

Minimally-Invasive Radical Hysterectomy for Cancer of the Cervix: The Perspective of the Society of Gynecologic Oncology of Canada (GOC)

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A randomized controlled trial¹ and a two-part cancer registry study,² published in the *New England Journal of Medicine*, report increased recurrence and mortality rates with the use of minimally invasive (MIS) radical hysterectomy as compared to laparotomy for women with cancer of the cervix.

These results have important implications that could lead to changes in practice in the surgical treatment of cancer of the cervix. Based on the findings in these two studies, careful scientific investigation is necessary to evaluate which biological, technical, or surgical factors may explain the observed deleterious effect of MIS in cervical cancer that have not been observed in randomized trials in other solid tumours, such as endometrial³ gastric,⁴ and colorectal cancer.⁵⁻⁷ Once the factors driving worse outcomes are better understood, practice guidelines can be updated to enhance the care of patients with cancer of the cervix in Canada.

LACC

The Laparoscopic Approach to Cervical Cancer trial (LACC) is a randomized international multicentre study including 631 patients with stage IA1-IB1, randomized either to MIS (319 patients, 84.4% by laparoscopy and 15.6% by robotic surgery) or laparotomy (312 patients).¹ Three-year disease-free survival was 91.2% in the MIS group compared to 97.1% in the open surgery group (HR 3.74; 95% CI 1.63–8.58), and the overall three-year

survival was 93.8% in the MIS group and 99.0% in the open surgery group (HR 6.00; 95% CI 1.77–20.30).

Comments

Although the survival in the open surgery group was higher than expected, the observed differences between the two groups are significant and concerning. As a result, the Society of Gynecologic Oncology of Canada (GOC) recommends withholding the *routine* use of MIS for radical hysterectomy in patients with cancer of the cervix. That being said, the study was performed in different areas of the world (Argentina, Australia, Brazil, Bulgaria, Canada [one centre], China, Colombia, India, Italy, Korea, Mexico, Peru, and United States) with well-established differences in incidence and outcome of cervical cancer.⁸ It is unknown if these differences would apply to the Canadian context.

Another important question raised by the study is whether different MIS techniques may have influenced outcomes, such as the use of intrauterine manipulators, the type of colpotomy (intraperitoneal vs. extraperitoneal), and the possible risk of intraperitoneal spread of cancer cells during specimen extraction.

COHORT STUDY

The second study provided data from two large cancer registries.²

Part 1: National Cancer Database

The first part evaluated 2461 patients with stage IA2-IB1 cervical cancer from the National Cancer Database between 2010 and 2013 who underwent minimally invasive radical hysterectomy (1225 patients, 79.8% by robotics) and who underwent open radical hysterectomy (1236 patients). The four-year survival was 90.9% in the MIS

Table. Risk factors in MIS and Open Surgery Groups

IA2-IB1 (2010-2013)	MIS (n=1225)	Open Surgery (n=1236)
4-year survival	90,9%	94,7%
Positive lymph nodes	10.7%	8.9%
Parametrial involvement	11%	9.5%
Positive margins	5%	4.4%
Presence of lymph vascular space involvement	31.9%	28%

MIS: minimally invasive surgery.

group and 94.7% in the open group (HR, 1.65; 95% CI 1.22–2.22).

Comments

This is a retrospective registry cohort study in which there were differences in risk factors between the MIS and open surgery groups on the final surgical pathology specimen (Table). These pathologic risk factors are strongly associated with survival and may have influenced the results, and no statistical analysis is provided.

Part 2: SEER database

The second part of this study evaluated the Surveillance, Epidemiology, and End Results (SEER) database for trends in 4-year relative survival rates in the U.S. (interrupted time-series analysis) and showed an increase in all-cause mortality over the years 2010 to 2016, coinciding with the increase in MIS uptake.

Comments

The time trend analysis does not appear to use age-standardized survival, so it is possible that their analysis may be confounded by increasing age at diagnosis. Although we do not have this type of data available in Canada, net cancer age-standardized cervical cancer survival has not declined over the past two decades.⁹

OVERALL: WHAT WE KNOW AND WHAT WE DO NOT KNOW

In these two studies, survival rates are worse when radical hysterectomy is performed by MIS compared to those of open procedures to treat early-stage cervical cancer. This difference cannot be ignored and could be specific to the biology of cervical cancer, or to specific technical aspects of the procedure leading to peritoneal contamination of tumours cells. Strategies proposed to decrease the risk of contamination include placing a suture on the unaffected

cervix at the beginning of surgery for easy retrieval and if possible to cover the tumour, using a vaginal vault cup without intrauterine manipulator, performing a colpotomy circumferentially intra-abdominally (rather than across the vagina) or via the vaginal route, and using specimen extraction techniques that mitigate intra-abdominal spillage.¹⁰

The survival difference in tumours greater than 2 cm is clear in the LACC trial, but the trial was not powered to evaluate oncologic outcomes in low-risk cervical cancers with tumours smaller than 2 cm, or in surgeries performed by robotic-assisted laparoscopy. Although not designed to answer the same question, CX.5 (SHAPE trial¹¹) may provide some informative data on the outcomes of patients with smaller tumours, most of whom were treated with MIS. In addition, a recent large Korean national database study on 6335 patients who underwent radical hysterectomy between 2011 and 2014 either by laparoscopy (n=3100) or laparotomy (n=3235) showed better survival in the laparoscopy group (HR=0.74; 95% CI 0.64–0.85), but no information on stage distribution or tumour size was provided.¹²

CONCLUSIONS

In view of the results of these two important studies, it is imperative to proceed with caution when counselling women with early stage cervical cancer about the approach to radical hysterectomy. In all circumstances, the information should be discussed thoroughly with patients.

While there are beneficial effects of MIS presented in multiple cohort studies, such as fewer complications, reduced blood loss, shorter hospital stays and less pain, the LACC study resulted in a higher rate of recurrence and mortality associated with minimally invasive radical hysterectomy for cervical cancer, with similar quality of life outcomes.¹³ For practice change, results of one randomized trial are usually confirmed by further randomized trials, as was the case for colorectal cancers.⁵⁻⁷ We currently do not know if the results of the LACC study can be directly transposed to the Canadian context, considering that only one Canadian centre participated in the trial. For that reason, GOC will launch a wide national initiative to survey cancer centres across Canada in order to obtain accurate data on outcomes following radical hysterectomy in relation to the surgical approach, and GOC encourages every centre to review their own data not only to inform the national effort, but also to inform patients on the results in their centre.

Lastly, due to the limited information available on the events reported in the LACC trial, and considering that all events occurred in 14 of the 33 recruiting centres, GOC will request that the source data be released for open access, so that further analysis can be done to replicate and understand the implications of the trial's results. The GOC will continue to update its guidance as more data and insights from these trials become available.

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