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Letter to the Editor

Regarding: "The LACC Trial and Minimally Invasive Surgery in Cervical Cancer"

To the Editor:

The Laparoscopic Approach to Cervical Cancer (LACC) trial [1] keeps stirring emotions and discussions [2–6]. The LACC trial can be criticized [7] because the surgical proficiency and the adequacy of the laparoscopic radical hysterectomy was not adequately evaluated, because radicality was not appropriately assessed, and because of the poorly defined inclusion of type II and type III surgery. However, our impression is that the main reason for this ongoing debate is because the LACC trial was a randomized controlled trial (RCT) and because many of us do not like or are not ready to accept the results.

This discussion highlights the problems of performing and of interpreting the value of an RCT in surgery. It is surprising that only the results of the smaller previous studies and meta-analyses were mentioned, but not the much larger excellent study with very similar results in the same issue of the *New England Journal of Medicine* [8]. Results are not only similar, but results were robust for laparoscopic or robot-assisted surgery and across histologic types and tumor sizes. Moreover, these results were recently confirmed in 4 other studies [9–12]

Randomization is essential to avoid inclusion bias. In addition, randomization is supposed to eliminate the effect of eventual cofactors. Therefore, randomization should be stratified for major factors that affect the outcome and that are not eliminated by randomization, such as the center and the surgeon in the LACC trial. In order to compare 2 techniques of surgery, the surgeon must be equally skilled in both techniques; otherwise, we are evaluating the surgeons' skills instead of the technique of surgery. Similarly, in cystic ovarian endometriosis surgery, it remains debated whether some results vary with the singer, not the song [13]. It is beyond the scope to discuss in detail the other problems of an RCT, such as blinding, extrapolation of results, and hidden subgroups in a nonhomogeneous population [14] and of the inadequacy for multimorbidity [15]. Other persisting problems for us clinicians, reviewers, and editors are how to estimate the value of a nonperfect RCT, and in surgical trials, how dependent and independent variables are treated. The value of a trial is the design, and the treatment of variables is the analysis of the study. The design, provided correct randomization, with stratification of the center and the surgeon, is rarely a problem in surgery when the outcome, such as mortality, is clear. However, in studies with outcomes such as pain, blinding is a major issue because of placebo effects and patient and observer bias [16]. A more frequent problem is the analysis, which rarely details explicitly how dependent and independent variables are treated. In an RCT, such as the LACC trial, the effect of cofactors or independent variables does not need to be evaluated by multivariate analysis because their eventual effects are considered neutralized by randomization. The dependent variables, however, are rarely explicitly analyzed. The effect observed for 1 variable, such as the type of surgery, will be equally valid for all other variables strongly associated with the type of surgery. This is implicitly addressed with the criticism that quality of surgery and skills might have been different for the laparoscopy and laparotomy group. However, other variables that are strongly associated with the type of surgery are not considered. They comprise, besides the carbon dioxide (CO_2) pneumoperitoneum in laparoscopy and the exposure to air with 20% of oxygen in open surgery, the many other subtle differences such as Trendelenburg, duration of surgery, anesthesia, and postoperative immune suppression.

The CO_2 pneumoperitoneum [17] and the 20% of oxygen in air cause mesothelial cell hypoxia and oxidative stress, respectively. Both result in an insufflation pressure and duration of exposure–dependent retraction of mesothelial cells, increased resorption of CO_2 with splanchnic metabolic acidosis during surgery, and acute inflammation in the entire abdomen after surgery. The severity and the duration of this acute inflammation and mesothelial cell retraction is a major cause of postoperative adhesion formation and pain in animal models and in humans [18]. These effects can be prevented by conditioning, which comprises, in order of importance, adding more than 5% of nitrous oxide to the gas environment, cooling the peritoneal cavity, and avoiding desiccation. Possibly relevant for the LACC trial is that conditioning also reduces the implantation of tumor cells in an animal model [19] both in laparoscopic and open surgery. Other effects of CO_2 as superficial cell hypoxia and the oxidative stress of open surgery on immunology and growth of cells, eventually cancer cells, have been poorly investigated.

In conclusion, the LACC trial [1] is a milestone trial, and we should learn from eventual shortcomings. As surgeons,

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we should realize the pitfalls and difficulties of an RCT and randomize or stratify for all factors that might affect the outcome, including the surgeon and the center. We should consider all strongly associated or dependent variables because their effect cannot be separated, unless a more elaborate design is used. Although highly unlikely, we cannot ascertain that the result of the LACC trial is due to the technique of surgery and not due to the gas environment, because both are certainly associated. A different gas environment also applies to the recent data with transvaginal closure [20]. If the outcome of a trial is not what was expected, our first goal should be to explore the causes of the discrepancy before suggesting that the result of the LACC trial is a spurious significance resulting from a lack of stratification or quality of surgery. Research data should be considered with an open mind and without emotion. Surprising results should be considered an opportunity to understand the mechanisms involved.

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