



Reconsider minimally invasive surgery for early cervical cancer

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Melamed A, Margul DJ, Chen L, *et al.* Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer. *N Engl J Med* 2018;379:1905-14.

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Human science and technology have developed rapidly since the 1990s, meanwhile, new energy and new materials have been continuously developed and applied to medicine, which has promoted clinical diagnosis and treatment progress (1,2). Gynecologic oncologists are constantly pursuing better surgical treatment with minimal surgical trauma. Tarasconi first reported a laparoscopic side accessory resection in 1981 (3). Harry Reich reported the first laparoscopic hysterectomy until 1988 (4). Then Querleu began laparoscopic pelvic lymphadenectomy (5). In 1993, Childers *et al.* reported laparoscopic staging of early endometrial cancer (6). In 1994, Querleu *et al.* first reported laparoscopic early ovarian cancer staging (7). Since then, laparoscopic reports on the treatment of gynecological malignancies have become more and more, and the scope of its application has become more and more extensive (8,9). Minimally invasive surgery, represented by laparoscopy, now accounts for 60% of all cervical cancer operations. Even among the criteria assessed by physicians, the assessment of the level of minimally invasive surgery has also become an important measure. In addition, minimally invasive surgery is also recommended as an acceptable surgical procedure in guidelines such as National Comprehensive Cancer Network (NCCN) (10).

Naik *et al.* (11) have reported a randomized phase II trial in which patients with early stage IB cervical cancer were randomized into a laparoscopically assisted radical vaginal hysterectomy (LARVH) group and radical abdominal

hysterectomy (RAH) group. The intraoperative blood loss, postoperative duration of bladder catheterization, and length of hospital stay were significantly shorter in the LARVH group. The limitations of this study were relatively limited sample size (nLARVH =7, nRAH =6) and lack of prognostic information. Some studies comparing laparoscopic and open radical surgery for early cervical cancer show that although there is no difference in the 5-year overall survival rate between the two surgical procedures, laparoscopic surgery has the advantages of shorter hospital stay, lower postoperative complications, less bleeding, and quicker recovery. However, these studies are retrospective and require more well-designed, multicenter prospective randomized controlled trials to further validate the long-term outcome of surgery and the safety of cancer treatment.

Two recent papers from *The New England Journal of Medicine* concluded that laparoscopic radical surgery for cervical cancer, which is widely practiced in the clinic, is not as effective as traditional open surgery, and the risk of death and recurrence after surgery is greatly increased. Ramirez *et al.* (12) conducted a phase 3, multicenter, randomized clinical trial to compare survival outcomes of patients with early-stage cervical cancer (IA1, IA2, and IB1) after minimally invasive surgery or open surgery from June 2008 to June 2017. A total of 631 patients from 33 centers worldwide were recruited. Among these, 319 patients randomly underwent minimally invasive surgery (84.4%

underwent laparoscopy and 15.6% robot-assisted surgery) while 312 underwent open surgery. Surprisingly, the 4.5-year disease-free survival rate was 86.0% for minimally invasive surgery and 96.5% for open surgery, with a difference of -10.6 percentage points [95% confidence interval (CI), -16.4 to -4.7]. Compared with open surgery, the overall survival rate of minimally invasive surgery was lower (3-year rate, 93.8% *vs.* 99.0%; hazard ratio for death from any cause, 6.00; 95% CI, 1.77 to 20.30). Furthermore, Melamed *et al.* (13) performed a cohort study involving 2,461 patients who received radical hysterectomy for stage IA2 or IB1 cervical cancer from 2010 to 2013 based on the Surveillance, Epidemiology, and End Results (SEER) program database. Of these, 1,236 patients received open surgery and 1,225 received minimally invasive surgery. After statistical analysis, the mortality rates were 9.1% and 5.3% among patients who performed minimally invasive surgery and open surgery, respectively (hazard ratio, 1.65; 95% CI, 1.22 to 2.22; $P=0.002$ by the log-rank test). From two studies we can draw a conclusion that minimally invasive radical hysterectomy in women with early cervical cancer was associated with a higher rate of recurrence and lower rates of disease-free survival and overall survival than the open approach. Hence, several centers include the Anderson Cancer Center, Johns Hopkins School of Medicine, Columbia University and Memorial Sloan-Kettering Cancer Center have stopped minimally invasive surgery for cervical cancer.

The choice of surgical methods for patients with early cervical cancer should also be reconsidered. Minimally invasive surgery has always been considered as an advance which help patients recover faster with smaller trauma. However, according to these two studies we indeed didn't obtain better or even the same security through minimally invasive surgery compared with open surgery. For such results, two papers have given some speculations. For example, when laparoscopic surgery is used to establish artificial pneumoperitoneum, it is necessary to fill the abdominal cavity with carbon dioxide, which will promote the proliferation and metastasis of cancer cells. It is also possible that the laparoscopic operation will not cut the tumor tissue completely, or the spread maybe caused by the surgery itself. Of note, the influence of the center or the surgeon cannot be ignored for relapsed patients are concentrated in 14 of the 33 centers in the first study. At the same time, the authors also suggested that such results could not be extended to patients with "low-risk" cervical cancer (tumor size, <2 cm; no lymph vascular

invasion; depth of invasion, <10 mm; and no lymph-node involvement), because the current results are insufficient to compare the survival outcomes of low-risk patients in two surgical procedures (12). While the second study did not show whether the scope of surgery in the minimally invasive group could match the open group. And the study lacked specific data on recurrence information and causes of death (13).

To sum up, we need to constantly reflect and treat the early stage minimally invasive surgery for cervical cancer. To further demonstrate the safety of minimally invasive surgery, we need to conduct prospective multicenter randomized controlled clinical trials in the other countries. Because laparoscopic surgery requires a long learning curve, in many cases, not minimally invasive surgery is inferior to open surgery, but the surgeon's laparoscopic skills are not mature enough. We need to carefully interpret these results and analyze the causes to continuously improve surgical procedures and techniques. For gynecologic oncologists, it is still based on standardized cancer treatment principles while performing laparoscopic surgery.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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