

Comment on the LACC Trial Investigating Early-stage Cervical Cancer by the Uterus Commission of the Study Group for Gynecologic Oncology (AGO) and the Study Group for Gynecologic Endoscopy (AGE) of the German Society for Gynecology and Obstetrics (DGGG)

Stellungnahme zur LACC-Studie bei frühem Zervixkarzinom der Kommission Uterus der Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) und der Arbeitsgemeinschaft Gynäkologische Endoskopie (AGE) der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)



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Key words

cervical cancer, laparoscopy, laparotomy

Schlüsselwörter

Zervixkarzinom, Laparoskopie, Laparotomie

received 9.7.2018

accepted 10.7.2018

Bibliography

DOI <https://doi.org/10.1055/a-0655-8112>
Geburtsh Frauenheilk 2018; 78: 766–767 © Georg Thieme
Verlag KG Stuttgart · New York | ISSN 0016-5751

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Deutsche Version unter:

<https://doi.org/10.1055/a-0655-8112>

The results of the LACC trial (Laparoscopic Approach to Cervical Cancer) were first presented in a lecture given at the 49th conference of the Society of Gynecologic Oncology (SGO) held in New Orleans on March 24–27, 2018 [1]. The primary objective of this international randomized phase III multicenter study was to compare disease-free survival (DFS) rates of women who underwent laparoscopic or robotic radical hysterectomy with the DFS of women who had abdominal radical hysterectomy (TLRH/TRRH versus TARH). Secondary goals of the study included rates of re-

currence, treatment-associated morbidity, overall survival, cost effectiveness, and quality of life. The trial was designed as a non-inferiority study of the laparoscopic treatment arm compared to the abdominal standard-of-care arm, with a follow-up of 4.5 years and a sample size of 740 patients. Patients with primary squamous cell carcinoma, adenocarcinoma or adeno-squamous carcinoma of the uterine cervix with FIGO stage IA1 (with lymphovascular space invasion, LVSI), IA2 or IB1 disease were included in the study. Each participating center had to submit 10 documented

cases who had undergone laparoscopic/robotic radical hysterectomy along with two non-edited complete video recordings to the study committee. The study was opened in June 2008 but was terminated prematurely for safety reasons by the Data Safety & Monitoring Committee after recruiting 85% of the patients because of the significant inferiority of the laparoscopic treatment arm.

Fewer than 20% of the patients were treated in centers in North America; the other study participants were recruited from centers in South America, India, China, Australia, Italy and Bulgaria. 312 women were treated in the abdominal arm and 319 women were recruited to the laparoscopic/robotic arm. Inclusion characteristics for both groups were highly comparable, particularly with regard to FIGO stage, histologic subtype, tumor differentiation, tumor size, resection margins and numbers of resected and affected lymph nodes. However, the staging, depth of invasion and tumor size were still unknown in 30% of cases at the time of presentation at the conference.

After a median follow-up of 2.5 (0.0–6.3) years with 39.2% of the datasets completed, the disease-free survival rate after 4.5 years was 97.6% (94.1–99.0) for the TARH group (per protocol) compared to 87.1% (81.0–91.3) for the TLRH/TRRH group, with a *p*-value of 0.88, meaning that the laparoscopic treatment arm had statistically failed to achieve the non-inferiority cut-off. Disease-free survival (DFS) rates were significantly higher in the abdominal standard-of-care arm (hazard ratio [HR]: 3.74; 95% confidence interval [CI]: 1.63–8.58; *p* = 0.002). Analysis of progression-free survival (PFS) rates also confirmed better outcomes with the abdominal approach (HR: 3.88; 95% CI: 1.79–8.41; *p* < 0.001). Only 7 (2.2%) of the 312 women who underwent open abdominal hysterectomy experienced recurrence, while there were 27 (8.5%) cases of recurrence in the laparoscopic/robotic arm, of which just under half were located in the vaginal vault or the lesser pelvis. The abdominal approach was also significantly superior with regard to overall survival (HR: 6.00; 95% CI: 1.77–20.3, *p* = 0.04). Of the 19 women in the laparoscopic arm who died, the cause of death in 14 cases was cervical cancer.

In addition to the above cited study, a retrospective analysis of the US National Cancer Database (NCDB) for the period 2010 to 2012 was also presented at this year's SGO conference. This retrospective study of 2221 women with FIGO stage IA2 to IB1 cervical cancer also reported significantly better survival rates for the cohort treated with abdominal surgery compared to the laparoscopic/robotic cohort. According to a secondary analysis (presented at the 2018 ASCO conference) this applied to cervical cancers with diameters between 2 and 4 cm, while the difference was not statistically significant for tumors with diameters of less than 2 cm [2].

In their respective summaries of the LACC and NCDB studies, neither of which have yet been published in full, the authors stated that laparoscopic radical hysterectomy was associated with a higher rate of recurrence and a poorer overall survival compared to open radical hysterectomy. It was recommended that patients with FIGO stage IA1 (with LVSI), IA2 and IB1 cervical cancer scheduled for radical hysterectomy should be informed about the results of the LACC trial.

Certain points of the study in its presented but not yet published form are still unresolved, including the selection criteria at the time of diagnosis (e.g. the time of randomization), the statistical validity for lower numbers of participants and shorter follow-up times and, given the incomplete datasets, the impact of a learning curve on surgeons, etc. Moreover, the very low rate of recurrence of just 2% in the open hysterectomy arm is remarkable – compared to the recurrence rates of around 10% reported in retrospective studies.

Only when the studies have been published in full will it be possible to start a discussion on whether a further randomized controlled study is needed.

The Uterus Commission of the AGO and the AGE would like to point out to all of their colleagues that because of the oncologic superiority of open radical hysterectomy as reported in the LACC study, the choice of surgical approach (i.e. laparoscopy versus abdominal surgery) must be discussed openly and frankly with patients – even if the study has not yet been peer reviewed and a final version of study has not yet been published in full.

Even surgeons with extensive experience of laparoscopic or robot radical hysterectomy to treat early-stage (up to FIGO stage IB1) cervical cancer should inform every patient in detail prior to surgery about the provisional results of the studies presented at the American conferences.

Conflict of Interest

The authors declare that they have no conflict of interest.

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