Optimal surgical approach for cervical cancer
LACC and SEER study results
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Abstract
In the management of patients with early stage cervical cancer, minimally invasive approach is considered to be the golden standard now days, and it is routinely performed.

Cervical cancer is one of the most frequent malignancies in women worldwide and is unfortunately diagnosed in advanced stages of the disease [1]. The goal of the LACC study, conducted by MD Anderson Cancer Center, an examination of the Surveillance, Epidemiology & End Result (SEER) database from the USA, was to investigate whether disease-free survival (DFS) among patients who underwent minimally invasive surgery (laparoscopic or robotic) was non-inferior compared to standard-of-care open radical hysterectomy.

The secondary outcome measures were to study the patterns of recurrence, costs, quality of life, pelvic floor distress inventory, overall survival, feasibility of sentinel lymph node biopsy, intra-operative, peri-operative, post-operative and long-term treatment related morbidity.

Minimal invasive surgery for any gynaecological pathology has become increasingly popular in recent years, and has been easily adopted across Europe. Many studies and systematic reviews, demonstrated the advantages of this approach: less complications, shorter hospital stay, lower transfusion rates, faster post operative recovery. [2-3]

Recently, results from studies of two groups, came as a surprise, and also as a concern, because of the suggestion that there might be lower overall survival rates and higher recurrence rates for minimally invasive approach to radical hysterectomy, compared to open surgery. One study from the MD Anderson Cancer Centre examining the Surveillance, Epidemiology and End Result (SEER) database and the other study, early data from the Laparoscopic Approach to Cervical Cancer (LACC) study. [4-5].

For both of the studies, the following inclusion criteria was mandatory:

• Histologically confirmed primary adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix;
• Patients with Histologically confirmed stage IA1 (with lymph vascular invasion), stage IA2, or stage IB1 disease;
• Patients undergoing either a Type II or III radical hysterectomy (Piver Classification);
• Patients with adequate bone marrow, renal and hepatic function:
• ECOG Performance Status of 0 or 1.
• Patient must be suitable candidates for surgery.
• Patients who have signed an approved Informed Consent
• Patients with a prior malignancy allowed if >5 years ago with no current evidence of disease
• Females, aged 18 years or older
Negative serum pregnancy test within <30 days of surgery in pre-menopausal women and women < 2 years after the onset of menopause.

A total of 319 patients underwent the minimally invasive procedure (16% robotics and 83% laparoscopy) and 312 patients had total abdominal radical hysterectomy. The majority of patients were stage IB1. There were no significant differences in postoperative histopathology between the two cohorts, except in the depth of invasion, with a higher rate of superficially invasive tumors in the minimally invasive group. There was also a slight difference in terms of the median number of lymph nodes between the two groups, but no difference in the rate of positive lymph nodes was observed.

Treatment arms were well proportioned on base line characteristics, including age (mean 46 years in both) and BMI. Conversion rate to laparotomy was 3%. The median follow-up was of 2.5 years. The non-inferiority boundary of ?7.2% for DFS at 4.5 years was breached (open access 97% versus minimally invasive 86%, difference ?10.6%, 95% CI ?16.4% to ?4.7%, P = 0.87). The minimally invasive arm was found to have over a 3-fold increase in DFS events (7/312 vs 27/319, HR = 3.74, 95% CI 1.63-8.58, P = 0.002), which was consistent when adjusted for stage of disease, age, BMI, lymph node involvement. The minimally invasive surgery arm was also associated with a decrease in overall survival (3/312 vs 19/319, HR = 6.00, 95% CI 1.48-20.3, P = 0.004). There were no differences in rates of intraoperative complications by treatment received (11% in both, P = 0.76).

Disease-free survival was significantly worse for patients who underwent minimally invasive surgery. The intention-to-treat analysis showed a 4.5-year disease-free survival rate of 96.5% in the open-surgery group and 86% in the minimally invasive arm. A per-protocol analysis showed 4.5-year disease-free survival rates of 97.6% and 87.1%, respectively.

The same study, showed higher survival rates for the open radical hysterectomy compared to the minimally invasive approach. The preliminary results for the minimal invasive radical surgery were so unexpected that the trial stopped prematurely after 85% recruitment.

There are many reasons that can be used to explain these results. For example, there was not enough evidence that the surgeons for the minimal invasive arm, that participated in the trial, were properly trained and if their learning curve had finished. For most of the surgeons, the problem was not why the results for the minimally invasive arm were so unexpected, but, that the control arm, with open surgery, performed extremely well.

**Learning curve**

In 2015, a study conducted by Conrad et al., [6] evaluated the patterns in use of minimally invasive procedures by members of the Society of Gynecologic Oncology and compared the results with those of their past surveys. Between 2007 and 2012, a very large increase in the proportion of surgeons who thought minimally invasive radical hysterectomy and pelvic lymphadenectomy was appropriate for cervical cancer (36.7% in 2007-81.6% in 2012). Also, between 2007 and 2012, there was an increase in conversion from minimally invasive surgery to laparotomy, and, according to the 2012 survey, 90.2% of members rarely or never referred a patient to a colleague for minimally invasive surgery, which was a significant increase from the 80.6% reported in 2004.

**Intracorporeal colpotomy**
There are some studies, cited in literature [7-8], that concluded that in case of minimally invasive surgery (total laparoscopic/robotic) intracorporeal colpotomy under CO2 pneumoperitoneum presents a risk of vaginal cuff margin and of intraperitoneal tumor spread in patients with early-stage cervical cancer treated by means of laparoscopic/robotic radical hysterectomy.

In the LACC study, the vault was the most common site of recurrence in cases of open surgery, whereas the pelvis was shown to be the most common site of recurrence in cases of laparoscopic/robotic surgery. Further, pelvic recurrence was not seen in cases of open surgery.

The recurrence pattern differed completely between the 2 groups, even though histopathological findings were identical.

**Uterine manipulator**

One of the fundamental moves during a laparoscopic procedure is applying upward traction to the uterus. Use of a uterine manipulator allows good exposure of the spaces around the uterus and a faster and safer procedure. However, some authors have raised concern that use of a uterine manipulator might help in the dissemination of malignant cells by disrupting the tumor [9-11]. Many authors have published data that have shown that use of a uterine manipulator during laparoscopic surgery for other types of cancer, such as endometrial cancer does not increase the incidence of positive peritoneal cytology or the risk of recurrence and that it has no influence on the overall survival [12]. However, use of a uterine manipulator during surgery for cervical cancer remains controversial. Rakowski et al., [13] reported that the use of uterine manipulator in robotic-assisted radical hysterectomy, did not show any clinicopathological differences in regards of depth of invasion, lymphovascular space invasion, or parametrial involvement compared those seen in cases of open surgery. On the contrary, artifactual displacement of cervical epithelium showing CIN III to fallopian tubes during laparoscopic hysterectomy performed with the use of an intrauterine balloon manipulator has been reported [14], which means that use of a uterine manipulator poses a theoretical possibility of peritoneal dissemination of cervical cancer.
These studies demonstrate the need to benchmark our work and audit our outcomes. With thousands of early cervical cancers treated with minimal access radical hysterectomies, now is already too late to be asking ourselves these questions regarding efficacy. Even if eventually it will be a choice between the risks of complications and chances of survival is not yet clear as we are still to find out the operative outcomes from the LACC study. For the time being, we have to continue to inform patients of all the data we know including that from the most recent studies and decide on the treatment strategy together. Presently, these studies have resulted in more questions rather than answers which will in turn undoubtedly prompt further trials.

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