHL (1872 to June 2011), Google Scholar and individual urological journals.

Terms used included the following: 'ureteroscopy', 'pregnancy', 'calculi', 'stones', 'laser' and 'urolithiasis'. Mesh phrases included the following: ('Ureteroscopy' [Mesh]) AND 'Pregnancy' [Mesh], ('Calculi' [Mesh]) AND 'Ureteroscopy' [Mesh], ('Pregnancy' [Mesh]) AND 'Stones' [Mesh], ('Pregnancy' [Mesh]) AND ('Lasers' [Mesh] OR 'Laser Therapy' [Mesh]), (('Lasers' [Mesh]) AND 'Calculi' [Mesh]) AND (('Pregnancy' [Mesh]), and ('Ureteroscopy' [Mesh]) AND ('Calculi' [Mesh])). Reference lists of selected papers and abstracts from the annual meetings of the American Urological Association, European Association of Urology and the World Congress of Endourology were also searched for further eligible studies. Finally, ongoing trials were searched using ClinicalTrials.gov. The search was performed by B.K.S. and K.A.L. and was limited to the English language. References of searched papers were evaluated for potential inclusion, and the more recently published version was included if the publication was duplicated. Authors of the included studies were contacted wherever data were not available or not clear. Disagreement between the reviewers was resolved by discussion. If agreement between the two reviewers could not be reached, a third author (T.B.L.L.) was consulted for arbitration and consensus.

The participants included pregnant women in all stages of pregnancy, who were 16 or over and who had failed conservative management for ureteric stones. The reasons for failure are outlined in the methodology section. They underwent URS ± lithotripsy/stone extraction under local, regional or general anaesthetic. Comparisons were made between immediate versus delayed stone treatment. Immediate treatment included URS ± lithotripsy ± stenting and URS + stone extraction. Delayed treatment included stent + delayed URS, stent + delayed shock wave lithotripsy (SWL), nephrostomy + delayed URS and nephrostomy + delayed SWL. The outcomes measured were safety and adverse effects, graded using the Clavien criteria. Efficacy was defined by the stone clearance rate and the need for additional procedures such as ureteric stenting. Process and recovery outcomes were measured by length of hospital stay, analgesic requirements and quality of life measures.

Criteria for Inclusion

All studies published between January 1990 and June 2011 were eligible for evaluation. To satisfy the criteria for inclusion it was necessary that the study report on URS in a population of pregnant women of at least 3 patients and that the method of stone extraction, success rate and urological and obstetric complications be documented. Complications were graded in accordance with the Clavien criteria wherever possible or as defined by the study authors.

Quality Assessment of Included Studies

Risk of bias assessment and assessment of quality of evidence were planned, but since only retrospective case series were identified, formal risk of bias and quality assessments were not performed.

Data Extraction

Studies relevant to the ureteroscopic management of pregnant patients were included. The following variables were extracted from each study: period of the study; country of origin of the study; stone size and location; patient demographics such as age, gestation and type of anaesthetic; number of URS performed; method of anaesthesia; method of stone extraction; ureteric stent insertion; use of fluoroscopy; stone-free outcome, and urological, obstetric and other complications.

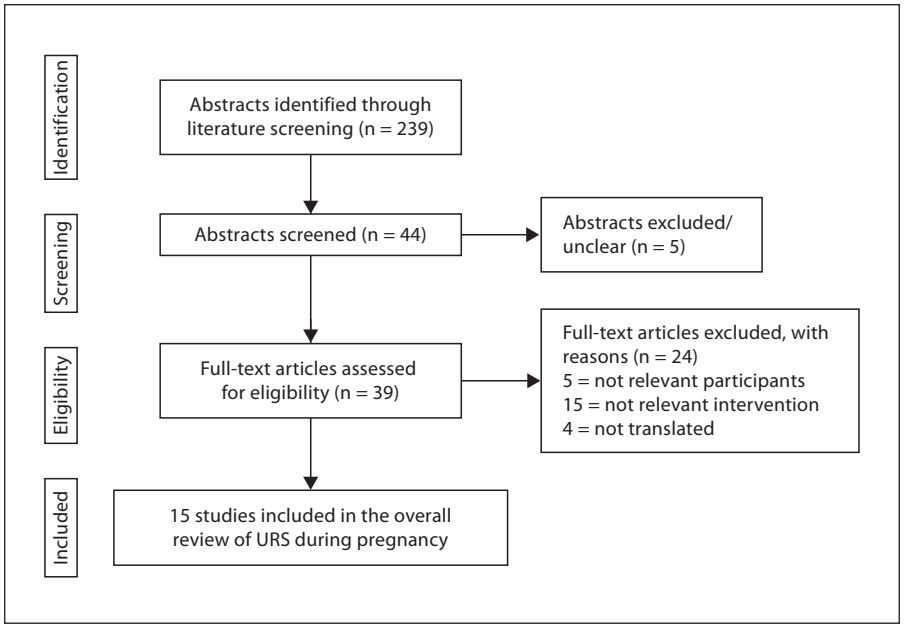

Fig. 1. Outcomes of the literature search.

Table 1. Summary of study information and patient demographics in the studies included

First author	Year	Country	Journal	Level of evidence	Patient age range, years	Trimester
Scarpa [16]	1996	Italy	J Urol	3	16–30	2, 3
Carringer [17]	1996	Sweden	Br J Urol	3	27–35	3
Ulvik [18]	1995	Norway	J Urol	3	20–41	1, 3
Juan [19]	2007	Taiwan	Kaohsiung J Med Sci	3	23–39	3
Akpinar [20]	2006	Turkey	J Endourol	3	24–33	1, 3
Yang [21]	2004	Taiwan	J Chin Med Assoc	3	not known	1, 2
Lemos [22]	2002	Brazil	Int Braz J Urol	3	20–34	1, 3
Lifshitz [23]	2002	USA	J Endourol	3	17–31	1, 2, 3
Watterson [24]	2002	Canada	Urology	3	21–36	1, 2, 3
Shokeir [25]	1998	Saudi Arabia	Br J Urol	3	22–33	2, 3
Parulkar [26]	1998	USA	J Urol	3	18–40	2
Denstedt [27]	1992	Canada	J Urol	3	not known	3
Rana [28]	2009	Pakistan	Urology	3	18–27	2, 3
Travassos [29]	2009	Brazil	J Endourol	3	not known	1, 2, 3
Cocuzza [30]	2010	Brazil	Urology	3	29.9 (mean)	2, 3

Results

A total of 15 reports of URS in pregnant women were identified in the literature search (fig. 1). All of these were retrospective case series. These reports included 116 pregnant women undergoing URS for ureteric stone disease (tables 1, 2). The mean age was 28 years (range 16–41); the majority of patients were in the 2nd or 3rd trimester of pregnancy. Most patients underwent the procedure under local anaesthetic or spinal/epidural anaesthesia. Ten procedures were performed under local anaesthetic, 46 under epidural/spinal anaesthesia and 44 under general anaesthetic, and the type of anaesthesia was not documented in 6 cases.

Table 2. Management and outcomes of patients in the studies included

First author	URS type and size	Imaging methods	Anaesthetic type	Position of stone	Stone size, mm	Fluoroscopy	Method of stone extraction	Stent	Complications	Follow-up
Scarpa [16]	13 rigid, 7.5 Fr	renal tract USS	8 GA 5 LA	2 distal 3 middle 3 upper 5 NA	NA	no	3 pulse dye laser 3 holmium laser 2 pneumatic 2 basket 3 displaced	13/13	nil	renal tract USS 2 days post-operatively 13/13 healthy full-term infants removal of stent post partum ESWL for stone clearance in 3/13
Carringer [17]	4 mini, 7 Fr (Candela Co.)	IVU	4 LA	3 distal 0 middle 1 upper 0 NA	7, 7, 8 16	no	4 pulse dye laser	0/4	nil	KUB on first post-operative day 4/4 healthy full-term infants
Ulvik [18]	13 rigid, 11.5 Fr	KUB + renal tract USS	12 epidural 1 LA	NA	NA	no	2 USL 1 forceps 10 basket	7/13	3 UTI[1] 1 premature uterine contractions (treated conservatively) 1 ureteric perforation (treated with stent and antibiotics)	IVU/USS 3 months post-operatively 1 neonate 7 weeks premature – not related to URS 1 neonate with cleft lip 11 healthy full-term infants
Juan [19]	3 semi-rigid, 6 Fr	renal tract USS	3 epidural	NA	NA	no	3 basket	0/3	nil	3/3 healthy full-term infants
Akpinar [20]	4 rigid, 8/9.8 Fr 2 FURS	renal tract USS	6 GA	3 distal 0 middle 3 upper 0 NA	7, 11, 9 8, 6, 6	no	6 holmium	4/6	2 prolonged admission due to pain (stayed 48 and 72 h post-operatively, respectively)	stents removed on 4th post-operative day 12/12 healthy full-term infants
Yang [21]	3 semi-rigid	renal tract USS	unknown	NA	NA	no	1 EHL 2 basket	0/3	nil	3/3 healthy full-term infants
Lemos [22]	13 rigid, 7/10 Fr	renal tract USS MRI	13 epidural	10 distal 2 middle 1 upper 0 NA	4–12 median 6	1/13	11 basket 2 USL	8/13	nil	13/13 healthy full-term infants
Lifshitz [23]	4 rigid (ACMI, 6.9 Fr) + FURS (Storz, 7.5 Fr; Olympus, 8 Fr)	renal tract USS limited IVU	4 epidural	3 distal 0 middle 1 upper 0 NA	4, 5, 3 0 5	4/4	4 basket	3/4	nil	4/4 healthy full-term infants removal of ureteric stent 1 day post-operatively
Watterson [24]	8 semi-rigid, 6.9 Fr	NA	8 GA	4 distal 1 middle 3 upper 0 NA	NA	4/8	8 holmium	4/8	nil	8/8 healthy full-term infants stent removal USS/IVU/KUB in post-partum period 2 ESWL post partum
Shokeir [25]	8 rigid, 11/9.5 Fr	renal tract USS	8 epidural	4 distal 1 middle 3 proximal 0 NA	NA	no	3 basket 2 USL 3 displaced	3/8	UTI – treated conservatively	stents changed every 6 weeks until delivery USS every 2 months until delivery and then 6 months following delivery 8/8 healthy full-term infants 3 ESWL post partum
Parulkar [26]	4 rigid	renal tract USS	4 GA	NA	NA	4/4	4 basket	0/4	nil	out-patient review 2–60 weeks following delivery
Denstedt [27]	3 rigid		unknown	NA	NA	3/3	3 basket	0/3	nil	NA
Rana [28]	18 semi-rigid (Storz, 6.9 Fr/ Wolf, 8 Fr)	renal tract USS 1 KUB	18 GA	8 distal 0 middle 10 proximal 0 NA	8–18 median 11	no	18 lithoclast	12/18	nil	18/18 healthy full-term infants renal tract USS, urine C+S post-operatively 3 ESWL post partum

Table 2 (continued)

First author	URS type and size	Imaging methods	Anaesthetic type	Position of stone	Stone size, mm	Fluoroscopy	Method of stone extraction	Stent	Complications	Follow-up
Travassos [29]	9 semi-rigid	renal tract USS	unknown	6 distal 0 middle 3 proximal 0 NA	6–10 median 8	no	9 basket	9/9	nil	removal of stent after 1 week 9/9 healthy full-term infants
Cocuzza [30]	6 semi-rigid (Wolf, 6.9 Fr), 1 FURS (Storz, 7.5 Fr)	renal tract USS	7 spinal	3 distal 2 middle 3 proximal 0 NA	mean 8.1 ± 4.8	7/7	4 basket 3 holmium	1/7	nil	7/7 healthy full-term infants stent removed 2 weeks following delivery USS 2 months following delivery

URS = Ureteroscopy; FURS = flexible ureteroscopy; GA = general anaesthetic; LA = local anaesthetic; USS = ultrasound scan; KUB = X-ray of kidneys, ureters, bladder; IVU = intravenous urogram; MRI = magnetic resonance imaging; NA = not available; EHL = electrohydraulic lithotripsy; SWL = shock wave lithotripsy; C+S = culture and sensitivity; UTI = urinary tract infection.

[1] Three patients with temperature <38.4 °C; of those 2 had documented UTI prior to URS (2 treated with antibiotics and discharged 3/7 days post-operatively, 1 re-admitted with pyelonephritis, which was treated conservatively).

Stone location was documented in 10 studies (86 patients). The stone location was in the proximal, middle and distal ureter in 31, 9 and 46 patients, respectively. Stone size was only documented in 7 studies (range: 3–11 mm for distal stones and 5–16 mm for proximal stones). The stone procedure was performed by rigid URS (n = 62, 53%), semi-rigid URS (n = 47, 45%), flexible URS (n = 3, 3%) or mini-ureteroscope (n = 4, 3%). During the procedure, fluoroscopy was used in 23 patients (20%). There were a number of methods used for stone extraction. The commonest method was basket extraction, which was used in 55 patients (47%). Laser and lithoclasts were popular for stone fragmentation, being used in 27 (23%) and 21 patients (18%), respectively. In a small proportion of patients, ultrasonic lithotripsy (USL) and a combination of techniques were required for stone extraction. The stone was extracted successfully in 100 patients (86%). In 6 patients, there was displacement of the stone into the renal pelvis necessitating SWL post partum. Sixty-four patients (55%) had a ureteric stent placed at the end of the procedure. The majority of procedures were performed without incident. There was 1 reported incidence of premature uterine contraction (Clavien criteria grade II), 5 UTIs (Clavien criteria grade I), 1 ureteral perforation (Clavien criteria grade III) and 2 cases of prolonged admission due to pain (Clavien criteria grade I). There were no maternal or foetal deaths reported.

Discussion

Retrograde stone extraction during pregnancy is becoming more common. The findings of this systematic review suggest that it is a procedure with high efficacy, with 86% of cases achieving complete stone clearance. Fluoroscopy and radiation exposure should be limited during pregnancy due to the risks to the foetus, and this was only required in 23 patients (20%). A number of techniques were used for stone extraction, including USL, basket extraction and lithoclast. A ureteric stent was placed in 55% of patients, which is disappointing as although they can allow adequate drainage of an obstructed system they are more prone to encrustation due to the increased concentration of calcium and urate in urine during pregnancy [13]. This encrustation can necessitate frequent stent changes, which can be as often as every 4–6 weeks. These additional procedures are associated with morbidity such as UTI, stent migration and pain, which can have adverse effects on the pregnancy. Nephrostomy for obstruction secondary to urolithiasis in pregnancy

[14] has also been described but is subject to similar complications and is not well tolerated, with a third of patients requiring removal of the nephrostomy tube due to pain, fever or drain obstruction [14]. Both are only temporary measures and do not provide definitive management of the obstructing calculus. To their advantage, ureteric stent insertion and nephrostomy placement can be successfully performed under local anaesthetic, thus reducing the potential risks of a general anaesthetic for the pregnant women. However, many of the URS procedures reported in this systematic review were performed under local or regional anaesthetic.

Technological advancements in endourology such as the development of the semi-rigid or flexible ureteroscope could be one of the reasons why URS is increasingly being used in pregnancy. There have also been improvements in the design of baskets used for retrieval, and the availability of laser, SWL and USL enables the atraumatic fragmentation of stones.

Complications were infrequent in pregnant women undergoing URS, with only 2 patients (1.6%) suffering a major complication. There was no mortality reported either for mothers or unborn children.

The review had some inherent limitations. Firstly, the paucity of well-designed randomised trials or comparative prospective studies assessing the role of URS in pregnant women was a clear limitation. Virtually all studies were retrospective case series without a control arm, and this inevitably introduces selection bias, as various confounding variables such as stone size, stone location and type of stones were not accounted for. This limits the evidence base somewhat. However, given the relative rarity of urolithiasis in pregnancy, especially complicated cases requiring surgical intervention, coupled with the high efficacy of URS and the lack of therapeutic alternatives, it may not be feasible nor pragmatic to conduct comparative studies on such women, let alone randomised studies. However, future studies should be prospective at the very least, with clearly specified objectives, an assessment of confounding variables such as stone size and location, and the measurement of clinically meaningful outcome measures, including quality of life outcomes.

Secondly, it was also unclear in the majority of studies how patients were selected, as there were no inclusion criteria in the majority of studies. This limitation may affect the external validity of the review findings. Thirdly, performance bias may also have been an issue, as it was not clear in the majority of studies what was the grade of the surgeon performing the URS. URS and in situ lithotripsy or stone retrieval is a complex procedure with a relatively long learning curve, and hence the surgical outcomes of experts and trainee surgeons are likely to be different. Finally, publication bias is also possible, as unfavourable results are less likely to have been reported or published. This assertion is supported by the apparent discrepancy between the relatively low number of patients in this review (n = 116 only) and the reported incidence of urolithiasis of up to 1 in 200 pregnancies, especially with 20–30% of patients failing expectant management. This observation suggests it is probable that more women are undergoing URS during pregnancy than is being reported, and our review was limited as only case series were included.

With these limitations in mind, the evidence base in regard to level 1–3 evidence for the role of URS in the treatment of urolithiasis in pregnancy is poor, and hence further well-designed, prospective studies which take into account selection bias, performance bias and the issue of confounding are required.

Conclusion

In spite of the various limitations, the findings from this systematic review suggest that URS appears to be a safe procedure during pregnancy, which can be performed under local or regional anaesthesia without the need of fluoroscopy. As such, it may be considered as a first-line treatment of ureteric calculi in those who have failed expectant management. To optimise outcomes in terms of efficacy and safety, URS in pregnancy should ideally be performed by experts in high-volume centres.

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7. Ureteroscopy for stone disease in the paediatric population – A systematic review.

With a rise in the incidence of paediatric stone disease, we wanted to look at the role of ureteroscopy for treatment of paediatric stones. A systematic review was conducted using MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, CINAHL, Google Scholar and individual urological journals between January 1990 and May 2013 for all English language articles reporting on a minimum of 50 patients ≤18 years treated with ureteroscopy for stone disease.

A total of 14 studies (1718 procedures) were reported with a mean age of 7.8 years (0.25-18 years). The mean stone burden was 9.8mm (1-30mm) with a SFR of 87.5% (58-100%) with initial therapeutic ureteroscopy. Majority of these stones were in the ureter (n=1427, 83.4%). There were 180 (10.5%) clavien I-III complications and 38 cases (2.2%) where there was a failure to complete the initial ureteroscopic procedure and an alternative procedure was performed. To assess the impact of age on failure rate and complications, studies were subcategorised into children below and above a mean age of 6 years. A higher failure rate (4.4% versus 1.7%) and a higher complication rate (24% versus 7.1%) were observed in children with a mean age under the age of 6 years.

Ureteroscopy for paediatric stone disease was shown as a relatively safe procedure with a reasonably good stone free rate.

Review

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Ureteroscopy for stone disease in the paediatric population: a systematic review

Hiro Ishii*, Stephen Griffin† and Bhaskar K. Somani*

*Departments of *Urology and †Paediatric Surgery, University Hospital Southampton NHS Trust, Southampton, UK*

The aim of the present review was to look at the role of ureteroscopy (URS) for treatment of paediatric stone disease. We conducted a systematic review using studies identified by a literature search between January 1990 and May 2013. All English-language articles reporting on a minimum of 50 patients aged ≤18 years treated with URS for stone disease were included. Two reviewers independently extracted the data from each study. A total of 14 studies (1718 procedures) were reported in patients with a mean (range) age of 7.8 (0.25–18.0) years. The mean (range) stone burden was 9.8 (1–30) mm and the mean (range) stone-free rate (SFR) 87.5 (58–100)% with initial therapeutic URS. The majority of these stones were in the ureter (n = 1427, 83.4%). There were 180 (10.5%) Clavien I–III complications and 38 cases (2.2%) where there was a failure to complete the initial ureteroscopic procedure and an alternative procedure was performed. To assess the impact of age on failure rate and complications, studies were subcategorized into those that included children with either a mean age <6 years (four studies, 341 procedures) or a mean age >6 years. (10 studies, 1377 procedures). A higher failure rate (4.4 vs 1.7%) and a higher complication rate (24.0 vs 7.1%) were observed in children whose mean age was <6 years. URS for paediatric stone disease is a relatively safe procedure with a reasonably good SFR, but there seems to be a higher failure and complication rate in children aged <6 years.

Keywords

paediatrics, calculi, laser, stone, ureteroscopy

Introduction

Paediatric stone disease has been on the rise in recent years [1,2]. The reason for this rise is multifactorial. Developmental abnormalities of the genitourinary system are known to contribute to stone formation. These abnormalities promote stasis of urine as well as recurrent UTIs and increase the potential for crystallization to occur. Metabolic abnormalities are also a major contributing factor in stone formation. These are more common in paediatric patients with stone disease. There is geographical variance in the location of the calculi. In South-East Asia and Africa, bladder calculi are frequent, whereas in the USA and Europe, upper ureteric calculi are most common [3]. The composition of the stone also seems to be influenced by geographic location; in Northern Thailand, there is a high incidence of pure calcium oxalate stones, compared with Europe, where the majority of the stones are infection-related [3].

Historically, the treatment of ureteric calculi in children has been by open surgical removal followed by prolonged hospital admission; however, with the advent of shockwave lithotripsy (SWL) in 1980 [4] and other endourological techniques, there has been a significant change in the management of paediatric stone disease.

In 1988, Ritchey et al. [5] used ureteroscopy (URS) for the extraction of lower ureteric stones in children. Early studies of ureteroscopic treatment of paediatric stone disease showed good results [6–12]; however, because of the fragility of the instruments and lack of experience, the majority of the stones extracted were located in the mid to distal ureter [2,12,13]. In the early 2000s, with improvements in the durability and quality of the instruments, several studies reported stone-free rates (SFRs) ranging from 84 to 100% after a single ureteroscopic procedure [2,13–16]. In 2008, Tanaka et al. [17] presented a review of 50 paediatric patients over a 3-year period who underwent URS for intrarenal calculi. Even though the SFRs were not as impressive as those for ureteric stones, this showed that intrarenal calculi could indeed be treated with URS in the paediatric population.

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In the last 3 years, studies have looked at various factors that may influence the morbidity associated with therapeutic URS in the paediatric population [18–20]; these include balloon dilatation of the ureteric orifice, use of ureteric access sheaths, the calibre of the actual scope used and the siting of a stent at the end of the procedure.

With constantly evolving technology and growing experience, this systematic review looks at the worldwide literature on the outcomes of ureteroscopic management of stone disease in the paediatric population.

Materials and Methods

Search Strategy

This review was conducted in accordance with the systematic review guidelines provided by the Cochrane Collaboration and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist. The search involved finding relevant studies from MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, CINAHL, Google Scholar and individual urological journals, published between January 1990 and May 2013.

The terms used in the search included the following: 'ureteroscopy', 'paediatric', 'pediatric', 'paediatrics', 'pediatrics', 'children', 'calculi', 'stones', 'laser', 'laser therapy' and 'urolithiasis'. Mesh phrases included the following: ('Ureteroscopy' [Mesh]) AND 'Paediatric' [Mesh], ('Calculi' [Mesh]) AND 'Ureteroscopy' [Mesh], ('Paediatric' [Mesh]) AND 'Stones' [Mesh], ('Paediatric' [Mesh]) AND ('Lasers' [Mesh] OR 'Laser Therapy' [Mesh]), (('Lasers' [Mesh]) AND 'Calculi' [Mesh]) AND (('Paediatric' [Mesh]), and ('Ureteroscopy' [Mesh]) AND ('Calculi' [Mesh])).

Only papers written in the English language were considered for inclusion. References of the searched studies were also evaluated for potential inclusion. Authors of the relevant studies were contacted to verify data if unclear or unavailable.

Inclusion Criteria and Outcomes of Interest

To be included in this systematic review studies were required to have reported on at least 50 cases of paediatric patients (aged ≤18 years) who underwent URS for stone disease, and their outcomes. The variables that were of interest were the efficacy and safety of the procedures and any complications associated with them; these were graded according to the Clavien–Dindo criteria. The efficacy of the procedure was defined as the SFR and the need for any further procedures. Recovery outcomes were defined by length of hospital stay, analgesic requirements and quality-of-life measurements.

Data Extraction

Two reviewers independently extracted the data which was then put into an Excel spread sheet. Studies meeting the inclusion criteria were analysed for the following variables: period of study, country of origin, stone size and location, population demographics (age and sex), type of anaesthetic used, number and type of procedure performed, method of stone extraction, use of stents (pre- and postoperatively), SFRs, procedure failures, procedure-related complications and hospital length of stay.

Results

A total of 14 studies (Fig. 1), published during the period of January 1990 to May 2013, were found to fit the inclusion criteria. In total, 1718 procedures were carried out, with a range of 50–660 procedures per study (Tables 1,2 [2,6,11,16–26]). The mean (range) age of the reported populations was 7.8 (0.25–18.0) years and the populations included 768 boys and 727 girls. One study did not mention their male and female patient numbers. The majority of the studies were from Turkey ($n = 5$) and the USA ($n = 4$). Of the 14 studies analysed, six were published in the last 3 years.

Stone location was recorded in all studies, with the majority of stones lying in the ureter ($n = 1427$, 83.4%) and most commonly within the distal ureter ($n = 862$, 50.4%). There were a total of 285 renal stones, most of which were in the lower pole ($n = 117$, 41.1%) and the PUJ/renal pelvis ($n = 51$, 18%). The mean (range) stone burden was 9.8 (1–30) mm with a mean (range) SFR of 87.5 (58–100)% after initial therapeutic URS.

Fig. 1 Outcome of literature search.

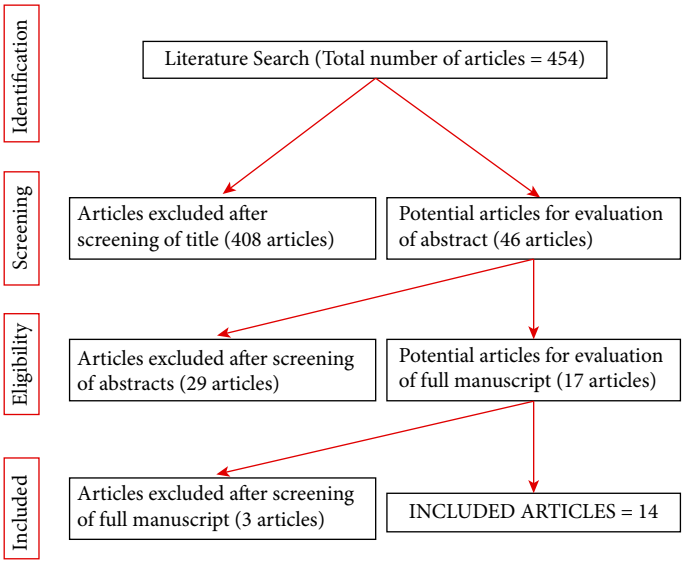

Table 1 Summary of study information and patient demographics.

Author	Journal	Year	Country	No. of cases	Mean age in years,(range)
Al Busaidy [6]	Br J Urol	1997	Oman	50	5.2 (0.5–12.0)
Bassiri [11]	J Endourol	2002	Iran	66	9.0 (2–15)
Minevich [2]	J Urol	2005	USA	81	7.5 (1–12)
Raza [21]	J Endourol	2005	UK	52	5.9 (0.9–15.0)
Gedik [22]	Int Urol Nephrol	2007	Turkey	54	8.5 (1–16)
Smaldone [16]	J Urol	2007	USA	115	13.2
Tanaka [17]	J Urol	2008	USA	50	7.9 (1.2–13.6)
Kim [23]	J Urol	2008	USA	170	5.2 (0.25–18.0)
Tanriverdi [18]	Pediatr Surg Int	2010	Turkey	65	9.1 (2–16)
Turunc [24]	J Endourol	2010	Turkey	66	8.1 (0.5–16.0)
Abu Ghazaleh [25]	Saudi J Kidney Dis Transpl	2011	Jordan	78	8.2 (6–14)
Nerli [26]	J Endourol	2011	India	88	9.5 (6–12)
Dogan [19]	J Urol	2011	Turkey	660	7.5 (0.33–17.0)
Atar [20]	Urol Res	2012	Turkey	69	4.3

The reporting of preoperative stenting was not as thorough as it was for postoperative stenting. Only eight studies [6,16,17,20,21,23,25,26] mentioned the proportion of their study population who underwent preoperative stenting. A mean (range) of 47.7 (0–100)% of patients were stented preoperatively in these studies. Post-procedure stenting was reported across all studies, with a mean (range) of 70 (31–100)% of the study population being stented.

In the 14 studies, there were 38 cases (2.2%) where there was a failure to complete the initial ureteroscopic procedure and an alternative procedure was performed. This was either because of peri-operative difficulties or intra-operative complications. Sixteen cases (0.9%) required SWL to render the patient stone-free as a result of stone migration during URS. There were 14 cases (0.8%) where the surgeon was unable to access the ureter/reach the stone. Finally, there were eight cases (0.47%) where the initial URS procedure had to be converted to an open procedure (ureterolithotomy, ureteroureterostomy or ureteroneocystostomy). In total, there were 180 (10.5%) complications. The most common complications were ureteric perforation, haematuria and UTI.

The mean hospital stay was reported in three studies [11,19,21]: the mean (range) length of stay was 2.5 (1–19) days. The follow-up period varied across the studies. Three studies [17,20,24] did not quantify the length of follow-up, while the mean (range) follow-up period for the other studies was 15.5 (1–120) months.

None of the included studies reported analgesic requirement postoperatively and quality-of-life scores after the procedure were not assessed in any of the studies.

To assess the impact of age on failure rate and complications, studies were subcategorized into those that included patients with a mean age of ≤6 years and those whose patients had a mean age of ≥6 years (Table 3 [6,20,21,23], Table 4 [2,11,16–19,22,24–26]). Four studies reported on patients with a mean age of ≤6 years, with a total of 341 procedures being performed. There were 15 (4.4%) failures with 82 (24%) complications. With regard to failures of URS, three cases (0.9%) were converted to open procedures, seven (2.1%) required SWL and in five cases (1.5%), the surgeon was unable to reach the stone.

The other 10 studies reported a mean patient age of ≥6 years, with a total of 1377 procedures. There were 23 (1.7%) failures with 98 (7.1%) complications. Of these procedures, five cases (0.36%) had to be converted into open procedures, nine (0.65%) required SWL and in nine cases (0.65%) an inability to access ureter/reach stone was reported. Although the failure and complication rates were found to be higher in the lower age group (Tables 5,6), the SFR was actually higher in the studies with patients aged ≤6 years (mean [range] SFR 91.7 [85.6–98.5]%), compared with the studies whose patients had a mean age of ≥6 years (mean [range] SFR 85.8 [58–98]%).

Discussion

The present review provides an insight into the practicalities of URS in the paediatric population in terms of efficacy and safety. With the recent rise in the incidence of paediatric stone disease, advancements in both instrumentation and experience in relation to URS have allowed surgeons to provide safe and effective alternatives to SWL, percutaneous nephrolithotomy and open surgery.

This review found there was a SFR of 86.3%, which compares well with the SFRs reported in studies of SWL in the treatment of paediatric stone disease. A recent study by Badawy et al. [27] reported SFRs of 83.4 and 58.5% in renal and ureteric calculi, respectively, in >500 patients. Bhageria et al. [28] have recently conducted a 10-year review on the use

Table 2 Management and outcomes of patients in the studies included.

Author	Procedures, *n*	Stone location, *n*								Mean stone burden, mm	SFR, %	Failures (*n*)	Complications (*n*)
		Upper ureter	Mid ureter	Lower ureter	Renal pelvis	Upper pole	Mid pole	Lower pole	Other stones				
Al Busaidy [6]	50	9	7	30						12.6	91.7	Required open ureterolithotomy (3)	Ureteric perforation (2)
Bassiri [11]	66	2	5	59						8.0 (5–15)	88.0	Unable to pass the ureteroscope (3)	Renal colic (1), haematuria (11), pyelonephritis (3)
Minevich [2]	81	16	14	28						Unknown	98.0	0	Ureteric stricture (1)
Raza [21]	52	0	3	72					2	8.8 (3–20)	91.0	0	Ureteric perforation (2), urinary retention (1), ureteric stricture (1), mild fever (5), mucosal tear (1)
Gedik [22]	54	3	16	25						7.1 (4–12)	77.8	Required open ureterolithotomy (2)	Pyrexia (3)
Smaldone [16]	115	19	11	37	6	10		17		8.3	91.0	0	Ureteric perforation/ extravasation (5), ureteric stricture (1)
Tanaka [17]	50				27			13	11	8.0 (1–16)	58.0	0	Re-admission because of nausea and vomiting (1)
Kim [23]	170		47	19				87	14	6.1 (3–24)	98.5	0	0
Tanriverdi [18]	65	5	2	33						9.5 (3–30)	89.2	Stones migrated requiring SWL (2)	Mucosal lacerations (2), minor haematuria (1)
Turunc [24]	66	7	9	50						8.2(4–20)	84.8	Stones migrated requiring SWL (5)	Pyrexia (1), prolonged hospital stay (1)
Abu Ghazaleh [25]	78				34	6	4		24	12.0 (9–15)	88.5	0	UTI (3), haematuria (1)
Nerli [26]	88	56							24	10.2 (7–16)	90.0	Required SWL after second look (2)	Intra-operative bleeding (6), self-limiting postoperative bleeding (8), pyrexia (4)
Dogan [19]	660	96	73	480					21	8.9	92.8	Conversion to open procedure (3), inability to access ureter/reach stone (6)	Stone migration (8), mucosal laceration (1), broken catheter (1), ureteric perforations (5), gross haematuria (2) (1 intraoperative, 1 postoperative), postoperative pain (2), febrile UTI (20), urinary retention (1), 1 urethral stone (1), late vesico-ureteric junction obstruction (4)
Atar [20]	69	6	9	54						7.2	85.6	Required SWL due to stone migration (7), inability to reach stone (5)	Mild haematuria (8), ureteric laceration (8), ureteric perforation (4), urinoma (1), urethral pain (7), renal colic (5), febrile UTI (9), urinary retention (7), bleeding/ false route/perforation intra-operatively (13)

SRF, stone-free rate; SWL, shockwave lithotripsy.

of percutaneous nephrolithotomy in the paediatric population and reported a SFR of 83% after a first-look procedure, which again is very competitive with the SFR of URS; however, the complication rate was somewhat higher in that study than that reported in the present review for therapeutic URS. The ability of URS to clear stones from virtually any location within the urinary system with minimal complication has brought this technique to the forefront.

Table 3 Studies in patients with mean age of ≤6 years.

Author	Procedures, *n*	Mean age, years	Stone location, *n*								Mean stone burden, mm	SFR, %	Failures (*n*)	Complications (*n*)
			Upper ureter	Mid ureter	Lower ureter	Renal pelvis	Upper pole	Mid pole	Lower pole	Other				
Al Busaidy [6]	50	5.2	9	7	30						12.6	91.7	Salvaged by uretero-lithotomy (3)	Perforations (2)
Raza [21]	52	5.9		3	72					2	8.8 (3–20)	91.0	0	Perforations (2), urinary retention (1), ureteric stricture (1), mild fever (5), mucosal tear (1)
Kim [23]	170	5.2		47	19				87	14	6.1 (3–24)	98.5	0	0
Atar [20]	69	4.3	6	9	54						7.2	85.6	Required SWL due to stone migration (7), inability to reach stone (5)	Mild haematuria (8), ureteric lacerations (8), perforations (4), urinoma (1), urethral pain (7), renal colic (5), mild haematuria (8), febrile UTI (9), urinary retention (7), bleeding/false route/perforation intra-operatively (13)

SRF, stone-free rate; SWL, shockwave lithotripsy.

Preoperative stenting was only mentioned in eight studies but had no correlation to the stone location and no obvious impact on the SFR. The postoperative stent insertion was mentioned in all the studies and varied greatly from 13 to 100%. The present review also highlights that failure and complication rates were influenced by the paediatric patient's age. Despite the higher rate of failures and complications in patients aged ≤6 years, the SFR was better in the studies in patients with a younger age group than those with the older age group (91.7 vs 85.8%). This may reflect easier spontaneous passage of stone fragments at younger ages.

Looking at the factors affecting the SFR for ureteric stones, Turunc et al. [24] in their retrospective review of 61 patients concluded that stone location and size affected the success, but that age and sex of patients did not seem to be significant. A similar study of 33 patients for ureteric stones suggested a favourable outcome for stones <10 mm in size [29]. Dave et al. [30] mention that, although paediatric URS for retrograde intra-renal surgery achieves reasonable results, polar stones require multiple sessions for complete stone clearance. Atar et al. [31] compared use of a 4.5-F mini-ureteroscope with use of a 7.5-F standard ureteroscope for treatment of ureteric stones in 69 preschool children; the SFR was significantly higher (93 vs 79%) for children treated with the mini-ureteroscope. Although this difference was significant for patients aged <3 years (94 vs 67%), it was not significant for children aged 4–7 years, with the authors recommending the use of a mini-ureteroscope for preschool children [20]. In another study by the same authors on ureteric stone treatment in 64 patients, laser lithotripsy had a significantly higher SFR and a lower complication rate compared with pneumatic lithotripsy [31].

The present review has two limitations. Firstly, the majority of the studies reviewed were retrospective; only three of the studies included were prospective studies [19,23,26], which are less likely to be the subject of various confounding factors and bias. The other limitation is that of publication bias. Despite the reported rise in the incidence of paediatric stone disease, only a small proportion reported significant volume (≥50 cases).

Conclusion

The evidence from the present review suggests that the use of URS in the paediatric population for stone disease as the first-line surgical management is a safe and highly effective procedure. This technique has been used in paediatric patients, with stones located throughout the urinary system, to good effect. The safety of this technique has been proven, with a relatively small proportion (8.7%) of the study population having minor complications; the most serious being Clavien grade III complications.

Conflict of Interest

None declared.

Table 4 Studies in patients with mean age of ≥6 years.

Author	Procedures, *n*	Mean age, years	Stone location (n)								Mean stone burden (mm)	SFR (%)	Failures	Complications
			Upper ureter	Mid ureter	Lower ureter	Renal pelvis	Upper pole	Mid pole	Lower pole	Other stones				
Bassiri [11]	66	9.0	2	5	59						8.0 (5–15)	88.0	Unable to pass the ureteroscope (3)	Renal colic (1), haematuria (11), pyelonephritis (3)
Minevich [2]	81	7.5	16	14	28						Unknown	98.0	0	Ureteric stricture (1)
Gedik [22]	54	8.5	3	16	25						7.1 (4–12)	77.8	Required open uretero-lithotomy (2)	Pyrexia (3)
Smaldone [16]	115	13.2	19	11	37	6	10		17		8.3	91.0	0	Perforations/ extravasations (5), ureteric stricture (1)
Tanaka [17]	50	7.9				27			13	11	8.0 (1–16)	58.0	0	Re-admission due to nausea and vomiting (1)
Tanriverdi [18]	65	9.1	5	2	33						9.5 (3–30)	89.2	Stones migrated requiring SWL (2)	Mucosal lacerations (2), 1 minor haematuria (1)
Turunc [24]	66	8.1	7	9	50						8.2 (4–20)	84.8	Stones migrated requiring SWL (5)	Pyrexia (1), prolonged hospital stay (1)
Abu Ghazalah [25]	78	8.2				34	6	4		24	12.0 (9–15)	88.5		UTI (3), haematuria (1)
Nerli [26]	88	9.5	56							24	10.2 (7–16)	90.0	Required SWL after 2nd look (2)	Intra-operative bleeding (6), self-limiting post-operative bleeding (8), pyrexia (4)
Dogan [19]	660	7.5	96	73	480					21	8.9	92.8	Conversion to open procedure (3), inability to access ureter/reach stone (6)	Stone migration (8), mucosal laceration (1), broken catheter (1), ureteric perforations (5), gross haematuria (2) (1 intra-op, 1 post-op), post-op pain (2), febrile UTI (20), urinary retention (1), 1 urethral stone (1), late vesico-ureteric junction obstruction

Table 5 Nature of complications, their frequency and Clavien grade.

Nature of complication	Number of complications (%)	Clavien criteria grade
Intra-operative bleeding/false passage/ureteric perforation/tear/laceration/submucosal wire	48 (2.8)	III
Haematuria	39 (2.3)	I
UTI/pyelonephritis	35 (2.0)	I
Mild fever/pyrexia post-operatively	14 (0.8)	I
Urinary retention	9 (0.5)	I
Postoperative pain requiring analgesia	9 (0.5)	I
Stone migration	8 (0.5)	III
Postoperative renal colic	6 (0.3)	I
Late vesico-ureteric junction obstruction	4 (0.2)	III
Ureteric strictures	3 (0.2)	III
Postoperative ureteric stone	1 (0.1)	III
Broken catheter	1 (0.1)	III
Re-admission because of nausea and vomiting	1 (0.1)	I
Urinoma formation	1 (0.1)	I

Table 6 Summary of ureteroscopy failure and complication rates between the sub-groups (age ≤6 years and 6 ≥ years).

	Studies in patients with mean age ≤6 years or below	Studies in patients with mean age of ≥6 years
Failures, *n*/*N* (%)	15/341 (4.4)	23/1323 (1.7)
Complications, *n*/*N* (%)	82/341 (24.0)	98/1323 (7.1)

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Correspondence: Bhaskar K. Somani, Department of Urology, University Hospital Southampton NHS Trust, Southampton SO16 6YD, UK.

e-mail: bhaskarsomani@yahoo.com

Abbreviations: SWL, shockwave lithotripsy; URS, ureteroscopy; SFR, stone-free rate.

8: Flexible ureterorenoscopy: Tips and tricks

There has been a big improvement in ureteroscopy technique with better fibre optics, digital imaging and smaller scopes. Improved imaging with better ancillary equipment such as graspers, baskets and laser technology have allowed more complex procedures. This paper aimed to provide a summary of flexible ureterorenoscopic procedures with "tips and tricks'' for success, providing techniques for various flexible ureterorenoscopic procedures including management of renal stones, calyceal diverticula and upper tract urothelial tumours.

The paper discussed the disposables used with flexible ureteroscopy including various types of guidewires, ureteral catheters, port seal, ureteral access sheath and a variety of stone extraction devices. Pre-operative patient positioning, set up, insertion and handling of the scope, stone fragmentation devices and post-operative drainage were also discussed. Tips to enhance scope durability and prevent costly repairs were also shared.

Our review concluded that flexible ureteroscopy is an effective, reproducible and minimally traumatic diagnostic and therapeutic technique perfectly adapted to disease of the upper urinary tract. Improvement in optics and ancillary equipment allowed access and treatment in all cases even those with anomalous or reconstructed urinary tract anatomy.

(Contribution 80%, writing the paper and doing the subsequent revisions).

Review Article

Flexible ureterorenoscopy: Tips and tricks

Bhaskar Kumar Somani, Omar Aboumarzouk[1], Aneesh Srivastava[2], Olivier Traxer[3]

Consultant Urological Surgeon and Stone lead, Southampton University Hospitals NHS Trust, [1]Department of Urology, Aberdeen Royal Infirmary, AB25 2ZN, Scotland, United Kingdom, [2]Consultant Urological and Transplant Surgeon, Consultant Urological and Transplant Surgeon, SGPGI, Lucknow, India, [3]Consultant Endourologist, Department of Urology, Tenon University Hospital, Pierre and Marie Curie University, 4 rue de la chine, Paris, France

Abstract

With advancement in technology, improvement in endoscope and ancillary equipment, more complex procedures can be performed using flexible ureterorenoscopy. In this review article we provide a summary of flexible ureterorenoscopic procedures with "tips and tricks" for success for each type of procedure. It looks at the disposables used with flexible ureterorenoscopic procedures, set up and patient positioning for gaining access, insertion and handling of scope and the use of urethral access sheath. We also provide techniques for various flexible ureterorenoscopic procedures including management of renal stones, calyceal diverticula and upper tract urothelial tumours.

Key Words: Calculi, flexible ureterorenoscopy, holmium laser, lithotripsy, laser vaporization

Address for correspondence:
Mr. Bhaskar K. Somani, Southampton University Hospitals NHS Trust, Southampton, United Kingdom. E-mail: bhaskarsomani@yahoo.com
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INTRODUCTION

The fibreoptic technology used in modern medicine was first demonstrated 150 years ago by John Tyndall in 1854. Young and McKay described the first ureteroscopy in 1929.[1] These Ureteroscopes were without any active deflection or working channel and were for diagnostic use only. It was not until 1978 before the first distal ureteroscopy was reported by Lyon and colleagues.[1,2] In association with Karl Storz, the first working Ureteroscope was developed in 1980 by Perez-Castro, a rigid ureteroscope with a separate optic and working channel. This was soon followed by the first electrohydraulic and ultrasonic lithotripsy a year later. The same year ureteroscopy and stone basketing under direct vision was reported by Das. The first flexible tip ureteroscope was introduced by Bagley and colleagues in 1983.[1,2]

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Last two decades have witnessed a huge improvement in flexible ureterorenoscope (F-URS) technology with smaller outer diameter, larger working channel, active deflection and better fibre optics.[2,3] With digital imaging and high definition television, the image quality has improved and the digital chip is now incorporated in the tip of the newer F-URS. In addition to the improvements in the endoscope, ancillary equipment such as graspers, baskets and laser technology have also progressed allowing more complex procedures. As the technology has improved, there has been a huge surge in the number of ureterorenoscopic procedures being performed.[4] The indications for F-URS procedures include management of calculus disease, diagnostic procedures, endoscopic management of upper tract tumors and endoureterotomy or endopyelotomy.[5-9] The aim of this paper is to provide a summary of flexible ureterorenoscopic procedures with "tips and tricks" for success for each type of procedure.

Disposables used with the flexible ureterorenoscopic (F-URS) procedure

Guide wires

Guide wires are used to gain access to renal collecting system and to allow passage of stents and catheters. The three important characteristics are tip flexibility, low friction and

Table 1: Examples of material, coating and types of guide wires and stents available

	Guide wire	Stent
Length (cm); Tip (cm)	145-150; 3-15	12-30
Material	Stainless steel, Nitinol	Silicone, Polyurethane, Polyester, Styrene/Ethylenebutylene, Hydrogel+Urethane, Biodegradable (Polylactic acid), Metallic (Polytetrafluoroethylene, nickel-titanium alloy)
Coating	PTFE, Hydrophilic polymer, Slipcoat	Hyaluronic acid, Hydrogel, Heparin, Silver, Tricoslan, Polyvinylpyrrolidone (PVP)
Types	Superstiff, Standard PTFE, Nitinol, Glidewire, Bentson, Roadrunner, Urowire	Percuflex, C-flex, Silitek, Tecoflex, Aquavene Polaris loop stent, Triumph, Radiance, InLay Optima, Resonance stent, TUDS

shaft rigidity, the later more useful as a coaxial system for passage of catheters or stents. Two 150-cm-long and 0.035 or 0.038 inch diameter guide wires (one 'safety' and one 'working' wire) should be used. The distal tip end must be flexible and atraumatic and its length varies from 3 to 15 cm [Table 1]. To reduce friction, guide wires are coated with polytetrafluroethylene (PTFE) or hydrophilic polymer. The latter is useful for negotiating difficult ureter; however these hydrophilic wires must be kept moist prior to its use. The working wire should be hydrophilic to protect the working channel of the scope. For difficult guide wire passage the following tricks can be helpful – advancing it via ureteral catheter, using a hydrophilic guide wire or Ureteroscopically passing it under vision and treating the underlying pathology such as stone fragmentation or balloon dilatation of stricture to allow access.[10] Difficult ureteral access can be negotiated (at times) with a 0.025 or 0.028 hydrophilic wire. Occasionally, for impacted ureteral stones direct disintegration is the only way to avoid false passage by guide wire, whatever the type or material of guide wire used. If a glide wire is used, once it is passed proximal to the stone, a 5Fr open ended catheter can be passed and the wire exchanged for a stiff wire.

Ureteral catheter

A 5-6F open tip ureteral catheter is used for retrograde pyelogram (RPG) or for positioning the guide wire in the ureter or to obtain urine sample from pelvicalyceal system for cytology/culture.

Ureteral access sheath

With expanding indication of F-URS, the use of access sheath is now becoming more common. It can facilitate ureterorenoscopy and retrieval of stone fragments (multiple withdrawals and reinsertions), whilst reducing the intrarenal pressure, improving irrigant flow, better visibility, decreasing operative time and costs.[11,12]

The access sheath is a 2-piece hydrophilic device: the sheath and the internal dilator [Table 2]. It is inserted over the working wire under fluoroscopic control and the internal dilator can be removed once the sheath is in place. Care should be taken while inserting it and forceful insertion should be avoided. It comes in various diameters (9.5-14 F internal diameter and 11.5-17.5 F external diameter) and lengths (20-55 cm).[13]

Table 2: Different accessories used with flexible ureteroscopic procedures

Ureteral access sheath
AquaGlide access sheath: hydrophilic sheath with additional channel for safety wire
Flexor access sheath
Flexor DL: dual lumen with secondary channel used for safety wire
UroPass: hydrophilic sheath with suture holes in end for securing sheath in place
Access Forte XE
Navigator access sheath
Ureteral occlusion device
NTrap: woven mesh of nitinol wires preventing stone fragment migration
Stone Cone: concentric coils to prevent stone fragment migration
Stone retrieval device
Baskets (1.5-3F) - Flat wire basket, parachute basket, helical basket, nitinol basket
NCircle: nitinol tipless basket
N-Compass: webbed mesh for small and multiple stones
Dimension stone basket: ti pless basket with teardrop shape
Escape stone basket: for use with laser fiber, holding the stone whilst fragmentation
Halo stone basket: tipless basket with rotary wheel to allow stone spinning for better fragmentation
Graspers (1.9-3F) – Two-prong, Three-prong, Four-prong, Nitinol
Types of lasers
Holmium:yttrium-aluminium-garnet (Ho:YAG)
Thulium
Pulse dye laser
Neodymium:YAG
Frequency-doubled, double-pulse neodymium:YAG (FREDDY)

Port seal

The seal is fixed on the working channel of the F-URS. The seal consists of an O-ring which allows the operator to conserve irrigant and preserve leaks whilst gripping the instrument (such as laser fiber).

Stone extraction devices

The extraction devices include stone-graspers, baskets and forceps [Table 2]. Most modern devices are made of nitinol, which have memory, resist kinking and cause minimal loss of deflection. To minimize complications it is important to carefully select the extraction device for the size and location of the stone, having a safety wire at all times, maintaining a good view at all times and avoiding forceful or blind manipulation. All extraction devices should be introduced in a straight scope (undeflected).

Baskets – Nitinol baskets are now standard device for stone retrieval.[2,13] The range from 1.5-2.2F and are flexible, designed not to damage the scope or intra-renal system. The smallest possible basket for the purpose should be used. Basket opening and closing are controlled by a proximal handle.

Graspers – These have 3 or 4 prongs that allow the impacted stone (in renal papilla or urothelial mucosa) to be extracted. They are also effective in removing stone from the kidney with the main advantage of being able to release the stone at any time.

Biopsy forceps – Allows taking biopsy sample from tumors or urothelial mucosa.

Irrigation

Saline is the standard irrigation used for F-URS. To improve the irrigant flow with an instrument in the working channel, it can be pressurized to get adequate flow at the distal tip of the ureteroscope. This can be done either by a manual pressure pump or pressure irrigation bag or a mechanical irrigator.[14,15]

Ureteral drainage

At the end of the procedure ureteral drainage may be required. This is done by leaving a ureteral catheter for up to 24 hours or a double J stent for several days. Stents are placed to prevent or relieve intrinsic or extrinsic ureteral obstruction. Various etiologies include ureteric calculi or stricture, retroperitoneal disease, trauma or iatrogenic injury and drainage post urinary diversion. A guide wire is positioned fluoroscopically or endoscopically prior to stenting. Care should be taken whilst cannulating the ureteric orifice so that it is atraumatic without creating a false passage, avoiding over distension and coiling of guide wire in the bladder. While the stent is being placed, the guide wire should be held taut and the stent position checked fluoroscopically and cystoscopically.

There is a wide variation in the size, shape and material of ureteric stents [Table 1]. The first generation polymeric stents were made of silicone which has now been replaced by polyurethane and newer polymers. To reduce bacterial adherence, biofilm formation and encrustation the newer stents are either made of modified polyurethane or other such polymers and some of them have additional coating. The coatings are either antibacterial agents (hydrogel, silver, PVP, heparin) or they are surface property enhancers (hyaluronic acid, heparin).[16]

Laser

Various different types of laser fibers have been used for ureteroscopic procedures [Table 2]. The Holmium-YAG laser is now the gold standard for use with the F-URS and delivers pulsatile energy.[2] It allows intra-corporeal lithotripsy, management of ureteral strictures and urothelial tumors.[2,17] The laser fiber must be placed right against the target (stone or tumor) for it to work. They can be single use or reusable and come in different sizes. The smaller diameter fiber (150-200 μm) deliver less energy but allow scope deflection, whilst the larger diameter fiber (350-400 μm) restrict scope deflection giving more power. There is a red aiming beam (green in some lasers) which shows where the fiber is in relation to the target.

Set-up and patient positioning and gaining access

Flexible ureteroscopy is usually performed under general anesthesia. Ensure that a urinalysis has been done preoperatively to rule out a urinary tract infection. Prophylactic antibiotics should be administered as per protocol. The patient is typically in dorsal lithotomy position.

Ensure that pressure points are protected. Fluoroscopy should be available and radiation symbol should be placed outside operating theatre. A cystoscopy is then performed to assess the position and size of ureteric orifice and to help insert a guide wire into the renal pelvis under fluoroscopic guidance. A RPG is then performed via a ureteric access catheter under fluoroscopy to visualize the ureteric and intra-renal anatomy and/or pathology. For all ureteroscopic procedures a 'safety wire', which provides access to the renal pelvis should be placed and kept secure at all times.[12,13,15] In males, the penis is held straight to straighten the urethra. Under fluoroscopy, F-URS (or the access sheath if it is being used) is then passed over a second 'working' wire.

Insertion, holding and handling of flexible ureterorenoscope

The handle of the ureterorenoscope is always held with dominant hand with the deflection control worked with the thumb, whilst the non-dominant hand controls the advancement/withdrawal of the scope. The scope should be kept straight without any distal tip deflection and inserted into the intra-renal collecting system over the working guide wire.[15] The working wire is then withdrawn and cold-light cable, the camera and irrigation system is attached. Recently wireless ureteroscopy has been described, but this is not standard practice and may be operator skill dependent.[15]

Ureteral dilatation and insertion of ureteral access sheath

After cystoscopy a safety guide wire is placed. Routine ureteric dilatation is not necessary.

For ureteral dilatation a ureteral balloon catheter is inserted over the working guide wire under fluoroscopic control.[13] Ureteral dilatation is then performed with inflation of balloon with contrast agent.

Ureteral access sheath is inserted over the working guide wire under fluoroscopic guidance.

The appropriate sheath based on its diameter and length should be selected on the anticipated use and ureteric anatomy.[13,15]

Management of kidney stones (other than lower-pole calculi)

Several options are available for managing kidney stones including percutaneous nephrolithotomy (PCNL), shock wave lithotripsy (SWL) and flexible ureteroscopy and lasertripsy (FURSL). We describe FURSL for managing renal stones. After the 'safety wire' and UAS is placed and secured, the F-URS is inserted over the working guide wire. Once the scope is in the pelvis, the working guide wire is withdrawn. The intra-renal collecting system is explored and the stone is located. The laser fiber (200 or 365 μm) is introduced into the working channel of the F-URS.[18] The fiber is advanced a few millimeters beyond the end of the working channel, the aiming beam is switched on and the laser is ready. The initial laser settings are of a frequency of 5-10 Hz and the power of 1-1.5 J (corresponding to 5-9 W).[19] The fiber is placed against the stone and fragmentation is commenced. Once fragmented, the fragments are captured with a grasper and withdrawn with the scope. If a UAS is not being used, the ureteroscope is withdrawn and must be repositioned over a working guide wire. If the fragment will not go through the UAS, the ureteroscope should be grasped against the distal end of the sheath and the entire unit (scope, grasper holding the stone and the access sheath) is removed in 'one piece', provided the fragment can be accommodated by the ureter. At the end of the procedure, the intra-renal system is re-inspected for any fragments. If the ureter needs to be drained, a ureteric catheter or an internal stent may be left in place, overnight or for a few days respectively.

Management of lower-pole calculi

Once the F-URS is in place, the lower pole calculus is located. A nitinol basket (1.5-2.4F) is inserted and the stone is captured and displaced to the upper pole calyx or renal pelvis. The stone is released and laser fiber is used to fragment the stone. If the stone cannot be displaced from lower pole calyx, it is fragmented *in situ* using a smaller laser fiber (150-200 μm).[5,20] For the introduction of the laser fiber, the scope must always be kept straight (undeflected) and scope deflection is only started after the fiber is at the tip of the endoscope.[21] The fragments are removed, the intra-renal system is re-inspected and ureter drained as described above.

Prevention of stone fragment accumulation in the lower calyx

If at the end of flexible ureterorenoscopy and lasertripsy (FURSL), many small stone fragments are left in the collecting system, there will be a risk of these fragments re-accumulating in the lower-pole calices. To prevent this, the lower pole calices can be sealed with an autologous blood clot. The ureteroscope is positioned in the lower group of calices.

Saline is then injected into the working channel of the scope, to flush the fragments towards the upper calices and the renal pelvis, and to clear any remaining contrast. Through the working channel of the scope, 5-10 ml of autologous blood (taken from peripheral venous line) is then injected.[22] The scope position in the lower caliceal group needs to be checked under fluoroscopy as the blood completely obscures the endoscopic vision. Once injected, the scope is withdrawn, and the surgeon waits 5-10 minutes for blood seal to form. RPG is then performed to check that the lower calyx is no longer visualized ensuring that the clot is providing a seal.

Management of calyceal diverticula

The decision to perform F-URS versus PCNL can be very difficult and the choice depends on the position, size and length of calyceal infundibulum. We describe the management of calyceal diverticula using F-URS. The F-URS is introduced into the intra-renal collecting system, as described above. A mixture of contrast and methylene blue or indigo carmine is injected through the working channel of the scope. Opacification of the diverticulum under fluoroscopy means that the neck of the diverticulum is patent.[23]

Saline is used to flush the intra-renal collecting system. The diverticulum is then observed for leakage of dye, with a delayed emptying of the diverticulum suggesting a narrow neck. A laser fiber (350-400 μm) is then passed through the working channel of the scope to incise the neck of the diverticulum. The scope is then inserted into the diverticulum and the stone can either be fragmented *in situ* or extracted intact with nitinol grasper.[24] Following treatment of the stone(s), the neck of the diverticulum is then generously incised with the laser, to allow the diverticulum to be marsupialised into the collecting system. A check for any residual fragments is made and a ureteral drainage with an internal stent is done with the pigtail of the stent in the marsupialised cavity (if possible).

Retrograde endopyelotomy

A RPG is performed and Uretero-pelvic junction (UPJ) obstruction is confirmed.[9] The extrinsic obstructing cause should be identified if the obstruction is from outside. A safety wire is secured and if required a short UAS is inserted under fluoroscopy. The F-URS is then inserted over the working guide wire. The position of the scope is then checked whether it is in the renal pelvis (if the UPJ is passable) or distal to UPJ (if it is not passable). The working wire is withdrawn and with the ureteroscope kept straight (distal tip undeflected), a 365 μm laser fiber is advanced a few millimeters beyond the end of the working channel. With the aiming beam switched on the laser is

set at a frequency of 12-15 Hz and a power of 1-1.5J (15-22 W).[19] If the scope is in the renal pelvis the UPJ is incised as the scope is being withdrawn towards the ureter, where as if the scope is below the UPJ the incision is made as the scope is being advanced towards the renal pelvis. Repeated passes are then made with the laser fiber, until the preiureteral fat appears. The F-URS is removed and a high-pressure ureteral balloon catheter is inserted over the safety wire. Under fluoroscopic guidance, the balloon is inflated with contrast agent to dilate the incised area.[6] The ureteral balloon catheter is removed and a RPG is performed, which would show extravasation of contrast for a correctly performed endopyelotomy. At the end of the procedure, a ureteral stent (8F or 12/8F) should be inserted and left in place for 4-6 weeks with a urethral catheter for 24 hours.

Retrograde endoureterotomy

A RPG is performed and the ureteric stricture identified. A safety wire is secured and if required and safe, a short UAS is inserted under fluoroscopy. The F-URS is then inserted over the working guide wire. The position of scope is checked, whether it is in the renal pelvis (ureteric stricture is passable) or distal to the stricture (not passable). The laser endoureterotomy is then done in the same was as retrograde endopyelotomy. Balloon dilatation is then done with contrast agent to dilate the incised area. For a correctly done endoureterotomy, a subsequent RPG will show extravasation of contrast from the ureter. An internal stent (12F) should be inserted and left in place for 6 weeks with a urethral catheter for 24 hours.

Antegrade flexible ureteroscopy

Although not frequently indicated, it can be useful in difficult retrograde access or in cases of urinary diversion.[25] Antegrade F-URS places mechanical stress on the scope and weakens it. In a prone position, the intra-renal collecting system is punctured under ultrasound or fluoroscopic guidance. A middle or upper calyceal system should be preferred as it helps scope alignment with the ureter. Contrast is injected through the puncture needle, to opacify the intra-renal collecting system and the ureter. The working guide wire is then inserted into the ureter under fluoroscopic guidance. The puncture needle is withdrawn and a dual-lumen catheter is inserted over the working guide wire. The safety guide-wire is then inserted through the second channel of the dual lumen catheter and is secured to the patient's body. Dual-lumen catheter is withdrawn and a high-pressure ureteral balloon catheter is inserted over the working guide wire. Under fluoroscopy, the balloon is inflated with contrast to dilate the tract. The ureteric balloon catheter is then withdrawn and UAS is inserted over the working guide wire. The F-URS is then inserted through the UAS over the working guide wire under fluoroscopic guidance. The working wire is removed and antegrade ureterorenoscopic procedure is carried out as indicated. At the end of the procedure the UAS is removed and a percutaneous nephrostomy tube is inserted under fluoroscopic guidance and secured to skin.

Management of urothelial tumors

Standard treatment of ureteric or renal pelvic tumors is nephroureterectomy. However, for patients with solitary kidney, chronic renal insufficiency or bilateral disease endoscopic management is an alternative option. Once the F-URS is in position, a saline wash of the intra-renal system may be obtained for cytology.[8,26] A RPG may be indicated to assist in localization of the lesion. However, it must not be done prior to cytological sampling as it interferes with the cytopathological examination. Trauma to the urothelium by advancement of guide wire should be avoided as it may cause mucosal trauma and can be confused as a lesion. Once the tumor is localized the choice of ablation techniques includes – 1) Debulking of tumor by cold-cutting it with a tipless nitinol basket for pathology, followed by laser vaporization of tumor base, or 2) Biopsy with forceps and vaporizing the entire tumor with a laser.[10,27] Vaporization is done with holmium: YAG laser (365 μm) with a frequency of 10Hz and a power of 1-1.2J (10-12 W).[19] For lower pole lesions, a smaller diameter fiber (200 μm) is used. Once the lesion is treated, inspect the rest of the intra-renal and ureteric surface. At the end, drainage is established either by a ureteral catheter left for 24 hours or a ureteric stent left for a few days. Adjuvant chemotherapy with instillation of topical agents may be given as appropriate.

Durability of the scope

With broadening indications of F-URS and high cost of purchase and maintenance, durability of scopes is extremely important.[28] The problems arise from loss of tip deflection, perforation of inner lining of the scope and loss of fibreoptic bundles. The newer generation of scopes seem to require fewer repairs especially in experienced hands.[29] The most common damage is to the working channel. This is done by working devices, especially laser fibers with the distal tip of F-URS deflected or if the laser is fired within the scope.[30] Hence, the damage can be avoided by keeping the scope straight before inserting the laser fiber and ensuring that it is not fired within the scope. Damage has also been reported during handling and sterilization of the scopes and hence adequate training to staff should be provided to minimize this.[31]

CONCLUSIONS

Flexible ureteroscopy with Holmium-YAG laser is an effective, reproducible and minimally traumatic diagnostic and therapeutic technique perfectly adapted to disease of the upper urinary tract. With digital technology, the new F-URS provide better image quality and hence, greater precision for diagnostic and therapeutic

procedures. Time and technology will continue to help with 'miniaturization' of the scope. Improvement in optics and ancillary equipment will allow access and treatment in all cases even those with anomalous or reconstructed urinary tract anatomy.

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9. Outcomes of flexible ureterorenoscopy and laser fragmentation for renal stones: Comparison between digital and conventional ureteroscope

Flexible ureterorenoscopes (FURSs) are now standard treatment for managing renal stones. Newer digital ureteroscopes (D-FURS) has better quality digital image compared to conventional scopes (C-FURS). We wanted to compare the outcomes of stone treatment using these two scopes. Prospective data was collected on 118 patients who underwent FURS for renal stones and the outcomes were compared between 59 patients in each group (D-FURS and C-FURS).

The ureteroscope characteristics of both the D-URS (Olympus URF-V) and C-URS (Olympus URF-P5) were compared. The patient demographics were comparable in the two groups. While the overall stone free rate (88% and 86%), and complication rate (0.9% and 1%) were comparable, D-FURS had slightly limited maneuverability but a statistically significantly shorter (44 minutes versus 54 minutes, $p<0.05$) mean operative time compared to C-FURS group. Our results showed that whilst the success rate with both digital and conventional ureteroscopes were comparable and good, the newer digital scope had a significantly shorter operative duration. This was due to the loss of visual clarity with C-FURS from the limitation in the number of optical fibres within the ureteroscope, while digital image (from D-FURS) lead to an improved image size and clarity.

(Contribution – 40%, analyzing the data and writing the paper)

Outcomes of Flexible Ureterorenoscopy and Laser Fragmentation for Renal Stones: Comparison Between Digital and Conventional Ureteroscope

Bhaskar K. Somani, Saeed M. Al-Qahtani, Sixtina Diez Gil de Medina, and Olivier Traxer

OBJECTIVE To compare the outcomes of flexible ureterorenoscopy and lasertripsy (FURS) using digital and conventional FURS for kidney stones.

METHODS From September 2007 to April 2011, 118 patients underwent FURS (by the same surgeon). The outcomes were compared between equal numbers of procedures (59 each) using a conventional flexible ureterorenoscope (C-FURS; Olympus URF-P5) and a digital flexible ureterorenoscope (D-FURS; Olympus URF-V). Although the deflection, working channel, and field view are similar in both, the initial and terminal diameter is 8.4F and 9.9F and 6.9F and 8.4F for the D-FURS and C-FURS, respectively. The mean stone fragmentation time was calculated by the size per operative time. The preoperative, operative, and postoperative data were retrospectively analyzed and compared.

RESULTS The patient demographics were comparable. The mean stone size was 12.8 and 12 mm in the C-FURS and D-FURS groups, respectively. The initial assessment of the entire pyelocaliceal system was possible in 58 of 59 cases (98%) in the C-FURS group and 56 of 59 cases (94%) in the D-FURS group. The mean operative time was significantly longer in the C-FURS group (53.8 $\pm$ 15.2 minutes vs 44.5 $\pm$ 14.9 minutes). The overall stone-free rate 1 month after the procedure was 86% in the C-FURS group and 88% in the D-FURS group.

CONCLUSION Although on comparison, the D-FURS had slightly limited maneuverability, comparable success rates can be achieved with both conventional and digital ureteroscopes. D-FURSs significantly reduced the operative time compared with C-FURSs. UROLOGY 82: 1017–1019, 2013. © 2013 Elsevier Inc.

Flexible ureteroscopy was introduced in 1964 by Marshall,[1] changing the face of endourology. Significant improvements in the field of flexible ureteroscopes have been made in the past 2 decades.[2,3] These have included improvements in ureteroscope deflection, flexibility, and durability, better optics and irrigant flow, and a reduction in the shaft diameter. Flexible ureterorenoscopes (FURSs) are now routinely used for the management of calculus disease. However, the poor image quality can be a limitation during these procedures. Although in a conventional FURS (C-FURS) the image acquisition is delivered by fibers, causing a grainy image, digital FURS (D-FURS) has "chip at the tip" technology, providing a fully digital image.[4]

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From University Hospitals Southampton National Health Services Trust, Southampton, United Kingdom; and Tenon University Hospital, Pierre and Marie Curie University, Paris, France

Reprint requests: Olivier Traxer, M.D., Ph.D., Department of Urology, Tenon Hospital, 4 rue de la chine, 75020, Paris, France. E-mail: olivier.traxer@tnn.aphp.fr

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With the higher resolution image, potentially better stone clearance can be obtained. However, the D-FURS has a relatively larger tip diameter because of the digital chip at the tip of the scope, potentially increasing the failure rate owing to a lack of adequate deflection for lower calices and an inability to negotiate through a smaller size access sheath. Our purpose of the study was to compare the outcomes of flexible ureteroscopy and laser fragmentation using C-FURSs and D-FURSs.

MATERIAL AND METHODS

From September 2007 to April 2011, 118 patients underwent FURS for renal stones (by the same surgeon). The data were collected prospectively in a database. The outcomes were compared between equal numbers of procedures (59 each) performed using C-FURS (Olympus URF-P5; Olympus, Center Valley, PA) and D-FURS (Olympus URF-V; Olympus). Although the deflection, working channel, and field view are similar in both ureteroscopes, the initial and terminal diameter is 8.4F and 9.9F and 6.9F and 8.4F for the D-FURS and C-FURS, respectively (Table 1).

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Table 1. Ureteroscope characteristics

	C-FURS (URF-P5)	D-FURS (URF-V)
Initial diameter (F)	6.9	8.4
Terminal diameter (F)	8.4	9.9
Working channel (F)	3.6	3.6
Up deflection (°)	180	180
Down deflection (°)	270	270
Field view (°)	90	90
Deep field vision (mm)	2-50	2-50

C-FURS, conventional flexible ureterorenoscope; D-FURS, digital FURS.

We used 2 stiff hydrophilic guidewires with a single floppy tip (Terumo 0.035 in.; Laboratoires Terumo, Guyancourt, France), 1 to introduce the device into the renal collecting system and 1 as a safety wire. All procedures were performed with the aid of an access sheath (12/14 Flexor, Cook Medical, Indianapolis, IN). The stone light holmium:yttrium-aluminum-garnet laser from American Medical Systems (Minnetonka, MN) was used, if needed, in certain patients. The working tools used in the present series (introduced through the working channel of the endoscope, measuring 3.6F) included holmium:yttrium-aluminum-garnet laser fibers from American Medical Systems (200, 273, and 365 μm), nitinol baskets (ZeroTip, 1.9F-2.4F, Boston Scientific, Natick, MA), and graspers (Triceps, 3.0F, Boston Scientific).

The stone volume was documented in accordance with the European Association of Urology 2012 guidelines ($3/4 \times \pi \times R^3$).[5] The mean stone fragmentation time was calculated as the size divided by the operative time. The preoperative, operative, and postoperative data were retrospectively analyzed and compared. The follow-up examination included a plain abdominal film on day 1 postoperatively and a noncontrast-enhanced computed tomography scan 4 weeks later. The stone-free rate was defined as the complete clearance of stones or fragments $\leq$2 mm.

RESULTS

Of the 118 patients, 59 each underwent C-FURS and D-FURS (Table 2). The mean age of the patients in the C-FURS group was 44 years, with a body mass index of 24.1 kg/m^2. The mean age of the patients in the D-FURS group was 42 years, with a body mass index of 23.7 kg/m^2. The mean stone size was 12.8 and 12 mm in the C-FURS and D-FURS group, respectively. The initial assessment of the entire pyelocaliceal system was possible in 58 of 59 patients (98%) in the C-FURS group and 56 of 59 patients (94%) in the D-FURS group. The mean operative time was significantly longer (P <.05) in the C-FURS group than in the D-FURS group (53.8 $\pm$ 15.2 vs 44.5 $\pm$ 14.9 minutes). The saving of 10 minutes in the D-FURS group represented 20%-22% of fragmentation time. The overall stone-free rate 1 month after the procedure was 86% in the C-FURS group and 88% in the D-FURS group. The overall complication rate for the C-FURS and D-FURS groups was 1% and 0.9%, respectively. At our institution, the average number of uses for C-FURS and D-FURS before repair was necessary was 67 and 54, respectively.

Table 2. Characteristics of patients and stones in both groups

	C-FURS (URF-P5)	D-FURS (URF-V)	*P* Value
Patients (n)	59	59	NS
Sex (n)			NS
Male	29	23	
Female	30	36	
Age (y)	44	42	NS
BMI (kg/m^2)	24.1	23.7	NS
Stone burden (mm)	12.8 (589 mm^3)	12 (508 mm^3)	NS
Site (%)			NS
Lower calix	14	17	
Middle calix	45	44	
Upper calix	41	39	
History of SWL (%)	28	30	NS
Operative time (min)	54	44	<.05
Mean $\pm$ SD	53.8 $\pm$ 15.2	44.5 $\pm$ 14.9	
Assessment of entire pyelocaliceal system	58/59 (98)	56/59 (94)	NS
Fragmentation time/min	10.7	11.6	NS
Stone free (%)	86	88	NS
Complication (%)	1	0.9	NS

BMI, body mass index; NS, not significant; SD, standard deviation; SWL, shock wave lithotripsy; other abbreviations as in Table 1.
Data in parentheses are percentages.

COMMENT

Our study results have shown that the clinical outcomes with the use of either type of ureteroscope are comparable. For both groups, the patient demographics were similar. Because a single surgeon performed all these procedures and used ureteroscopes manufactured by the same company (Olympus), the risk of bias was minimized. Although the operative time was significantly less with D-FURS, the entire pelvicaliceal system could not be accessed in more patients in this group.

The loss of visual clarity with C-FURS mainly results from the limitation in the number of optical fibers within the ureteroscope. Digital image acquisition leads to improved image size and clarity. The image quality of the D-FURS (Olympus URF-V) is about 3 times greater than that for the C-FURS (Olympus URF-P5).[4] In addition to improved visibility, improved maneuverability has been reported with the use of digital ureteroscopes.[6,7] Similar to our findings, Binbay et al[8] reported a lower operative time for D-FURS than for C-FURS. However, in their study, different manufacturers had manufactured the ureteroscopes. The C-FURS was a Karl-Storz Flex-X2 (Karl Storz Endoscopie, Guyancourt, France), and the D-FURS was an ACMI DUR-D (Gyrus ACMI, Southborough, MA).

The larger distal tip has led to an increase in access sheath use, potentially increasing access sheath injury and postoperative stent usage.[9] An increase in the use of balloon dilation and an access sheath was also reported in a study comparing conventional and digital ureteroscopes.[8] An in vitro study between the Olympus URF-V D-FURS and Olympus URF-P3 fiberoptic FURS showed a better image size, resolution, and color reproducibility with the former.[10]

The present study is 1 of the largest studies to compare the outcomes of C-FURS and D-FURS from the same manufacturer (Olympus). One of the limitations was that the patients were not randomized and the stone composition was not available for all patients and hence was not compared between the 2 groups.

CONCLUSION

The clinical outcomes for renal stone laser fragmentation were similar with the use of conventional and digital ureteroscopes. Although the digital ureteroscope significantly reduced the operative time, this did not translate into better stone clearance. FURS is a minimally invasive and effective technique for the management of renal stones.

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10. Surgical management for upper urinary tract transitional cell carcinoma (UUT-TCC): A systematic review

Upper urinary tract transitional cell carcinoma (UUT-TCC) is conventionally treated with radical nephroureterectomy (NU). To reduce morbidity and safeguard nephrons, a number of nephron-sparing techniques, e.g. ureteroscopic management, percutaneous approaches, and distal ureterectomy are being used. We wanted to review the evidence comparing various surgical techniques including open nephroreterectomy (ONU), laparoscopic nephroureterectomy (LNU), conservative localized ureteric resection, ureteroscopic management and surveillance, and open surgical handling of lower ureter end compared with endoscopic- or laparoscopic-assisted methods. We systematically reviewed the literature comparing surgical and oncological outcomes for various surgical techniques using MEDLINE, EMBASE, Cochrane Library, CINAHL, British Nursing Index, AMED, LILACS, Web of Science, Scopus, Biosis, TRIP, Biomed Central, Dissertation Abstracts, ISI proceedings, and PubMed.

Of the 400 potentially relevant publications identified and screened for retrieval, only one randomized trial was identified, which compared early surgical and oncological outcomes between LNU and ONU. In all, 32 observational studies comparing ONU and LNU, five comparing various techniques to deal with the lower end of the ureter, three comparing nephron sparing surgery (NSS) with radical NU and one comparing radical NU with percutaneous approaches were identified.

LNU group had a significantly lower blood loss and hospital stay and lower urinary tract recurrence than ONU. There was no difference in overall cancer specific survival (CSS) and recurrence-free survival between NSS and NU. Various surgical

techniques of lower ureteric management did not show any difference in oncological outcomes.

There has been a paradigm shift in the surgical management of UUT-TCC in recent years. Although most of the evidence came from retrospective single-center studies, our review concluded that LNU is now the standard of care in the surgical management of UUT-TCC and has favorable preoperative outcomes compared to ONU.

(Contribution 25%, helping with the review and proofreading/correcting the paper)

(Selected in Best of British papers published in BJUI to celebrate BAUS 2013).

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COCHRANE REVIEW

Surgical management for upper urinary tract transitional cell carcinoma (UUT-TCC): a systematic review

Bhavan Prasad Rai, Mike Shelley*, Bernadette Coles†, Bhaskar Somani‡ and Ghulam Nabi

*Department of Urology, Medical Research Institute, Ninewells hospital and Medical School, Dundee, *Cochrane Prostatic Diseases and Urological Cancers Unit, Research Department, Velindre NHS Trust, †Cancer Research Wales Library, Cardiff University, Velindre Hospital, Cardiff, and ‡Department of Urology, Southampton General Hospital, Southampton, UK*

Accepted for publication 10 May 2012

- Surgical management of upper urinary tract transitional cell carcinoma (UUT-TCC) has significantly changed over the past two decades. Data for several new surgical techniques, including nephron-sparing surgery (NSS), is emerging.
- The study systematically reviewed the literature comparing (randomised and observational studies) surgical and oncological outcomes for various surgical techniques
- MEDLINE, EMBASE, Cochrane Library, CINAHL, British Nursing Index, AMED, LILACS, Web of Science, Scopus, Biosis, TRIP, Biomed Central, Dissertation Abstracts, ISI proceedings, and PubMed were searched to identify suitable studies. Data were extracted from each identified paper independently by two reviewers (B.R. and B.S.) and cross checked by a senior member of the team.
- The data analysis was performed using the Cochrane software Review manager version 5. Comparable data from each study was combined in a meta-analysis where possible. For dichotomous data, odds ratios with 95% confidence intervals (CIs) were estimated based on the fixed-effects model and according to an intention-to-treat analysis. If the data available were deemed not suitable for a meta-analysis it was described in a narrative fashion.
- One randomised control trial (RCT) and 19 observational studies comparing open nephroureterectomy (ONU) and laparoscopic NU (LNU) were identified. The RCT reported the LNU group to have statistically significantly less blood loss (104 vs 430 mL, $P < 0.001$) and mean time to discharge (2.30 vs 3.65 days, $P < 0.001$) than the ONU group. At a median follow-up of 44 months, the overall 5-year cancer-specific survival (CSS; 89.9 vs 79.8%) and 5-year metastasis-free survival rates (77.4 vs 72.5%) for the ONU were better than for LNU, respectively, although not statistically significant.
- A meta-analysis of the observational studies favoured LNU group for lower urinary recurrence ($P < 0.001$) and distant metastasis. The meta-analyses for local recurrence for the two groups were comparable.
- One retrospective study comparing ONU with a percutaneous approach for grade 2 disease reported no significant differences in CSS rates (53.8 vs 53.3 months).
- Three retrospective studies compared NSS and radical NU, and reported no significant differences in overall CSS and recurrence-free survival between the two approaches.
- Five retrospective studies compared various techniques of *en bloc* excision of the lower ureter. No technique was

What's known on the subject? and What does the study add?

Upper urinary tract transitional cell carcinoma (UUT-TCC) is an aggressive disease. The mainstay in the treatment of UUT-TCC is surgical intervention, with oncological control the primary objective. UUT-TCCs have been conventionally treated with radical nephroureterectomy (NU). This procedure involves removal of the kidney, ureter and ipsilateral excision of a bladder cuff. Whilst open NU has traditionally been the approach used, laparoscopic NU (LNU) is now an increasingly popular and established approach for UUT-TCC. It is argued that LNU reduces postoperative morbidity without compromising oncological efficacy. With technological evolution, robotic NU has now been attempted in some centres as well. In addition, several techniques have been described to manage the bladder cuff with no agreement as to the most efficacious approach. In a further attempt to reduce morbidity and safeguard nephrons, there have been advocates of a number of nephron-sparing techniques, e.g. ureteroscopic management, percutaneous approaches, and distal ureterectomy. These approaches obviously raise concern on oncological efficacy with requirement for more stringent long-term surveillance protocols.

This study comprehensively reviews and summarises the evidence comparing various surgical techniques in the management of UUT-TCC. The review additionally evaluates and critically appraises the quality of evidence available, which currently informs practice.

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reported to be better (operative and oncological) than any other.
- This review concludes that there is a paucity of good quality evidence for the various surgical approaches for UUT-TCC. The techniques have been assessed and reported in many retrospective single-centre studies favouring LNU for better perioperative outcomes and comparable oncological safety. The reported observational studies data is further supported by one RCT.

KEYWORDS

transitional cell carcinoma, nephroureterectomy, laparoscopy, minimally invasive techniques, ureterectomy

INTRODUCTION

Upper urinary tract TCCs (UUT-TCCs) are uncommon and aggressive tumours. For clinically localised disease, surgical excision in the form of radical nephroureterectomy (NU) is considered as 'standard of care'. The procedure entails *en bloc* excision of the kidney, ureter and an ipsilateral cuff of the urinary bladder around the ureteric orifice. Major resections such as this, are not uncommonly associated with significant morbidity in the form of blood loss, postoperative pain and therefore prolonged hospitalisation. To mitigate some of the morbidity, there has been considerable advancement in minimally invasive techniques, with a clear focus on reducing blood loss, length of incision, postoperative pain, hospital stay and earlier convalescence. As a result, many viable alternates to open NU (ONU) are offered including laparoscopic NU (LNU), ureteroscopic resection/fulguration, and segmental resection or percutaneous management. However, the fundamental goal in surgical resection of cancer is oncological control and this should not be compromised at the cost of better immediate operative outcomes. Since the development of minimally invasive techniques in the surgical management of UUT-TCC there has been a considerable amount of evidence published comparing various surgical techniques; reporting on both immediate operative and oncological outcomes. Despite advances in surgical techniques and technologies many uncertainties continue to exist in clinical practice.

The aim of the present study was to systematically review the literature (randomised and observational studies) on the comparative surgical approaches in the management of UUT-TCC and comprehensively present the reported clinical data. Comparisons included radical ONU vs LNU, NU vs conservative localised ureter resection, open surgical resection (local or NU) vs endoscopic management and surveillance, and open surgical handling of lower ureter end compared with endoscopic- or laparoscopic-assisted methods.

MATERIALS AND METHODS

A sensitive search strategy was developed for MEDLINE to identify published clinical studies that compared different surgical techniques for treating UUT-TCC. Specific search terms were used in conjunction with the Cochrane highly sensitive search strategy for randomised control trials (RCTs). Other databases searched included EMBASE, Cochrane Library, CINAHL, British Nursing Index, AMED, LILACS, Web of Science, Scopus, Biosis, TRIP, Biomed Central, Dissertation Abstracts, ISI proceedings, and PubMed. A list of titles and abstracts of potentially relevant clinical studies were generated by the search strategy and imported in to bibliographic software (EndNote®). This list was screened by two authors independently (B.R. and B.S.) and fully published papers were retrieved where appropriate. Data were extracted from each identified paper independently by two reviewers (B.R. and B.S.) and cross checked by a senior member of the team.

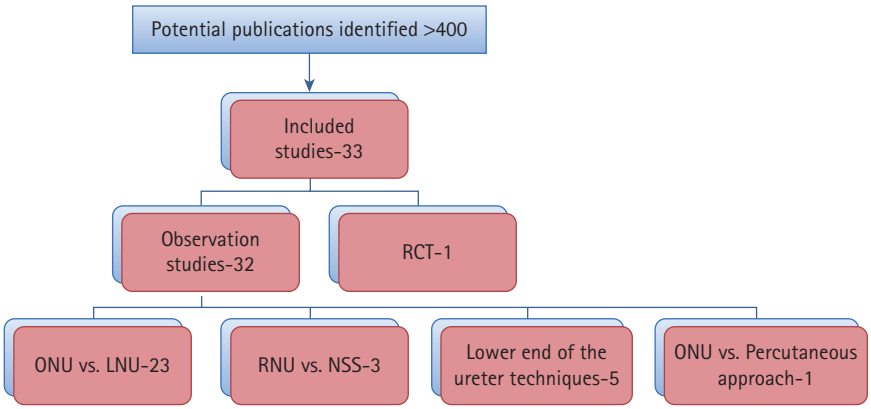
The primary outcomes of interest were surgical outcomes, e.g. operative duration, blood loss, and hospital stay. Secondary outcomes included oncological safety, e.g. bladder tumour recurrence, local recurrence, and the development of metastases, recurrence-free survival (RFS), progression-free survival (PFS), cancer-specific survival (CSS) and overall survival (OS). The extracted data included information on trial design, participants, types of interventions, and outcome measures. Data analyses compared radical surgery with other primary surgical methods and comparisons were made for each of the outcomes. Also, comparisons were made between different surgical approaches.

The data analysis was performed using the Cochrane software Review Manager version 5. Comparable data from each study were combined in a meta-analysis where possible. For dichotomous data, odds ratios (ORs) with 95% CIs were estimated based on the fixed-effects model and according to an intention-to-treat analysis. If the data available were deemed not suitable for a meta-analysis it was described in a narrative fashion.

RESULTS

Of the 400 potentially relevant publications identified and screened for retrieval, only one RCT was identified, which compared early surgical and oncological outcomes between LNU and ONU [1]. In all, 32 observational studies comparing ONU and LNU [2–24]; five comparing various techniques to deal with the lower end of the ureter [25–29], three comparing nephron-sparing surgery (NSS) with radical NU [30–32] and one comparing radical NU with percutaneous approaches were also identified [33] (Fig. 1). A risk of bias graph for the single identified RCT was generated (Fig. 2). A quality assessment of the observational studies comparing ONU and LNU was performed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Table 1).

FIG. 1. Studies identification in the review.



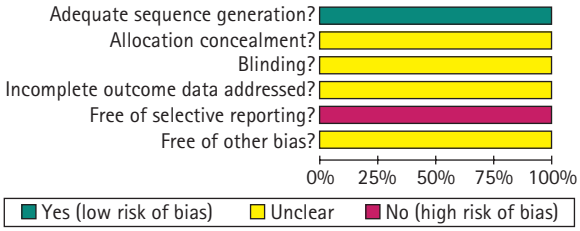


FIG. 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

RCT OF LNU VS ONU

This review identified one RCT comparing perioperative and oncological outcomes between LNU and ONU [1], it was a single institutional study with all procedures (both ONU and LNU) undertaken by one experienced surgeon. In all, 40 patients with non-metastatic UUT-TCC were recruited for both the approaches. Perioperative outcomes were compared using Student's *t*-test and oncological outcomes were compared using the log-rank test. Further analysis was performed after stratification by grade and stage. This trial showed that LNU had statistically significantly better outcomes for blood loss (104 vs 430 mL, $P < 0.001$) and mean time to discharge from hospital (2.30 vs 3.65 days, $P < 0.001$) than ONU. At a median follow-up of 44 months, the overall 5-year CSS (89.9 vs 79.8%) and 5-year metastasis-free survival rates (77.4 vs 72.5% for ONU vs LNU) were seemingly better for LNU but not statistically significant. The bladder tumour-free rates for the two groups were similar.

OBSERVATIONAL STUDIES COMPARING LNU VS ONU

SURGICAL OUTCOMES

Observational data from 19 studies suggest that laparoscopic surgical interventions either complete or combined with open excision of the lower end, reduced intraoperative blood loss, postoperative pain, and hospital stay compared with open surgery [2–9,11–14,17,18,20–23,34] (Table 2). There was lack of consistency in reporting data including statistical methods. In all, 16 studies reported primary surgical outcomes as means [2–9,11–14,17,18,20,21,23,34], while three contemporary studies reported primary surgical outcomes as medians [21–23]. The range of mean blood loss for the LNU and ONU groups was 144–580 mL and 299.6–750 mL, respectively. The range of mean hospital stay for the LNU and ONU groups was 2.3–13 days and 4.2–21.1 days, respectively. The operative duration appears to be longer in the LNU groups, as the range of mean operative durations for the LNU and ONU groups was 164.8–462 min and 156.2–324 min, respectively. Only four studies reported a better operating time with LNU [8,12,35].

SECONDARY ONCOLOGICAL OUTCOMES

Meta-analysis was performed on observational studies reporting lower urinary tract (bladder and urethra) recurrence, local recurrence and distant metastasis. In all, 17 observational studies reported on lower urinary tract recurrence [2,3,5,7,9–15,17,18,20,21,23,36], 15 on local recurrence [2,3,5,7,9–13,15,17,18,23,36] and 16 on distant metastasis [2,3,5,7,9–15,17,18,22,23,36]. The pooled OR between the LNU and ONU approaches for lower urinary tract recurrence favoured the LNU group (OR 0.64, 95% CI 0.50–0.82, $P < 0.001$; Fig. 3). The pooled OR between the LNU and ONU approaches for local recurrence did not differ markedly between the groups (OR 0.71, 95% CI 0.40–1.46, $P = 0.25$; Fig. 4). The pooled OR between the LNU and ONU approaches for distant metastasis favoured the LNU group (OR 0.72, 95% CI 0.54–0.97, $P = 0.03$; Fig. 5).

SURVIVAL RATES

In all, 17 observational studies reported survival rates [2,3,10–12,14,15,17–24,34,36] (Table 3). All studies consistently reported comparable oncological safety between LNU and ONU. The range of 5-year CSS for LNU and ONU was 95.2–71% and 92.6–63.5%, respectively. The range of 5-year RFS for LNU and ONU was 90.47–52.5% and 88.8–50.7%, respectively. The longest follow-up was reported by Stewart *et al.*

TABLE 1 Observational studies comparing ONU and LNU: quality assessment using STROBE guidelines

Study	Design	Technique for lower ureter, -ONU/LNU	A	B	C	D	E	F	G	H	I
Gill *et al.* 2000 [2]	Retrospective	Open bladder cuff/transvesical detachment	P	N	N	P	Y	N	Y	N	P
Shalhav *et al.* 2000 [3]	Retrospective	Open bladder cuff/extravesical stapling	P	N	N	P	Y	N	Y	N	P
Stifelman *et al.* 2001 [4]	Retrospective	Open bladder cuff/transvesical detachment									
Goel *et al.* 2002 [5]	Retrospective	Open bladder cuff/open bladder cuff	P	N	N	P	Y	N	Y	N	P
Matsui *et al.* 2002 [6]	Retrospective	Open bladder cuff/open bladder cuff	Y	P	N	P	Y	N	Y	N	P
Kawauchi *et al.* 2003 [7]	Retrospective	Open bladder cuff or TUR/open bladder cuff or TUR	P	N	N	P	Y	N	Y	N	P
Klinger *et al.* 2003 [8]	Unclear if retrospective or prospective	Open bladder cuff/open bladder cuff	Y	N	N	P	Y	N	Y	N	P
Hsueh *et al.* 2004 [9]	Retrospective	Open bladder cuff/open bladder cuff	Y	N	N	P	Y	N	Y	N	P
Rassweiler *et al.* 2004 [11]	Retrospective	Open bladder cuff/open bladder cuff	P	N	N	P	Y	N	Y	N	P
Hattori *et al.* 2006 [12]	Unclear if retrospective or prospective	Open/lap or open	Y	N	P	P	Y	N	Y	N	P
Raman *et al.* 2006 [13]	Retrospective	Open-intravesical/extravesical techniques or TUR de-roofing/open-intravesical/extravesical techniques or TUR de-roofing	P	N	N	Y	Y	P	Y	N	P
Rouprêt *et al.* 2007 [14]	Retrospective	Open bladder cuff/open bladder cuff	Y	P	N	Y	Y	P	Y	N	Y
Manabe *et al.* 2007 [15]	Retrospective	Open bladder cuff/open-intravesical/extravesical techniques	Y	N	N	P	Y	N	Y	N	P
Hsueh *et al.* 2007 [10]	Retrospective	Open bladder cuff/open bladder cuff	Y	N	N	Y	Y	N	Y	N	P
Taweemonkongsap *et al.* 2008 [17]	Retrospective	Open bladder cuff/open bladder cuff	Y	N	N	P	Y	N	Y	N	Y
Hemal *et al.* 2008 [16]	Retrospective	Open bladder cuff/open bladder cuff or laparoscopic stapling using Endo-GIA device or laparoscopic excision with scissors and free hand intracorporeal suturing or 'pluck' technique	Y	N	N	P	Y	N	Y	N	P
Waldert *et al.* 2009 [18]	Retrospective	Open bladder cuff/open bladder cuff	Y	P	N	Y	Y	N	Y	N	P
Capitanio *et al.* 2009 [19]	Retrospective multicentre study	Without excision of a bladder cuff or open or laparoscopic cuff excision or cuff excision via endoscopy/without excision of a bladder cuff or open or laparoscopic cuff excision or cuff excision via endoscopy	Y	N	N	Y	Y	Y	Y	N	Y
Greco *et al.* 2009 [20]	Unclear if retrospective or prospective	Open bladder cuff/laparoscopic approach	Y	N	N	Y	Y	N	Y	N	P
Favaretto *et al.* 2010 [21]	Retrospective	Open bladder cuff/open or laparoscopic or TUR	Y	Y	P	Y	Y	Y	Y	N	Y
Stewart *et al.* 2011 [23]	Retrospective	Extra- or transvesical mobilisation of the lower ureter and bladder cuff/'pluck' technique or formal open cystotomy, and combined extra- and transvesical dissection	Y	N	N	Y	Y	P	Y	N	P
Ariane *et al.* 2011 [22]	Retrospective multicentre study	Open bladder cuff or 'pluck'/open bladder cuff or 'pluck'	Y	N	N	Y	Y	P	Y	N	P
Walton *et al.* 2011 [24]	Retrospective multicentre study	Abercrombie technique or bladder cuff excision/ Abercrombie technique or bladder cuff excision	Y	N	N	Y	Y	Y	Y	N	Y

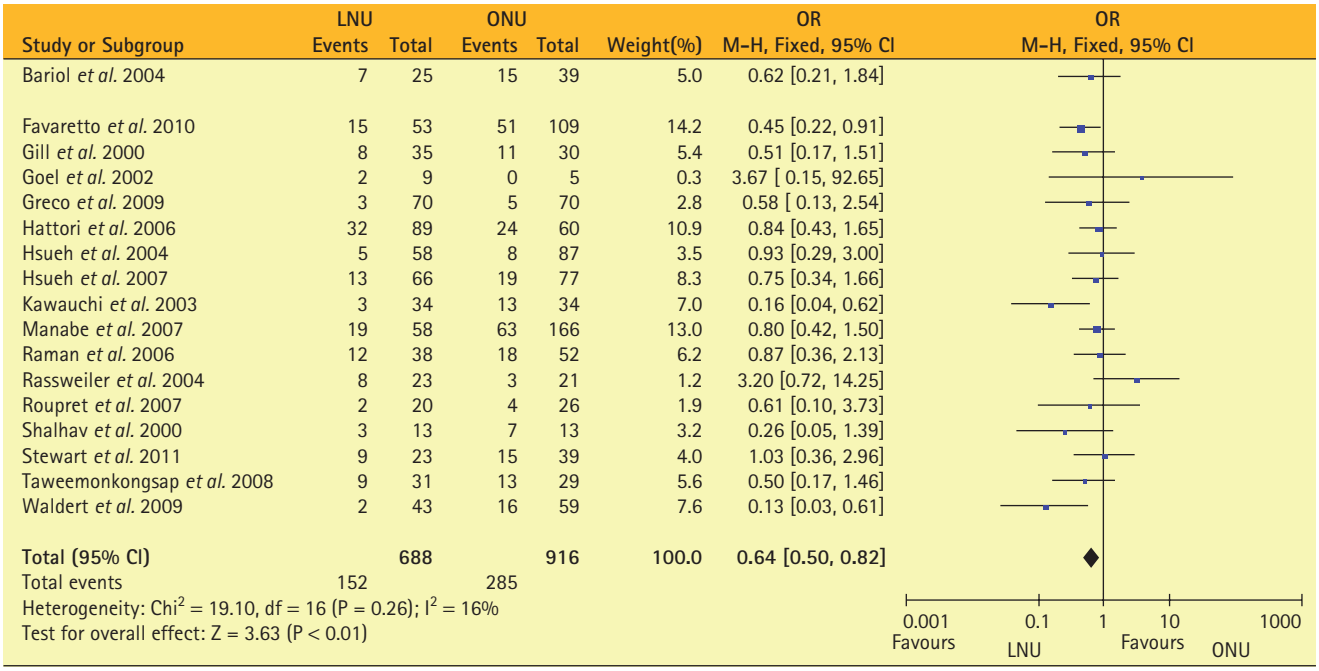
***A**, Objectives and pre-specified hypothesis in the introduction; **B**, Eligibility criteria of cohort in methods; **C**, Methods for recruitment of participant; **D**, Mention of outcomes, exposure, and confounder; **E**, Study size calculated; **F**, Potential biases addressed; **G**, Statistical methods described; **H**, Mention of how missing data was handled; **I**, Limitation of the study and the generalisations mentioned; **Y**, Yes; **N**, No; **P**, Partially. TUR, transurethral resection.*

[23] with a median of 163 months, reporting comparable oncological outcomes for 5-, 10-, and 15-year OS, PFS and CSS for the two approaches. Three retrospective multicentre studies [19,22,24] were identified. Capitanio *et al.* [19] reported oncological outcomes comparing LNU and ONU in 1249 patients. The 5-year RFS estimates were 86.8% and 76.2% for LNU and ONU, respectively. The 5-year cancer-specific-mortality-free survival estimates were 85.8% and 73.1% for LNU and ONU, respectively. Walton *et al.* [24] reported on a cohort of 773 patients. The estimated 5-year RFS was 63.4% and 73.7% for LNU and ONU, respectively ($P = 0.124$). The estimated 5-year CSS were 75.2% and 75.4% for the LNU and ONU groups, respectively

TABLE 2 Early surgical outcomes from observational studies for LNU vs ONU

Study	Operative duration, mean, min	Blood loss Mean, mL	Hospital stay Mean, days
Gill *et al.* 2000 [2]	224.8 vs 280.2	242 vs 696	2.3 vs 6.6
Shalhav *et al.* 2000 [3]	462 vs 234	199 vs 441	6.1 vs 12
Stifelman *et al.* 2001 [4]	291 vs 232	144 vs 311	4.6 vs 6.1
Goel *et al.* 2002 [5]	189 vs 184	275 vs 570	5.1 vs 9.2
Matsui *et al.* 2002 [6]	286.8 vs 239.5	151 vs 299.6	2.7 vs 4.2
Kawauchi *et al.* 2003 [7]	233 vs 236	236 vs 427	13 vs 21.1
Klinger *et al.* 2003 [8]	198 vs 220	282 vs 532	8.1 vs 13.3
Hsueh *et al.* 2004 [9]	259.1 vs 230.2	410 vs 750	9.3 vs 12.6
Rassweiler *et al.* 2004 [11]	200 vs 188	450 vs 600	10 vs 13
Hattori *et al.* 2006 [12]Pure LNU vs. Combined LNU vs. ONU	258 vs 306 vs 324	354 vs 580 vs665	
Raman *et al.* 2006 [13]	244 vs 243	191 vs 478	4.6 vs 7.1
Rouprêt *et al.* 2007 [14]	164.8 vs 155.2	274.5 vs 337.7	3.7 vs 9.2
Taweemonkongsap *et al.* 2008 [17]	258.9 vs 190.7	289.4 vs. 313.8	9.32 vs 8.69
Hemal *et al.* 2008 [16]	219.2 vs 156. 2	299.4 vs. 525.88	4.84 vs 6.88
Waldert *et al.* 2009 [18]	220 vs212	300 vs. 542	8.1 vs13.8
Greco *et al.* 2009 [20]	240 vs190	–	–
Favaretto *et al.* 2010 [21]	265 vs164 (median)	200 vs.250 (median)	3 vs 5 (median)
Stewart *et al.* 2011 [23]	165 vs180 (median)	280 vs 398 (median)	7 vs 10 (median)
Ariane *et al.* 2011 [22]	240 vs 180 (median)	–	8 vs 9 (median)

FIG. 3. Meta-analysis of observational studies reporting on lower urinary tract recurrence.



($P = 0.897$). Ariane *et al.* [22] reported oncological outcomes in 609 patients. The 5-year RFS was 52.2% and 50.7.7% for LNU and ONU, respectively ($P = 0.7$). The 5-year CSS were 90.7% and 78% for the LNU and ONU, respectively ($P = 0.06$). All the three studies on a multivariate analysis showed that the surgical approach (ONU or LNU) used did not influence the oncological outcomes.

OBSERVATIONAL STUDIES COMPARING RADICAL NU VS NSS

Three studies [30–32] compared NSS and radical NU (Table 4). Giannarini *et al.* [32]

FIG. 4. Meta-analysis of observational studies reporting on local recurrence.

Study or Subgroup	LNU Events	LNU Total	ONU Events	ONU Total	Weight(%)	OR M-H, Fixed, 95% CI
Bariol *et al.* 2004	2	25	6	39	15.2	0.48 [0.09, 2.58]
Gill *et al.* 2000	0	35	0	30		Not estimable
Goel *et al.* 2002	0	9	0	5		Not estimable
Hattori *et al.* 2006	7	89	6	60	23.3	0.77 [0.24, 2.41]
Hsueh *et al.* 2004	0	58	2	87	7.0	0.29 [0.01, 6.20]
Hsueh *et al.* 2007	2	66	2	77	6.3	1.17 [0.16, 8.56]
Kawauchi *et al.* 2003	0	34	0	34		Not estimable
Manabe *et al.* 2007	1	58	2	166	3.6	1.44 [0.13, 16.17]
Raman *et al.* 2006	0	38	0	52		Not estimable
Rassweiler *et al.* 2004	0	23	1	21	5.4	0.29 [0.01, 7.54]
Roupret *et al.* 2007	2	20	5	26	13.8	0.47 [0.08, 2.70]
Shalhav *et al.* 2000	2	13	0	13	1.4	5.87 [0.25, 135.15]
Stewart *et al.* 2011	1	23	0	39	1.2	5.27 [0.21, 134.77]
Taweemonkongsap *et al.* 2008	2	31	1	29	3.4	1.93 [0.17, 22.51]
Waldert *et al.* 2009	0	43	6	59	19.2	0.09 [0.01, 1.73]
Total (95% CI)		**565**		**737**	**100.0**	**0.71 [0.40, 1.26]**
Total events	19		31			

Heterogeneity: $Chi^2 = 7.32$, df = 10 (P = 0.69); $I^2 = 0\%$
Test for overall effect: Z = 1.16 (P = 0.25)

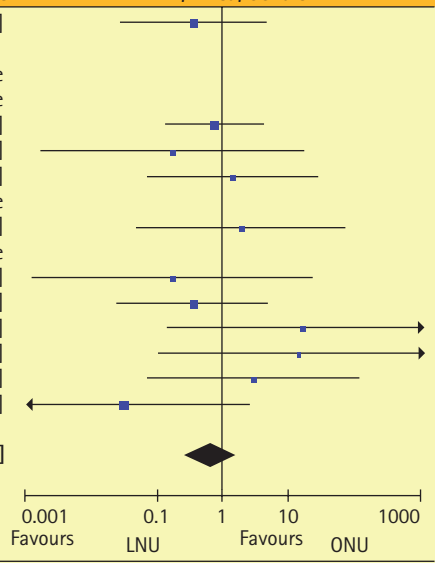
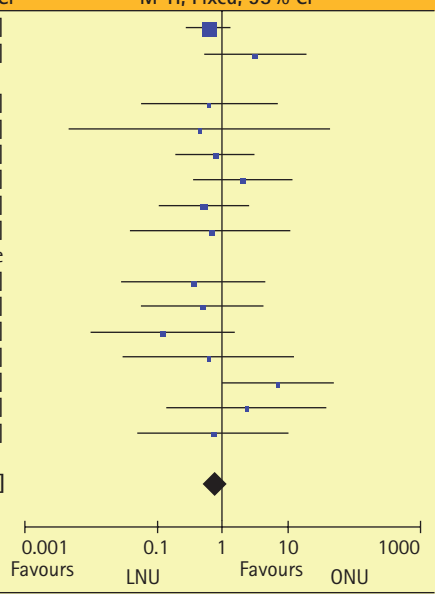


FIG. 5. Meta-analysis of observational studies reporting on distant metastasis.

Study or Subgroup	LNU Events	LNU Total	ONU Events	ONU Total	Weight(%)	OR M-H, Fixed, 95% CI
Ariane MM *et al.* 2012	21	150	97	459	38.9	0.61 [0.36, 1.01]
Bariol *et al.* 2004	7	25	7	39	3.7	1.78 [0.54, 5.88]
Gill *et al.* 2000	3	35	4	30	3.7	0.6 [0.13, 2.97]
Goel *et al.* 2002	1	9	1	5	1.1	0.50 [0.02, 10.25]
Hattori *et al.* 2006	11	89	10	60	9.9	0.71 [0.28, 1.78]
Hsueh *et al.* 2004	6	58	7	87	4.7	1.32 [0.42, 4.14]
Hsueh *et al.* 2007	6	66	12	77	9.5	0.54 [0.19, 1.53]
Kawauchi *et al.* 2003	2	34	3	34	2.7	0.65 [0.10, 4.13]
Manabe *et al.* 2007	0	58	0	166		Not estimable
Raman *et al.* 2006	2	38	6	52	4.5	0.43 [0.08, 2.24]
Rassweiler *et al.* 2004	4	23	6	21	4.9	0.53 [0.13, 2.21]
Roupret *et al.* 2007	2	20	9	26	6.7	0.21 [0.04, 1.11]
Shalhav *et al.* 2000	2	13	3	13	2.4	0.61 [0.08, 4.41]
Stewart *et al.* 2011	7	23	5	39	2.4	2.98 [0.82, 10.83]
Taweemonkongsap *et al.* 2008	3	31	2	29	1.8	1.45 [0.22, 9.34]
Waldert *et al.* 2009	2	43	4	59	3.0	0.67 [0.12, 3.84]
Total (95% CI)		**715**		**1196**	**100.0**	**0.72 [0.54, 0.97]**
Total events	79		176			

Heterogeneity: $Chi^2 = 11.95$, df = 14 (P = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 2.13 (P = 0.03)



compared outcomes of 43 patients who underwent either distal ureter resection with bladder cuff excision and ureter re-implantation (19 patients) or radical NU for distal ureteric tumours (24). The 5- and 10-year bladder cancer-free survival (log-rank test, $P = 0.117$), OS (log-rank test, $P = 0.693$), and CSS (log-rank test, $P = 0.896$) were similar for the two groups. Hence, the study suggested distal ureterectomy as an option in distal ureteric tumours. Dragicevic *et al.* [30] and Lucas *et al.* [31] both compared conservative approaches with radical NU and reported equivalent oncological outcomes between the two groups in selected cases.

OBSERVATIONAL STUDIES COMPARING RADICAL NU VS PERCUTANEOUS NU

One retrospective study was identified comparing ONU with a percutaneous approach [33]. This study showed the CSS rates after radical ONU and percutaneous NU for grade 2 disease were 53.8 and 53.3

TABLE 3 Survival rates for LNU vs ONU

Study	Follow-up, months	Survival rates, %
Shalhav *et al.* 2000 [3]	Mean 24	Crude survival 77 vs 69
		CSS 77 vs 77
Gill *et al.* 2000 [2]	Mean LNU 11.1, ONU 34.4	Crude survival 97 vs 94 ($P = 0.59$)
		CSS 97 vs 87 ($P = 0.59$)
Rassweiler *et al.* 2004 [11]	60	2-yearr survival 89 vs 83
		5-year survival 81 vs 63
Bariol *et al.* 2004 [36]	Median LNU 101, ONU 96	1-year metastasis-free survival rate 80 vs 87.2 ($P = 0.33$)
		5-year metastasis-free survival rates 72 vs 82.1 ($P = 0.26$)
		OS 56 vs 59 ($P = 0.26$) at median follow-up of 7 years
		CSS 72 vs 82 ($P = 0.516$) at median follow-up of 7 years
Hattori *et al.* 2006 [12]	Median ONU 35, LNU + open lower ureter 31, LNU + laparoscopic lower ureter 17	1-year CSS 95 vs 93 vs 93 ($P = 0.89$)
		3-year CSS 81 vs 86 vs 80
		5-year CSS 78 vs 81
		1-year estimated extravesical RFS 77 vs 80 vs 89 ($P = 0.91$)
		3-year estimated extravesical RFS 71 vs 76 vs 71
		5-year estimated extravesical RFS 71 vs 71
		1-year estimated bladder RFS 65 vs 78 vs 72 ($P = 0.38$)
		3-year estimated bladder RFS 51 vs 65 vs 45
		5-year estimated bladder RFS 51 vs 56
Rouprêt *et al.* 2007 [14]	Median LNU 68.5, ONU 78	5-year CSS 90 vs 61.5 ($P = 0.31$)
		5-year tumour-free survival rate 71.6 vs 51.2 ($P = 0.59$)
Manabe *et al.* 2007 [15]	Median LNU 13.6, ONU 28	2-year disease-free survival rate 75.6 vs 81.7
		2-year CSS 85.2 vs 87.0
		2-year OS 83.7 vs 83.6
Hsueh *et al.* 2007 [10]	Mean	5-year CSS pT1 92 vs 88.1 ($P = 0.745$)
	LNU 37.6	2-year overall recurrence rate 23 vs 27 ($P = 0.95$)
	ONU 53.6	
Taweemonkongsap *et al.* 2008 [17]	Mean LNU 26.4, ONU 27.9	2-year CSS 86.3 vs 92.5 ($P = 0.823$)
		2-year OS 86.3 vs 83.3 ($P = 0.863$)
Hemal *et al.* 2008 [16]	Median LNU 53, ONU 57	5-year RFS 90.47 vs 88.8 ($P = 1.0$)
		5-year CSS 95.2 vs 92.6 ($P = 1.0$)
		5-year OS 85.7 vs 85.2 ($P = 1.0$)
Waldert *et al.* 2009 [18]	Mean LNU 41, ONU 41	5 year CSS 85 vs 80 ($P = 0.62$) (ES)
		5-year tumour free-survival rate 79 vs 76 ($P = 0.82$) (ES)
Capitanio *et al.* 2009 [19]	Median 49	5-year RFS 86.8 vs 76.2
		5-year CSS 85.8 vs 73.1
Greco *et al.* 2009 [20]	Median 60	5-year disease-free survival 75 vs73 ($P = 0.037$)
Favaretto *et al.* 2010 [21]	Median 23	2-year RFS 42 vs 38 ($P = 0.9$)
		2-year CSS 82 vs 86 ($P = 0.9$)
Stewart *et al.* 2011 [23]	Median 163	5-year OS 61 vs 64
		5-year PFS 76 vs 79
		5-year CSS 71 vs 80
		10-year OS 56 vs 48
		10-year PFS 76 vs 79
		10-year CSS 71 vs 80
		15-year OS 11 vs 34
		15-year PFS 76 vs 79
		15-year CSS 64 vs 74
Ariane *et al.* 2011 [22]	Median 27	5-year RFS 52.2 vs 50.7 ($P = 0.7$)
		5-year CSS 90.7 vs 78 ($P = 0.06$)
Walton *et al.* 2011 [24]	Median 34	5-year RFS 63.4 vs 73.3 ($P = 0.124$)
		5-year CSS 75.2 vs 75.4 ($P = 0.897$)

ES, estimated survival.

TABLE 4 Studies comparing outcomes of NSS and radical NU

Study	Objectives	Findings and survival rates, %
Giannarini *et al.* 2007 [32]	Distal ureter resection with bladder cuff excision and ureter re-implantation vs radical NU with bladder cuff excision	CSS at 5 and 10 years was not statistically significantly different (log-rank test, $P = 0.896$) OS at 5 and 10 years was not statistically significantly different (log-rank test, $P = 0.693$)
Dragicevic *et al.* 2009 [30]	Open conservative surgery vs radical NU	5-year survival rates 59 vs 55. 5-year survival rates for imperative and elective indications 41 vs 75. Radical NU had statistically significantly poorer outcomes for the disease on univariate analysis (HR 2.2, 95% CI 1.1–4.6; $P = 0.030$)
Lucas *et al.* 2008 [31]	NSS vs radical NU	Low-grade disease: 5-year OS 75.4 vs 66.4 ($P = 0.281$) 5-year CSS 86.2 vs 87.4 ($P = 0.909$) High-grade disease: 5-year OS 45 vs 71.5 ($P = 0.077$) 5-year CSS 68.6 vs 75 ($P = 0.528$)

HR, hazard ratio.

TABLE 5 Studies comparing the various techniques of en bloc *excision of the lower ureter during the NU procedure*

Study	Objectives	Findings with recurrence and metastasis rates, %
Romero *et al.* 2007 [25]	Extravesical laparoscopic control of the bladder cuff vs extravesical open control of the bladder cuff	Overall recurrence rates 66.7 vs 33.3 ($P = 0.09$). Local recurrence rates16.7 vs 0 ($P = 0.239$). Bladder recurrence rates 50 vs 33.3 ($P = 0.233$). Distant metastasis 25 vs 8.3 ($P = 0.248$).
Ko *et al.* 2007 [28]	Open excision of a bladder cuff (OC) vs transurethral incision of the ureteric orifice (TUIUO)	The bladder recurrence rates were similar in the OC group (22.2; 6/27) and the TUIUO group (26.3; 5/19). There were no pelvic recurrences in either group.
Salvador-Bayarri *et al.* 2002 [26]	Open excision of a bladder cuff vs endoscopic resection of ureter	Bladder tumour recurrence 39 vs 34.5 (no statistical significance).
Matin *et al.* 2005 [29]	Extravesical laparoscopic control of the bladder cuff vs cystoscopic secured detachment and ligation method	Bladder tumour recurrence 41.7 vs 13.9 (not statistically significant). Retroperitoneal metastasis 8.3 vs 5.6 (not statistically significant). Distant metastasis 25 vs 8.3 (not statistically significant).
Walton *et al.* 2009 [27]	Endoscopic ureteric detachment vs open bladder cuff excision	Bladder tumour recurrence 54.4 vs 47.9 (not statistically significant). RFS and CSS similar for both groups

months, respectively ($P > 0.05$), and concluded that the percutaneous NU should be an option in patients with solitary kidneys, those at risk of chronic renal failure, and healthy individuals with normal contralateral kidneys who are willing to comply with a strict and lengthy follow-up protocol.

OBSERVATIONAL STUDIES COMPARING VARIOUS TECHNIQUES FOR DEALING WITH THE LOWER END OF THE URETER

There were five retrospective studies identified in our search that compared various techniques of *en bloc* excision of the lower ureter [25–29] (Table 5). Bladder recurrence was reported by all the studies and ranged between 13.9% and 54.4% depending on the technique used. Other oncological outcomes reported were local recurrence, retroperitoneal and distant metastasis, recurrence and CSS. However, none of the studies reported statistically significant advantage of one technique over the other.

DISCUSSION

The search strategy for this review included a comprehensive search of electronic databases, meticulous hand searching of relevant journal articles and abstracts. Despite laparoscopic and minimally invasive approaches being common place in contemporary urological practice for more than two decades, there is a paucity of good quality RCTs comparing surgical techniques (one RCT in 400 publications; 0.25%). Apart from this RCT, current evidence to guide surgical practice is based on a large number of retrospective observational studies. The reported data suggests significantly better perioperative outcomes with laparoscopic and minimally invasive approaches with equivalent long-term oncological control of the disease. A meta-analysis of the

observational studies comparing LNU and ONU reporting on bladder recurrence and distant metastasis favoured the laparoscopic group. However, we would strongly recommend caution in interpreting these results, given the various methodological problems with the retrospective study design, particularly the selection biases, small sample sizes and lack of statistical power. Indeed the OS, CSS, RFS after adjustment for confounding factors, particularly stage and grade, show consistent oncological equivalence between the two approaches in all the studies. All the studies reporting on immediate outcomes consistently show laparoscopic superiority for reduced intraoperative blood loss and hospital stay. Operative durations tended to be longer in the laparoscopic group. There continues to be lack of clarity about the best approach to deal with the lower end of the ureter. There has been some suggestion of a high risk of progression with the 'pluck' techniques, although this risk is not clearly established. The five studies identified in this review did not show a particular approach to be better and current practice remains an issue of surgeon's preference and experience [25–29]. With evolving minimally invasive approaches in the surgical management of UUT-TCC, NSS is a further extension. The early evidence would suggest that these approaches may have similar oncological outcomes in comparisons with radical NU for organ-confined disease, particularly for low-grade small tumours.

This review reflects that urological surgeons over the years have accepted the results of weaker clinical studies with retrospective designs and selection bias for the surgical management of UUT-TCC. Surgical technology appears to have disseminated rapidly in surgical practice without good scrutiny for assessing its clinical effectiveness. There are several established issues in conducting a well-designed RCT in surgery. Patient choice remains the most important and perhaps poorly understood factor in performing a RCT. Elective participation by an individual in a RCT is dependent on the information presented in an unbiased way. In addition, surgeons may have personal preference for certain techniques, which may reflect their own previous training and expertise [37]. With the introduction of robotic technology, a trial assessing robot-assisted LNU vs conventional LNU would be an ideal beginning. Considering the challenges associated with performing a RCT in surgical practice it has been suggested that progressive surgical research will have to be reliant on good quality non-randomised trials.

CONCLUSIONS

There has been a paradigm shift over the years in the surgical management of UUT-TCC, with LNU being the standard of care in most institutions. However, there is a paucity of good quality evidence for the various surgical approaches for UUT-TCC. The techniques have been assessed and reported in many retrospective single-centre studies favouring the laparoscopic approach for better perioperative outcomes and comparable oncological safety. The reported observational studies data are further supported by one RCT.

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CONFLICT OF INTEREST

None declared.

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Correspondence: Ghulam Nabi, Department of Urology, Ninewells Hospital, Academic Surgical practice, Population Sciences Division, College of Medicine, Dentistry & Nursing, University of Dundee, Dundee DD1 9SY, UK.
e-mail: g.nabi@nhs.net

Abbreviations: **CSS**, cancer-specific survival; **NSS**, nephron-sparing surgery; **(L)(O)NU**, (laparoscopic) (open) nephroureterectomy; **OR**, odds ratio; **OS**, overall survival; **PFS**, progression-free survival; **RCT**, randomised control trial; **RFS**, recurrence-free survival; **STROBE**, the Strengthening the Reporting of Observational Studies in Epidemiology; **UUT-TCC**, upper urinary tract TCC.

11. Oral 5-aminolevulinic acid in simultaneous photodynamic diagnosis of upper and lower urinary tract transitional cell carcinoma – a prospective audit

We wanted to evaluate the diagnostic accuracy of photodynamic diagnostic (PDD) ureterorenoscopy for upper urinary tract urothelial tumours (UUT-TCC). This is the first reported series worldwide on the use of oral 5-Aminolevulinic acid (5-ALA) for PDD in UUT-TCC.

A prospective audit of 26 patients (39 procedures) who required upper urinary tract endoscopic assessment for diagnosis, treatment and follow-up for UUT-TCC was done. Patients received 20 mg/kg bodyweight of 5-ALA dissolved in 50 mL water, given orally 3 – 4 h before the ureteroscopy. Following standard white light cystoscopy and ureterorenoscopy, PDD ureteroscopy was performed to detect fluorescent areas suggestive of tumour. Biopsies were then carried out from all suspicious areas, noting if lesions were detected under white or blue light or both.

Sixty-two biopsies were performed for suspicious urothelial lesions (35 bladder, 26 ureter/renal pelvis and 1 from prostatic urethra). Twenty-four (68.5%) bladder biopsies were taken from lesions seen only under blue light and 45.8% of these were malignant. Similarly, ten (38.5%) ureteric/renal pelvicalyceal lesion biopsy were seen only under blue light of which 70% were malignant. With no major complications, and six minor complications (2 transient asymptomatic hypotension and 4 facial skin photosensitive reaction), our results confirmed that PDD using oral 5-ALA is safe and feasible with additional advantages of detecting lesions not visualised with conventional white light ureteroscopy.

(Contribution 35%, creating the database, help with writing and proof reading)

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Oral 5-aminolevulinic acid in simultaneous photodynamic diagnosis of upper and lower urinary tract transitional cell carcinoma – a prospective audit

Sarfraz Ahmad, Omar Aboumarzouk, Bhaskar Somani, Ghulam Nabi and Slawomir Grzegorz Kata

Department of Urology, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK

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Study Type – Therapy (case series)
Level of Evidence 4

OBJECTIVE

- To evaluate the diagnostic accuracy of photodynamic diagnostic ureterorenoscopy after oral administration of 5-aminolevulinic acid (5-ALA) for upper urinary tract urothelial cancers.

PATIENTS AND METHODS

- In this audit, twenty-six patients underwent thirty-nine procedures (cystoscopy/ureterorenoscopy) following oral administration of 5-ALA for photodynamic diagnosis (PDD).
- Twenty mg/kg body weight of 5-ALA was given orally 3–4 hours prior to the planned endoscopic visualisation.
- Following standard white light cystoscopy and ureterorenoscopy, photodynamic diagnostic endoscopy was performed using D-light system (Olympus PDD cystoscope and 7.5Fr KARL STORZ PDD Flex-X ureterorenoscope) to detect fluorescence.
- Biopsies were carried out from all suspicious areas, noting if lesions were detected under white or blue light or both.

RESULTS

- A total of sixty-two biopsies were performed for suspicious urothelial lesions (35 bladder, 26 ureter/renal pelvis and 1 from prostatic urethra).
- Of the 35 bladder biopsies, 11 lesions were seen under both white and blue light and 91% of these were malignant.
- While 24 (68.5%) biopsies were taken from lesions seen only under blue light and 45.8% of these were malignant.
- Similarly, of the 26 ureteric/renal pelvicalyceal biopsies, 11 were concurrent in both white and blue light and 100% of these were malignant.
- While 10 (38.5%) lesions were seen only under blue light and 70% of these were malignant.

CONCLUSIONS

- Photodynamic diagnosis using oral 5-ALA is safe and feasible with additional advantages of detecting lesions not visualised with conventional white light endoscopy.
- This may translate into more complete treatment thereby decreasing subsequent recurrences and possibly progression of the upper urinary tract urothelial cancers.

KEYWORDS

photodynamic diagnosis, transitional cell carcinoma, ureterorenoscopy

What's known on the subject? and What does the study add?
The idea of using photosensitizing agents to enhance visualization of cancer tissue dates back to 1900. 5-Aminolevulinic acid (5-ALA) was first suggested for photodynamic diagnosis (PDD) of transitional cell cancer (TCC) of the bladder in 1992. Since then, PDD with intravesical application of 5-ALA or its ester hexaminolevulinate (Hexvix) has proven to be superior over standard white-light cystoscopy in detection of carcinoma *in situ* and dysplasia as well as enhancing margins of TCC. PDD of upper urinary tract TCC is under-studied because of trouble with delivery of the photosensitizer. Fluorescence after oral 5-ALA was initially reported in 1956. Oral 5-ALA for photodynamic therapy was suggested for upper urinary tract TCC in 1998 and for refractory non-muscle invasive bladder cancer in 2001. A study in 2012 on oral and intravesical application of 5-ALA for bladder PDD showed no difference in diagnostic accuracy for each modality.

To our knowledge our series is the first report on use of oral 5-ALA for PDD in detection of upper urinary tract tumours. We published our initial results in 2010. We think that our recent audit is quite encouraging. PDD ureterorenoscopy resulted in detection of additional urothelial tumours that could have been missed by the conventional white-light endoscopy. We suggest that this technique should be used in large multicentre trials to replicate our results.

INTRODUCTION

Transitional cell carcinoma (TCC) of the bladder is a common urological malignancy whereas upper urinary tract transitional cell carcinoma (UT-TCC) is infrequent, accounting for around 7% of urothelial tumours. Standard diagnostic modalities for these tumours are white-light endoscopy and radiological imaging. For UT-TCC, the role of pretreatment histological diagnosis is controversial. However, ureterorenoscopy with a brush or forceps biopsy is required in cases where the diagnosis is in doubt, or the management would be significantly altered by endoscopic findings [1].

White-light endoscopy can detect obvious and sizeable urothelial TCC whereas subtle mucosal lesions may be missed. Diagnosis of these occult lesions is important because these have important implications for disease progression and management decisions. Photodynamic diagnosis (PDD) is a step forward in enhancing diagnostic accuracy for urothelial TCC. Successful clinical application of the fluorescence has been reported in dermatology, brain, tracheobronchial tree and more recently in bladder tumours [2]. Kelly and Snell were the first to suggest that a haematoporphyrin-derivative could be used as an aid to the diagnosis and treatment of bladder cancers [3]. PDD uses fluorescence to localize these lesions by selective accumulation of protoporphyrin IX in the tumours. PDD cystoscopy has high sensitivity for detecting bladder tumours, in particular carcinoma *in situ* [4]. Both hexaminolevulinate and 5-aminolevulinic acid (5-ALA) induced PDD can enhance the diagnostic accuracy of cystoscopy for bladder carcinoma [5–10]. Additionally, PDD with these photosensitizers decreases the rate of recurrent non-muscle invasive bladder tumours by enhancing their initial diagnosis and treatment [8,11,12]. One-hour intravesical instillation of these agents is required 1 h before fluorescence cystoscopy, which is resource dependent and may not be available widely.

Diagnosis of UT-TCC is more challenging especially when radiological investigations are not conclusive. The use of blue-light-assisted ureterorenoscopy in UT-TCC is still in its early stages. We previously reported a short case series of oral administration of 5-ALA for PDD of UT-TCC [13]. Now we present a prospective audit of the results of a simple and practical technique of PDD for upper and lower urinary tract TCC using oral 5-ALA as photosensitizer. We aim to explore the role of 5-ALA in detecting abnormal tissues in the upper urinary tract.

TABLE 1 Indications for photodynamic diagnosis in study participants

Previous history of TCC		New patients (suspicious UT-TCC on CTU)	
Location of TCC	No. of patients	Location of TCC	No. of patients
Bladder TCC*	6	Renal pelvis	2
UT-TCC	4	Ureter	6
Both bladder and UT-TCC	8		

*TCC, transitional cell carcinoma; UT-TCC, upper tract transitional cell carcinoma; CTU, computed tomography urogram. *Patient with history of bladder tumours and a new suspicious UT-TCC on follow-up CTU.*

PATIENTS AND METHODS

This prospective audit includes all patients who required upper urinary tract endoscopic assessment for diagnosis, treatment and follow-up for UT-TCC. The photodynamic diagnostic ureterorenoscopy was approved by the 'Improvement and Quality Committee' of our institute. All patients gave their consent before the procedures.

Each patient received 20 mg/kg bodyweight of 5-ALA (Medac, Stirling, UK) dissolved in 50 mL water, then mixed with 50–100 mL orange juice to flavour the drink. The mixture was given orally 3–4 h before the planned endoscopy [14]. After oral administration, patients were kept away from direct sunlight or strong room light for 24 h. This protocol was based on the Scottish Photodynamic Therapy Centre and the Scottish Adult Neurosurgical Network guidelines for the use of oral 5-ALA.

A single urologist performed all procedures. The technique of ureterorenoscopy and biopsy followed principles recommended by Tawfiek *et al.* [15] and by Grasso *et al.* [16]. The bladder and upper urinary tract were mapped first under white light and then under blue light. Following standard white-light cystoscopy and ureterorenoscopy, PDD endoscopy was performed using a D-light system (Olympus PDD cystoscope with 12-degree and 70-degree telescopes and a 7.5 Fr KARL STORZ PDD Flex-X ureterorenoscope) to detect fluorescence using a xenon arc lamp with a blue light with a 380–440 nm wavelength. Biopsies were carried out from all suspicious areas noting if lesions were detected by white or blue light, or both. Random biopsies from normal mucosa were taken from upper urinary tract only if reported as suspicious on CT urogram. Upper tract tumours suitable for endoscopic management (visible under white or blue light) were ablated with a holmium : YAG laser (with curative intent).

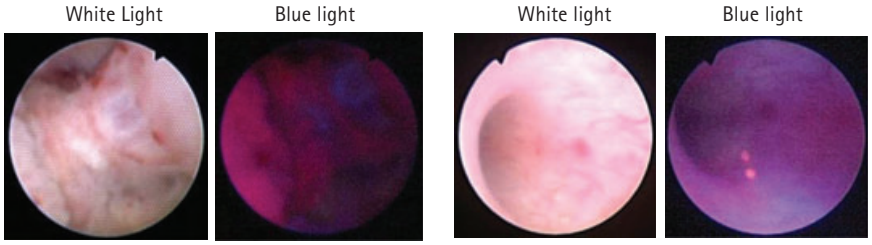
The biopsy specimens were fixed in formalin and processed as standard for haematoxylin & eosin staining. The WHO 1973 histological grading system and 2004 WHO consensus classifications are used in parallel in our institute.

Data were collected for all patients included in the study. The primary outcome variable of the statistical analysis was the difference in abnormal lesions seen under white and blue light endoscopically and pathological outcomes. MICROSOFT EXCEL 10.0 was used to manage and analyse the data.

RESULTS

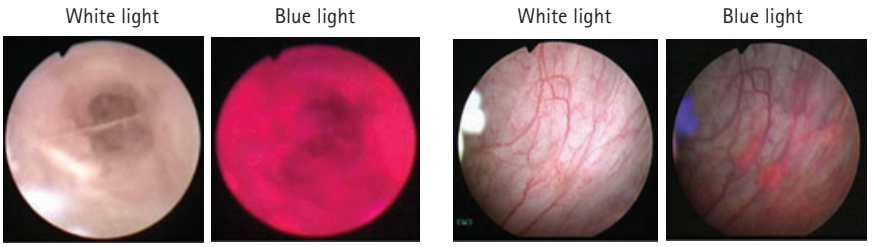
Twenty-six patients were included in the audit with a mean (±SD) age of 70.3 years (±11) and a male to female ratio of 22:4. The indications for PDD are summarized in Table 1. Thirty-nine procedures were performed using 5-ALA and 62 biopsies were taken, 35 from bladder, 26 from upper urinary tract, and one patient underwent diagnostic TURP for strong fluorescence from the prostatic urethra. During the study

FIG. 1. Comparisons of endoscopic visualization under white and blue light. (a) Renal calyx, diffuse fluorescence seen under blue light, biopsy confirmed pTaG2 transitional cell carcinoma. (b) Ureter – dot-like fluorescence, biopsy from these areas showed a carcinoma in situ. (c) Ureter – diffuse fluorescence under blue light, biopsy confirmed carcinoma in situ. (d) Bladder – biopsy from the fluorescence areas confirmed pTaG2 transitional cell carcinoma.



a) Renal Calyx – diffuse fluorescence under blue light

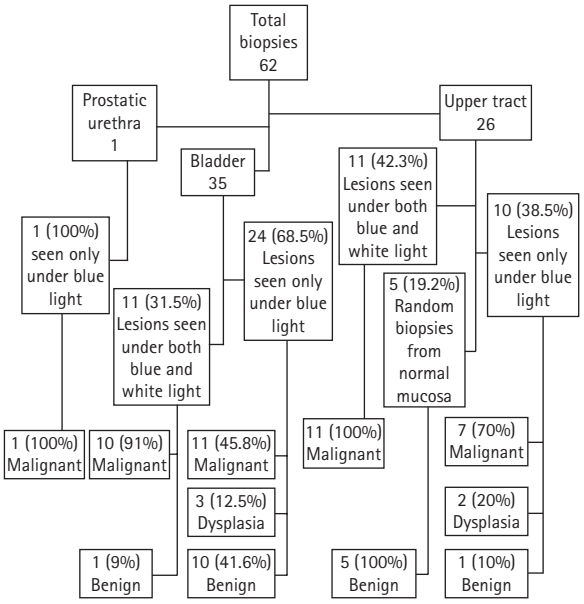
b) Ureter – patchy fluorescence under blue light



c) Ureter – diffuse fluorescence under blue light

d) Bladder – fluorescence under blue light

FIG. 2. Algorithm of endoscopic findings and pathological results of bladder and upper tract biopsies.



period, 15 patients underwent PDD ureterorenoscopy once, nine patients had the procedure twice and two patients thrice.

Thirty-five biopsies were taken from suspicious bladder mucosal lesions and one from fluorescent prostatic urethra. Among the bladder biopsies, 11 (31.5%) were taken from lesions seen with both white and blue light. Histological analysis showed that 10 (90.9%) of these biopsies were malignant. Twenty-four (68.5%) biopsies were taken from mucosal lesions seen under blue light only. Ten of these biopsies (41.6%) were benign while 11 biopsies (45.8%) were malignant (nine pTaG2, one pT1G3, one carcinoma *in situ*). Three biopsies (12.5%) showed dysplasia (Figs 1 and 2). Biopsy from prostatic urethra (diagnostic TURP) revealed pTaG3 TCC. Patients with negative biopsies were followed up with flexible cystoscopy, only if they had a history of bladder TCC.

Twenty-six biopsies were taken from renal pelvi-calyceal systems or ureters. Eleven of these biopsies were taken from lesions identified under both white and blue light and all of these were malignant. Five random biopsies were taken from mucosa with normal appearance in both white and blue light (reported as suspicious on CT urogram), all of which turned out to be benign. Ten biopsies (38.5%) were taken from the abnormal mucosal areas seen only in blue light (seven malignant pTaG2, two dysplasia and one benign) (Figs 1 and 2). The subsequent biopsy (after 3 months) in one ureteric dysplastic area was confirmed as pTaG2 tumour.

Biopsies from most (90%) of the fluorescent areas seen under blue light were abnormal (malignant or dysplasia). One patient with benign histology had a repeat CT urogram and urinary cytology at 6 months. Both investigations were normal.

Additionally, 10 upper urinary tract lesions were visible only under blue light. The corresponding CT urograms were reported as normal in half of these patients and urine cytology was suspicious (C4) in only one of these five patients. Hence, with standard white light ureterorenoscopy these tumours could have been missed.

The median operation time was 30 min (range 15–60 min). The variability of time was the result of the additional procedures required, i.e. cystoscopy +/– biopsy/resection of bladder tumour and ureterorenoscopy +/– biopsy/ tumour ablation +/– stent(s) insertion. The cost of 1 vial of 5-ALA (1.5 g) was £110. PDD cystoscopy was being used as a diagnostic tool in our institution before we implemented PDD ureterorenoscopy, so purchase of the 7.5 Fr KARL STORZ PDD Flex-X ureterorenoscope (approximately £12 000) was the only additional cost.

No major complications were seen in the audit cohort. Two patients developed transient asymptomatic hypotension before endoscopy and four patients developed a facial skin photosensitive reaction. The

patients were managed symptomatically and responded well without any long-term or serious outcomes.

DISCUSSION

We have shown that PDD ureterorenoscopy with oral 5-ALA is beneficial for the detection of malignant urothelial lesions that are not seen under standard white light. Appropriate management and prediction of prognosis of the urothelial TCC are dependent on careful endoscopic evaluation of the whole urinary tract. Concomitant urothelial tumours in the bladder and upper urinary tract, especially carcinoma *in situ*, are an important risk factor for tumour recurrence and progression [17–19].

In our audit, the oral 5-ALA-induced PDD ureterorenoscopy provided promising results in localization and detection of malignant urothelial lesions of the upper urinary tract as well as the bladder. Most of the blue-light-guided biopsies were malignant (70% upper urinary tract and 45.8% from the bladder). The higher percentage of positive biopsies from the upper urinary tract than from the bladder is possibly a result of the study population selected, which included patients with suspected UT-TCC or being followed up for UT-TCC. The aim of this audit was to investigate the role of oral 5-ALA PDD for UT-TCC diagnosis. However, additional bladder tumours were also depicted. This audit does not recommend systemic (oral) 5-ALA for PDD diagnosis of lower urinary tract lesions. Bladder TCC can be found using white-light cystoscopy in 8–13% at the time of diagnosis of UT-TCC and bladder recurrence rate varies between 17% and 47% after endoscopic treatment of UT-TCC [20]. We showed that the use of oral 5-ALA for PDD ureterorenoscopy allows simultaneous blue-light inspection of the bladder to diagnose small/occult concomitant bladder TCC.

In addition to the detection of overt malignant urothelial lesions, strong fluorescence was also observed in areas of urothelial dysplasia. The urothelial dysplasia is characterized by architectural distortion, variable degree of atypia and scanty mitotic activity in the basal and intermediate cell layers. Diagnosis of these dysplastic lesions is also clinically significant because there is evidence that dysplasia shares some abnormalities with carcinoma *in situ* and has a high tendency to develop into cancer [21]. In this present audit, PDD ureterorenoscopy detected three dysplastic lesions in the bladder and two in the upper urinary tract, indicating that these precursor lesions can be identified during PDD ureterorenoscopy. These findings showed that simultaneous blue-light-assisted cystoscopy at the time of PDD ureterorenoscopy detects additional malignancies within the lower urinary tract that could be missed under white light. Hence the diagnostic credibility of PDD ureterorenoscopy was superior with oral 5-ALA use.

Localization and the reliability of the pathological specimens from upper urinary tract lesions remain the most important difficulties in UT-TCC ureteroscopic diagnosis. We have shown that the targeting of the upper urinary tract lesions was improved by PDD ureterorenoscopy. However, the biopsies were taken with standard ureteric biopsy forceps so no real improvement was observed in the quality of the specimens. In this audit, none of the specimens from the upper tract included muscular fibres, so pTa stage, or non-invasive papillary urothelial carcinomas, can be considered doubtful. Various authors considered that tumour grade could be just as predictive concerning disease evolution and prognosis of the patients [22]. Furthermore, it has been established that protoporphyrin IX concentration in the muscular layer of the bladder is minimal and PDD cannot be used as a staging tool [14].

Accurate and timely detection of the recurrent urothelial TCC is important to prevent tumour progression. Routine follow-up cystoscopy may not identify all recurrent bladder TCC [23]. In our audit, both new patients and those undergoing follow-up for UT-TCC were included. For both of these subgroups, detection of the abnormal mucosal lesions under blue light was superior to the standard white light endoscopy. However, its significance and its effect on management and long-term benefits for both new and follow-up patients need to be addressed in separate studies.

There are a few limitations to this paper that warrant mention. First, this is an observational audit evaluating the concept that the oral 5-ALA-induced PDD ureterorenoscopy may improve detection of urothelial TCC. Although, the results are encouraging, randomized trials are required to establish the superiority of this newer technique over standard diagnostic modalities for UT-TCC. Second, this technique is operator dependent so estimation of the degree of fluorescence is questionable. A standard fluorescence grading system is required to overcome this issue. Furthermore, our data include both new ($n = 14$) and recurrent ($n = 12$) UT-TCC, and because of the small number of patients in these groups it is not possible to draw meaningful statistical differences in the role of PDD ureterorenoscopy for new and recurrent UT-TCC. Finally, because of the lack of long-term follow-up, correlation of this endoscopic diagnosis with more robust endpoints such as recurrence-free and overall survival could not be established.

In summary, PDD ureterorenoscopy seems to represent a valuable diagnostic technique for UT-TCC, showing considerable improvement of tumour visual accuracy as well as tumour detection rate. This may translate into more complete endoscopic treatment thereby decreasing subsequent recurrence and possibly progression. Further studies are needed to evaluate the role PDD in the diagnosis of the upper urinary tract lesions in addition to clarifying the impact of this technique on the recurrence rates and on tumour-free and overall survival.

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CONFLICT OF INTEREST

None declared.

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Correspondence: Department of Urology, Sarfraz Ahmad, Ninewells Hospital and Medical School, University of Dundee, Dundee, DD1 9SY, UK.
e-mail: drsarfrazrana@hotmail.com

Abbreviations: **TCC**, transitional cell carcinoma; **UT**, upper urinary tract; **PDD**, photodynamic diagnosis; **5-ALA**, 5-aminolevulinic acid.

12. Mitomycin C (MMC) instillation following ureterorenoscopic laser ablation of upper urinary tract carcinoma

Nephroureterectomy is the gold standard treatment for upper tract transitional cell carcinoma (UUT-TCC). Ureteroscopic management of UUT-TCC is a minimally invasive technique with lower morbidity and helps to preserve the renal function. With the success of adjuvant intravesical Mitomycin C (MMC) treatments for non-muscle invasive bladder carcinoma in reducing recurrence rates, we adopted a similar approach for UUT-TCC using MMC instillation in the UUT. Our aim was to develop and evaluate a protocol for a single dose MMC instillation following ureteroscopic laser ablation of upper urinary tract transitional cell carcinoma (UUT-TCC).

All patients diagnosed with new and recurrent suspected UUT-TCC were selected after an informed consent. After ureteroscopic ablation of tumour, MMC was instilled via an infusion pump.

Twenty UUT units (19 patients) were managed for UUT-TCCs using our MMC protocol. At a mean follow-up of 24 months 13/20 (65%) of the UUT units remained cancer-free, 3 (15%) UUT units developed stricture and were treated with endoscopic dilatation, only one of these developed long-term stricture that needed a nephrectomy. None of the patients developed renal impairment or systemic side-effects. Our results confirmed that endoscopic ablation with protocol-based adjuvant MMC for UUT-TCC, in low-grade lesions seems to be effective in reducing recurrences with good preservation of kidney function and a low rate of long-term local complications.

(Contribution – 25%, creating the database and proofreading/correcting the paper).

Original Article

Mitomycin C instillation following ureterorenoscopic laser ablation of upper urinary tract carcinoma

Omar M. Aboumarzouk[1], Bhaskar Somani[2], Sarfraz Ahmad[3], Ghulam Nabi[3], Nicholas Townell[3], Slawomir G. Kata[3]

[1]Wales Deanery, Department Urology, Cardiff, UK and Islamic University of Gaza, College of Medicine, Gaza, Palestine, [2]Southampton University Hospitals NHS Trust, Southampton, [3]Department of Urology, Ninewells Hospital and Medical School, Dundee, UK

Abstract

Introduction: Instillation of Mitomycin C (MMC) should prevent implantation of cancer cells released during endoscopic treatment and prevent recurrences as seen in carcinoma of the bladder.

Aim: To develop and evaluate a protocol for a single dose MMC instillation following Holmium: YAG laser ablation of upper urinary tract transitional cell carcinoma (UUT-TCC).

Setting and Design: A single institute prospective study.

Materials and Methods: MMC instillations protocol was designed and offered to patients between August 2005 and April 2011. Following tumor ablation, MMC was instilled into upper urinary tract (UUT) over 40 minutes. All the patients were regularly followed up.

Results: Twenty UUT units (19 patients) were managed for UUT-TCCs using our MMC protocol. Two UUT units had G1pTa tumors, 14 had G2pTa, 2 had G3pTa, and 2 had G3pT1. At a mean follow-up of 24 months (range 1-72 months), 13/20 (65%) of the UUT units remained cancer-free, 3 (15%) UUT units developed stricture and were treated with endoscopic dilatation, only 1 (5%) of these developed long-term complications. None of the patients developed postoperative renal impairment or systemic side-effects.

Conclusions: Using a set standard protocol, MMC can safely be instilled into the UUT after TCC ablation with minimal complications or side effects, good preservation of renal function, and with a low recurrences rate comparable to the literature.

Key Words: Mitomycin C, transitional cell carcinoma, upper urinary tract, ureteroscopy

Author for correspondence:
Mr. Omar M. Aboumarzouk, Wales Deanery, Urology Department, Cardiff, Wales and Islamic University of Gaza, College of Medicine, Gaza, Palestine.
E-mail: aboumarzouk@gmail.com

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INTRODUCTION

Nephroureterectomy has been the gold standard for the management of upper tract transitional cell carcinoma (UUT-TCC).[1] With the development of smaller diameter flexible ureteroscopes in conjunction with flexible laser fibers and improved optics, endoscopic management can be a safe alternative.[2] This minimally invasive approach can reduce the morbidity of treatment whilst preserving renal function. With the expanding role of renal sparing technique, low grade lesions in patients with normal contralateral kidneys can also be treated ureterorenoscopicaly.[1,3] Recent reports suggest that endoscopic management can be an alternative treatment option for low grade superficial tumors even as a first line management.[4-6]

However, with a recurrence rate between 30-65% following complete endoscopic treatment, the importance of frequent endoscopic surveillance is emphasized.[7] Not surprisingly, this is higher for high grade lesions with a third of patients proceeding to nephroureterectomy with a long-term

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follow-up.[8] Contemporary success of adjuvant intravesical treatments for non-muscle invasive bladder transitional cell carcinoma in reducing recurrence and progression rates has encouraged urologists to adopt a similar approach for UUT-TCC using BCG or Mitomycin C (MMC).[9-15]

The existing methods for MMC instillation either depend on gravity drainage instilled via nephrostomy tube or bladder instillation with an objective to develop a reflux via JJ stents or instilled via retrograde open-ended ureteric catheter. Each method has potential drawbacks, such as tumor seeding from the nephrostomy tract as well as the risk of extravasation and absorption of the topical agent if the percutaneous method is done.[16] Furthermore, various doses and delivery schedules for instillation have been tried with a variable recurrence rate.[9-17]

Therefore, we adopted a protocol for endoscopic management and adjuvant MMC installation with an aim to assess the recurrence and complication rates, effect of adjuvant MMC on renal function, and the need for further radical surgery for patients with UUT-TCC.

MATERIALS AND METHODS

Between August 2005 and April 2011, 15 men and 4 women with a mean age of 72 years (range: 57-83 years) underwent ureterorenoscopic UUT-TCC Holmium: YAG laser ablation followed by administration of topical MMC following the adopted algorithm protocol [Figure 1]. One man also developed UUT-TCC in his other UUT, bringing the total UUT units involved to 20. All patients diagnosed with new and recurrent suspected UUT-TCC were selected after an informed consent and institutional audit board approval. The study was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice and the Declaration of Helsinki (September 2004 version). The exclusion criteria were tumor size >1.5 cm, multiple (technically impossible to ablate in one session) tumors, or known high grade G3 tumors prior to surgery.

Semi-rigid ureteroscope 7 F Karl Storz or 7.8 F Richard Wolf and 7.5 F Karl Storz Flex X flexible ureterorenoscope were used for the procedure. Laser ablation was done with a curative intent using holmium laser (365 μm or 210 μm fibers) with power levels for ablation ranging from 1.0 J to 1.2 J, and the pulse frequencies from 12 Hz to 15 Hz. For ablation, the laser fiber was directed at and placed in close approximation to the tumor without touching the tissue. Multiple biopsies were taken from the tumor both before and after ablation using a 3 F Karl Storz reusable biopsy forceps for flexible ureteroscope for flat lesions and Nitinol zero tip basket for exophytic lesions. Sterile water was used for irrigation with low pressure gravity flow.

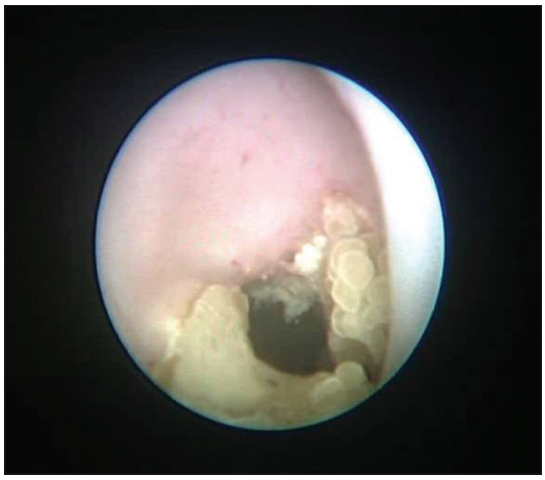

Figure 1: Proposed algorithm for management of UT-TCC (CTU: CT Urogram, UT-TCC: Upper tract transitional cell carcinoma, URS: Ureterorenoscopy, MMC: Mitomycin C)

Saline was not used for irrigation as diathermy ablation was intended to complete the treatment. As we did not observe any complications related to upper urinary tract irrigation for stone treatment between 2005 and 2009, we decided on water rather than Glycine. Both were reported previously as appropriate and safe for irrigation.[18]

After reviewing all published reports on MMC instillations into upper urinary tract [Table 1], we established a protocol for all patients undergoing endoscopic management of UUT TCC [Figure 1]. Following complete endoscopic ablation of the tumor, 5F open-ended ureteric catheter was left within pelvicalyceal system proximal to ablated area. Forty milligrams of MMC was dissolved in 40 ml of 0.9% normal saline and instilled via an infusion pump over 40 minutes (1 ml/minute). Post installation, the ureteric catheter was clamped for 20 minutes and was only released earlier if the patient complained of pain or discomfort. The ureteric catheter was secured to the 14 F Foley catheter with adhesive tape and was placed to gravity drainage. For tumors in the pelvicalyceal system, the ureteric catheter was removed the following day, whereas for tumors in the ureter, the ureteric catheter was exchanged for a ureteric stent the next day under general anesthetic to prevent stricture formation. Two patients with ureteric TCC had inserted Contour Injection Percuflex stent (Boston Scientific) following laser ablation and did not require coming back to theater following day. Patients were discharged the following day from the hospital with a strict surveillance schedule in place. This involved a 3-monthly check ureterorenoscopy in the first year, a 6-monthly check URS for 2 years followed by an annual URS. This was combined with an annual CT Urography. Follow-up, tumor recurrence, renal function, and need for radical surgery were analyzed retrospectively, and data was kept on a departmental database. Blood MMC levels were not monitored as none of the patients developed any systemic symptoms or deterioration in renal function [Table 2].

RESULTS

Twenty UUT-TCCs underwent endoscopic ablation followed by instillation of Mitomycin C using the protocol mentioned [Table 2]. All new tumors and recurrences were biopsied prior to complete ablation using Holmium: YAG laser followed by MMC instillation. No significant bleeding was observed during or after the procedures. Seven patients needed a second ablation and MMC re-instillation for recurrences at a mean follow-up of 4 months, all of whom have been tumor-free since their last follow-up.

The mode of presentation was frank hematuria (n = 9), surveillance of bladder tumor (n = 9), of which 2 patients had previous contralateral nephroureterectomy for TCC, with 1 patient being investigated for suspected stones, and another patient was under surveillance check for a bowel cancer, which picked up the ureteric tumor causing obstruction.

The American Society of Anesthesiologists (ASA) score was 2 in 12 patients and 3 in 7 patients. The location of the tumor, side, grade and stage, and renal function are detailed in Table 2.

Nine tumors were in the pelvicalyceal system while 10 in the lower ureter and only 1 in the mid-ureter. Two UUT units had G1pTa tumors, 14 had G2pTa tumors, 2 had G3pTa tumors with one also having a CIS, and 2 had G3pT1 tumors (high grade tumors were pathologically diagnosed after ablation and not known before surgery, otherwise would have been excluded) [Table 2].

The recurrence rate of UUT-TCC was 35% (7/20 urinary tracts). However, at a mean follow-up of 24 months (range: 1-72 months), 13 UUT units remain clear of tumor on the last ureteroscopic assessment. Of those with recurrences, 1

Table 1: A literature review of reported results of topical adjuvant treatment post ablation of UT-TCC

Author	Year published	Journal	Retrograde or percutaneous	Agent used	Patients (tumors)	Grade/stage	Recurrence rate (%)	Nephroureterectomy (NU) or progression (*P*) (%)	F/U (months)
Keeley[10]	1997	J Urol	Retrograde 1-3 days after treatment	MMC (40 mg)	19 (21)	G1-5 G1/2-2 G2-8 G3-4	54	NU-4/19 (21) P-0	30 m
Eastham[9]	1993	J Urol	Percutaneous	MMC (40 mg)	7	G2/3 Ta-3 G2/3T1-3 CIS-1	28.5	Cystectomy-1/7 (14)	1-12 m
Goel[16]	2003	J Urol	Retrograde or percutaneous (after a week)	MMC (40 mg)/ epirubicin (50 mg)	24	Low grade-15 High grade-5 SCC-2	50	NU-10 (42) P-2 (8)	64 m
Present series			Retrograde	MMC (40 mg)	19 (20)	G1/2 Ta-16 G3Ta-2 (1 also with CIS) G3T1-2	35	NU-1 (5) Cystectomy-1 (5) P-0	1-72 m (mean 24 m)

TCC: Transitional cell carcinoma, UT: Urinary tract, Urol: Urology, MMC: Mitomycin C, CIS: Carcinoma *in situ*, F/U: Follow-up

Table 2: Summary of patients with UT-TCC managed endoscopically with adjuvant MMC instillation

Age	Sex	Side	Presentation	Location	Ureteric tumor staging and grade	Creatinine; eGFR pre/post procedure	ASA
57	M	Left	Hematuria	Renal pelvis	G2pTa	103/108;60/60	2
65	M	Right	Bladder tumor F/U	Renal pelvis	G2pTa	80/80;60/60	2
80	M	Right	Bladder tumor F/U	Renal pelvis	G2pTa	114/122;42/56	2
		Left		Lower ureter	G1pTa	122/123;56/60	2
70	M	Right	Bladder tumor F/U	Lower ureter	G3pT1	185/156;30/45	2
72	F	Left	Hematuria	Renal pelvis	G2pTa	67/66;60/60	3
72	M	Left	Hematuria	Renal pelvis	G1pTa	84/92;60/60	2
79	M	Right	Hematuria	Renal pelvis	G2pTa	77/77;60/60	2
75	F	Left	Bladder tumor F/U	Lower ureter	G3pTa+CIS	210/142;20/19	2
73	F	Right	Bladder tumor F/U	Lower ureter	G3pTa	67/69;60/60	3
78	M	Left	Stone search	Renal pelvis	G2pTa	69/69;60/60	2
79	M	Right	Bowel cancer F/U, CT ureteric obstruction	Mid ureter	G2pTa	69/70;60/60	2
77	M	Left	Hematuria	Renal pelvis	G2pTa	70/70;60/60	3
60	M	Right	Hematuria	Lower ureter	G2pTa	91/82;60/60	3
71	M	Left	Hematuria	Lower ureter	G2pTa	103/84;60/60	2
67	M	Right	Hematuria	Lower ureter	G3pT1	76/85;60/60	2
83	M	Left	Bladder tumor F/U	Lower ureter	G2pTa	96/93;60/60	3
69	M	Left	Bladder tumor F/U	Lower ureter	G2pTa	74/78;60/60	3
72	F	Left	Hematuria	Renal pelvis	G2pTa	72/64;52/52	2
73	M	Right	Bladder tumor F/U	Lower ureter	G2pTa	103/110;60/59	3

eGFR: Estimated glomerular filtration rate, ASA: American society of anesthesiologists score, F/U: Follow up, TCC: Transitional cell carcinoma, UT: Urinary tract, MMC: Mitomycin C

patient had a G3pT1 tumor, but was not keen for a NU and had a recurrent G2pTa tumor, 1 patient with a high grade lower ureteric disease (G3pT1) and a previous contralateral NU and underwent a ureterectomy and ileal substitution, and 1 patient developed muscle invasive TCC around the right ureteric orifice and underwent a cystectomy. The remaining 4 patients with recurrent TCCs underwent ureterorenoscopic ablation followed by MMC instillation and remained tumor-free on check ureterorenoscopies.

COMPLICATIONS

Only 1 patient did not tolerate instillation of MMC, which was stopped after 15 minutes of initiation due to severe loin pain. However, none of the patients developed any clinical systemic side-effects. Initially, in 3/20 cases (15%), we observed local complications, all of which were benign ureteric strictures, which were dilated during their ureteroscopic check and have not recurred since. However, only 5% ($n = 1/20$ upper urinary tracts) developed a significant long obstructing benign stricture, which lead to a nephroureterectomy due to the kidney being non-functioning on a renogram. Two of the patients that developed strictures were also seen to have benign calcified debris attached on the wall of upper urinary tract. Patient who didn't tolerate instillation developed a renal stone stuck to the renal pelvis and lower calyx [Figure 1], which was successfully disintegrated with Holmium: YAG laser 6 months after MMC instillation, and he remains recurrence free.

In 1 patient, we successfully dilated stenotic segment of proximal ureter [Figure 2a and b] with Uromax 12 F Balloon Dilator with no evidence of contrast extravasation on retrograde ureteropyelogram after the procedure [Figure 2c], and the ureter was wide for endoscopic inspection 3 months following dilatation [Figure 2d].

None of the patients developed worsening renal function; Table 2 details pre- and post-operative renal function. Furthermore, none of the patients had local or distant disease progression, and none of the tumors have been upgraded on subsequent biopsies.

These complications can be classified as Grade IIIb under the Clavien Classification of Surgical Complications.[19]

DISCUSSION

The principle finding of this study was that endoscopic ablation of UUT-TCC followed by adjuvant Mitomycin C delivered using a standardized protocol has minimal complications and tumor recurrences comparable to those reported in the literature.[7] However, it is worth noting that none of the patients with low grade lesions needed nephroureterectomy, and they were all tumor-free on their last follow-up (mean - 24 months). A good cancer control was achieved in 65% of the ureters with preservation of renal function in all patients.

The limitations of this study were that this was a single center small study with significant observations for clinical practice. Also, no formal measurement of the intrarenal pressure as well as the degree of filling of the upper urinary tract was taken whilst instilling the MMC through the infusion pump. With only 19 patients with 20 UUT-TCCs and a mean follow-up of 24 months, some would argue the need for larger numbers, but for a relatively uncommon tumor, our figures are comparable to other published series [Table 1].

The strength of this study compared to other similar studies was the careful selection of UTT-TCC patients for endoscopic laser ablation for effective delivery of adjuvant MMC according to a set standardized protocol meant that all the patients had the same method of treatment.

The adjuvant MMC instillation was started within 6 hours following ablation of tumor, in contrast to previous reports where retrograde instillation of MMC, was done 1-3 days after endoscopic treatment.[10] The proven benefits of immediate adjuvant MMC post bladder tumor resection have changed clinical practice of non-muscle invasive bladder cancer.[20] Based on this, we believe that timing of MMC delivery into upper tract is crucial to its efficacy, hence the basis of the protocol. Unlike previously reported studies, all our patients were discharged 1-2 days postoperatively, and none of the patients developed any treatment related systemic side effect.[11-14] Sepsis, aplastic anemia, toxic agranulocytosis have been reported with the use of MMC; however, none of the patients in this study experienced any of these.[8]

In a comparison of open nephroureterectomy versus percutaneous resection for management of UTT-TCC, Lee *et al.* reported a comparable disease-free survival outcome for grade 1 and 2 disease in a 13-year follow-up.[4] In another study over a 9-year period, 19 patients were given percutaneous BCG at 6 weekly installations via a pre-placed nephrostomy tube starting at day 7 after second look nephroscopy, done a week after the percutaneous resection, and found no statistically improvement in survival of those who received BCG when compared to those who did not receive it.[4] Whilst low grade lesions can be treated endoscopically, both studies recommended treating high grade lesions with NU.[4,5] A more recent study also evaluated the cost effectiveness and survival of endoscopic management of UT-TCC with NU, and found the former to be more favorable for low grade superficial tumors.[6]

Possible mechanism and implications for future policy and practices was that endoscopic ablation with adjuvant instillation

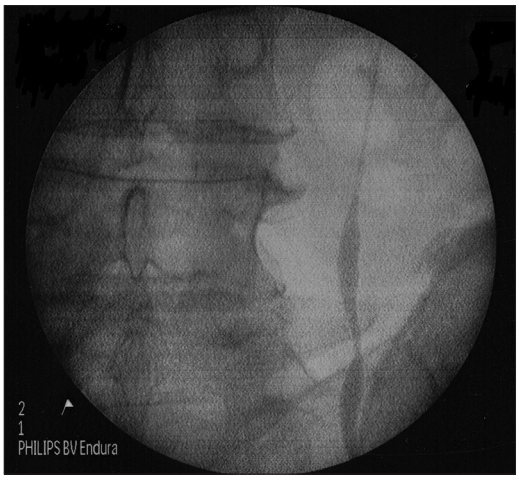

Figure 2a: Stenosed ureter pre-dilatation

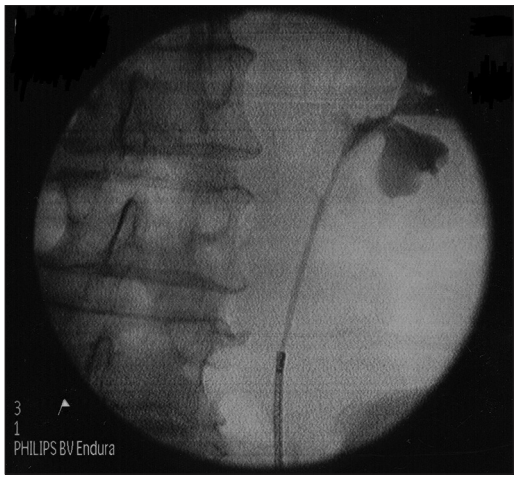

Figure 2b: Dilating stenotic segment of proximal ureter with uromax 12 F balloon dilator

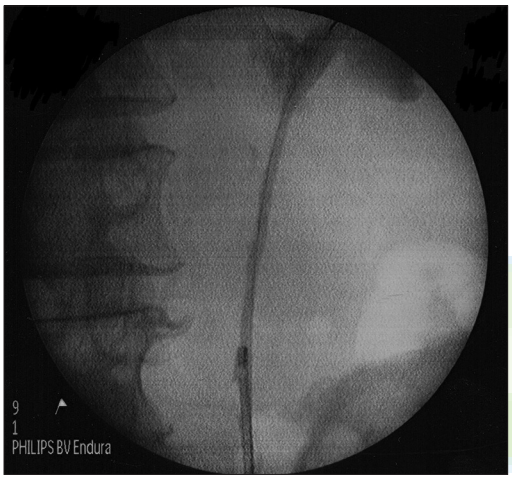

Figure 2c: Post procedure, showing no evidence of contrast extravasation on retrograde ureteropyelogram

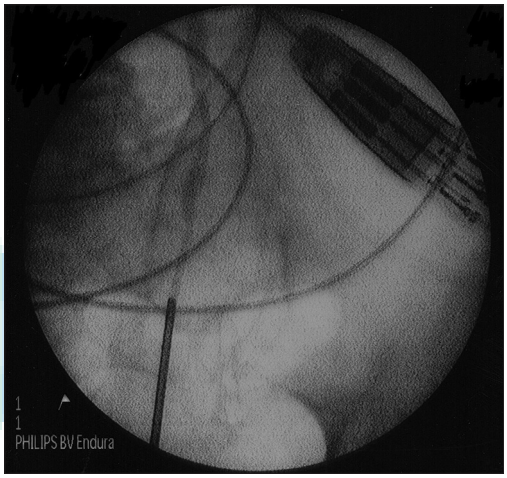

Figure 2d: Wide ureter for endoscopic inspection 3 months following dilatation

of Mitomycin C into upper urinary tract can be offered to a carefully selected group of patients, in particular low grade, even with normal contralateral kidneys and good general condition. The high grade and multifocal tumors have a higher risk of recurrence and progression as seen in our study and in other similar studies.[4,5] More aggressive intervention still remains the current recommendation for these cases.[21] As most studies using topical Mitomycin C in UUT-TCC [Table 1] are either small or retrospective, a well-designed prospective multicenter randomized trial is needed to address the issues such as dosage, frequency of installation, and time duration for the adjuvant agent to be in the system.

CONCLUSION

Endoscopic ablation with protocol-based adjuvant MMC for UUT- TCC, in particular low grade lesions seems to be effective in reducing recurrences and tumor progression with good preservation of kidney function and a low rate of MMC related long-term local complications. Though there is a risk of subsequent stricture complication, the majority of which can be easily dilated with no further recurrences.

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Conclusions:

The work done in my thesis through these 12 papers shows the role of MIS in the management of benign and malignant renal conditions. The first two papers show the role of laparoscopic partial nephrectomy and its success in obese patients and the outcomes when compared to robotic surgery. The next six papers show the use of ureteroscopy and its outcomes for stone management in difficult situations such as in pediatrics, pregnancy, obesity, patients with bleeding diathesis and very large stones. The comparison and advantages of modern digital scope with traditional fiber optic ureteroscope is also done with the expert 'tips and tricks' of doing ureteroscopy. The final three papers discuss the diagnosis and management of upper urinary tract tumours including the role of PDD for diagnosis and of adjuvant MMC post tumour ablation. In addition, there is a systematic review of literature discussing all types of surgical management of upper urinary tract tumors with advantages of laparoscopic Nephroureterectomy.

Although the reviews included in my thesis were done in an impartial and systematic manner in line with the Cochrane standard, the data was limited by the lack of non-randomised and prospective studies. The studies also had a high risk of selection bias. Despite the limitations, these MIS have advantage over the traditional counterparts and have gradually achieved acceptance for more complex disease conditions pushing the surgical boundaries to new frontiers.

These papers in my thesis throw new insight into areas of minimally invasive benign and malignant renal conditions. Although laparoscopy and ureteroscopy is well established, the current evidence will help clinicians and patients in informed decision making for several other conditions not previously treated in a minimally invasive

way. The advantages of MIS including reduced morbidity, low length of stay and good outcomes were observed even for treating difficult and challenging conditions.

Minimally invasive surgery is a step in the right direction for management of various benign and malignant renal conditions. My work demonstrates evidence-based outcomes, which will ensure widespread adoption of these techniques in future.

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