

Peer Review File

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Reviewer A

Comment 1: The text is relatively well-organized with logical formatting, and it is of appropriate length.

Reply 1: Thank you!

Changes in the text: no changes according to this comment.

Comment 2: This was the first study investigating the usability of a rMSI endoscopic system during a bladder tumor biopsy.

Reply 2: Exactly, thank you.

Changes in the text: no changes according to this comment.

Comment 3: This study has inevitably limitations especially the ex vivo test conditions.

Reply 3: We absolutely agree with that.

Changes in the text: To highlight this aspect according to your comment, we modified the text (see page 16, line 350-352).

Reviewer B

Comment 1: Isn't this paper similar in content to "Endourological training using 3D printed bladder phantoms - development and prospective evaluation" that the authors have published separately in the Journal of Endourology?

Reply 1: The article "Endourological training using 3D printed bladder phantoms - development and prospective evaluation" published in the Journal of Endourology in February 2021 aimed to introduce a realistic and user-friendly bladder phantom and to evaluate it in the context of endourological training. The current study uses a modified version of this phantom, that allows to evaluate fluorescence imaging. The current study however pursues a very different research question: The aim was to test the usability of the novel rMSI endoscopic system, but not to evaluate the bladder phantom.

Changes in the text: Because the article by Waldbillig et al. had not been published at the time of our initial submission in November 2020, we have added it as a citation (see page 14, line 287-290, page 23, line 514-516).

Comment 2: What was the difference in experience between the 15 urologists?

This paper mentions experience with ex vivo studies, but what about years of doctors' clinical experience, gender, age, etc.?

Do you think that affected the results of this study?

Do you think that the rMSI had an educational effect?

Reply 2: Thank you for the suggestion to report on sociodemographic data and on the clinical experience of the participating physicians in more detail. So far, we only describe the total number of cystoscopies performed (on patients) (page 11, line 236-237). Of our 15 physicians, 10 were residents

and 5 were board certified urologists. 4 physicians were female, 11 were male. They were on average 30 years old.

Following your suggestions, we compared the execution times (time till removal of the last lesion and time to surgeons' certainty of a complete biopsy) between residents and urologists. There was no statistically significant difference between the subgroups for any of the times measured. This analysis however is limited by the number of physicians.

Consequently, we think that the investigators' experience does not influence her/his performance of biopsy in this setting. Because the investigators used the two different endoscopes only once each, our study does not allow us to draw any conclusions about a learning effect.

Changes in the text: As suggested, we have added sociodemographic information as well as information on the previous clinical experience of the participating physicians (see page 11, lines 233-237). Moreover, we have added the finding, that execution times did not differ between residents and urologists (see page 12, line 245-248).

Comment 3: Is a t-test sufficient for statistical analysis? I don't think that the ability of doctors is normally distributed?

Reply 3: Thank you very much, for this important comment. Due to the non-normally distribution of the data, we now applied the Wilcoxon ranked-sum test for group comparison, which did however not result in changes of significance.

Changes in the text: We modified the statistical analysis as advised (see page 4, line 86-87; page 12, line 239-248; page 14, line 311-312; page 24, Tab. 1).

Comment 4: In this study, the lesion's position was on the lower side for the convenience of the phantom, but in actual cases, the lesion may be in a difficult location. What do you think will be the effect in this case? I think that cystoscopy operation will be more dependent on experience.

Reply 4: Thank you for this comment. As described on page 11 line 228-231, we excluded the first 3 trials from the statistical analysis because here, the patches on the ceiling of the phantom could not be removed with the forceps, neither for the conventional, nor for the rMSI endoscope. The fact that these areas of the bladder phantom were difficult to reach for both endoscopes is due to its rigid construction (page 16, lines 352-353). We fully agree that, tumors (in actual cases) can be localized in areas difficult to reach by a rigid endoscope. In such cases, tumor biopsy or transurethral resection of the bladder tumor certainly requires greater experience of the surgeon. Based on the findings of our study, it can be assumed that the rMSI system performs at least as well as a conventional endoscope even in these difficult cases. It is also possible that the simultaneous visualization of different imaging modalities may facilitate biopsy/TUR-B, especially in challenging tumor positions. This needs to be evaluated in in-human studies.

Changes in the text: As suggested, we have added these considerations to our discussion (see page 16, line 355-358).

Comment 5: Isn't this kind of diagnostic support system necessary for skilled users?

How would you rate the ability to see as doctors get used to it?

Reply 5: Thank you for these interesting questions. To the best of our knowledge, there is no study to date that has demonstrated that the use of e.g. PDD offers no advantage to experienced urologists in terms of better detection of a Carcinoma in situ, or rather that only inexperienced surgeons benefit from PDD. As mentioned earlier, our study showed no difference in detection rate or execution time between the experienced and inexperienced investigators. Consequently, we think that the rMSI system can comparably support inexperienced and experienced users in the biopsy of bladder tumors. Changes in the text: no changes according to this comment.

Additional comment to the editor and reviewer:

Meanwhile the paper "Multiparametric cystoscopy: is the future here yet?" by Ahmadi and Daneshmand was published in TAU. We included this current paper that discusses potential and limitations of multispectral endoscopy in our introduction section (see page 7, line 138-140).