

Expert Opinion



How should gynecologic oncologists react to the unexpected results of LACC trial?

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Conflict of Interest

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In March, the results of the Laparoscopic Approach to Carcinoma of the Cervix (LACC) trial were announced at the 2018 Society of Gynecologic Oncology (SGO) annual meeting, bringing in a significant wave. Minimally invasive surgery has been shown to have better surgical outcomes with equivalent survival rates in patients with endometrial, colorectal, and gastric cancer in previous randomized controlled trials [1-4]. It was expected that the same result would be obtained in cervical cancer, but the disease-free survival and overall survival rate of minimally invasive radical hysterectomy (MIS RH) surgery group was significantly lower than that of open radical hysterectomy (ORH) surgery in LACC trial. In the retrospective analysis using National Cancer Institute (NCI)'s Surveillance, Epidemiology, and End Results (SEER) data in the US, the introduction of MIS was associated with an increase in the mortality rate due to cervical cancer, thus further strengthening the results of the LACC trial. These results have already been published outside the medical community, will affect the practice of gynecologic oncologists, and are likely to change the treatment guideline of cervical cancer. However, before accepting the results of the LACC trial, we must go through a lot of important things that were not considered and controlled, and thus biased the results in the LACC trial and the analysis using NCI's SEER data in the US.

The first problem is that the survival rate of the open surgery group was too good and much higher than that reported previously. Only 7 of 319 (2.2%) patients in open surgery group had recurrence in the LACC trial. In previous large studies with long term follow-up, the recurrence rate after ORH for stage IA2-IB1 cervical cancer is about 10% [5]. The reason for low recurrence rate in the LACC trial should be explained. Short follow-up time of the LACC trial may be one of the reasons. The duration of follow-up time in this trial ranged between 0 to 75 months. It should be reevaluated after at least more than 2 years of follow-up from now on.

Second, the high recurrence rate of the MIS group may be due to surgical technique or carelessness of the operator, not because of the MIS itself. In the case of cervical cancer, the use of uterine manipulator during MIS RH causes tumor injuries and tends to break tumors. Therefore, if the vagina is cut in the pelvic cavity, broken tumor fragments may flow into the pelvic and abdominal cavity and peritoneal seeding may occur. Because the patient has a stiff trendelenburg down position during MIS RH, the tumor spillage into the pelvic and abdominal cavity becomes worse. Intracorporeal colpotomy under CO₂ pneumoperitoneum was an independent risk factor for recurrence after MIS RH in previous studies [6,7]. In these cases, recurrence usually occurs in the form of peritoneal seeding in the pelvis and occurs

shortly after surgery. In LACC trial, this factor was not considered and the recurrences after MIS RH were mainly pelvic recurrences which were occurred shortly after surgery. In order to reduce the incidence of peritoneal seeding from broken tumor fragments during MIS RH, the stiff trendelenburg down position should be changed to supine position and vaginal cuff resection and repair should be performed with vaginal approach. Irrigation of vagina and pelvic cavity should be performed rigorously before repairing the vaginal stump.

Third problem is the surgeon proficiency for MIS RH in LACC trial. The surgeon proficiency criteria for MIS RH in the LACC trial was only 10 cases. However, the grounds for this criteria are insufficient. The well-known disadvantage of laparoscopic surgery is the difficulty in learning, and the learning curve for laparoscopic radical hysterectomy (LRH) is especially very long because of the complexity of surgical procedure. For good operative outcomes, the surgical proficiency may be achieved with 30 to 40 cases if the surgeon is good at ORH and has some experience in laparoscopic surgery. However, to achieve enough radicality and sufficient oncologic outcomes, over 40–50 cases are required for surgical proficiency [8,9]. In our initial experience, the resected parametrial tissue size in LRH was smaller than that of ORH [10]. The recurrence rate after LRH was equivalent only for small tumor less than 2 cm [10]. The recurrence rate was significantly higher for LRH in tumor larger than 2 cm [10]. After around 50 cases of LRH, the recurrence rate in larger tumor was the same between LRH and ORH. Even after 100 cases of LRH, the recurrence rate decreased further. Robotic radical hysterectomy (RRH) is easier to learn, but surgeon proficiency criteria for sufficient oncologic outcomes will be similar to LRH [11]. There is a high probability that the radicality of surgery is not fully achieved through MIS in LACC trial.

Fourth problem is that the results of subgroup analysis have not been reported. This analysis should be performed to determine which group has higher recurrence rate after MIS RH. This should include tumor size, stage, histology, surgery type (type II vs. III radical hysterectomy), surgeons' experience, and nationality or ethnicity, etc.

Fifth problem is that the participation in countries where MIS RH has become surgery of choice has been low. In countries where MIS RH has already been recognized as an operation that should be selected first, most of the patients assigned to ORH withdrew their participation in the study.

In conclusion, the report of outcomes in this trial is too early, and it should be reevaluated after at least 2 years. The poor survival outcome of the MIS RH group is not a problem of the MIS itself, but is probably due to the inadequate control of the operator and the surgical technique in LACC trial. Therefore, a new study which is controlled for these factors is needed.

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