Minimally invasive approach is preferred for clinical stage 1 endometrioid-type endometrial cancer

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In recent years, minimally invasive surgery (MIS) has become one of the leading advanced therapeutic technology in the management of patients with various types of benign diseases, not only due to successful transformation of the treatment landscape but also clear demonstration of many advantages, such as small wound, better cosmetics, less wound pain, sooner recovery, and easy fulfillments of enhanced recovery after surgery (ERAS) programs compared to conventional exploratory laparotomic approach.[1–6] However, for the management of patients with malignant tumors, there are many debated issues and controversies, although many studies have confirmed that MIS can be successfully in place of traditional exploratory laparotomy in the management of many kinds of malignancies, based on the validated effectiveness and safety of MIS.[7–12] Among the aforementioned cancers, the gynecological organ-related cancers may be one of highly debated issues, because the preferred surgical therapy for endometrioid-type endometrial cancer (E-EC) is an MIS (laparoscopic surgery or robotic surgery) and the choice of treatment for epithelial ovarian cancer (EOC) is a standard midline incision-based exploratory laparotomy.[12–15] In the 2024 January issue of the *Journal of the Chinese Medical Association* (*JCMA*), entitled "Long-term outcome of minimally invasive staging surgery for clinical stage I endometrial cancer: A single institute experience in Taiwan," which attempted to evaluate the immediate and long-term outcomes of the women with clinical stage 1 E-EC either treated with MIS or treated with conventional exploratory laparotomy.[12]

Lu et al[12] retrospectively analyzed 665 women with clinical stage 1 E-EC underwent either MIS (n = 412) or conventional exploratory laparotomy (laparotomy) (n = 253) at Taichung Veterans General Hospital between 2009 and 2020. They found women in the MIS group had significant better favorable immediate outcomes than those in the laparotomy group, including lower complication rate (8.5% vs 38.7%), such as lower perioperative complication rate (2.7% vs 5.5%); lower postoperative complication rate (5.8% vs 33.2%); shortening operative time (240 vs 265 minutes); less estimated blood loss (75 vs 430 mL); and better recovery presented by shortening postoperative hospital stay (2.0 vs 7.0 days).[12] Parameters of women with clinical stage 1 E-EC addressing immediate surgical outcomes are all significantly better in the MIS group compared to in the laparotomy group.[12] Additionally, primary outcome using the 5- or 10-year progression-free survival (PFS) as target demonstrated the better PFS in women treated with MIS compared to with laparotomy (95.9% vs 88.6% in 5-year PFS rate and 94% vs 86.3% in 10-year PFS rate, respectively), although after adjusting bias, such as age (< and ≥65 years), clinical stage (1A and 1B), pathological stage (1A, 1B, and ≥2), histology type (pure and mixed), and grade (1-2, and 3), there was no statistically significant difference of both 5- and 10-year PFS rates with hazard ratio (HR) of 0.95.[12] For evaluating the secondary outcome, in term of overall survival (OS) rates, the MIS group also showed the statistically significant better 5- and 10-year OS rates than the laparotomy group (99.4% vs 94.9% in the 5-year OS rate, and 98.5% vs 92.5% in the 10-year OS rate, respectively) by univariate analysis.[12] Similar to the other bias factors impacting on PFS, after adjusting confounding factors, such as clinical stage, pathology stage, histology, and grade, the HR of MIS was 0.45 compared to laparotomy in OS rate, although it did not reach the statistically significant difference.[12] However, the trend related to favorable outcome is directing to MIS, and OS was dramatically better in the MIS group than in the laparotomy group. All suggest that the use of MIS may be a better choice in the management of women with clinical stage 1 E-EC.[12] The current study using the real-world data to clearly demonstrate the reality of outcomes in our day routine clinical practice for the treatment of clinical stage 1 E-EC patients is worthy of further discussion.

First, EC is a surgical illness. In early EC, the standard surgery is a total hysterectomy with bilateral salpingo-oophorectomy via a minimally invasive laparoscopic approach (similar to MIS), which is recommended by Endometrial Cancer Staging Subcommittee, the International Federation of Gynecology and Obstetrics (FIGO) Women's Cancer Committee for FIGO staging of endometrial cancer: 2023.[14] In addition, the majority of society-guidance guidelines have been aware of that as MIS does not compromise the oncologic prognosis and has a significant advantage in perioperative and postoperative outcomes over open surgery, it should be recommended where possible.[15] Therefore, there is no doubt that nearly all patients had better be encouraged to receive MIS as well as all gynecologic oncologists should have an ability to perform MIS for EC patients, particularly for those early-stage E-EC patients, if no contraindicated exists. However, this suggestion may not be easy to be followed. Many gynecologic oncologists did not believe that MIS is a good alternative for the management of three common gynecology-organs-related cancers (EC, cervical cancer, and EOC), even for those women with early-stage E-EC, based on their thought that lymph node dissection is not possible laparoscopically, especially

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in obese patients and safe margin is not easily conducted or dissemination of tumor during the operation is more common in the MIS approach (the high intraabdominal pressure and the use of intrauterine manipulator). Additionally, the loss of tactile sense during MIS, may result in the failure to identify metastatic diseases, especially high left para-aortic lymph nodes just under the left renal vein that would have been otherwise palpable during laparotomy.[16] In previous study derived from one of the biggest medical centers in Taiwan, Dr. Wu[9] mentioned that nearly 70% (69.3%, 159/518) of surgical stage 1 EC patients had been treated by laparotomy. Another study derived from the other biggest medical centers mentioned by Dr. Lu[12] showed that less half of early-stage EC patients were treated by MIS (46.4%, 70/151), even though the patients apparently belonged to the lowest risk group patients (clinical stage 1 and tumor mass ≤2 cm). By contrast, nearly two-thirds of clinical stage 1 E-EC patients (62.0%, 412/665) were treated by MIS in the current study. We should give a big hand to congratulate the authors' success and advance in the management of early-stage E-EC patients.

Second, it is interesting to find that the percentage of women treated with para-aortic lymphadenectomy in the MIS group was statistically significantly lower than in the laparotomy group (33% vs 75.5%), but the percentage of pelvic lymphadenectomy was similar between two groups (94.7% vs 93.3%).[12] Although the number of retrieval lymph nodes of pelvic or para-aortic area was similar between two groups, we found that the number of retrieval para-aortic lymph nodes in the MIS group had a trend to be higher than in the laparotomy group (10 vs 6), and this observation was also found in consideration of the number of retrieval pelvic lymph nodes (18 vs 17). Even though, many patients treated with MIS did not receive para-aortic lymphadenectomy, the outcomes (both PFS and OS) were excellent, which may raise the question of whether the para-aortic lymphadenectomy is needed or not in the clinical stage 1 E-EC patients (belonging to low-risk population), because the technique to perform MIS para-aortic lymphadenectomy is relatively difficult, particularly for those patients with bizarre anatomy.[17] Besides the challenge of technique to perform para-aortic lymphadenectomy via MIS, the need to perform lymph node dissection for E-EC patients is a still highly debated issue.[16] It is reasonable that the more lymph nodes removed, the better chance of detecting metastatic diseases, which can offer the important information about the need of adjuvant therapy and give the better prediction for future prognosis either by therapeutic effects or by adjuvant therapy effects, but at the cost of possible adverse events (AEs), such as increased immediate perioperative morbidities (prolonged operative time, increased blood loss, and damaged vessels, nerves or surrounding organs) and long-term sequelae, including lymphedema, lymphocysts, intestinal obstruction, and deep venous thrombosis, leading to a poor quality of life (QoL) of survivals.[16] All result in surgeons who always face the dilemma of "understating" or "overtreating" the patient during their routine clinical practice. However, based on Dr. Lu's study[12], even though two-thirds of clinical stage 1 E-EC patients did not receive MIS para-aortic lymph node dissection, the prognosis was excellent. In fact, among the enrolled subjects in Dr. Lu's study,[12] except few subjects, nearly all of them belonged to a low-risk group population, who were a good candidate to omit the lymphadenectomy procedure. Additionally, it is reported that nearly 80% of the high-risk group of patients did not have positive lymph node metastases after comprehensive lymphadenectomy in the literature review.[16] All hint to us that positive rate of lymph node metastases in the clinical stage 1 E-EC patients may be really low. In fact, fewer than 4.8% (30/626) of clinical stage 1 E-EC patients had lymph node metastases in Dr. Lu's study.[12] Additionally, the information addressing pelvic lymph node metastases or para-aortic lymph node metastases or both was not shown by authors, contributing to difficulty to identify the reality of lymph node metastases in these clinical stage 1 E-EC patients. Without the true prevalence of rates of lymphadenopathy in the clinical stage 1 E-EC patients, it is uncertain to know the real benefits for patients which should outweigh the risk of performing lymphadenectomy, contributing to the need to re-consider whether the extensive lymphadenectomy, particularly for lymph nodes located on the para-aortic area is really needed for those low-risk population.

Although some uncertainties might require clarification in the current study, and the current study is limited by its retrospective nature, the efforts made by the authors to attempt to provide the real-world data to compare the difference of clinical stage 1 E-EC patients between MIS and laparotomy are worthy of applause. Although it is still too premature, their efforts may further enhance our belief that MIS for clinical stage 1 E-EC patients (low-risk group population) may be a better alternative compared to the conventional laparotomy, except for those patients with contraindication to MIS procedure. This is of paramount importance.

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