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Is It Time to Call for Improvement in Surgical Techniques for Minimally Invasive Radical Hysterectomy?

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INTRODUCTION

Cervical cancer is the most common pelvic cancer in women worldwide with an annual incidence of 569,847 and 311,365 deaths expected in 2018.[1] In the United States, about 13,000 women are diagnosed each year with cervical cancer. Radical hysterectomy (RH) and chemoradiation therapy are both treatment options for women with early-stage cervical cancer. Retrospective studies suggest that RH is as effective as radiation therapy (RT). The only randomized clinical trial comparing these two modalities for women with stage Ib-IIa cervical cancer showed equivalent 5-y overall survival (OS) and disease-free survival (DFS).[2] RH as primary treatment is preferred over RT in women who desire the preservation of ovarian function and is associated with fewer long-term sexual dysfunction.[3–5]

In the recent noninferiority study published in the New England Journal of Medicine by Pedro Ramirez et al., 631 women with stage IA1 (with lymphovascular invasion), IA2, and IB1 cervical cancer were randomized to undergo RH by minimally invasive surgery (MIS) (319 patients) or exploratory laparotomy (RAH) (312 patients) approach; in the MIS group, 84.4% underwent laparoscopic and 15.6% robotic-assisted laparoscopic RH. The RAH group had a slightly more than 10% advantage in 4.5-y DFS over MIS RH (96.5% vs 80.0%). Similarly, a 5% OS advantage at 3 y (99% vs 93.8%) was observed in the RAH group.

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After the first report of laparoscopic radical hysterectomy with pelvic and paraaortic lymphadenectomy by Nezhat et al. multiple studies have shown that both approaches resulted in equivalent DFS and OS, which is contrary to the results recently reported by Ramirez et al.[6,7] Additionally, MIS was associated with benefits such as shorter length of stay, less blood loss, and fewer short- and long-term risks.[8–13] Further evaluation of these surgical approaches was reported in seven retrospective studies (**Table 1**).

In 2014, Nam et al. reported a higher recurrence rate of 8.5% in the MIS RH group as compared with 2.1% in the RAH group. Patients with larger tumor volume had a significantly higher recurrence rate of 42.9% than those with small volume disease (2.5%). However there was no difference in the 3-y DFS between the two approaches in the group with small volume diseases.[14] In a subsequent follow-up study performed by the same group, there was no increased risk of recurrence or death associated with laparoscopic radical hysterectomy (LRH). For the patients with tumors >2 cm, the risk for recurrence and survival remained equivalent.[9] The equivalent survival rates seen with two different surgical approaches is in agreement with five other studies in which the average tumor size was greater than 2 cm.[8,10,13,15,16]

Although retrospective in nature, the large number of subjects (total of 1328) included in these multiple previous studies provide compelling evidence for the notion of the safety of LRH or MIS when compared with the RAH. A meta-analysis by Wang et al. found no significant differences in the 5-y OS and DFS following MIS or RAH for early-stage cervical cancer.[17] A subsequent meta-analysis by Cao et al. on 2922 patients noted no differences in OS and DFS in patients who underwent LRH vs RAH.[11] Meta-analyses have inherent advantages, such as an increased sample size and ability to compare data across multiple trials, as well as limitations, such as their tendency to incorporate biases. Overall, they can be instrumental in verifying the consistency of a finding.[18]

The current international trial led by Ramirez et al. consists of researchers from multiple sites including China, Korea, Brazil, Colombia, Peru, Italy, and Australia. Although the institutions involved were subjected to trial-related mon-

Table 1.
Disease-free Survival Following MIS vs RAH

Authors (country)	Year	Number of cases (MIS vs RAH)	Follow-up (MIS vs RAH in months)	Survival
Steed (Canada)[13]	2004	71 vs 205	17 vs 21	DFS at 2 years: 94% vs 94% (average tumor size: 2.3 vs 2.6 cm)
Nam (Korea)[4]	2004	47 vs 96	34.5 vs 43.5	86.7% vs 98.9% (DFS at 3 years); no differences if the tumor volume was less than 2 cm
Jackson (United Kingdom)[15]	2004	57 vs 50	52 vs 49	OS: 94 vs 96% (average tumor size 1.6 vs 1.7 cm)
Li (China)[16]	2007	90 vs 35	26	Mortality rate 10% vs 8% (average tumor size 2.8 vs 2.6 cm)
Malzoni (Italy)[8]	2009	62 vs 65	71.5 vs 52.5	DFS: 92.4% vs 96.3% (average tumor size 2.3 vs 2.7 cm)
Lee (Korea)[10]	2010	8 vs 16	78 vs 75	DFS at 5 years: 90.5% vs 93.3% (did not address average tumor size)
Nam (Korea)[9]	2011	263 vs 263	91 vs 92	DFS at 5 years: 94.4% vs 92.8% (average tumor size 1.8 vs 1.8 cm)
Ramirez (Multiple)[6]	2005–2011	259 vs 232	54 vs 54	DFS at 4.5 years: 96.5% vs 80.0% (average tumor size 1.2 vs >1.2 cm)

MIS, minimally invasive surgery; RAH, exploratory laparotomy; DFS, disease-free survival; OS, overall survival.

itoring, audits, institutional review board monitoring, and regulatory inspections by providing direct access to source data/documents, there were limitations in standardization of cancer staging and histopathology. Surgical randomized clinical trials can be limited by the variable technical skills of surgeons involved.[19] An effort was made to standardize surgical techniques by video review, but these videos have not been made available for review.

Importantly, there was no centralized review of the pathology specimens. Interobserver discrepancies exist in cervical cancer staging and patient with high-risk diagnoses based on histopathology have poorer outcomes than patients with non–high-risk diagnosis.[20] To limit interobserver bias, a centralized pathology review is an important tool in the execution of clinical trials.[21] This is particularly important because high-quality pathology and laboratory medicine services are often lacking in low- and middle-income countries (LMIC), as defined by the World Bank based on per-capita gross income.[22–24] Because more than half of the patients included in this trial were accrued from LMICs, it would be important to have a centralized pathology review to determine the accuracy of the pathology specimens. Failure to accurately assess various risk factors may affect the selection of adjuvant therapy for patients with high-risk factors.[25]

Additionally, there was no standardization in preoperative evaluation and imaging to ensure all patients were appropriately staged before being included in the study. Historically, because of a higher incidence in resource-limited LMICs, cervical cancers were staged clinically. Changes to International Federation of Gynecology and Obstetrics cervical cancer staging guidelines, made in 2018, allow for utilization of any preoperative imaging modality including ultrasound, computed tomography, magnetic resonance imaging, and positron emission tomography. Although imaging can now contribute to staging, the guidelines acknowledge that imaging modalities are often limited in LMICs and continue to allow clinicians to stage cervical cancers based on the resources that they have available.[26] Because of the lack of standardization of preoperative evaluation in this study, it is possible that the same cancer may have been staged differently in two different countries or institutions, impacting survival outcomes.

In this study, adjuvant therapies were delivered in about 27% of the patients who either underwent open or minimally invasive surgery. There were no differences in the deliveries of chemotherapy or radiotherapy or the days of completion of radiotherapy; however, there was a difference in the recurrence sites between the two approaches. Specifically, vaginal vault recurrences were seen more

often in RAH, whereas all the recurrences in the nonvaginal vault pelvic areas occurred with MIS. Most recurrences in both groups occurred in the pelvis or vaginal vault. This difference was clustered in 14 of 33 recruiting centers; there were within-trial differences in the outcomes; thus, the finding of the study may be heterogenous across the study sites.

Nonetheless, the finding of this study is significant in that a 4-fold increase in the risk of death was observed in women with early cervical cancer who underwent MIS when compared with RAH. The approach of MIS has previously been shown to have equal survival outcomes with improved quality of care for women with endometrial cancers.[27,28] It thus came as a surprise that this noninferiority study by Ramirez et al.[6] showed an opposite finding of inferior survival outcomes by a minimally invasive approach for a different gynecologic cancer. The surgical approaches between hysterectomy for endometrial and cervical cancers have many similarities and differences; one fundamental difference is the location of the tumor, with cervical cancer being directly exposed to the abdominal and pelvic cavity during the surgical resection, whereas endometrial cancer is confined within the uterine corpus. Therefore, a surgical approach such as hysterectomy for cervical cancer carries a higher risk of a spread pattern in the pelvis and abdominal cavity, which differs from the typical recurrence of cervical cancer in the vagina and retroperitoneal nodes.[6]

Although the Ramirez et al.[6] trial was not designed to assess possible mechanisms for poorer survival in the MIS group, they do note the previous studies have associated specific surgical techniques with worse outcomes. These techniques include use of uterine manipulators and the route of vaginal cuff closure. It is unclear how many of the patients in the MIS group had a uterine manipulator used during the surgery. It is possible that the use of uterine manipulator may have led to the disruption and dissemination of the disease. In a large retrospective analysis of 704 patients, a 2.37-fold higher odds of recurrence were observed in patients undergoing MIS with the use of a uterine manipulator for early-stage cervical cancer.[29]

The method of vaginal cuff closure has been similarly shown to have a survival impact in cervical cancer patients. Kong et al. demonstrated that intracorporeal closure of the colpotomy was associated with higher rates of recurrence than with vaginal approaches.[30] It was hypothesized that high pressure CO_2 used in MIS directly led to intraperitoneal spread. During a RH the cervix is not exposed to CO_2 until after the colpotomy. An enclosed colpotomy technique ligates the upper portion of the vagina prior to transection of the upper one third of the vagina. By preventing exposure of the cervix to CO_2 and to the peritoneal cavity, an enclosed colpotomy may decrease recurrence rates with MIS.[31–33]

Specific surgical techniques have been associated with worse outcomes in other gynecologic pathology. For example, patients who underwent morcellation for uterine fibroids had a 3-fold higher mortality risk than those who did not have morcellation. This result mirrored that reported in the current 4-fold increased risk in death when surgery was performed with a minimally invasive surgical approach. Our gynecologic community has come a long way through learning from the risk of morcellation of uterine fibroids in the abdominal cavity and has sought to improve surgical techniques and patient outcomes.[34]

Whereas we applaud the findings from Ramirez et al. in bringing an awareness of the potential risks to women with cervical cancer, it is important to note that many of the studies comparing RAH with MIS accrued data prior to 2010. Over the past decade, robotic surgery techniques have improved, and continue to improve, dramatically. We have an obligation to continue to strive for the innovative surgical approach that is safe and offer superior surgical outcomes for our patients. One of these approaches may be the consideration of the containment of cervical cancer tumor mass similar to what is being researched on for safe morcellation for uterine fibroid.[35] The current practice of laparoscopic or robotic radical hysterectomy for cervical cancer or to a lesser extent for endometrial cancer should be used with caution until we find a way to contain cancer that is potentially exposed and may be disseminated to the abdominal cavity.

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