

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Laparoscopic lateral lymph node dissection in two fascial spaces for locally advanced lower rectal cancer" (No.: 61575). These comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our research. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the comments are as follow:

Responds to the Reviewers' comments:

Reviewer #1:

Comment: Your study was very interesting as it confirmed the anatomy with cadaver. The concept of two-space anatomy, formed by urogenital fascia and vesicohypogastric fascia in the lateral lymph node region, is not a new method in LLND, but a standard operating technique. How did you perform LLND so far? Is it possible to compare the surgical results with the previous method and this method?

Response to comment: Special thanks to you for your good comment. By cadaveric dissection, we found that urogenital fascia, vesicohypogastric fascia and parietal fascia lie side by side and formed two spaces (Latzko's pararectal space and paravesical space) which were the surgical area for LLND. From July 2018 to October 2020, we have performed laparoscopic LLND in two fascial spaces successfully in 20 patients, and the preliminary results showed that it was a feasible and safe surgical approach. With the accumulation of surgical experience, the operating time has been reduced from 243 minutes at the beginning to about 150 minutes now.

In this study, we focus on the introduction of this new technique. As the sample size of this study is small and the follow-up time is short, at this stage, it may not be

appropriate to compare the surgical results with the previous method (a Japanese clinical trial -JCOG2012 showed that urinary dysfunction and postoperative complications occurred in 59% and 5% of patients, respectively). Over the next year, we plan to enroll another 30 patients, and make a full evaluation, including disease-free survival, postoperative complications, postoperative urination function and sexual function. Then we can make a full comparison with the previous method. In addition, as mentioned in Comment 4, whether inferior vesical artery (IVA) should be removed in LLND is an important research topic we are exploring. We believe that, with the progress of our study and the increase of operations, the surgical procedure will be further optimized and popularized in the clinic.

Reviewer #2:

Comment: I read the paper very carefully and I would like to congratulate the author on a job well done. This topic is extremely interesting and controversial, which per se should be considered as publishable material after minor revision.

Response to comment: We appreciate you for carefully and patiently reviewing our manuscript. We have made correction carefully according to the reviewers' comments. In addition, the manuscript has been revised by someone with expertise in technical English editing. We hope that the language is now acceptable for the next review process.

Reviewer #3: I really appreciate you giving me an opportunity to review an interesting manuscript regarding laparoscopic lateral lymph node dissection. Although this paper is well written especially in detailed intra-pelvic anatomy, there are concerns as follows.

Comment 1: In current series, uni-LLND was performed in all patients with locally advanced lower rectal cancer although there should be a certain number of patients who had whole or semi-whole circumferential lesions. The authors should show persuasive reasons for not performing bilateral lymph node dissection.

Response to comment 1: Thanks a lot for your good suggestions. All patients

underwent pelvic MRI examination before surgery to detect lateral lymph node (LLN) enlargement (the largest short diameter > 7 mm). In this study, all 20 patients showed uni-LLN enlargement, and no bilateral LLN enlargement was found. So, uni-LLND was performed. In other words, the selection of either uni- or bilateral LLND is decided according to the preoperative MRI result; it's not that we don't perform bilateral LLND. In the last month, we performed two LLNDs, including one bilateral LLND.

Comment 2: I consider that about 3 hours of time requiring for uni-LLND is a bit too long, while the number of dissected lymph node and the blood loss volume were seemed to be acceptable. Please show the author's future perspective of shortening the operative time.

Response to comment 2: We performed the first LLND operation in July 2018, and it took 243 minutes to finish. With the accumulation of surgical experience, the operating time for uni-LLND has been reduced to about 150 minutes. In addition, as you mentioned in Comment 4, the inferior vesical artery (IVA) was preserved in these 20 patients (as the removal may affect postoperative urination function), but the lymph nodes located along IVA were cleaned up. This delicate surgical procedure took about 20 minutes to complete. In a recent operation, we started trying to sever IVA and found that the postoperative urination function was not affected. If our further study confirms this finding, it means that IVA can be routinely removed in LLND, and it also means that the operating time can be further reduced. We believe that, with the optimization of surgical procedures, LLND in two fascial space will be faster and safer.

Comment 3: Detailed postoperative complications not only for lateral lymph node dissection alone but for overall operative procedures of rectal cancer based on Clavien-Dindo classification should be demonstrated.

Response to comment 3: Many thanks for your positive comment. It should be pointed out that we are not just reporting postoperative complications for LLND, but

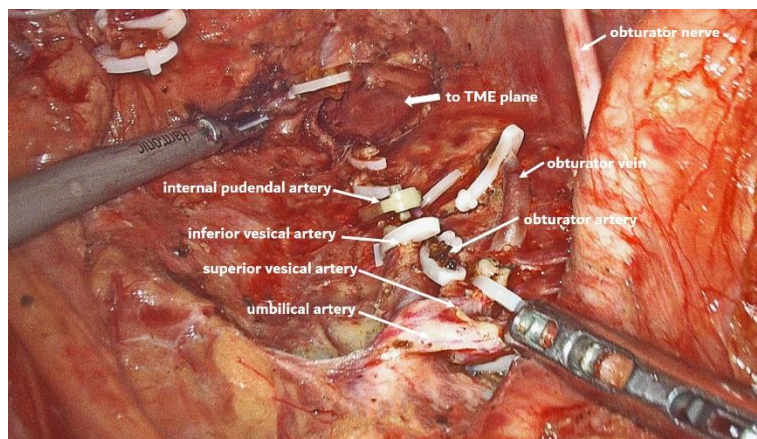
all complications for overall operative procedures (laparoscopic TME plus LLND). We reviewed the original medical records of these 20 patients, and made sure that no other postoperative complication was observed. We have made a more detailed description in the revised manuscript, as described below: Postoperative complications included lymph leakage in 1 case and lower limb pain in 1 case (grade I based on Clavien-Dindo classification). No other postoperative complication was observed. The former was cured after fasting for 4 days, and the latter resolved spontaneously 1 month after hospital discharge.

Comment 4: In your procedure of LLND, the inferior vesical artery (IVA) is routinely preserved although you mentioned that this area was a common site for internal iliac lymph node metastasis. I am believing that the IVA should not be preserved to achieve an enough radically. Please discuss this issue.

Response to comment 4: In the book of “Laparoscopic Lateral Pelvic Lymph Node Dissection”, Konishi T suggested that the inferior vesical artery (IVA) is a common site for internal iliac lymph node metastasis. Miki J et al also indicated that IVA was one of the two predominant sites for sentinel lymph nodes based on patterns of pelvic lymphatic drainage (DOI: 10.1002/pros.23486). However, it is still controversial whether IVA should be removed in LLND, mainly because the removal may affect postoperative urination function. As a result, in this study, IVA was preserved in all 20 patients, but the lymph nodes located along IVA were cleaned up. Recently, we have followed up 7 patients to assess the urination function (by IPSS score) one year after surgery, and found that their urination function was negatively affected compared with that before surgery.

Actually, whether IVA should be removed in LLND is an important research topic we are exploring. In a recent operation, all the branches from the internal iliac vessels were severed at their origins, including umbilical artery, superior vesical artery, inferior vesical artery, internal pudendal artery and obturator vessels (as shown in the following figure). Interestingly, this patient did not show any discomfort in urination

after surgery. It suggested that the removal of IVA might not affect urination. However, a controlled prospective study is required to pursue this initial observation. Hopefully, we could give an answer in 1-2 years.



Comment 5: If I understand your manuscript correctly, the lateral border of the Latzko space was not demonstrated. Are the umbilical artery and the vesical artery included in the Latzko space? In my understanding, the Latzko space is bordered with the vesicohypogastric fascia as well as the para-vesical space.

Response to comment 5: As shown in Figure 9C, from the perspective of “fascia anatomy”, Okabayashi's pararectal space is the space between the fascia propria of the rectum and the urogenital fascia; Latzko's pararectal space is the space between the urogenital fascia and vesicohypogastric fascia; and the paravesical space is the space between the vesicohypogastric fascia and parietal fascia. Latzko's pararectal space and paravesical space were the surgical area for LLND.

As shown in Figure 8 and 9, the vesicohypogastric fascia is a triangle-shaped structure, and its boundaries are formed by the umbilical artery, the tendinous arch of the pelvic fascia and the lateral surface of the bladder. As the inferior vesical artery (IVA) is located near to the tendinous arch of the pelvic fascia, IVA can also be deemed as the base of this triangle. So, strictly speaking, the umbilical artery and IVA are the boundaries of the vesicohypogastric fascia, but not included in the Latzko's pararectal space.

Figure 8 The vesicohypogastric fascia is a triangular fascia composed of umbilical artery, tendinous arch of pelvic fascia and bladder (red shadow). The urogenital fascia (yellow shadow) and the vesicohypogastric fascia blend with each other and appear as a V-shape (yellow dotted line). The ureter is pulled up and the actual position is shown in blue shadow.

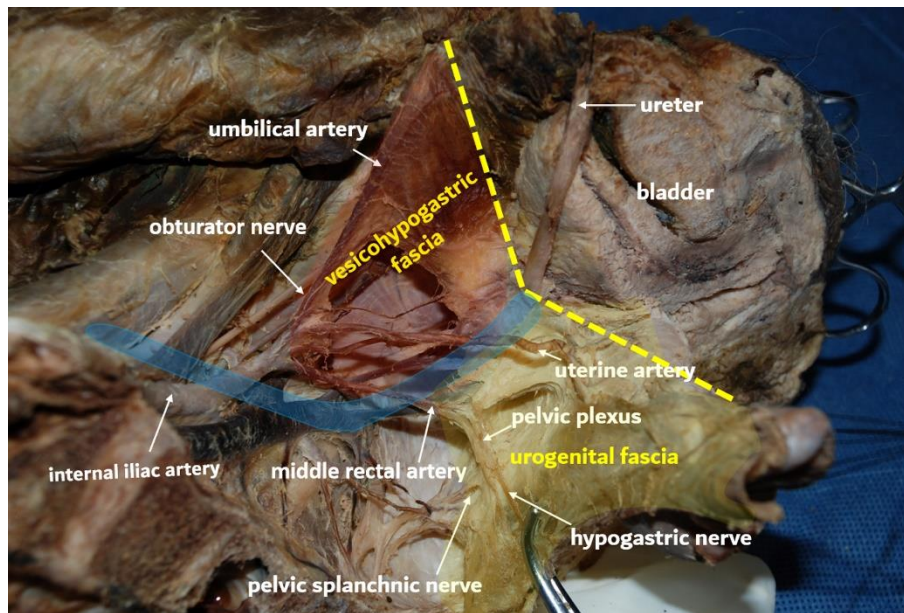
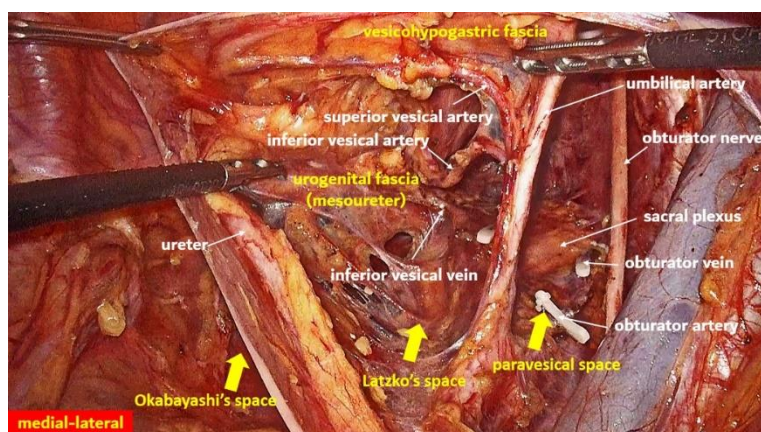
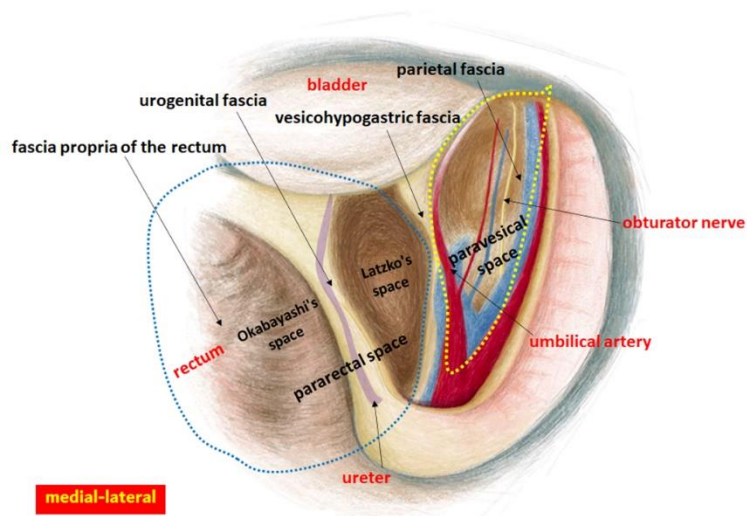
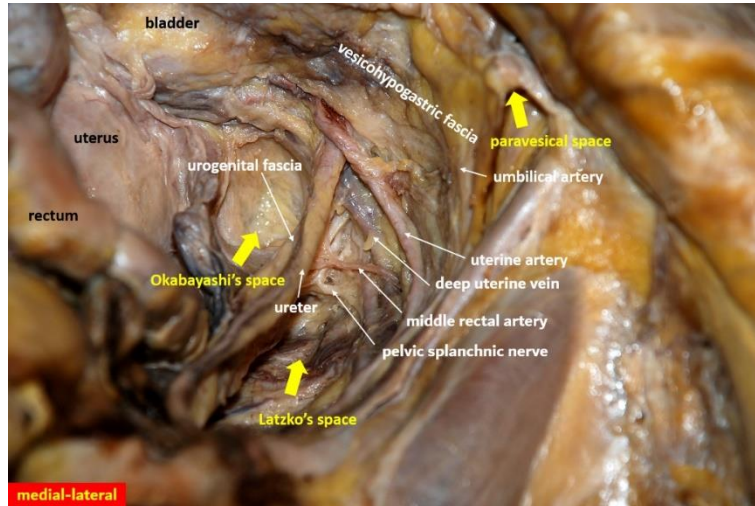


Figure 9 The fascial spaces related to rectal cancer surgery are showed in photograph of operation (A), photograph of cadaver dissection (B) and diagram (C). The pararectal space (blue dotted line) can be divided into Okabayashi's space and Latzko's space. Fascia propria of the rectum, urogenital fascia, vesicohypogastric fascia and parietal fascia form Okabayashi's, Latzko's space and paravesical space (yellow dotted line). The last two spaces are the surgical area for LLND.





We appreciate for Editors and Reviewers' warm work earnestly, and hope that the revised version will be acceptable for publication in "Oncotarget".

Once again, thank you very much for your comments and suggestions. We look forward to your reply about our revised paper.

Yours sincerely,

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