

# End of the minimal invasion surgery in cervical cancer?

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Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related death in women worldwide [1,2]. For early clinical stage, surgery remains the primary treatment with the greatest effect on long-term survival. Radical hysterectomy with pelvic lymphadenectomy (LDN) remains the standard for patients with cervical cancer in early clinical stage. Randomized clinical trials demonstrated that survival after minimally invasive surgery (MIS) is similar to survival after open surgery in patients with cervical cancer, early-stage colorectal or gastric cancer, hysterectomy due to MIS has led to lower risk of infection and recovery faster than open surgery. The first laparoscopic radical hysterectomy for cervical cancer was reported in 1992. Since then, numerous observational studies have shown that it is feasible and associated with less blood loss, short postoperative hospitalization and fewer complications than open surgery [3]. The current guidelines of the National Comprehensive Cancer Network and the European Society of Gynecological Oncology indicate that laparotomy (open surgery) or minimally invasive surgery (MIS) performed with laparoscopy or robotics is acceptable [4,5]; However, the presence of positive surgical margins after surgery is directly related to the risk of relapse and poor survival [5]; open radical hysterectomy; It is associated with complications, including risk of lymphedema, bladder and sexual dysfunction. To reduce surgical morbidity the MIS suggest that the results are better [3,6-9].

Retrospective studies have shown that laparoscopic radical hysterectomy is associated with less intraoperative blood loss, shorter length of hospital stay and a lower risk of postoperative complications than open abdominal radical hysterectomy. These recommendations have led to the widespread use of MIS for radical hysterectomy; there are few retrospective studies on survival outcomes after MIS equivalent to those obtained by open surgery, in women with cervical cancer in early stage [7-10]; The Laparoscopic Approach to Cervical Cancer Study (LACC), which compared radical hysterectomy by MIS with radical hysterectomy by open surgery, found that the rate of disease-free survival at 4.5 years was 96.5% with open surgery and 86% with MIS; even after adjusting for age, weight, early stage and lymph node status; with MIS, survival was not good, mortality rates at four years were 5.3% with open surgery and 9.1% with MIS. women with cervical cancer in early stage had been treated in hospitals accredited for MIS had lower overall survival rate in the 4 years after diagnosis than those with open surgery (90.9% vs. 94.7%,  $P=0.002$ ) with progressive decrease s 4 years of 0.8% per year [3,8,10]. MIS has been associated with lower rates of survival without disease or overall survival at 5 years than open surgery; even robotic surgery was associated with better perioperative outcomes than open surgery in retrospective studies. Recurrence and survival rates did not differ significantly between both types of surgery [11-13]; These results should be discussed with patients scheduled for radical hysterectomy. The technical feasibility and oncological safety of radical hysterectomy due to MIS is described [3-5,8], when open radical hysterectomy versus MIS is compared the surgery time

was ( $>26.9$  minutes) longer, loss of blood volume ( $<268.4$ ml) lower, hospital stay ( $-3.22$  days) shorter. The intraoperative complication rate is comparable, but the postoperative complications are lower with MIS. The number of lymph nodes collected, amount of parametrial tissue excised, prevalence of positive surgical margins and the rate of general survival 5-year DFS is similar in both procedures; MIS for radical hysterectomy is widely accepted and an alternative to open radical hysterectomy; however some studies are opposed to this treatment and create confusion and propose the abandon of MIS for treatment of cervical cancer [3,10,12,13].

The factors related to these results are the learning curve in MIS between 2007 and 2012, increase for radical hysterectomy with LDN in cervical cancer (36.7% in 2007 to 81.6% in 2012); as well as the conversion of MIS to open surgery (with 2.8% conversion rate  $>5\%$  in 2007 and 23.6% in 2012; the 90.2% of surgeons rarely or never referred the patient to a colleague expert in MIS. Laparoscopic radical hysterectomy requires an experience of 25 to 50 cases [3,10,12-17] for optimal surgery, therefore conversion rates to open surgery increased between 2007 and 2012 due to lack of experience, where reports that the 1% reduction in 4-year survival in women treated for cervical cancer for each year after 2006 was related to the lack of experience, it takes years to confirm these actual results. Another aspect during the laparoscopic procedure, is the application of traction of the uterus upwards which is fundamental. The use of a uterine manipulator allows a good exposure of the spaces around the uterus and makes the surgery to be fast and safe; the uterine manipulator could alter the tumor spread of malignant cells; it has not been reported in endometrial cancer, where the incidence of positive peritoneal cytology or risk of recurrence is not increased, nor does influence global survival; but the use of the uterine manipulator in cervical cancer remains controversial; the use of uterine manipulator in radical hysterectomy with robotics did not produce clinico-pathological differences in the depth of the invasion of the lymphovascular space or parametrial compromise compared to open surgery, contrary to the artificial displacement of the cervical epithelium showing HSIL in the tubas during the laparoscopic hysterectomy performed with an intrauterine balloon, the use of the uterine manipulator suggests a theoretical possibility of peritoneal dissemination of cervical cancer [3,10,15,16,18-22].

A partial explanation of why these results are so surprising is that previous studies have overwhelmingly focused on surgical outcomes,

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**Received:** December 13, 2018; **Accepted:** January 31, 2019; **Published:** February 04, 2019

rather than clinical ones; the surprising finding of the trial was not the worst result with minimally invasive surgery (compared to an expected disease-free survival rate of 90% at 4.5 years), but the best results as expected with open surgery (unlike previous randomized trials with similar patients, with disease-free survival rates of 80 to 94.6%), all cancer recurrences in the LACC trial were grouped into 14 of the 33 participating cancer centers, raising questions about whether these centers recruited more patients, recruited them earlier or if they had unique factors of patients or surgeons. In addition, the incidence of locoregional recurrence was greater with MIS than in open surgery. The use of uterine or cervical manipulators and carbon dioxide gas (CO<sub>2</sub>) in radical hysterectomies by MIS can spread the tumor locally; pneumoperitoneum with CO<sub>2</sub> contributes to the promotion of tumor recurrence (with this last factor it is likely that it contributes to abdominal and port metastasis for locoregional spread); In addition, other factors, such as surgical technique, degree of procedure radicality and peritoneal immunity can contribute to clarify these issues [3,10,12,13,17,23].

Another factor in the MIS showed that laparoscopic intracorporeal colpotomy under pneumoperitoneum with CO<sub>2</sub> is a prognostic factor related to the recurrence of the disease and represents a risk of positive surgical margins in the vaginal vault and intraperitoneal tumor spread; which can cause tumor leakage to the intraperitoneal space, which leads to intraperitoneal dissemination, even, it was shown that the vaginal vault is the most common site of recurrence together with pelvic recurrence. The patterns of recurrence differ in MIS or open surgery, although the histopathological findings (tumor size, SIL, parametrial margin and vaginal margin) are identical; the LACC study, which includes the use of uterine manipulators and colpotomy [3,10]; if we abandon MIS with a return to open surgery it will lead to 85 additional complications, 70 hemotransfusions, will save 4.75 lives per-1,000 cases.

This meta-analysis, did not reveal significant differences in the 5-year overall survival rate (death risk index, 0.91, 95% CI, 0.48 to 1.71, P=0.76) or 5-year disease-free survival rate. (risk index for recurrence or death due to CaCu, 0.97, 95% CI, 0.56 to 1.68, P=0.91) between the two approaches, only four studies had data on survival without disease, and two studies [12,23] on global survival; another meta-analysis of laparoscopic surgery and open surgery; found that the survival rate without disease, overall survival rate and recurrence rate did not differ significantly between the two groups; although, long-term oncological results after laparoscopic radical hysterectomy are unknown [3,10,14,15]. Similarly, radical hysterectomy for robotic surgery compared with open surgery recurrence and death rates did not differ significantly between the two approaches with recurrence rate (10.1% and 10.4% respectively; P=0.73), the oncological outcomes were similar with the two approaches [3,10,16]; Surgical trials are difficult to perform and pose particular practical and methodological challenges.

Additional limitations that may justify a future study include imperfect assessments of cervical cancer, endometrial cancer, lack of follow-up and missing data in selected patients, with respect to race and ethnic group, standardization of adjuvant treatment and failure to review the pathology and these studies pointing out the death sentence for MIS in the treatment of cervical cancer is not necessarily, until more details are known, surgeons should proceed with caution, advise their patients about the results of these collective studies and assess the individual risks and benefits of each woman with respect to MIS compared with open surgery [3,6,10,11].

In conclusion, radical hysterectomy for MIS in cervical cancer was associated with a rate of recurrence and disease-free survival and lower

overall survival, which with open surgery at 4.5 years was 96.5% with open surgery and 86% with MIS. Even after adjusting for age, weight, early stage and lymph node status; Four-year mortality rates were 5.3% with open surgery and 9.1% with MIS.

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