



Editorial

The change in landscape after a new landmark is constructed: Radical hysterectomy for early cervical cancer and Minimally Invasive Surgery



A landmark event is defined as “an event or development that marks a turning point or stage” [1]. A landmark study is one that is regarded by “workers in a field as a seminal study or which had substantial impact on the area of knowledge” [2]. The laparoscopic or robotic radical hysterectomy vs abdominal hysterectomy trial in patients with early-stage cervical cancer randomized controlled trial (aka, the LACC trial) is for certain such a landmark event and study [3]. This editorial is not meant to be an in-depth critique of the LACC trial. However, it is impossible to ignore aspects of the trial as it has marked a turning point with substantial impact in our field. All future studies will be published and critiqued in the context of the results of the LACC trial and the authors of the current study heavily referenced it.

Minimally invasive surgery (MIS) has also been a landmark transformative event in surgical innovation in many surgical subspecialties. Irrespective of any published study results, I have personally seen the benefit I am offering to my patients with MIS over laparotomy. The GOG LAP2 and LACE studies provided level I evidence of this benefit in patients undergoing surgery for endometrial cancer [4,5]. In cervical cancer, multiple retrospective studies also had demonstrated the same benefit for patients until the LACC trial was presented and published. My first thoughts were that I may have been hurting patients all these years with my surgery. The LACC trial made me stop and take an honest look at my outcomes and that of my colleagues. The true impact of the LACC trial is not that it should change standard of care across the board but rather that we put some real effort into understanding the results and our own practices. An all-or-none approach does not benefit patients nor those caring for them. The LACC trial was a well-designed trial with excellent internal validity. However, as with any other trial, especially where a complex surgical technique is being tested, it is the external validity (i.e. “does it apply to all and more specifically my practice?”) that we are trying to determine and are struggling with. Should the unexpected outcome at mostly 14 hospitals in the world dictate care for all women with cervical cancer across the globe and for the remainder of time?

In this issue of the Journal, Dr. Kim and colleagues have taken a careful look at their experience in response to the LACC trial results [6]. The current study reports the results of a retrospective cohort, not case-control, analysis at a single institution comparing non-robotically assisted laparoscopic and open radical hysterectomy in patients with cervical cancer. The very obvious, and easy, first critique is that this is a retrospective study with all of the known limitations, biases and criticisms with which I agree. However, retrospective data can be quite useful and can provide real-world data if done correctly and if all cases are truly identified and included [7,8]. Such real-world data helps to inform

us in healthcare in the application of results from randomized controlled trials (RCTs) and can also provide insights that may not be appreciated in such RCTs [7]. The “confirmatory” study that accompanied the LACC trial publication was also merely a retrospective analysis using national databases [9]. Therefore, we must not be quick to completely discount all retrospective analyses in favor of a single RCT, especially if they are not “confirmatory”. RCTs are also far from perfect. A well-known limitation of randomized trials that is often not discussed is the pre-trial selection bias that occurs. The cohorts enrolled and randomized represent only a fraction of all the truly eligible patients which may have significant impact on the external validity of the findings in a real-world setting. A well done, single institution retrospective analysis, despite the limitations, will include all cases and then describe the outcomes based on the treatment delivered to an entire cohort as the current study has done.

Kim and colleagues included cases with FIGO stage IB1 to IIA2 which is not the exact same cohort as in the LACC trial. Patients with FIGO stage IB2 and higher are probably best treated with primary chemoradiation in current times as the likelihood of having pathologic risk factors necessitating postoperative radiation therapy is quite high. The authors also provided the outcomes specifically in patients with FIGO stage IB1 who also underwent a preoperative MRI. In the overall cohort, there was no statistical difference in either PFS or OS between MIS and open cases. However, they mention a trend to worse PFS in MIS cases. One must be careful with “trends” as they can easily change in either direction with the addition of more cases. It could also be that the lack of statistical significance, and therefore only a “trend”, in PFS could very well be the result of a lack of power to provide statistical significance. Having said that, the absolute difference in PFS in the overall cohort was 6% which falls within the LACC trials acceptable non-inferiority boundary. Further subgrouping by histology revealed the same message but with even less power as the numbers got smaller for each subgroup. The one subgroup that seemed to have a larger and statistically significant difference in PFS, but not OS, was those with FIGO stage IB1 disease and tumor size >2 cm on preoperative MRI. A concern of the current study in terms of PFS outcomes is that it seems that the follow-up was shorter in the MIS cases as compared to the open cases in reviewing the Kaplan-Meier curves. The authors report a median of follow-up of 106 months overall but did not provide the median follow-up in each group. This does affect the PFS analysis. It is possible that with longer follow-up the PFS differences may become more pronounced. Interestingly, OS was always the same without even a “trend” in both MIS and open arms despite the groupings analyzed. This suggests that the majority of cases that recurred were salvaged or could also just be a reflection

of the shorter follow-up time in the MIS group. It does remain unclear to me why there was such a poor salvage of recurrent cases in the LACC trial that also led to an inferior OS not to mention the much better than expected PFS and OS in the open cases.

The analysis of MRI results and association with outcomes in the current study brings up a few points for thought. It is time that we stop accepting clinical staging alone (i.e. pelvic exam either in the office or under anesthesia) as the primary method of making decisions about appropriate surgical or non-surgical intervention. It is akin to a colorectal surgeon deciding whether to operate based on merely a digital and endoscopic rectal examination. MRI is routine in the assessment of newly diagnosed anorectal cancers and it should also be so in newly diagnosed cervical cancers. MRI is much more readily available around the world and is certainly available in the United States, Europe and in the institutions that enrolled in LACC trial as well as in Korea from where the current study originates. A pelvic MRI that reveals a tumor <4cm confined to the cervix is extremely accurate in predicting for the absence of extrapelvic disease. Therefore, pelvic MRI (or ultrasound performed by truly expert clinicians) could be the only imaging modality needed in this specific cohort of patients. This would ensure with a higher degree of certainty, although not perfect, that we are operating on tumors that are truly FIGO stage IB1.

The emphasis on tumor size in terms of outcomes and for selection for surgical approach also brings up another important question. How do we best assess tumor size especially when trying to associate this factor with PFS or OS? Clinical examination is unreliable and should be abandoned as the sole determinant of size. Preoperative MRI (or ultrasound) is likely the best option currently, but it is also not perfect. Also, should the amount of tumor in a prior conization be added to the current MRI determined size? In the current study, MRI was performed after a prior conization. I wonder whether it is more important the total amount of tumor at diagnosis or what amount of tumor, if any, is remaining when the procedure is actually performed. One may argue that it should be the final pathologic size determined in the hysterectomy specimen because this is the most accurate as compared to clinical examination or MRI. But, again, do we add conization dimensions with final hysterectomy dimensions? In the current study, it seemed that preoperative MRI noting a tumor greater than 2 cm after conization was associated with outcome. Is 2 cm the right cutoff? Does it matter where the tumor is located? So many questions but I can think of one situation in which I cannot imagine a plausible biologic or mechanistic explanation as to how any surgical intervention would have an impact on PFS or OS. This is the situation where there is absolutely no cancer remaining in the cervix pathologically at the time of hysterectomy since the prior conization had removed all tumor. Beyond this, we all need more thoughtful assessment and data which in the meantime will likely be in the form of retrospective data.

Surgical technique is so varied and extremely difficult to control for with any randomization or multivariate adjustment process. Therefore, it is extremely difficult to extrapolate and externally validate findings from any study, whether the LACC trial or the current one, to all other surgeons. There is also a likelihood that the enthusiasm with MIS led many to overlook the basic tenet of oncologic surgery which is to maintain integrity of the tumor and avoid, at all costs, tumor spillage in grossly visible and exposed tumors. This surgical variation may explain why some may not see the same outcomes in their own experience. Individual "experience" should not be merely anecdotal but assessed objectively. This may also explain why the method of colpotomy in the current study did not affect outcomes if tumor containment was not maintained not matter how colpotomy was performed. It would also

possibly explain why in the current study, "experience" as measured by "early introduction" and "post-dissemination" stages was not associated with outcomes. I would not expect it to be different if tumor containment methodology was the same throughout all cases.

An all-or-none approach is of no value in medicine and surgery. RCTs are the highest level of evidence but certainly can also be subject to many biases and the surgical quality and technique bias among individual surgeons and institutions is nearly impossible to overcome. There are even greater limitations with retrospective analyses. But, well done retrospective analyses do provide real-world data that complement findings from RCTs, and at times, may be more reliable in a certain cohort. MIS is still an acceptable option in properly selected cases and with qualified surgeons who have objectively assessed their outcomes. It is difficult to provide strict criteria that would apply to all surgeons as to which cases may be appropriate for a MIS approach. I can say that an all-or-none approach in all patients with cervical cancer and for all surgeons is not the road forward in our current landscape of surgery for cervical cancer. There is enough doubt and equipoise to justify the conduct of another RCT with improved patient selection and quality control of surgical technique. I would encourage all to continue to objectively assess outcomes in a retrospective fashion until another landmark surfaces. All well done retrospective studies should be objectively assessed for merit for publication and not biased against if they do not "confirm" the LACC trial results.

Conflict of Interest

Dr. Leitao reports personal fees from Intuitive Surgical, outside the submitted work.

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