**Author's response to reviews**

**Title:** The role of diagnostic ureteroscopy in the era of computed tomography urography.

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Re: MS: 4421673711349165, “The role of diagnostic ureteroscopy in the era of computed tomography urography”

Dear Editor,

Thank you for your letter of April 9th regarding the above-referenced manuscript. We have carefully read the insightful comments of the reviewers and have amended the manuscript in accordance with their suggestions. Our point-by-point reply appears below.

Reviewer 1

1. Page 4 line 89, you could discuss the controversy between the Campbell’s Urology and the 2014 EAU [Introduction].

We agree with the reviewer and modified the text accordingly [Lines 89-93]:
“…In the last edition of "Campbell's urology" the authors do not support a routine ureteroscopic confirmation of UTUC, while the European guidelines on UTUC (2015 version) advocate the use of diagnostic ureteroscopy with biopsy, especially in cases where additional information will impact treatment decisions…”

2. It will be interesting to mention which ureteroscopes were used.

The information was added to the text as follow [Lines 113-116]: 
"Ureteroscopy was performed following a retrograde study, using 8FR rigid ureteroscope (Wolf), advancing the instrument as much as possible. Renal inspection was performed using flexible ureteroscope (DUR-8 (ACMI) or in later years the Flex- X™ (Storz))."

3. You should incorporate the following sentence of the results section (page 2, line 139-141) in the method section “Complete endoscopic examination of the ureter, renal pelvis and calyx has been performed in all patients”.

We agree with the reviewer. This sentence was moved to line 112 in the methods section.

4. Is flexible-URS was systematic for renal examination?
   Yes. To clarify this point the text was modified [line 115]:
   “… Renal inspection was performed using flexible ureteroscopy…”

5. About histology, you should use the WHO 2004 classification for tumor grade and the TNM 2009 for UTUC [Methods]

   Because many patients were treated before 2009 we used TNM 2002. References were added to the text. [lines 117-119]

6. What was the follow-up for patients with chronic kidney disease?

   CKD patients were referred to a nephrologist in addition to the required urologic follow-up. A comment was added to the text [lines 130-131]: “…Patients with chronic kidney disease were referred to a nephrologist for consultation…”

7. You should mention the number of patients with chronic kidney disease.
   22 patients had chronic kidney disease and therefore they did not perform CTU. This data was added to the text [lines 151-152]: “… CTU was not performed
in 22 patients with chronic renal failure and 3 patients with severe contrast allergy…”

8. Please, mention the inclusion dates. Because you mentioned you did 1818 between 2003 and 2008 but when did the first patient included undergo surgery? Even for the last one. I ask this question because the improvements in technology during the study period.

This data was added to the text as follow [lines 144-145]: “The study cohort included 116 patients who underwent diagnostic ureteroscopy between November 2003 and December 2010…”

During the study period we were using active deflection ureteroscopes, initially the DUR-8 (ACMI) and later on the Flex-X (Stortz) [lines 113-116]. We usually did not encounter difficulties in approaching the suspected renal lesions. The challenging aspect of diagnostic ureteroscopy is gaining a proper biopsy, in that respect (regretfully) there was no significant progress during the study period

9. The complications should be classified according to the Clavien Dindo classification. Furthermore, you have to mention that in the section method (not in the discussion). [Results]

We agree with the reviewer. Text was modified and data added accordingly [lines 126-127]: “… Intra- and peri-operative complications were reviewed and staged according to Clavien-Dindo classification⁹…”

and lines 160-165 : “All complications observed in this study were Clavien grade I or II. Intraoperative complications included contrast extravasation, observed during ureteroscopy, in 4 patients (3%). All patients were managed with ureteral stent for one week with no clinical sequel. Febrile UTI and renal colic were observed after ureteroscopy in 7 (6%) and 4 (3%) patients, respectively. Conservative treatment was successfully applied in all cases”.
10. **It could be interesting to calculate the sensitivity and specificity for CTU, ultrasound and urine cytology.**

   We preferred using positive and negative predictive values because they are measures of diagnostic tests, describing their performance [lines 134-136].

11. **One of the limitations is the use of ultrasound as modality to undergo URS. This imagery modality is unfortunately subjected to inter-observer bias and has a lack of accuracy (in obese patients for example). I am not sure that it is a good idea to include these patients because ultrasound is no recommended as imagery modality for the diagnosis of UTUC.**

   We agree with the reviewer. This was previously explained in the text [lines 105-107]: "Although ultrasound is not accepted as a standard modality for UTUC investigation, we reported on ultrasound results when it was available (either performed as first imaging modality in the community or in cases of chronic renal failure or severe contrast allergy)."

12. **I think you just have to include patients with positive CTU and those with positive urine cytology and negative cystoscopy.**

   Indeed, the study presents our experience with diagnostic ureteroscopy but in the conclusions we focused on patients with positive findings on CT. In order to clarify this point for the reader we modified the phrasing of our main conclusion [lines 268-269]:
   “… In this retrospective study, nephroureterectomy was spared from 42% of patients with presumptive UTUC, demonstrated on CTU…”

13. **I think you have to describe clearly the objective: the first endpoint is to assess the accuracy of URS compared to the other technics and the secondary endpoint**
is to assess the efficacy of URS treatment.

In line with this view we rephrased the aims of the study in the introduction [lines 94-96]: “… The purpose of this study was to evaluate the diagnostic value of ureteroscopy in patients who underwent workup for suspected UTUC and to assess the impact of ureteroscopy on the management of UTUC…”

Reviewer 2

1. Introducing the utility of an endoscopic management of UTUC, I would describe more precisely the indications and which are the selected cases eligible.

The text was modified to clarify this issue [lines 120-124]:

“…Patients with histologically confirmed UTUC were referred to nephroureterectomy usually within one month following the diagnostic procedure or, in selected cases, managed conservatively with endoscopic resection. Patients with low grade, <1 cm UTUC were eligible for endoscopic treatment…..”

2. In my opinion, it's more appropriate a reference to specific guidelines (i.e. american or european guidelines) rather than to an urologic text even if it's 'Campbell Urology'

We agree with the reviewer and modified the text - please see our reply to reviewer 1 (comment 1).

3. Referring to patients subjected to nephroureterectomy, it’s not specified if ureterorenoscopy was performed immediately before open surgery or it was a distinct operation followed by nephroureterectomy in subsequent days or weeks.

The text was modified for clarification [lines 120-122]:
"…Patients with histologically confirmed UTUC were referred to nephroureterectomy usually within one month following the diagnostic procedure…"

4. In the description of follow-up of the patients managed endoscopically, I would add the possibility of a topical adjuvant therapy (have you treated some patients in your experience?)

We have limited experience with instillation for UTUC and therefore it was not described in the current paper.

We hope you find the revised version of our manuscript suitable for publication in BMC Urology.

Sincerely,

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