Is robot-assisted laparoscopy safe for surgical treatment of cervical cancer?

In Scandinavia, conventional laparoscopy never gained acceptance for complex oncological procedures including radical hysterectomy for early stage cervical cancer (CC). However, following the FDA-approval of robot-assisted laparoscopy for gynecological indications in 2005, a dramatic increase of minimally invasive procedures has been observed in Scandinavia. Several case series and a couple of meta-analyses have consistently shown clinical benefits of robotic radical hysterectomy compared with the abdominal approach.\(^1\)\(^2\) Also, and as expected, the oncological safety seemed reassuring.\(^3\)\(^4\) As a result, several societies and national guideline committees advocated the use of robotic surgery for the surgical treatment of CC.

The Scandinavian healthcare systems have gradually adjusted to the increasing use of robotic surgery with shorter hospitalization and significant investments in robotic systems and surgical training. With this in mind, it was anticipated that the international LACC trial (Laparoscopic Approach to Cervical Cancer), the first randomized controlled trial exploring the oncologic safety of minimal invasive surgery (MIS) for CC, merely would confirm the perceived safety.\(^5\) But it did not. In fact, it turned out that MIS was associated with almost four times higher risk of disease recurrence and six times higher risk of death. The trial has been scrutinized in detail and the reactions from the scientific community have shifted from surprise to disbelief. The critiques of the trial include early termination, lack of central pathology and inadequate proficiency assessment of participating surgeons. The latter has drawn most of the attention since it could be expected that many surgeons were in their early learning curve for the laparoscopic and robotic procedures. However, these potential shortcomings are overshadowed by the lack of a plausible biological cause for the reported inferiority of MIS. Although factors such as the use of intrauterine manipulators, intraabdominal colpotomy and CO\(_2\) gas have been proposed, none are substantiated by scientific data. Data from the LACC trial also questioned the safety of MIS for fertility-sparing treatment of CC. The trial was not powered to answer this question, although data deriving from tumors <2 cm seem reassuring. However, the ongoing international IRTA study has retrospectively assessed survival between laparotomy and MIS for women treated with radical tracheectomy.\(^6\) Preliminary data suggest that MIS is safe and it is highly unlikely that a randomized controlled trial (RCT) can be conducted for this procedure.

Following the publication of the trial, several large collaborative series have been published, many of them supporting the outcomes of the LACC trial.\(^7\)\(^8\) This is of particular interest since up until the publication of that trial, not a single study suggested that robotic surgery would be inferior to laparotomy in terms of disease-free survival. Whether this is a result of publication bias is unknown but the results from the LACC trial may have enticed surgeons to submit results contradicting the common perception of robotic surgery for cervical cancer. The majority of these retrospective series are limited by selection and time trend bias. The only nationwide, population-based cohort study on the subject was published earlier this year from Sweden.\(^9\) Based on close to 900 women treated in 2011–2017 with either open or robot-assisted approach, no difference was observed for disease-free and overall survival. Similar results have been obtained from the Danish register (unpublished data) and these observations have in common that the nearly all MIS cases were carried out using the robotic approach. Conventional laparoscopic radical hysterectomy is probably one of the most difficult minimally invasive procedures and the rapid adoption of robot-assisted surgery in Scandinavia may account for the results. Perhaps more importantly, the management of gynecological cancer in Scandinavia stands out in several ways. National strategies to centralize cancer treatment have been successful and resulted in high-volume centers, allowing for adequate surgical training and clinical research. The indications for primary treatment, surgery as well as chemoradiation, are similar and a majority of patients are entered into national quality registries. The data from Sweden and Denmark suggest that these circumstances are critical for the oncologic outcome, especially when novel technologies are implemented. However, it is important to stress that registry-based studies, regardless of the quality, cannot replace well-conducted randomized controlled trials. It could be argued that the RCT is an inappropriate method to evaluate procedural interventions, since multiple factors, apart from the treatment allocation, affect the outcome. The RCT allows the investigators to control for baseline parameters but is highly dependent on operator proficiency, thus any surgical RCT has inherent pitfalls, which in turn may compromise its external validity. Consequently, trials conducted when operators are in their early learning curve may result in type II errors. Indeed, RCTs such as the EORTC trial and the CHORUS trial for advanced ovarian cancer have been heavily criticized for poor surgical quality and the strong suspicion of type II errors, justifying the ongoing TRUST trial. Clearly, any study on underlying causes for an observed difference should be preceded by high-quality RCTs that minimize the risk of learning-curve bias. However, assessing operator proficiency is challenging, and most efforts to address this issue remain highly subjective. Conversely, setting the proficiency standards too high creates a study-specific situation far from the normal, clinical situation. Such a trial would be difficult to reproduce and would not reflect how most patients are treated.
So how do we limit the risk of type II errors in RCTs investigating procedural interventions? Perhaps by only including institutions in which the procedure in question has become part of the established treatment algorithm. In the ongoing international RACC trial, recruiting sites are only accepted if they have had an established robotic program for at least 3 years and meet certain volume criteria. These standards do not preclude type II errors but at least they reflect the current clinical situation in high-volume centers with established robotic programs. The results from the RACC trial may not be generalizable for low-volume centers and the results will not be available for another 5 years. Until then, we support the recently published European Society of Gynaecological Oncology (ESGO) statement that women with early stage cervical cancer should be offered laparotomy outside clinical trials.

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REFERENCES