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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 For early-stage disease, surgical removal of the uterus remains the primary treatment and has the greatest effect on long-term survival. However, abdominal (“open”) radical hysterectomy is associated with complications, including a risk of lymphedema in the legs and bladder and sexual dysfunction.² Recently, a greater emphasis on reducing surgical morbidity has led to the development of minimally invasive techniques. Despite a paucity of randomized trials, retrospective data suggesting superior surgical and similar oncologic results led to widespread acceptance of minimally invasive radical hysterectomy.^{2,3} Laparoscopy-based and robotic techniques are currently the dominant methods of performing radical hysterectomy in the United States.

Ramirez and colleagues now report in the *Journal* the results of the Laparoscopic Approach to Cervical Cancer (LACC) Trial, a phase 3 trial comparing minimally invasive (laparoscopic or robotic) radical hysterectomy with open radical hysterectomy in women with early-stage cervical cancer.⁴ Midway through the trial, the data and safety monitoring committee called for early closure of the trial after an interim analysis revealed a disease-free survival rate at 4.5 years that was lower with minimally invasive surgery than with open surgery (86.0% vs. 96.5%; difference, –10.6 percentage points) and a lower 3-year rate of overall survival (93.8% vs. 99.0%; hazard ratio for death, 6.00). A companion population-based study by Melamed and collaborators, also now appearing in the *Journal*, showed similar survival trends in a two-part analysis.⁵ The first analysis, which used propensity-score weighting, showed that women with early-stage cervical cancer who had been treated at Commission on Cancer–accredited hospitals with minimally invasive radical hysterectomy had a lower rate of overall survival within 4 years after diagnosis than those who had been treated with open radical hysterectomy (90.9% vs. 94.7%, $P = 0.002$). The second analysis, a time-interrupted study of a similar population that used data from the Surveillance, Epidemiology, and End Results program database, showed a progressive decrease in the 4-year relative survival rate by 0.8% per year that coincided with the initial period of adoption of robot-assisted surgery in the United States (2007–2010) ($P = 0.01$ for change of trend). Taken together, the LACC Trial and the epidemiologic study call into question the equivalency of cancer outcomes with open as compared with minimally invasive radical hysterectomy for cervical cancer.

A partial explanation of why these results are so striking is that previous studies have focused overwhelmingly on surgical, rather than clinical, outcomes.⁶ In addition, comparisons of previous randomized and nonrandomized studies in other clinical settings have shown that results can be divergent in direction as well as magnitude.⁷ Some have argued that the surprising finding of the trial was not the poorer results with minimally invasive surgery (as compared with an expected disease-free survival rate of 90% at 4.5 years), but rather the better-than-expected results with open surgery (in contrast to previous randomized trials involving similar patients, with disease-free survival rates of 80 to 94.6%).^{8–10} However, at least two of the previous trials were enriched for patients at intermediate or high risk for recurrence, whereas the population-based study by Melamed et al. and the LACC Trial had similar study populations and similar survival outcomes. Furthermore, the randomized trial involved 33 centers in 13 countries and the participation of vetted, high-volume cervical-cancer surgeons. The surgical-volume requirement and quality assessment of the participating surgeons' skills and postoperative outcomes distinguish this trial from previous phase 3 cervical-cancer trials and may have contributed to the more favorable outcomes with open radical hysterectomy than those observed in the previous trials.

Curiously, all cancer recurrences in the LACC Trial were clustered at 14 of the 33 participating cancer centers, which raises questions about whether those centers enrolled more patients, enrolled them earlier, or had unique patient or surgeon factors. In addition, the cumulative incidence of locoregional recurrence was surprisingly higher in the minimally invasive surgery group than in the open-surgery group. The use of uterine or cervical manipulators and carbon dioxide (CO₂) gas in minimally invasive radical hysterectomies is postulated to encourage local tumor spread.¹¹ Yet, statistics on manipulator usage were not presented in the LACC Trial, and data from randomized trials are mixed regarding the contributions of CO₂ pneumoperitoneum to the promotion of tumor recurrence (with the latter factor more likely to contribute to abdominal and port-site metastases than to locoregional disease spread).¹¹ Other factors, such as surgical technique, degree of procedural radicality, and peritoneal immunity, may also contribute. Ad hoc studies that evaluate manipulator use and its association with recurrence as well as surgical techniques to minimize cervical tumor spread may help clarify these questions.

Although the results of the LACC Trial and the epidemiologic study are powerful, scientific scrutiny demands consideration of potential study-design or study-conduct issues that may affect outcomes unexpectedly. Surgical trials are difficult to conduct and pose particular practical and methodologic challenges.⁷ One concern is the early closure of the trial, with enrollment of 85% of planned participants and somewhat reduced power for the primary outcome; however, the trial statistics are valid on the basis of the wide margin of difference and nonoverlapping 95% confidence intervals in the disease-free survival rates of the surgical cohorts. Additional limitations that may warrant future study include the imperfect assessments of cervical-cancer stage, the lack of follow-up data and missing data in select patients, the lack of data regarding patient race and ethnic group, nonstandardization of adjuvant treatment, and non-performance of central pathology review. However, for most outcomes, these trial shortcomings appeared balanced between the two groups. Limitations of the epidemiologic study included the retrospective data sets, the heterogeneous methods

of cancer staging, and the fact that the time frame of the study coincided with the earlier part of the robotic-surgery learning curve for radical hysterectomy.

Do these studies signal the death knell for minimally invasive radical hysterectomy in cervical-cancer treatment? Not necessarily, but this approach has been dealt a great blow. Although the data are alarming, select patient subgroups may still benefit from a less invasive approach. No patients with stage IA2 disease and only one with stage IB1, grade 1, disease had a recurrence in the LACC Trial. In addition, patients with a tumor size of less than 2 cm did not have worse outcomes with minimally invasive surgery than with open surgery in either study. Until further details are known, however, surgeons should proceed cautiously, counsel their patients regarding these collective study results, and assess each woman's individual risks and benefits with respect to minimally invasive as compared with open radical hysterectomy.

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