To Whom It May Concern,

The authors would like to thank the Reviewer for providing a thorough and invaluable feedback on the Manuscript. All points raised by the Reviewer are addressed below.

Q1 Missing citation are detected in Introduction. For example, para 1 line 2-12, para 2 line 5-9. In my opinion, citation is needed for such important points to avoid biasness in writing.

A1 Missing citations have been added to the manuscript.

Para 1 line 2-12:

2 Maurer CA, Renzulli P, Kull C, Kaser SA, Mazzucchelli L, Ulrich A, Buchler MW. The impact of the introduction of total mesorectal excision on local recurrence rate and survival in rectal cancer: long-term results. Ann Surg Oncol 2011; 18: 1899-1906 [PMID: 21298350 DOI: 10.1245/s10434-011-1571-0]

3 Swedish Rectal Cancer Trial, Cedermark B, Dahlberg M, Glimelius B, Pahlman L, Rutqvist LE, Wilking N. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997; 336: 980-987 [PMID: 9091798 DOI: 10.1056/NEJM199704033361402]

Para 2 line 5-9 has been re-written:

"The use of three-dimensional models, both virtual and 3D printed, presents the information obtained from the two-dimensional radiological images in a way that resembles the complex three-dimensional pelvic space encountered intraoperatively."

The phrase "more closely" has been removed to avoid biasness.

Q2 I suggest author to add another new section to explain in details the general processes and mechanisms for constructing the 3D model or images for application of rectal cancer surgery.

A2 A new section has been added and incorporated into the Discussion para 12-13 to explain the process of the construction of the 3D model through segmentation of a radiological image.

"The main factors that contribute to the slow uptake of the 3D modelling technology in rectal cancer surgery are related to the methodology of 3D image generation. 3D models are generated through the segmentation of a two-dimensional radiological image, which can be described as dividing an image into multiple labelled areas representing organs or tissues. Image segmentation relies on the principle that different tissues are characterised by specific range of pixel intensities. It can be performed manually, where each pixel of each slice of the radiological image is labelled manually, semi-automatically or fully automatically, where algorithms that recognise pixel distribution according to a pre-specified threshold are used.

3D modelling has an established role in surgical planning in maxillofacial, orthopaedic and liver surgery[3, 4]. Organs, such as bones and muscles, with large contrast between pixel intensities between different tissues on radiological images, lend themselves well to the automatic or semi-automatic segmentation. Radiological MR images of the pelvis require manual segmentation due to close proximity of pixels with similar intensity representing separate organs. This can be extremely labour- and time-consuming. Hamabe et al.[10] reported time of construction of virtual model of up to 40 hours, however, it did significantly decrease with experience."

Q3 Section of Results (from 1. feasibility of application of 3D modeling technology until 4. Surgical device design), throughout the text, it looks like a list of previous studies. No critical comments on literature are done by the authors. I suggest author to compare the advantages and drawbacks of previous studies and give some critical comments on the methodology and results of previous studies. For me, this is one of the major weakness of this manuscript.

A3 The authors have carefully considered this point of the reviewer's comments. The Results have been indeed presented as a list of studies identified in this

systematic review. For the descriptive purposes, they are grouped into four categories. Each study has been summarised to present its methodology and main findings.

The critical comments on the clinical significance have been provided throughout the Discussion. The methodology has been addressed in the Results – Study Characteristics, while the limitations of the methodology is addressed in the Discussion para 17.

Q4 Addition of figures from previous studies would make the manuscript more interesting.

A4 Unfortunately no high quality figures or figures adding value to the manuscript were available.

Q5 Section of discussion, Lack of discussion on future direction of three-dimensional modelling technology in rectal cancer surgery. I suggest authors to add recommendation on improvements of 3D modelling and printing for rectal cancer surgery.

A5 A new section has been added to the Discussion, para 18-22, to address the future direction and recommendations for the use of 3D modelling in rectal cancer surgery.

"The future directions of development of the 3D modelling technology in rectal cancer concluded from this review should focus on three main areas – improvement of the 3D modelling technology, validation of the technology and assessment of the benefits and limitations of its application in surgical practice. Firstly, the automation or semi-automation of the segmentation of the two-dimensional radiological image should be sought to reduce the time and workload required for the construction of the three-dimensional model. This can be achieved through the application of the artificial intelligence and machine learning algorithms.

Secondly, the fidelity of 3D models of rectal cancer and pelvis ought to be assessed through well-designed blinded studies validating the prediction of rectal cancer staging provided by the 3D model against the histological assessment of the surgical specimen. Similarly, the accuracy of the patient-specific pelvic anatomical information needs to be validated against the intra-operative findings.

Thirdly, the future randomised controlled studies are required to establish the impact of the application of 3D models on the surgical and oncological outcomes, compared to the established practice of the use of traditional two-dimensional radiological studies in the process of surgical planning. Well-designed multi-centre, randomised trials are required to assess whether there is a statistically significant difference in outcomes, such as surgical time, blood loss, complication rate, R0 resection, CRM, cancer recurrence rate or cancer-free survival, when the use of 3D models and 2D radiological images in operative planning are compared.

The current systematic review identified the need for the future exploration of the application of the three-dimensional models in surgical training. The two examples identified in this review[25,26] indicate a level of interest in this area and show a perceived and objective improvement in anatomical knowledge with the use of 3D models in normal pelvic anatomy and anatomy specifically relevant to LPLND. However, further well-designed randomised controlled studies are needed to establish the impact of the use of the three-dimensional models on the acquisition of pelvic and rectal anatomy understanding, as well as practical surgical skills relevant to the performance of surgical tasks during the rectal cancer surgery, such as TME procedure or minimally invasive rectal cancer approaches.

Lastly, the systematic review revealed the lack of application of 3D modelling technology in patient interaction. The future exploration of this technology needs to also focus on this aspect of the rectal cancer surgical care. It will be necessary to explore the possibility and the impact of the use of 3D models in the process of patient consultation, discussion of the treatment options and obtaining an informed consent.

The future exploration of the 3D modelling technology in rectal cancer surgery should also address the question whether the 3D printed models present any

additional benefits compared to the 3D virtual models. This will be relevant to all the fields of application of this technology – surgical planning and operative rehearsal, as well as in the acquisition of the anatomical knowledge or surgical skills, and in patient interaction. In parallel, the technological improvements in the 3D printing materials are required for the construction of clinically relevant 3D printed models and are expected to allow for the creation of physical models, which can more accurately resemble human tissues."

Q6 The conclusion is very weak and should be a little more detailed. Please rewrite it to reflect the content of current study.

A6 The conclusion has been revised and re-written to reflect the content of the study.

"The systematic review provides a complete, practical and comprehensive review of the current role of 3D modelling in rectal cancer surgery. It identifies the main areas of interest in this novel approach to patient-tailored image-guided surgery for rectal cancer, and it demonstrates its limitations and directions for the future development and research.

There is an increasing interest in the application of 3D modelling technology in surgical planning and navigation, as well as education, within the realm of rectal cancer surgery. The sixteen studies identified in the review were largely represented by the feasibility or pilot studies, suggesting the relative infancy of the application of this technology in rectal cancer surgery and the need for further research to evaluate its benefits and limitations in clinical practice.

3D modelling can be applied to construct the three-dimensional models, both virtual and physical, of normal pelvic and rectal anatomy, as well as different stages of rectal cancer, including those invading other pelvic structures. 3D models can be applied in surgical planning and navigation in TME, TaTME, beyond-TME surgery or lateral pelvic lymph node dissection. They have been showed to improve perceived and objective anatomical knowledge relevant to rectal cancer surgery.

However, thus far, 3D models of rectal cancer have not been employed in the patient education or interaction.

Further developments in the 3D modelling methodology and technological developments in 3D printing, as well as future well-designed randomised controlled trials, are necessary for the 3D modelling technology to become clinically applicable in rectal cancer surgery."