

## Expert Opinion



# Unexpected result of minimally invasive surgery for cervical cancer



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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Author Contributions

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In 2 separate studies presented at the March 2018 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer, held in New Orleans, women with early cervical cancer treated by minimally invasive radical hysterectomy, either conventional or robot-assisted minimally invasive radical hysterectomy, were shown to have a significantly higher risk of disease recurrence and poorer long-term survival than those of women treated by open surgery.

One of the 2 studies revealed a 48% higher risk of death from any cause within 4 years after minimally invasive radical hysterectomy and pelvic lymphadenectomy for stage 1A2–1B1 cervical cancer. The retrospective analysis, which included data from 2 national U.S. databases and was presented by J. Alejandro Rauh-Hain, MD, revealed a statistically significant decline in survival as adoption of minimal invasive surgery (MIS) for early-stage cervical cancer increased.

The other of the 2 studies, “the phase III randomized trial of laparoscopic or robotic versus abdominal radical hysterectomy in patients with early-stage cervical cancer: LACC trial,” presented by Pedro T. Ramirez, MD, also revealed an unexpected outcome of MIS performed for stage 1A1, 1A2, and 1B1 cervical cancers. The number of disease recurrences after laparoscopic or robotic-assisted procedures was almost four times higher than the number of recurrences after open surgery, and this translated into a hazard ratio for disease-free survival (DFS) of 3.74 (at 4.5 years) for MIS versus open surgery. Significantly more patients who underwent MIS died during a median follow-up of 2.5 years (19 patients vs. 3 who underwent open surgery), meaning that women who underwent MIS were 6 times as likely to die during the follow-up period. DFS at 4.5 years after minimally invasive radical hysterectomy was shown to be inferior to that after open surgery. Minimally invasive radical hysterectomy was associated with a higher rate of locoregional recurrence. Results of this trial should be discussed with patients scheduled to undergo radical hysterectomy.

The technical feasibility and oncological safety of laparoscopic radical hysterectomy, including that performed under robotic assistance, have been described in numerous reports [1-7]. A systematic comparative review of open versus laparoscopic radical hysterectomy conducted by Wang et al. [8] found operation time (+26.9 minutes) to be longer, blood loss (–268.4 mL) volume to be lower, hospital stays (–3.22 days) to be shorter, the intraoperative complication rate to be comparable, and the postoperative complication rate to be lower for the laparoscopic procedure. The number of harvested lymph nodes, the amount of parametrial tissue excised, the prevalence of positive surgical margins, and the 5-year disease free and overall survival (OS)

rates were similar between the two procedures [8]. For these reasons, laparoscopic radical hysterectomy is widely accepted as an alternative to open radical hysterectomy.

Results of the 2 studies presented at the SGO Annual Meeting were opposite those mentioned above, and we are confused whether we should abandon MIS for early-stage cervical cancer. However, there are several limitations to these 2 studies that should be considered in our decision making.

## LEARNING CURVE

Conrad et al. [9] evaluated the current patterns in use of MIS procedures by SGO members and compared the results against those of their 2004 and 2007 surveys. Between 2007 and 2012, there was a very large increase in the proportion of SGO members who thought minimally invasive radical hysterectomy and pelvic lymphadenectomy was appropriate for cervical cancer (from 36.7% in 2007 to 81.6% in 2012). Also between 2007 and 2012, there was an increase in conversion from minimally invasive surgery to laparotomy (with 2.8% of SGO members reporting a conversion rate >5% in 2007 and 23.6% of members reporting that same rate in 2012), and, according to the 2012 survey, 90.2% of members rarely or never referred a patient to a colleague for minimally invasive surgery, which was a significant increase from the 80.6% reported in 2004 ( $p=0.0004$ ).

Several authors have noted that mastery of laparoscopic radical hysterectomy requires experience in at least 25 and up to 50 cases [10,11], which means that optimal surgical outcomes of MIS for cervical cancer, which was first adopted in 2006, are just now coming about. Perhaps the rate of conversion to laparotomy increased between 2007 and 2012 because surgeons lacked the required experience or were reluctant to make referrals.

Rauh-Hain reported a 1% decrease in 4-year survival of patients treated for cervical cancer for each year after 2006 on the basis of an interrupted time series analysis of data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program. It was speculated that the decline was due to surgeons' lack of experience and disinclination toward making referrals, and we think that analysis of patient survival over the more recent years is necessary to confirm the "real" outcomes of MIS.

## UTERINE MANIPULATOR

During the laparoscopic procedure, applying upward traction to the uterus is considered fundamental. Use of a uterine manipulator allows good exposure of the spaces around the uterus and thus a faster and safer procedure [12]. However, some authors have raised concern that use of a uterine manipulator might further disrupt the tumor and thus result in dissemination of malignant cells [13-17]. Several authors have shown that use of a uterine manipulator during laparoscopic surgery for endometrial cancer does not increase the incidence of positive peritoneal cytology or the risk of recurrence and that it has no influence on OS [18-20]. However, use of a uterine manipulator during surgery for cervical cancer remains controversial. Rakowski et al. [21] reported that the use of uterine manipulator in robotic-assisted radical hysterectomy, did not yield any clinico-pathological differences in depth of invasion, lymphovascular space invasion (LVSI), or parametrial involvement compared those seen in cases of open surgery [21].

On the contrary, artifactual displacement of cervical epithelium showing CIN III to fallopian tubes during laparoscopic hysterectomy performed with the use of an intrauterine balloon manipulator has been reported [22], which means that use of a uterine manipulator poses a theoretical possibility of peritoneal dissemination of cervical cancer.

## INTRACORPOREAL COLPOTOMY

On the basis of results of an experimental animal study, Volz et al. suggested that intraperitoneal tumor spread may be connected to inadvertent presentation of cancerous tumor cells to the circulating pneumoperitoneum CO<sub>2</sub> gas and disturbance of the superficial mesothelial layer caused by the high CO<sub>2</sub> pressure; this may provoke cancer cell implantation [23]. Kong et al. [24] investigated the pattern of recurrence after open versus laparoscopic/robotic radical hysterectomy in patients with early cervical cancer, and multivariate analysis of factors in the MIS group showed laparoscopic intracorporeal colpotomy under CO<sub>2</sub> pneumoperitoneum to be a strong prognostic factor related to disease recurrence. They concluded that total laparoscopic/robotic intracorporeal colpotomy under CO<sub>2</sub> pneumoperitoneum may pose a risk of a positive vaginal cuff margin and of intraperitoneal tumor spread in patients with early-stage cervical cancer treated by means of laparoscopic/robotic radical hysterectomy.

Several studies have shown that recurrence patterns differ according to the colpotomic approach because exposure of the cervical mass to circulating CO<sub>2</sub> during intracorporeal colpotomy may result in tumor spillage into the intraperitoneal space, leading to intraperitoneal dissemination [25,26]. In the Laparoscopic Approach to Cervical Cancer (LACC) study, the vault was shown to be the most common site of recurrence in cases of open surgery, whereas the pelvis was shown to be the most common site of recurrence in cases of MIS. Further, pelvic recurrence was not seen in cases of open surgery. The recurrence pattern differed completely between the 2 groups, even though histopathological findings (tumor size, LVSI, parametrial margin, and vaginal margin) were identical.

In the LACC study, a fair amount of data, including the use of uterine manipulators and the precise colpotomic approach, are unknown. We must judge the usefulness of MIS for early-stage cervical cancer dispassionately and objectively on the basis of all pertinent data.

Finally, we quote Shitanshu Uppal, MD, the discussant of the two studies presented at the SGO Annual Meeting, "What will happen if we abandon minimally invasive surgery? A return to open surgery for all patients would result in 85 additional complications, 70 additional transfusions, and 4.75 lives would be saved per 1,000 cases."

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