

Should we abandon minimally invasive surgery for cervical cancer?

Recent data infer that, as a specialty, we should consider an open surgical approach

Mary M. Mullen, MD, and David G. Mutch, MD

A minimally invasive approach for gynecologic surgery increasingly has become the surgical modality of choice (vs open surgery) due to decreased perioperative and postoperative morbidity for many gynecologic cancers.¹⁻³ This has included radical hysterectomy for cervical cancers. Until recently, retrospective evidence supported its use, suggesting decreased perioperative and postoperative complications with similar survival outcomes between patients undergoing minimally invasive and open radical hysterectomy.^{4,5} In November 2018, two new studies were published in the *New England Journal of Medicine*, and another study was presented at the American Society of Clinical Oncology (ASCO) annual meeting challenging this practice paradigm. These studies reveal a higher risk of disease recurrence and decreased overall survival

with minimally invasive surgery (MIS) compared with open surgery for Stages IA-IB1 cervical cancer. These findings have resulted in a change in practice nationwide.

RCT findings astonish specialty

The first study, the Laparoscopic Approach to Cervical Cancer (LACC) trial, authored by Ramirez and colleagues was a noninferiority randomized controlled trial evaluating MIS versus open radical hysterectomy for patients with cervical cancer (Stage 1A-1B1) conducted from 2008-2017.⁶ The primary outcome was disease-free survival at 4.5 years. Secondary outcomes included recurrence and overall survival rates. Power analysis suggested a sample size of 740 patients to provide greater than 80% power with a noninferiority margin of -7.2% between disease-free rates of the two groups. However, the study was closed prematurely at enrollment of 631 patients (85% recruitment) by the Data Safety Monitoring Committee due to the astounding differences in survival between the two groups.

The rate of disease-free survival at 4.5 years was 86.0% with MIS and 96% with open surgery. There were 27 recurrences (8.5%) in the MIS group and only 7 (2.2%) in the open-surgery group, accounting for a hazard ratio (HR) for disease recurrence or death from cervical cancer of 3.74 (95% confidence interval [CI], 1.63-8.58). This difference remained after adjusting for confounding variables. There were 22 deaths—19 (5.9%) in the

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Mary M. Mullen, MD, is Fellow, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University School of Medicine and Alvin J. Siteman Cancer Center, St. Louis, Missouri.



David G. Mutch, MD, is Ira C. and Judith Gall Professor of Obstetrics and Gynecology and Vice Chair of Gynecology in the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University School of Medicine and Alvin J. Siteman Cancer Center. He serves on the OBG MANAGEMENT Board of Editors.

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MIS group and 3 (0.1%) in the open-surgery group (HR, 6.56). Although patient characteristics between groups appeared to be similar, more than one-third of patients in each group had missing data regarding histology at the time of surgery, grade, tumor size, lymphovascular space invasion, and depth of invasion. Interestingly, intraoperative, perioperative, and postoperative complications between the two groups were similar (with rates of 11%, about 40%, and about 25%, respectively).

Surprising findings continue in NEJM

The second study, by Melamed and colleagues, was a retrospective cohort study using data from the National Cancer Database (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) database evaluating women with stage IA2 or IB1 cervical cancer who underwent either minimally invasive or open radical hysterectomy between 2010 and 2013.⁷ The primary outcome was time to death.

Participant characteristics. A total of 2,461 women were included: 49.8% underwent MIS and 50.2% underwent open surgery. According to the raw data, patients undergoing MIS were more likely to be white, privately insured, reside in an area associated with higher income, undergo surgery at a nonacademic institution, have adenocarcinoma, and have smaller, lower-grade tumors. After propensity-score weighting, demographic and clinical characteristics were similar between groups. Median follow-up was 45 months.

Results. A total of 164 deaths occurred: 94 in the MIS and 70 in the open-surgery group. The risk of death during study follow-up was 9.1% in the MIS group versus 5.3% in the open-surgery group, and women who underwent MIS had shorter overall survival ($P = .002$; HR, 1.65; 95% CI, 1.22–2.22). Mortality rates remained higher in the MIS group after adjusting for adjuvant therapy (HR, 1.62; 95% CI, 1.2–2.19). However, the HR for death with MIS was not statistically significant in a subgroup analysis evaluating tumors 2 cm in

size or less (HR, 1.46; 95% CI, 0.70–3.02). The authors demonstrated that the adoption of MIS for radical hysterectomy corresponded to a drop in the 4-year survival rate of 0.8% per year ($P = .01$).

ASCO meeting data emphasize lower mortality and survival rates for MIS

A third important, but less publicized study, is a retrospective cohort study by Marguland and colleagues that was presented at the ASCO annual meeting and is pending publication. This study evaluated the 5-year survival of women with stage IB1 cervical cancer after MIS or open radical hysterectomy from 2010 to 2013.⁸ The findings demonstrated similar results to the above studies with decreased 5-year survival rates in patients with a tumor size of 2 cm or greater in the MIS group (81.3% vs 90.8; HR, 2.14; 95% CI, 1.36–3.38; $P < .001$). These results hold true when controlling for confounding clinical variables. Interestingly, in a subset analysis evaluating patients with tumors less than 2 cm, survival rates were similar between groups. This study confirms decreased morbidity and cost associated with MIS radical hysterectomy.

A consistent message emerges from 3 independent studies

We must take the study findings seriously and evaluate the quality of the evidence. There are many strengths to the above studies. First and most importantly, the LACC study is the only prospective randomized controlled trial (RCT) to evaluate this very important clinical question. RCTs are the gold standard for understanding the effectiveness and safety of an intervention compared with an established treatment. The study was well designed in that the study population was clearly defined with detailed inclusion and exclusion criteria. The intention to treat analysis was similar to the per-protocol analysis, and the study followed Consolidated Standards of Reporting Trials (CONSORT) guidelines. While the study was stopped early, there was still 84%

FAST TRACK

Recent findings from an RCT, a retrospective study, and data presented at ASCO are consistent that an open approach is superior to MIS for cervical cancer

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power for the primary outcome. Therefore, when it comes to MIS for cervical cancer, this study provides the soundest data we have available. It is also extremely noteworthy that two additional large retrospective studies evaluating this question separately found similar results.

Criticisms remain, but older research has drawbacks

A main concern with these studies is that the findings challenge previously published research, which overall suggest similar survival outcomes between MIS and open surgical approaches. However, in evaluating the previously published retrospective data it is clear that the studies have considerable limitations.

Long-term survival not always evaluated in research. First, the majority of studies comparing MIS and open treatment modalities specifically evaluated perioperative complications and did not consider long-term survival.^{4,9,10} Of those studies that did consider survival outcomes, the groups often were not balanced and were skewed toward the open surgery patients having larger tumors and higher-stage disease.⁵

Difficult to compare “apples to apples.” These findings are complicated by the fact that open radical hysterectomies were essentially replaced by MIS radical hysterectomies, and therefore, the comparisons are not equivalent since they are comparing different treatment times. For instance, throughout the time period many of these studies were conducted, the treatment paradigm for early-stage cervical cancer changed regarding who received adjuvant therapy and imaging techniques. Therefore, these studies are not comparing apples to apples.^{11,12}

Are we going to increase morbidity? Another common concern when considering abandoning MIS for cervical cancer is the increase in morbidity that our patients may incur immediately postoperatively due to open surgery. Multiple studies have associated minimally invasive radical hysterectomies with decreased blood loss, shorter hospital

stay, lower transfusion rates, and decreased time until return of bowel function.^{4,10,13}

While we recognize that open surgery is associated with increased morbidity, we do argue that, with the almost-universal implementation of Enhanced Recovery Pathways (ERP) in gynecologic oncology, the disparities between the two groups will be minimized and likely are much smaller than that reported in historical literature.¹⁴ Notably, there were no differences in peri-, intra-, or postoperative complications between the two groups in the LACC study, indicating that MIS may not be saving our patients as much morbidity as we think.

Surgical ability differences. Despite the vast strengths associated with the studies we have discussed they certainly embody limitations as well. First, surgical aptitude is difficult to evaluate and tease out. This is extremely pertinent given perioperative, and postoperative, outcomes in cervical cancer, as well as survival outcomes, in multiple surgically managed cancers, which are directly associated with the volume and proficiency of the surgeon.¹⁵⁻¹⁹ Additionally, the mode of minimally invasive surgery that was most commonly utilized was different from practice in the United States. Eighty four percent of the patients in the MIS group of the LACC study underwent laparoscopic and 13.6% underwent robot-assisted radical hysterectomy. This is starkly different from US practice, where 75% of gynecologic oncologists report performing radical hysterectomies only robotically.²⁰

Take-home points

Consider this latest evidence in your surgical planning. Most importantly, the evidence is the evidence. In other words, we can attempt to explain away the findings, but despite arguments against these studies, these data are the most reliable evidence we have to date regarding outcomes for cervical cancer with MIS versus open approaches. These data demonstrate that MIS may be harming our patients and so we must take this into careful consideration during surgical planning.

FAST TRACK

Although previously published research show similar survival rates for open and MIS approaches, those data are lacking and retrospective

For small cancers, MIS may be the best option. MIS radical hysterectomy may still be the best approach for patients with tumors less than 2 cm in size. The LACC study is not powered to evaluate oncologic outcomes in this subset of patients and the two retrospective studies suggest no difference in survival in this cohort.

We must work to understand the driving force between the disparate outcomes. Are the increased rates due to the open surgical approach, the uterine manipulator, circulating CO₂ gas, or tumor exposure to the intraperitoneal cavity as the authors suggest? Or is it due to surgical expertise, tumor biology, tumor size, or mode of MIS? At this point the impelling cause is unknown.

New NCCN guidelines are to come. Up to this point the National Comprehensive Cancer Network (NCCN) guidelines stated that

“radical hysterectomy procedure may be performed either via laparotomy or laparoscopy.” Given these recent studies, however, new NCCN guidelines will be released cautioning the use of the MIS approach. In short, these data have transformed the standard of care.

At our institution, the majority of radical hysterectomies will be performed open. Continued discussion remains regarding small lesions, but even in these cases most surgeons will proceed with open surgery in an attempt to maximize survival.

As providers, it is our duty to honestly reflect on published data and comprehensively counsel patients about the risks and benefits associated with each approach, including the fact that recurrence may be higher with a minimally invasive approach. Patients and providers must then collectively decide what is best for each individual case. ●

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