Editorial Commentary

Minimal invasive surgery in cervical cancer in the light of the LACC trial

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After a recent publication in the *New England Journal of Medicine* the world of gynaecologic oncology was shaken by the reported safety issue of minimally invasive surgery (MIS) in the treatment of early cervical cancer. These so far widely used surgical techniques are characterized by fast recovery, short hospital stays, and less perioperative complications like blood loss, thrombosis and infections. The LACC trial, a phase III study published by Pedro Ramirez showed a significantly higher risk of relapse and death in patients with cervical cancer from 2 to 4 cm managed with minimal invasive surgery, with a 99% 3 years overall survival after open surgery 3 years, versus 93.8% after MIS (1). A national American database survey (2) provided similar findings.

The LACC study has provided the only available level 1 evidence, and must be taken into account as a major source of knowledge and drive of clinical practice. However, the study was criticized, for several reasons. First of all methodological issues were identified: the primary statistical objective was not achieved; the confidence interval of the risk crosses the boundary of non-inferiority; the power of the study, which was interrupted after accruing 85% of the planned inclusions, is 84%, below the 90% standard of non-inferiority trials (3). Furthermore, the power is automatically even lower when it comes to evaluating tumors smaller than 2 centimeters. Other criticisms were related to a substantial number of missing date, and differences in patients and tumor characteristics between groups, with a higher rate of parametrial involvement in the group of MIS (7% *vs.* 4%), non-standardized adjuvant treatment, higher rate of non-cancer deaths in the laparoscopy group, and recurrence and mortality uncharacteristically low in open group. Finally the proficiency in MIS of the investigators was questioned, with an average of 2 cases per center per year.

In contrast, many well-conduced retrospective studies such as a Korean study in a highly experienced center (4). A meta-analysis published in 2015 presented the outcome of 1,539 cervical cancer patients with similar prognosis for patients treated with open and MIS (5).

In response to LACC trial many researchers started to collect their own data. Conflicting results were published, some confirming the findings of the LACC trial, others showing similar results whatever the approach. For example, a Swedish nationwide study did not show any difference in survival in 5-year observation, when robotic surgery was used compared to open approach (6). As robotic assistance has never been found to be superior to standard laparoscopic approach, this finding can be extrapolated to all modalities of MIS. A European Society of Gynaecologic Oncology (ESGO) study of a retrospective cohort found that while MIS seems to be detrimental in tumors larger than 2 cm, MIS might be safe in smaller size tumors and after cone biopsy. The latter SUCCOR study (Surgery in Cervical Cancer Observational Retrospective) collected data from 89 European Centres (7). Comparable to LACC trial the authors showed more oncological risk related to MIS (OS open surgery 4.5 years =98%, OS MIS po 4.5 years =87%). Interestingly, these results were not confirmed in patients with tumors smaller than 2 cm, after cone biopsy, when uterine manipulator was not used and when protective manoeuvers were performed [closure of the vagina over the tumor at the beginning of the procedure (8), specimen extraction performed within a bag, colpotomy performed vaginally at the end of procedure]. Some groups have already started new, prospective trial, which results are eagerly awaited.

Following current recommendations, we can state that in the light of the LACC study, the open surgery is the gold standard approach in the treatment of cervical cancer patients, but that there are indications that MIS is still feasible in low volume disease, at the condition that specific precautions are taken, by proficient surgeons in high volume hospitals. Patients should be informed about the available prospective and retrospective evidence on survival, also about the benefits of minimal invasive surgery. After the LACC publication, the majority of international societies published statements. For example, the ESGO stated (9): the ESGO encourages that all minimally invasive surgical procedures for cervical cancer are prospectively recorded, including tumours characteristics and technical details, and performed only in highly specialized centres by appropriately trained surgeons. Patients must be informed about the available prospective and retrospective evidence on survival, complications and quality of life relating to the two surgical approaches. If minimal access surgery is offered, and accepted by the patient, every effort should be made to avoid spillage of tumour cells in the peritoneal cavity (e.g., avoiding crushing lymph nodes, banning vaginal or uterine manipulators, and closing the vaginal cuff in order to avoid any contact between tumour and peritoneal cavity).

In our perspective LACC study is not a step back forward in gynaecologic oncology surgery, it is a warning and an incentive for improvement of MIS techniques and a reminder that meeting the oncological standard is a mainstay of MIS. Consequently, the results of the LACC study can be explained by two biases. The *surgeon bias* reflects the fact that an equal experience proficiency in two substantially different techniques, a traditional one and an innovative one is an extremely rare situation. The *oncological concept bias* refers to the use of a technique that does not meet the necessary oncological requirements. Poorer survival outcomes are the end of the story and the explanation might well be before the beginning. It is likely that the difference in favor of open surgery in the LACC randomized trial, the US database review and other retrospective studies is not the fault of the MIS, but of a misuse of it.

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