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Expert Opinion

Minimally invasive surgery for cervical cancer: consequences for treatment after LACC Study

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For many years, the mainstay of treatment for early cervical cancer has been radical hysterectomy. The original procedures performed by Ernst Wertheim, Friedrich Schauta, and Vincent Meigs had high mortality rates. Some were performed prior to the introduction of anaesthesia and patients might have had no recourse to chemotherapy and radiotherapy if adjuvant treatment was required. Furthermore, in the early days, there were no antibiotics if infection ensued. Over the next half a century, improvements in medicine made surgery more acceptable but the operative techniques for radical hysterectomy remained largely unchanged.

Over the last 2 decades, efforts have been concentrated on reducing the morbidity of surgery. This has been achieved by selecting out women for upfront chemo-radiotherapy using new imaging techniques, providing less radical surgery for earlier stage disease, performing fertility sparing surgery for selected patients, using sentinel lymph node (LN) dissections, and utilising minimally invasive surgical techniques such as standard laparoscopy or robotics. In addition, a new understanding of malignant progression in embryologically based permissive tissue compartments [1] may change the surgical approach in other groups [2-4]. The combination of the above has changed practice unrecognisably in a relatively short time period. Furthermore, the utilization of radical hysterectomy is now less frequent. For example, a recent survey in the UK demonstrated that only about 300 such procedures were being performed annually [5].

Minimal access approaches to radical hysterectomy for cervical cancer have become increasingly popular in the last decade and have been adopted broadly across Europe and the Americas. Systematic reviews of observational studies have shown that a minimal access approach with either standard laparoscopy or robotics was associated with a shorter hospital stay, less complications, less blood loss, and lower transfusion rates [6-8]. This is in the background of recurrence rates being reported as similar in both minimally invasive and open arms [9-13].

Recently, emerging data from two groups have suggested that there might be a higher recurrence rate and lower overall survival for a minimal access approach to radical hysterectomy for cervical cancer compared to open [14-16]. This has caused surprise, reflection, and concern as to how to counsel patients when choosing a route for radical hysterectomy. More importantly, it is vital to examine what we know about both these studies to see how they might influence outcomes now and what further studies are needed in the future.

The first of these studies came from the MD Anderson Cancer Center and was an examination of the Surveillance, Epidemiology & End Result (SEER) database from the USA [14]. In this retrospective study,

the 4-year mortality risks were 5.8% for open surgery and 8.4% in the minimal invasive surgical arm, respectively. The hazard ratio (HR) was 1.48 (95% CI 1.10–1.98). The strength of this study lies with the absolute numbers of patients with 2,221 women included in the analysis. However, the results differ from numerous other series that contain combined numbers of subjects that are much greater [9-13].

Other criticisms of the MD Anderson analysis include the fact that only total survival, not disease-free survival was assessed and that the difference was not evaluated in a multivariate analysis. As the authors admitted, there were a large number of women in the minimally invasive arm who were in the learning phase of a surgeon's series. Furthermore, there appeared to be bias towards the open abdominal hysterectomy arm with less women with adenocarcinomas and large tumors. Although not individually significant, the larger proportion of women with tumors of more than 2 cm in size, parametrial involvement, margin involvement, and positive LNs in the minimally invasive arm means that a multivariate analysis was important. In addition, it seems that the selection criteria was unknown with potentially a large number of women included who might have had up-front chemo-radiotherapy in other centers judging by the amount of women with poor histological oncology outcomes post-operatively. In its own right, this paper was interesting but would not supersede the large number of other papers of arguably better quality that showed no difference in recurrences with less complications for a minimally invasive approach.

The data from the SEER database might have gone unnoticed if it was not for the results from another group [15,16]. The early data from the Laparoscopic Approach to Carcinoma of the Cervix (LACC) study also showed improved survival with open radical hysterectomy for cervical cancer compared to a minimally invasive approach. The LACC study was a randomized controlled study powered to 90% to show non-inferiority for minimal access radical hysterectomy at 4.5 years. The disadvantage for minimal invasive radical approach was so great (HR for disease-free survival = 3.74), that the Data Safety Monitoring Committee stopped the trial prematurely after 85% recruitment.

On the surface, this study might change clinical practice so it needs careful assessment and scrutiny. The trial design attempted to eliminate participating centers' learning curve accounting for any abnormal outcomes by insisting that contributing surgeons submitted outcome data from ten minimal access cases and 2 unedited videos. Many feel that this was not enough supporting evidence that properly trained surgeons were participating in the minimally invasive arm. Furthermore, the minimal access arm recruited an average of only 2 patients per center per year raising the question as to whether all surgeons had the chance to maintain sufficient experience during the decade of accrual. The number of eligible patients not recruited is unknown. However, it is not that the minimally invasive arm performed so much worse in the LACC study but that the control arm (open surgery) performed unexpectedly well. There were only seven recurrences in 312 (2.2%) women. This is an extremely low result for recurrences. On the other hand, 27 (8.4%) recurrences in the minimally invasive surgery (MIS) arm corresponded well to the data reported in most large studies comparing robotic surgery with open surgery for cervical cancer [8-13]. These studies have had similar recurrence rates for abdominal radical hysterectomy varying between 9.1%

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and 14.3%, respectively [8-13]. On the other hand, one big single center study reported for MIS recurrence rates as low as 0% to 4% (n=933) [17].

The LACC study differs so greatly from others in its recurrence rate for open surgery that we have to ask why. There is no hypothesis as to why open abdominal hysterectomy should suddenly perform so well in this group of women and we have to understand why this trial produced such an unusual result. It may be due to the incomplete data presented. Histological data on tumor size was missing in a third of abdominal hysterectomy cases. The incidence of lymph-vascular space invasion was missing in 5% of cases. Data on parametrial and vaginal involvement was missing in 7% and 10% of cases respectively in the abdominal arm of the trial. However, these parameters have been shown to have tremendous influence on recurrence-free survival even in multivariate analysis, which could additionally be influenced by the extent of the radical hysterectomy [18]. It seems a shame that in such a well-designed trial systematic reporting of histology did not occur and that this was not reviewed centrally. Only 39.2% of cases had complete data at the endpoint of 4.5 years and the average follow-up was only 2.5 years. With such a large amount of missing data it lends the question as to whether or not it is possible to get reliable results and draw valid conclusions.

When this paper reaches peer review, great care will be needed to look at the criteria used to select women for surgery such as magnetic resonance imaging, positron emission tomography, and histological analysis. Parameters for initial randomization should be clearly addressed. Individual units will need to be assessed to see if they were outliers that adversely affected the whole trial group. Sub-analyses will need to be performed to assess if the effect was predominantly seen in higher risk tumors such as those with unexpected parametrial involvement with a risk of tumor cell spilling or cut-through during surgery. Most importantly, we hope that the study group will be able to reassess the tumor size in as many patients as possible, as an asymmetric distribution of this parameter would explain the results entirely.

If the final analysis still produces a similar result to that recently presented, the authors will need to hypothesize why there is a difference. Is it due to adverse effects of the minimally invasive approach such as exposure of the tumor into the peritoneal cavity, carbon dioxide insufflation, or uterine manipulation? To answer this, they may need to obtain more data from the surgeons such as whether or not they regularly instrument the uterus, seal-off the Fallopian tubes, sew the vagina together to seal-off the tumor, or use humidified carbon dioxide and limit the intraperitoneal pressure. In addition, pattern of recurrences – vaginal, retroperitoneal in the Müllerian compartment, pelvic lymph compartment, peritoneal carcinomatosis or trocar site is of crucial importance. With respect to the influence of potential tumor cell spillage and seeding in remnants of permissive organ or lymph compartments that might be more likely in the MIS arm, an analysis as to whether there is a greater difference of recurrence between the groups in the not-irradiated compared to the irradiated patients; this would be informative since radiation should correct, at least in part, for any cell spillage in the radiation field. The authors would need to explore these and other potential adverse factors in a multivariate analysis. As the recurrence rate in the minimally invasive arm was at or slightly below the level expected, they will need to explain why their outcomes in the abdominal arm were so much better than expected than even the SEER data which showed a 7.4% probability of death within 5 years in the abdominal hysterectomy group. Can the result be explained by better surgery for open abdominal hysterectomy or better selection?

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The data presented is interesting and challenging. In spite of the weaknesses discussed, this study is extremely valuable to the discussions concerning the best surgical procedure for our patients depending on their individual circumstances. Keeping this in mind, we have to take care not to over-react to these 2 trials that report different information to that previously published in peer review journals. On the other hand, we must not ignore it either. At present, we are not at a position where we should change our practices and should remember the benefits of a minimally invasive approach in terms of blood loss, complications and quality of life. Nevertheless, we should continuously monitor our own data to identify worse results compared to the benchmark and correct for it. What we could do immediately, is to implement precautions to effectively avoid tumor cell contamination and tumor traumatization during surgery, in spite of the fact that it has not been proven that this is a significant cause for recurrence. In addition, we should tailor the surgical approach according to the patients' individual risk situation and preference. Unfortunately, even when we have the results of the LACC study there will still be no completed randomized controlled trial comparing minimal access surgery with an open approach.

What these studies do demonstrate is the need to benchmark our work and audit our outcomes. With many thousands of minimal access radical hysterectomies already performed for early cervical cancer now is probably too late to be asking ourselves these basic questions regarding efficacy. Many feels that the cat is already out of the bag and we as surgeons need to know how to speak to our patients. Whether it will eventually be a choice between the risks of complications and chances of survival is not yet clear as we are still to know the operative outcomes from the LACC study. In the meanwhile, we have to continue informing patients of all the known data including that from the most recent two studies and decide on the treatment strategy in collaboration with patients as part of the informed consent process. Presently, these studies have resulted in more questions rather than answers which will in turn undoubtedly prompt further trials.

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