

Editorial

Reconsider the safety of laparoscopic surgery in endometrial cancer



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General introduction

The 20th century witnessed the development of laparoscopic surgical technologies and its successful applications in gynecological and general surgeries. In 1901, Russian doctor Dimitri Ott, for the first time, inspected the human abdominal cavity with a speculum through a small incision, which marked the origin of the concept of minimally invasive techniques.¹ During the following decades, clinical diagnosis of intra-abdominal lesions was performed by some doctors in Europe and the U.S. with instruments similar to modern laparoscopy. But it was until 1980s that modern-sense laparoscopic surgeries, including laparoscopic appendectomy and laparoscopic cholecystectomy, were conducted.^{2,3} In 1989, Dr. Reich Harry performed the first laparoscopic hysterectomy,⁴ which is regarded as a cornerstone in the history of gynecologic surgery. Afterwards, laparoscopic surgery rapidly stepped into the mainstream of gynecology practice during the 1990s, delivered for both benign and malignant diseases. Starting from the 2000s, the master-slave mode robotic system, exemplified by the da Vinci® robot, has been accepted worldwide, and currently, robot-assisted laparoscopic approaches have taken up a major proportion of general, urologic and gynecologic surgeries, especially in developed countries.⁵ From a historical perspective, the broad application of laparoscopic surgeries nowadays stands on solid foundations established in decades of technical revolutions and refinements.

Application of laparoscopic surgery in endometrial cancer treatment

During the past two decades, the safety of laparoscopic surgery for oncological treatment has been evaluated. Some studies, including several prospective clinical trials, have been conducted to assess the short-term and long-term safety of laparoscopic surgery in endometrial cancer. Two largest clinical trials, the Gynecologic Oncology Group (GOG) LAP2 trial and the Laparoscopic Approach to Cancer of the Endometrium (LACE) trial both concluded that laparoscopic surgery was

non-inferior comparing with open surgery in terms of long-term survival in treating early-stage endometrial cancer.^{6,7} In the LAP2 trial, a total of 2616 stage I-IIA endometrial cancer patients were included (1696 in the laparoscopic surgery group and 920 in the open surgery group). The three-year recurrence rate was similar between the two groups (11.39% in the laparoscopy group vs 10.24% in the laparotomy group; the difference falls within the noninferiority bound of 5.3%). And both groups showed a five-year survival rate of 89.8%.⁶ In the other international multi-center study, the LACE trial, both disease-free and overall survival were similar between stage I endometrioid endometrial cancer patients receiving laparoscopic and abdominal hysterectomy.⁷ Besides, in both trials, the post-operative complications were significantly fewer in the laparoscopy group.^{8,9} These results were further confirmed by a meta-analysis of 9 randomized controlled trials.¹⁰

Notably, in the LAP2 trial, 492 patients of non-endometrioid subtypes were included. In subgroup analyses, laparoscopic surgery did not bring additional survival risk in any of these subgroups, yet the sample size was relatively small for each subgroup (ranging from 42 to 289).⁶ Recently, a retrospective study based on the National Cancer Database (NCDB) including 6981 non-endometrioid endometrial cancer patients proved that in all pathological subtypes (including serous, clear cell, carcinosarcoma, etc.) the survival outcome after two surgical approaches was similar.¹¹ Based on all the evidences above, a general consensus of adopting laparoscopic surgery for treating early-stage endometrial cancer was reached in the gynecologic oncology community globally, considering its acceptable long-term safety and relative advantages.

New concerns about the safety of laparoscopic surgery

With emerging new evidences, especially after the publication of the Laparoscopic Approach to Cervical Cancer (LACC) Trial data,¹² more concerns about laparoscopic surgeries were brought out to the gynecologic oncology community, leading to the reconsideration of its clinical applications. In the LACC trial, a higher risk of recurrence was noted in

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the laparoscopic surgery cohort compared with the open surgery cohort for early-stage cervical cancer patients. There are several reasons proposed to account for that. First, the influence of uterine manipulator and insufflation gas may promote the intraperitoneal seeding of tumor cells.^{12,13} In a recent large-sample retrospective study from European countries (the Surgery in Cervical Cancer, Observational, Retrospective [SUCCOR] study), the application of uterine manipulator was associated with a significantly higher risk of relapse in early-stage cervical cancer patients undergoing laparoscopic surgery.¹⁴ Second, the method of colpotomy in laparoscopic surgery, which is thought to enhance the chance of intraperitoneal tumor exposure, may also facilitate tumor relapse.^{12,13} Indeed, in the SUCCOR study, the recurrence rate was significantly lower in patients receiving laparoscopic surgery with vaginal closure compared to those without.¹⁴ Finally, the qualification of cancer centers and surgeons' learning curve for laparoscopic radical hysterectomy procedures could also influence the prognostic outcome.^{15–17} Recently, more retrospective studies from American, European and Asian hospitals also supported the superiority of open surgery in early-stage cervical cancer treatment,^{18–21} and this result was further proved by a meta-analysis of 15 observational studies including cases ranging from International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IA1 to IIA.²² All the above evidences urged the modification of the National Comprehensive Cancer Network (NCCN) guideline to adopt open abdominal radical hysterectomy as the standard approach of care for early-stage cervical cancer.²³

These study results also led us to reconsider the safety of laparoscopic surgery in endometrial cancer. Indeed, there are emerging evidences showing that laparoscopic surgery was associated with more rapid recurrence in certain endometrial cancer subgroups,^{24–27} as shown in Table 1. Thus, could the factors mentioned above also influence the safety of endometrial cancer patients receiving minimally invasive surgery? Mechanistically, uterine manipulators used during surgeries could also have direct contact with the endometrium and the tumor, which might facilitate peritoneal tumor dissemination through the fallopian tube or lymphovascular space invasion. But currently, only retrospective data are available, with conflicting results about such putative associations.^{28–30} In addition, there are still controversies regarding the effect of uterine manipulator on endometrial cancer patients' prognosis.^{31,32} In a retrospective multicenter study by Uccella et al.,³¹ the use of uterine manipulator did not show significant influence on patients' prognosis. However, in a more recent study by Padilla-Iserte et al.,³² which included a larger cohort (2661 cases from 15 centers), the uterine manipulator group showed worse disease-free and overall survival. Specifically, the difference in survival was significant only in stage I-II patients, and the most common recurrence patterns included peritoneal

carcinomatosis and visceral metastasis. This is possibly through peritoneal seeding via the fallopian tube, or due to the disruption of normal uterine wall structure. While in stage III patients, in which case extra-uterine disease already existed, such effects might be less prominent. Nevertheless, all these results are based on retrospective studies. More prospective clinical trials are needed to address this issue.

Another concern regarding laparoscopic surgery is the efficacy of radiation therapy delivered after surgery. In a recent study by Kim et al.,²⁷ for stage II endometrial cancer patients, the recurrence rate was significantly higher in the laparoscopic surgery group than in the open surgery group (37.5% vs. 5.3%, $p = 0.013$). In the study, a higher rate of postoperative radiation therapy was observed in the open surgery group (84.2% vs. 66.2%, $p = 0.006$). However, in the open surgery group, there were more other risk factors including larger tumor size and higher rate of lymphovascular space invasion, which may also influence the clinical decision of radiation therapy delivery. Recently, there are some other evidences that may provide mechanical explanations. In some studies, robot-assisted hysterectomy is found to be associated with a higher risk of vaginal cuff dehiscence, which may cause a prolonged interval between surgery and initiation of postoperative radiation therapy.^{24,33} And an interval beyond 8 or 9 weeks was proved to be associated with a higher risk of disease recurrence in endometrial cancer.^{34,35} In a recent retrospective study by Song et al.,²⁴ the survival after robotic surgery and open surgery was compared. The results indicated that robotic surgery was associated with a higher recurrence rate in intermediate-risk endometrial cancer, since all 8 recurrent cases in this 135-case cohort were from the robotic surgery group. In this study, the median time interval to postoperative radiation was 19 days longer in the robotic surgery group than that in the open surgery group (85 days vs. 66 days), which may partly explain the results.²⁴ However, more studies are needed to support such speculations.

Suggestions for surgical approach selection in endometrial cancer

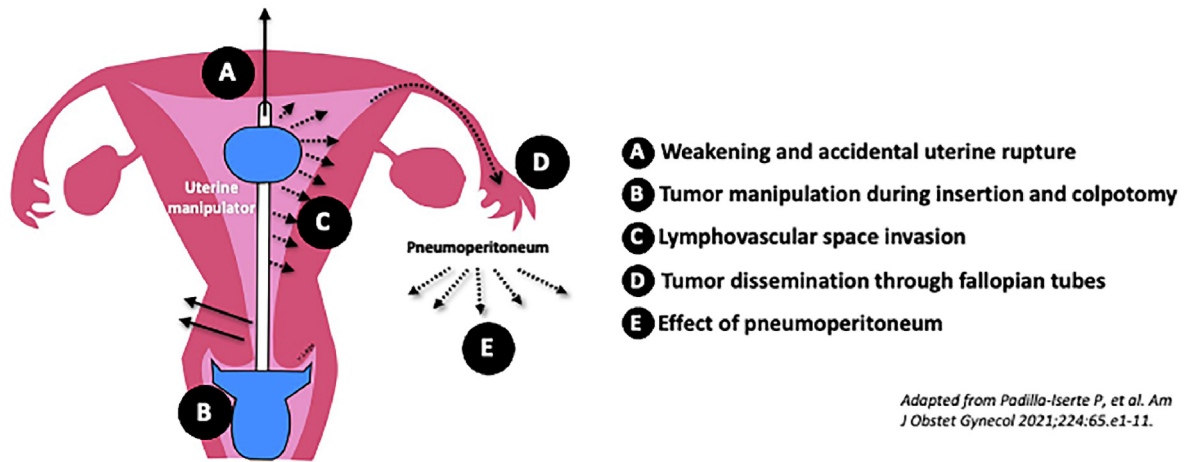
Since the publication of the molecular subtypes of endometrial cancer by the Cancer Genome Atlas (TCGA) Research Network in 2013,³⁶ molecular features, as a supplement to traditional clinicopathological information, has been paid increasingly more attention in patients' clinical evaluations. Recently, it was incorporated into the endometrial cancer risk stratification system in the European Society of Gynaecological Oncology (ESGO) guideline.³⁷ It is reasonable to reconsider the possibility of incorporating molecular testing information into patients' surgical management, and there are emerging new evidences indicating the possible associations.

Some studies analyzed the safety of laparoscopic surgery in patients of distinct molecular subgroups. In our recent study based on TCGA data, laparoscopic surgery and open surgery showed comparable survival outcome in microsatellite-unstable (MSI) cases. But laparoscopic surgery was associated with significantly shorter recurrence-free survival in microsatellite-stable (MSS) endometrioid endometrial cancer patients.³⁸ Furthermore, among recurrent cases of this cohort, more locoregional relapses were observed in the minimally invasive surgery group compared with the open surgery group, though statistical significance was not reached.³⁸ These results reminded us of the shorter locoregional recurrence-free survival of the minimally invasive surgery cohort in the LACC trial.¹² A possible explanation for that is the influence of uterine manipulator and insufflation gas used during minimally invasive surgeries. In the article by Padilla-Iserte et al.,³² a mechanistic explanation for the negative influence of uterine manipulator during endometrial cancer surgery was proposed. It is hypothesized that due to the macroscopic and microscopic injuries in the uterine wall caused by manipulators, tumor cells may more easily spread to the peritoneal cavity. These effects, plus the influence of insufflation gas (Fig. 1), could possibly lead to higher locoregional recurrence rate in the MSS subgroup. Nevertheless, in the MSI subgroup, these negative effects could be balanced by stronger anti-tumor immunity trigger by higher tumor mutation burdens

Table 1

Recent studies showing inferior survival outcome after minimally invasive surgery in endometrial cancer.

Year	Author	Study design	Patient subgroup of interest	Major findings
2020	Song et al. ²⁴	Retrospective	Stage I, intermediate risk	Minimally invasive surgery group showed higher recurrence rate.
2021	Philp et al. ²⁵	Retrospective	Stage I-II, high-intermediate risk	Minimally invasive surgery group showed higher risk of and shorter time to recurrence.
2021	Dai et al. ²⁶	Retrospective	All stages, TP53 mutant	Minimally invasive surgery group showed shorter recurrence-free survival.
2021	Kim et al. ²⁷	Retrospective	Stage II	Minimally invasive surgery group showed shorter disease-free survival.



Adapted from Padilla-Iserte P, et al. Am J Obstet Gynecol 2021;224:65.e1-11.

Fig. 1. Mechanisms of tumor cell dissemination in laparoscopic surgery(32).

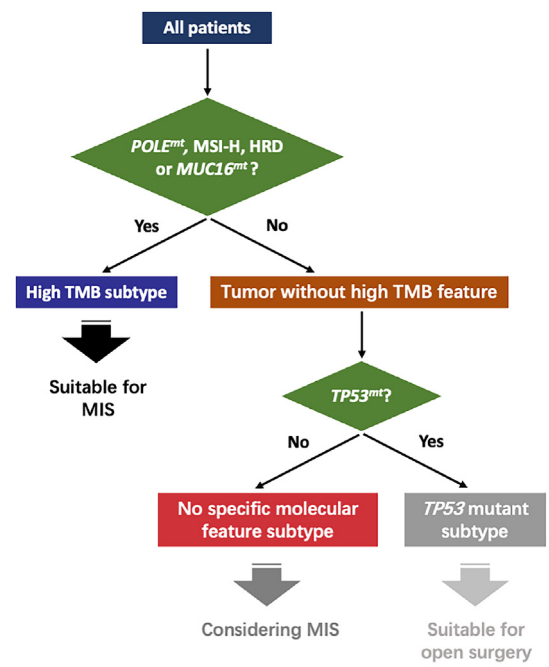
and more neoantigens, and are therefore not revealed in patients' survival.

Recently, further analyses indicated that in patients with *POLE* mutations, MSI high, homologous recombination repair pathway mutations or *MUC16* mutations, survival after two surgical approaches was similar, while in patients with *TP53* mutations, laparoscopic surgery was associated with compromised survival.²⁶ In accordance with the assumption mentioned above, the negative effects of laparoscopic surgery might be especially prominent in the highly invasive subtype, the *TP53* mutant subtype. While *POLE* mutations, MSI high, homologous recombination repair pathway mutations and *MUC16* mutations all indicate higher tumor mutation burden and more effective antitumor immune reactions, which may facilitate the eradication of disseminated tumor cells.^{39–42} A scheme for selecting surgical approach was proposed accordingly (Fig. 2). Still, mechanistic studies and prospective trials are needed to validate these hypotheses.

Furthermore, some clinicopathological factors should also be reconsidered for surgical decisions of endometrial cancer. Accumulating data over the past decades indicated that optimal debulking surgery is essential for better survival outcome in advanced-stage endometrial cancer patients.^{43,44} Considering the ability of intraoperative detection and completeness of resection, open surgery would be better for diseases that extend beyond the uterus. Besides, in a recent multi-center retrospective study from Korea, for stage II endometrial cancer patients, the recurrence rate was significantly higher in the laparoscopic surgery group compared with the open surgery group.²⁷ Similar to cervical cancer surgeries, the method of colpotomy and direct contact with the tumor by uterine manipulators during laparoscopic surgery might account for the results. Above all, we recommend open surgery in endometrial cancer patients of high-risk group, diseases with cervical involvement, patients with extra-uterine diseases, and patients with large uterus during initial treatment, while for the remaining part of patients in intermediate and high-intermediate groups, though there are novel evidences indicating compromised survival after laparoscopic surgery,^{24,25} more studies are needed before any updated recommendations could be put forward.

Prospective

Tumor treatment is a complex and evolving field, and we can hardly draw the final conclusion or make recommendations based on any single evidence or results from one clinical trial. Besides, emerging new evidences should always lead us to reconsider the possibilities of revising formerly established conclusions. The fierce argument about the LACC trial results, even after formal revision of the NCCN and other international guidelines, indicate that the optimal surgical approach for early-



From Dai Y, et al. Front Oncol 2021; 11: 634857.

Fig. 2. Scheme for selecting proper surgical approach in endometrial cancer(26). Note: *POLE*^{mt}, *POLE* mutation; MSI-H, microsatellite-instability high; HRD, homologous recombination defect; *MUC16*^{mt}, *MUC16* mutation; TMB, tumor mutation burden; MIS, minimally invasive surgery; *TP53*^{mt}, *TP53* mutation.

stage cervical cancer is still inconclusive. Simultaneously, for endometrial cancer, new research data also shed light on possibilities of re-adopting open surgery in certain cases. In the future, we should rely on international collaborations to design rigorous clinical trials to test the above conclusions and hypotheses. In the future studies, molecular features of endometrial cancer should be incorporated and analyzed in addition to traditional clinicopathological parameters, with an aim of developing personalized treatment strategies for guiding better patient care.

Author contributions

DY: Wrote the manuscript and prepared the figures. WZ: Revised the manuscript. WJ: Acquired the funding and revised the manuscript. All

authors approved the final version of the manuscript as current form.

Conflict of interest

The authors declare that they have no conflict of interest.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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