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Minimally Invasive or Abdominal Radical Hysterectomy for Cervical Cancer.

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Minimally Invasive or Abdominal Radical Hysterectomy for Cervical Cancer

TO THE EDITOR: In the trial reported by Ramirez et al. (Nov. 15 issue),[1] the authors observed lower survival rates among women with early-stage cervical cancer who underwent minimally invasive surgery than among those who underwent open surgery. These results suggest that factors such as CO_2 gas insufflation might cause early spread of tumor cells, which in turn compromises outcomes. Similar findings were observed in the accompanying retrospective study conducted by Melamed et al.[2]

We tested the replicability of these findings in patients with other pelvic cancers, using selection criteria and methods similar to those used by Melamed et al. Our inverse probability of treatment–weighted analysis (involving 3928 patients with data in the National Cancer Database in the period 2010–2011) showed that patients who underwent cystectomy by means of minimally invasive surgery had similar 4-year mortality as their counterparts who underwent open surgery (45.7% and 45.9%, respectively; P=0.07). Likewise, our interrupted time-series analysis (with the use of data from the Surveillance, Epidemiology, and End Results [SEER] 18-registry database for the 2000–2010 period) showed no significant change in trend in 4-year relative survival among patients who underwent cystectomy before the adoption of minimally invasive surgery (i.e., in years 2000–2003; −0.3%; 95% confidence interval [CI], −2.5 to 1.2)[3] as compared with those who underwent surgery after 2003 (1.5%; 95% CI, 0.6 to 2.4) (P=0.20 for trend). Similar results were observed in patients who underwent prostatectomy (data not shown), which suggests that the findings reported regarding cervical cancer may not be generalizable to all pelvic cancers.

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TO THE EDITOR: The unexpected results of the trial conducted by Ramirez et al. have brought a great debate within the academic arena. Under the umbrella of the European Society of Gynecological Oncology (ESGO), we recently conducted a survey entitled "after LACC [Laparoscopic Approach to Cervical Cancer] trial," which had 400 responses. We found that 83% of the survey respondents did not anticipate these trial results. Respondents attributed the outcomes in the minimally invasive surgery group to several factors, such as a less radical technique than with open surgery, incorrect manipulation, and spread of the tumor because of CO_2 gas insufflation. A total of 57% of the ESGO members who responded to the survey have changed their approach to open surgery, and 50% consider minimally invasive surgery to be appropriate only for small tumors. Almost 90% of the respondents reported that they intend to share this article with every

patient, and 75% consider it unethical not to discuss the trial results with surgical candidates.

The results of this trial are now on the table, but the final conclusions regarding its effect have to be elucidated. It is time to discover why minimally invasive surgery has done so poorly and, if possible, how to improve it.

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TO THE EDITOR: On the basis of the results of the LACC trial conducted by Ramirez et al. and the National Cancer Database report from Melamed et al., we performed a subanalysis of our recently published results,[1] including only the population with the highest risk of recurrence (stages IB1 through IIA1, according to the FIGO [International Federation of Gynecology and Obstetrics] 2009 criteria, with tumors measuring 2 to 4 cm in the greatest dimension), and the data are presented here. No uterine manipulators were routinely used. Instead, a vaginal probe was used to delineate the vaginal fornices.

Of 111 patients, 57 underwent minimally invasive surgery (laparoscopic or robotic) and 54 underwent laparotomy. The rates of lymphovascular invasion (46% and 45%, respectively) and positive nodes (16% and 18%) were similar in the two groups. With a median follow-up of 8.6 years, there were no differences between the minimally invasive surgery group and the laparotomy group in rates of recurrence (14% and 17%, respectively; P=0.69), cancer-specific survival (calculated from the date of surgery to the date of death from cervical cancer or last follow-up; 88% and 87%, P=0.77), disease-free survival (calculated from the date of surgery to the date of first recurrence or last follow-up in patients without relapse; 86% and 77%, P=0.34), and overall survival (88% and 78%, P=0.20).

We found similar results for the same subgroup of patients when we used the tumor–node–metastasis classification. Whether the use of a uterine manipulator is a factor for recurrence remains to be determined.

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

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DRS. RAMIREZ AND OBERMAIR REPLY: Chiva et al. comment on the ESGO survey that was conducted after the results of our randomized trial were presented at the Society of Gynecologic Oncology meeting in March 2018. It should be highlighted that this survey was conducted before the final publication of our article. Nevertheless, they found on the basis of preliminary data that 57% of the respondents had switched from minimally invasive to open radical hysterectomy. The respondents attributed outcomes in the minimally invasive surgery group to less radical technique and incorrect uterine manipulation. In our trial, the open-surgery group and the minimally invasive surgery group were balanced for histologic subtype, grade, stage, tumor size, and lymph-node status. In addition, there was no significant difference in parametrial involvement or vaginal margins, which thus argues against inadequate radicality in the minimally invasive surgery group.

The survey also pointed to the issue of incorrect uterine manipulation. Clearly, this is a subjective observation and more a commentary than a scientific fact, given that there are no data as to what defines adequate uterine manipulation. Pertaining to tumor dissemination and effect of CO_2 gas insufflation on tumor implantation, we agree with this hypothesis[1] and discuss it in our article. We are encouraged to learn that 90% of the respondents planned on sharing the results of our trial with patients. It would be interesting

to see results from this same survey being conducted after the final publication of the article.

In response to Gil-Moreno and Magrina: our prospective, randomized trial was not designed to determine the cause of the inferior outcomes observed in the minimally invasive surgery group. The concept that a uterine manipulator is a potential factor that may increase the risk of recurrence is speculative. The results presented by their group in this correspondence are based on a retrospective comparison of a very small cohort of patients.[2] Such comparisons highlight the flaws of retrospective sequential comparisons with limited numbers of patients. The groups that were compared may not be balanced with regard to selection of the patients, risk factors, adjuvant therapy, surveillance strategies, or documentation and confirmation of recurrences. In addition, in retrospective data, the duration of follow-up ought to be evaluated for each group, given that there is usually shorter follow-up in the minimally invasive surgery group than in the open-surgery group, thus leading to a lower likelihood of time allowed for the manifestation of recurrent events. The reported recurrence rate of 14% in their minimally invasive surgery group far exceeds that of the same approach in our prospective trial (8.4%).

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Since publication of their article, the authors report no further potential conflict of interest.

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DR. MELAMED AND COAUTHORS REPLY: Abdollah and colleagues note that the increased risk of death related to minimally invasive radical hysterectomy that was observed in our study may not be generalizable to other operations for pelvic cancers. Two randomized trials have shown the oncologic safety of minimally invasive hysterectomy for endometrial carcinoma.[1,2] Furthermore, our observational study[3] showed that minimally invasive staging surgery for epithelial ovarian cancer was not associated with shorter survival than laparotomy. The safety and effectiveness of minimally invasive surgery must be evaluated independently for specific oncologic indications whenever feasible. Extrapolation of study findings across anatomical locations, histologic types, and tumor stages should be undertaken with extreme caution.

The comments of Gil-Moreno and Magrina present an opportunity to address the limitations of small, retrospective studies that compare the risk of recurrence and death between minimally invasive surgery and open radical hysterectomy for cervical cancer. With only 111 patients and a recurrence rate of approximately 16%, the progression-free survival estimates reported by Gil-Moreno and Magrina are based on no more than 17 recurrences. As such, their study is severely underpowered. Furthermore, the small number of events makes adjustment for multiple confounders challenging. The absence of a significant difference in rates of recurrence and survival reported by Gil-Moreno and Magrina, and in studies of similar design, is likely to be due to the limitations inherent to the study design. Interpreting these findings as strong evidence in support of the safety of minimally invasive radical hysterectomy for cervical cancer is imprudent.

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