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Editorial

Post-LACC era: critical assessment not "all-or-none" is needed

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An all-or-none approach has been adopted by many since the landmark LACC trial, which unexpectedly reported higher recurrence and mortality rates in patients randomized to a minimally invasive surgical (MIS) approach to perform radical hysterectomy (RH) [1]. We have watched with great interest as subsequent retrospective studies that have reported findings in line with LACC trial results have been touted as "confirmatory" and highlighted as plenary presentations at national and international meetings and published in high impact journals. It is quite interesting that other retrospective studies that differ in their findings have not been highlighted and considered of low quality by many [2].

In this current issue, Li et al. [3] report comparable oncologic outcomes between laparoscopic RH (LRH) and open RH (ORH) among patients with 2009 FIGO stage IB1 cervical cancer and tumor size <2 cm. This multi-institutional retrospective cohort study includes 1,484 patients (LRH, n=585 vs. ORH, n=899) and is certainly among the largest to date. It is a sound and high quality retrospective study and, of course, will still suffer from the inherent limitations of any retrospective study. There was no observed differences in disease-free survival (DFS) and overall survival (OS) between the two groups, both unmatched and after appropriate propensity score matching. Not even a "trend" that would lead many to suggest that this study suffers from an underpowering issue. Also, the number of cases included are many more than randomized in LACC which further likely negates any concern about power. They also performed subgroup analyses according to the visibility of tumor and found that LRH was not associated with recurrence and mortality rates both in the visible tumor and invisible tumor subgroups. Of course, there are limitations as this study may only apply to the surgeons who contributed cases, the method of follow-up is debatable and assessment of PFS in a retrospective fashion is quite challenging and heterogeneous. But, whether someone has died and the date of death is not so challenging when determining OS if patients have appropriate follow-up. It is important to remember that randomized controlled trials (RCTs) also only include a small fraction of the entire cohort of patients with a particular disease or who are undergoing a procedure. RCTs are the highest level of discovery but are also quite limited by the inability to include all eligible cases and their external validity is critical. Well done retrospective studies have the potential to report outcomes on all cases and not just a sampling. The current one is such an example.

A number of retrospective studies have been published around the world since we asked for continued critical assessment on this issue [4]. Many studies have reported similar

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concerning findings to the LACC trial but others have not. Kim et al. [5] reported that LRH did not influence disease recurrence of 2009 FIGO stage IB1 patients with cervical mass ≤2 cm in their early single-institutional retrospective cohort study [5]. Therefore, they suggested this subgroup as a safe candidate for LRH. However, these studies differ in terms of tumor size measurement. While Li et al. [3] (current study) used clinical or pathologic tumor size, Kim et al. [5] used preoperative magnetic resonance imaging (MRI) to determine cervical mass size. Such a difference might originate from the wide utility of MRI in Korea. This brings up an important criticism of the current study and others. What is the best way to assess tumor size? Postoperative tumor size does not always reflect preoperative tumor size assessments. Decisions to operate are based on preoperative factors and not final pathologic findings.

In contrast to the above and current study, Uppal et al. [6] reported results of their multi-institutional retrospective cohort study and noted that patients with tumor ≤2 cm on final pathology also exhibited significantly inferior DFS when RH was performed by MIS. However, in this analysis, cases with no residual tumor were excluded, while 2009 FIGO stage IA1 (lymphovascular space invasion positive), IA2, and IB1 were included. Interestingly, Uppal et al. [6] reported that conization before surgery was associated with lower recurrence risk, similar to Kim et al.'s study [5].

In the SUCCOR study, an international European retrospective cohort study, patients with 2009 FIGO stage IB1 cervical cancer who had a tumor less than 4 cm on preoperative MRI were included, whereas those who received conization before surgery were excluded [7]. Uniquely, inverse probability weighting was conducted and resulted that MIS RH was associated with higher recurrence and mortality rates compared to the ORH. However, in a subgroup of patients with a tumor ≤2 cm, similar survival outcomes were observed between the MIS RH and ORH.

Why does a cervical tumor size matter? Well, tumor size matters in many cancers not just cervical cancer. The ability to properly contain and handle tumors as they increase in size is a concern not just with cervical, but many cancers. This is further complicated when MIS approaches are used. Tumor containment and handling must be approached using basic oncologic principles whenever tumor is still present and there is potential for tumor spillage and unwanted contamination no matter the surgical approach. This might be supported by a protective effect of preoperative conization on recurrence, suggested by many retrospective studies. Moreover, the use of uterine manipulators during MIS RH seems to promote tumor breakdown and spillage further. The SUCCOR study noted that patients who underwent MIS RH without using a manipulator seemed to have similar recurrence rate compared to those who underwent ORH [7]. Additionally, increasing tumor size is correlated with the presence or absence of pathologic high-risk factors, such as parametrial extension, extracervical and nodal metastases. The LACC trial and many retrospective studies, including the current one, did not utilize routine preoperative MRI. Improper patient selection may also have factored into the results noted by LACC and other studies.

It is important that results of well-done retrospective large cohort studies continue to be highlighted and not simply negated because they do not support the LACC findings. An all-or-none approach is not the way to make decisions for patients. Not all patients with cervical cancer should undergo surgery, not all should have MIS and not all surgeons should perform MIS. Similarly, not all patients should just be opened. It seems extreme to us to perform an ORH for a patient with cervical cancer after a cone has been done and has negative margins

while at the same time, if fertility is desired, a cone alone may suffice and MIS reported to be safe if doing radical trachelectomy. This continued critical assessment is needed and provides greater equipoise as we continue to enroll patients on much needed additional RCTs such as the RACC trial (ClinicalTrials.gov Identifier: NCT03719547) and others in development. It will be frustrating that these trials may take some time to complete. However, there is enough justification from both a scientific basis and study results, such as the current, that additional RCTs are needed before we simply abandon MIS.

We are living in a post-LACC era. What are we to do? Because of MIS's many advantages, although LACC also suggested no advantage to MIS, it is difficult to abandon all MIS RH in the management of early-stage cervical cancer. We must be illuminated by LACC, a truly landmark study, and learn from it and critically assess why the results were what they were. We need to refine our selection process as well as technique and return to core surgical oncologic principles. Tumor spillage should be avoided and is completely a surgeon- and technique-related event. Köhler et al.'s 'transvaginal closure technique of vaginal cuff' [8] and Kanao et al.'s 'no-look no-touch technique' [9] would be great examples of trying to prevent tumor spillage as well as other methods. We also must be more careful when selecting cases for a possible MIS approach. A simple pelvic examination and clinical tumor assessment to decide primary surgical treatment, nevermind MIS or not, are not acceptable anymore. MRI, or high-quality ultrasound by experienced sonographers, must be a part of the initial preoperative assessment of these patients.

In conclusion, the possible advantages of MIS as seen in many other procedures should not be simply given up because of the unexpected findings from the LACC trial. We hope that MIS RH continues to be critically assessed with thoughtful discussion, rather than decay and be abandoned forever for these women. Ongoing RCTs and future ones are needed and should be strongly supported. There is enough equipoise to conduct such RCTs and enroll patients.

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