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Forum

Can minimally invasive surgery still be done for cervical cancer patients considering the LACC trial?

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1. Background

For the past several decades, minimally invasive surgery (MIS) has been advantageous for the treatment of cervical cancer compared to open surgery. MIS is favored due to reduced blood loss, decreased post-operative complications, rapid recovery, and shorter hospitalization time. In 2018, results from the Laparoscopic Approach to Cervical Cancer (LACC) trial, an international multicenter randomized phase III trial of women with early-stage cervical cancer comparing the survival outcomes among different surgical approaches[1] and a real-world study published in the New England Journal of Medicine,[2] showed that patients with early-stage cervical cancer undergoing minimally invasive radical hysterectomy have a lower rate of progression-free survival and overall survival (OS) than those who undergo an abdominal radical hysterectomy. As a result, the latest National Comprehensive Cancer Network (NCCN) guidelines no longer suggest minimally invasive radical hysterectomy, but rather open surgery as the standard approach. Though the results were in contradiction with most surgeons' experiences, more surgeons tend to perform the laparotomy approach of radical hysterectomy in cervical cancer patients to avoid legal problems. Nonetheless, more researchers are seeking new evidence to verify the feasibility of and find a way to reestablish the MIS approach in cervical cancer patients. Literature has reported no significant differences in survival between different surgical approaches in early cervical cancer patients without risk factors. Additionally, surgeons are improving their techniques such as avoiding using a manipulator which may raise potential risk of tumor spread and performing a transvaginal closure or vaginal cerclage of the cervix isolating the tumor.

To discuss in depth the controversial use of MIS for cervical cancer, the International Society of Gynecological Endoscopy (ISGE) and Peking University (PKU) jointly organized the virtual symposium on minimally invasive surgery for cervical cancer on June 19th, 2021.

Dr. Jianliu Wang, president of the forum, and Dr. Jianming Song, chair of ISGE China Effort, jointly moderated the meeting. Numerous

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experts from China, Europe, the United Kingdom, and the United States attended virtually to discuss the contrasting studies in depth concerning MIS for cervical cancer and the issues involved on how to improve the MIS approach in these situations.

2. Expert lectures

Dr. Samar Nahas, Chair of the Department of OB&GYN/Division Director of Gynecologic Oncology and Minimally Invasive Surgery at the University of California Riverside, was invited to present the "Current status and future prospect of minimally invasive surgery for cervical cancer in the United State-in the light of LACC trial".

Dr. Nahas first reviewed the history of abdominal radical hysterectomy, radical trachelectomy, and vaginal radical hysterectomy. A meta-analysis confirmed no oncologic safety differences between vaginal radical trachelectomy and vaginal radical hysterectomy. Given that studies have found that the rate of parametrial invasion in patients with tumors less than 2 cm occurs in less than 1% of patients, simple trachelectomy has been shown to promote comparable survival rates to radical trachelectomy in many studies.[3,4] When laparoscopic radical hysterectomy was developed, researchers began to compare three techniques of radical hysterectomy (abdominal, laparoscopic, and robotic) and found that minimally invasive surgery may be a more effective and safer option for the surgical treatment of early-stage cervical cancer. Then, Dr. Nahas reviewed the results of the LACC trial which caused a significant debate amongst the crowd and provoked a significant switch to favor open surgery in the academic world. Even though the results were inconsistent with surgeons' own experiences and literature, it was hard to defend personal experience in the face of the randomized trial, particularly in the face of conflicts concerning medical insurance and lawsuit. The debates on the LACC trial were mainly focused on the quality of the study such as the surgeon's qualification and the quality control of surgery. The current consensus amongst the audience concerning the LACC trial was that the issue cannot be definitively settled until another prospective randomized trial that includes single pathologist review, preoperative MRI, parametrical measurements, and quality indicators of radical hysterectomy is performed on a sufficient number of patients. Additionally, well-trained, certified gynecologic oncologists will have to be selected to conduct such a trial. Furthermore, if MIS is performed, in-depth counseling and consultation with the patients before the surgery is necessary.

Dr. Zhiqing Liang of Southwest Hospital of Army Medical University (AMU) presented the Chinese colleagues' opinion of MIS for cervical cancer based on data analysis of Chinese multi-center and technology improvement. His team's study showed promising results in OS rates in local advanced-stage patients when using laparoscopic radical hysterectomy and lymphadenectomy for cervical cancer.[5,6] He believes that the key point of laparoscopic surgery, in such a case, is the transection of the vagina with a cold knife and the removal of the specimen through the vagina. These results have been supported by studies in other countries. In 2015, a systematic review[7] found that though laparoscopic surgeries required a longer time to perform, there is less blood loss and a more rapid recovery. In 2020, Chinese experts retrospectively compared the long-term oncological outcomes between laparoscopic and abdominal surgery in stage IA1 (lymph-vascular space invasion-positive, LVSI positive) to IB1 cervical cancer patients with different tumor sizes in 4891 patients from 2009 to 2016.[8] They found that the modified laparoscopic-vaginal radical hysterectomy demonstrates a significantly better OS rate at 5 years (96.1%) compared to 92% for the total laparoscopic surgery. Furthermore, the disease-free survival (DFS) rate at 5 years of stage IB1 was 98.6% in the modified laparoscopic-vaginal radical hysterectomy group, which is significantly higher than that of the laparoscopic radical hysterectomy. Dr. Liang then pointed out that the DFS and OS differences found in LACC trials are secondary endpoints and should be considered tentative. An additional randomized trial should be required to determine the efficacy of minimally invasive radical hysterectomy in cervical cancer patients. Lastly, he pointed out the principle of tumor-free surgery should be adapted up to the end of the operation. He suggested some technological improvements focusing on tumor-free surgery as follows.

1. The operation procedure in LACC was to transect the vagina completely during the laparoscopy, which will inevitably lead to tumor cell spreading and also spilling into the pelvic cavity, which might be the primary reason for pelvic recurrence. It is suggested that lymphadenectomy and para-uterine tissue dissection should be completed by laparoscopy and that the hysterectomy and vaginal opening should be performed transvaginally to avoid tumor cell spread.
2. Using a uterine manipulator will damage the epithelial cell layer of the vagina and make it easier for the detached tumor cells to implant in the vaginal mucosa. Also, tumor cells may be stimulated by the force applied on the manipulator and thus be squeezed into the interstitial vessels of the cervix, causing the tumor to spread. Vaginal closure or vaginal cerclage may be an improved technique.
3. The enlarged lymph nodes should be removed completely to assure the integrity of the tumoral tissue.
4. If necessary, one should be advised to wash the abdominal cavity and trocar sites with chemotherapy drugs and to clean the vagina with distilled water or cisplatin after suturing the vagina.

Dr. Sichen Liang from Peking University People's Hospital showed data derived from their retrospective study[9] comparing laparoscopy and open surgery in 237 patients with locally advanced cervical cancer from 2009 to 2018. With similar baseline and clinical-pathological features in the two different surgical approaches, there were no significant differences in the complications which commonly consisted of urinary retention, urinary system injury, hydronephrosis, intestinal injury, intestinal obstruction, hernia, lymphocyst, lymphedema of lower limbs, thrombotic diseases, and infections. The 5-year OS rates of the laparoscopy group and the laparotomy group were 86.8% and 87.8%, respectively, and the 5-year tumor-free survival rates were 81.7% and 84.6%, respectively, with no significant differences. During the follow-up period, the recurrence rate in the laparoscopy and the laparotomy group were 15.7% and 12.3%, without significant differences. Dr. Liang's team concluded that the prognosis between laparoscopic surgery and open surgery in locally advanced cervical cancer patients with stage IB2 to IIA2 did not appear to be significantly different.

Dr. Sha Wang from Peking University People's Hospital presented another study[10] on comparing pelvic floor dysfunction and quality of life (QoL) between laparoscopic and abdominal radical hysterectomy in cervical cancer patients at Peking University People's Hospital. 150 patients who underwent radical hysterectomy with either laparoscopic hysterectomy (LRH) or abdominal approach (ARH) were included. The validated versions of the pelvic floor distress inventory-short form 20 (PFDI-20), the overactive bladder symptom score (OABss), and the Euro quality of life five dimensions questionnaire (EQ-5D) system were used in detailed evaluation of postoperative lower urinary tract symptom (LUTS), anal distress, and QoL. The results showed that there were significant differences in the total score of PFDI-20 and OABss between the LRH group and the ARH group ($P < 0.05$). Patients who underwent LRH suffered from more severe symptoms of LUTS and anal distress. There were no significant differences in the EQ-5D scores between the two groups ($P < 0.05$). Multiple analyses confirmed that LRH was a risk factor for LUTS and OAB after controlling for other factors. LRH was also a risk factor for anal distress based on colorectal-anal distress inventory (CRADI) scores. They concluded that compared to abdominal surgery, the laparoscopic approach seems to increase postoperative distress concerning the lower urinary tract and defecation. Therefore, the overall conclusion is that laparoscopic surgery should be carefully selected in clinical practice.

3. Participant discussions

After the lectures, the attendees shared ideas on the significance and weaknesses of the LACC trial and raised possible suggestions to improve our clinical management.

Dr. Bruno J. van Herendael, Medical Director of ISGE, pointed out that in LACC trial, experienced oncologic surgeons should have been selected to conduct the trial. Laparoscopy gives a surgeon better vision during surgery. We may find superiority in the laparoscopy procedure with a well-designed randomized trial.

Dr. Adel Shervin, Ex-Director of the Accreditation Council of ISGE, suggested that we should not ignore the dark side of laparoscopy and find solutions to such problems, such as the effect of CO_2 pneumoperitoneum on tumor growth and metastasis.

Dr. Guenter Noe, the Vice President of ISGE, stated that a single randomized controlled trial (RCT) should not have such a strong influence on medical procedures. He also reiterated Dr. Van Herendael's point of needing to design a more scientific trial with experienced oncologic surgeons.

Dr. Omer Devaja, Director of National Health Service (NHS) gynecological oncology training in the UK, shared his experience. At his center, simple hysterectomy and radical hysterectomy are equally efficient for tumors under 2 cm. Therefore, a prospective single-center trial might give more information than a multi-center trial because surgeons have different skillsets and potentially different practices.

Dr. Jvan Casarin from Italy stated that laparoscopic surgery does have some risks and doctors should modify the technique.

Dr. Yang Xiang from Peking Union Medical College Hospital pointed out that doctors should learn from the LACC trial, be aware of the tumor-free concept in laparoscopic surgery and modify the technique in some ways such as abandoning the use of the uterine manipulator. In addition, future clinical practice should be based on the results of well-designed RCT trials, some of which are still ongoing in many hospitals in China.

Dr. Zeyi Cao made a short conclusion about the stand of the Chinese doctors' opinion concerning laparoscopic surgeries in cervical cancer cases. He stated that the MIS approach still has advantages for low-risk patients. It is the obligation of doctors to ensure that patients are fully aware of the pros and cons of both approaches.

4. Summary

The experts from panel discussions expressed that although the LACC trial was evidence-based, consists of selected low-risk patients, and required fully informed consent of the surgery and careful operation, there is still space for laparoscopy in the treatment of cervical cancer. However, in most Western countries, the costs sustained for the robotic assisted laparoscopic surgery are no longer covered by insurance companies for cervical cancer patients. Furthermore, after being fully informed about the evidence-based potential risks of laparoscopic surgery, most patients preferred open surgery.

In conclusion, experts in the meeting agreed that one RCT should not necessarily lead to a change in practice and MIS should not be abandoned as an "all-or-nothing" change. Several steps need to be taken into consideration when MIS is being performed for cervical cancer patients. First, subspecialized training in gynecologic oncology is required for surgeons to perform MIS for cervical cancer. Second, only by conducting another prospective randomized trial that includes a single pathologist review, preoperative MRI, parametrical measurements, quality indicators of radical hysterectomy, and unified criteria for the performance of different extents of surgeries can surgeons draw conclusions in the matter.[11] Thirdly, MIS may be offered in properly-selected patients based on past experiences and qualifications such as low-risk level (tumor diameter less than 2 cm, depth of invasion less than 1 cm, without lymph node metastasis, or lymph vascular space invasion, and a well-differentiated pathologic type) early-stage patients.

Participants of discussion (*listed in alphabetic order of the surnames*)

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Declaration of competing interest

The authors have no conflicts of interest to disclose.

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