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Modify or abandon: minimally invasive radical hysterectomy for early-stage cervical cancer

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"One of the greatest pains to human nature is the pain of a new idea." -Walter Bagehot

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The Laparoscopic Approach to Carcinoma of the Cervix (LACC) trial was arguably the most provocative trial in the gynecologic oncology literature in recent times.[1] The current work by Köhler et al is evidence that it continues to leave many gynecologic oncologists incredulous.[2] The LACC trial compared minimally invasive radical hysterectomy for early-stage cervical cancer to open radical hysterectomy. The results showed that the oncologic outcomes of minimally invasive surgery were inferior to open surgery. In the same issue of the *New England Journal of Medicine*, an accompanying study by Melamed *et al* using the National Cancer Database added another blow to the use of minimally invasive radical hysterectomy. It showed a declining 5-year survival over the years that corresponded to increasing uptake of the minimally invasive approach for the treatment of early-stage cervical cancer in the United States.[3]

So why did these studies create such a stir? There are likely several reasons. First, given the high success rate of the minimally invasive surgery arm in the LACC trial (disease-free survival of 86.0% at 4.5 years), most individual surgeons are unlikely to observe a substantial number of recurrences in this patient population. This could render incomprehensible the concept that minimally invasive surgery is inferior. Second, that the minimally invasive approach could have inferior oncologic outcomes was unexpected given the proven safety of laparoscopy and robotic surgery in other cancer sites like uterine and prostate cancer.[4] Third, is that neither study could provide an explanation as to why minimally invasive radical hysterectomy would have inferior survival. It would, however, be an unfair standard to demand from the LACC trial that it provide the reasons for inferior survival in the minimally invasive arm. Randomized controlled trials (RCTs) have never purported to answer *why* one treatment is better or worse than another - only *which*.

Several reasons have been proposed to explain why minimally invasive radical hysterectomy had higher recurrence rates and a greater risk of death. The three most obvious ways in which minimally invasive surgery differs from its open counterpart are the necessity for pneumoperitoneum, the common practice of using a uterine manipulator, and the method of colpotomy that might expose the cervix and corresponding tumor to the abdominal cavity. Even with these hypotheses, however, the true reason may be something else entirely.

To circumvent these differences and avoid tumor exposure, Köhler et al developed a modified technique of vaginally assisted laparoscopic radical hysterectomy.[2] In this journal issue, they present the results of this modified procedure in 389 patients with inclusion criteria similar to the LACC trial. Their technique essentially requires creating a covering over the cervix using the vaginal tissue and strictly avoiding the use of a uterine manipulator. The reported disease-free survival at 4.5 years of 95.8% by Kohler et al is higher than 86% in the minimally invasive arm of the LACC trial.

It is possible that the proposed surgical technique could truly produce similar outcomes to the open arm of the LACC trial if compared directly. Alternatively, it is also possible that the oncologic outcomes of Kohler et al are due to the meticulous selection of patients most appropriate for this procedure (ie, excluding those who are likely to receive post-operative radiation or those with larger tumors). It could also be due to other factors such as their expertise in performing this procedure since all these centers are very high volume (with a combined average of 80 radical hysterectomies per year).

We must not ignore the very real possibility for systematic bias that exists in a single-arm observational study that does not have a comparison group, let alone one that is randomized. The argument of whether all treatment should be guided by an RCT is beyond the scope of this editorial.[5] But, the fact that a randomized study is the best way to control for systematic bias and confounding - for both known and unknown factors - is incontrovertible. Prior to the LACC study, we had numerous data points suggesting that the minimally invasive approach was as safe as the open approach. However, now there is a well-designed, well-executed, well-monitored, and thoughtfully presented randomized study on the subject that has answered the question. The minimally invasive approaches offered to most women with early-stage

cervical cancer result in more cancer recurrences and more deaths than the open approach.

As we deal with the post-LACC management challenges of early-stage cervical cancer, we are left with two potential pathways: either modify the minimally invasive technique *and prove its equivalence* or abandon it altogether. Abandoning it would be the easiest option. However, there are convincing reasons to be innovative and thoughtful about minimally invasive techniques. One cannot deny the benefits of combining significantly improved peri-operative outcomes with equivalent survival like those demonstrated by the Gynecologic Oncology Group LAP2 Study for endometrial cancer patients.[4] Köhler et al's modified technique seems to have the biologic rationale and robust retrospective results with over 10 years of follow-up that make it a worthwhile technique to be considered in future RCTs.

"Don't throw the past away. You might need it some rainy day."
-Peter Allen & Carole Bayer

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