

Is There a Role for Minimally Invasive Surgery in Cervical Cancer Treatment: Carry on, Discard, or Modify? A Literature Review and Case Series Presentation

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Rezumat

Mai are oare vreun rol chirurgia minimal invazivă (laparoscopică sau robotică) în tratamentul cancerului de col uterin: să continuăm, să renunțăm sau să modificăm tehnica?

Chirurgia oncologică evoluează constant. Ghidurile și recomandările sunt revizuite periodic în urma progreselor terapeutice înregistrate. Chirurgia minimal invazivă (laparoscopică și robotică) a reprezentat o etapă importantă în tratamentul cancerului de col uterin. Date noi din literatura medicală au pus însă sub semnul întrebării indicațiile acestei abordări. În 2018, studii noi au readus în actualitate întrebarea: mai există un rol al chirurgiei minimal invazive în tratamentul cancerului de col uterin? Tehnica chirurgicală propusă de Köhler (închiderea de tip bursă a vaginului) pare să rezolve unele dintre probleme ridicate de chirurgia minimal invazivă. Höckel propune excizia totală a mezometrului pentru scăderea ratei de recidivă locală. Se prezintă aceste două tehnici operatorii realizate pe cale laparoscopică. Scurta serie de cazuri prezentată argumentează fezabilitatea celor două tehnici. Pentru evaluarea riscurilor și beneficiilor sunt desigur necesare studii prospective.

Cuvinte cheie: chirurgie minimal invazivă, cancer de col uterin, excizia totală a mezometrului, chirurgie robotică, închiderea tip bursă a vaginului

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Abstract

Oncological surgery is constantly evolving. Recommendations and guidelines are updated periodically in light of new research. Since surgery is a key step in the treatment of cervical cancer in Romania and considering the new findings, this study aims to assess the new guideline recommendations and the surgical treatment options available. The paradigm shift that took place in 2018 left the question: does minimally invasive surgery still play a role in the treatment of cervical cancer? Köhler surgical technique seems to address some of the issues raised by the minimally invasive surgery with good results. Höckel proposes total mesometrial excision to decrease the risk of recurrence. This study presents 3 cases of cervical cancer patients with stages ranging from IB1 to IIIB that had undergone total mesometrial excision and vaginal cuff closure using the laparoscopic approach to minimize the risk of local recurrence. The case series presented showed that it is feasible and safe to merge these techniques. Further prospective studies are needed in order to assess the risk and benefits of these techniques.

Key words: minimally invasive surgery, cervical cancer, vaginal cuff closure, total mesometrial excision, robotic surgery

Introduction

The incidence and mortality rates from cervical cancer in Romania are among the highest in Europe (1). Even though in countries with national screening programs the incidence and mortality have a marked downward trend, according to the estimates in the GLOBOCAN Project, Romania ranks 5th place in Europe in 2018. Many guidelines recommend a treatment plan based solely on chemotherapy and exclude surgery from the treatment options in locally advanced cervical cancer (2). In Romania, the gap between scientific literature recommendations and effective implementation is maintained by late enrollment to radiotherapy and low access to specialized centers. The therapeutic strategy for locally advanced cervical cancer may differ somewhat from the European recommendations (2). Many patients are still referred to surgery in various stages of diagnosis and treatment (2).

Oncological surgery is constantly evolving, recommendations and guidelines are updated periodically in light of new research. In recent years, minimally invasive surgery (MIS) for gynecological pathology has taken a considerable lead since complication rate and

postoperative recovery time have decreased considerably (3). MIS has become the preferred option for many gynecological disorders (4). Since surgery is an important step in the treatment of cervical cancer in Romania and considering the new findings, this study aims to assess the new surgical treatment options and the new guideline recommendations.

The Paradigm Shift

The guidelines accepted both MIS and open surgery (OS) for performing the radical hysterectomy in IA2 to IIA stages of cervical cancer (5). These recommendations led to the widespread use of MIS despite the few prospective randomized studies assessing the survival outcomes (5) and the limited data from the retrospective studies. In 2018, Ramirez et al (5) conducted a prospective multicenter randomized trial to properly evaluate the survival outcomes after MIS or OS in early-stage cervical cancer. The results would lead to a major paradigm shift in cervical cancer surgery. The enrollment of patients was closed early by the data and safety monitoring committee because MIS was linked to higher rates of death (5). The 3-year rate of disease-free survival was lower for MIS

than for OS, even after adjustment for age, body-mass index, stage of disease, lympho-vascular invasion, and lymph-node involvement, as well as a lower rate of overall survival (5). Evaluated at 4.5 years, the rate of disease-free survival was 86% for MIS and 96.5% for OS (5).

In addition, Melamed et al. (6) conducted an epidemiological study that would indisputably link the MIS to shorter survival rates than OS for IA2 and IB1 cervical cancer patients. The adoption of MIS coincided with a decline in the 4-year relative survival rate of 0.8% per year after 2006 (6).

Since then, ESMO (7) has included in the clinical practice guidelines that MIS cannot be regarded as the preferred treatment option and that patients should be counselled about the risks and benefits of the different types of surgery. NCCN (8) updated the principles of evaluation and surgical staging as follow: OS is the standard and recommended approach.

Moreover, in 2020 a systematic review and meta-analysis revealed once more the high risk of recurrence and death associated with the MIS compared with OS (9). Subsequently, many studies linked MIS to lower overall survival and disease-free survival (10-14). Some studies emerged claiming improved disease-free survival for MIS approach (15) or at least non-inferiority (16-22). Considering the new findings, in the United States, there is a decreasing utilization of MIS hysterectomy in cervical cancer patients associated with an increase in perioperative complications and longer hospital admissions (23). Even in Europe, 57% of the total European Society of Gynecological Oncology members who responded to a survey shifted to open surgery and 50% consider MIS to be appropriate only for small tumors (24). This unexpected result left the scientific community divided, but obliged to further investigate the matter and impartially evaluate the results taking into consideration both sides.

Controversies

As with other major paradigm shifts in medical

fields, debates emerged. One of the controversies is on the surgical proficiency. Vergote et al (25) acknowledged that the surgical proficiency should be considered the most important issue of a surgical trial pointing out that in the LACC trial some of the participating surgeons had not completed a fellowship in gynecological oncology and some were general surgeon with surgical oncology fellowships, and most had not published their results in MIS hysterectomies. The measurements of the length of parametria as a parameter of the radicality had not been performed (25). Another argument as identified by Kimming et al (26) was that the MIS arm recruited an average of only 2 patients per center per year raising the question if all surgeons had the chance to maintain sufficient experience during the decade of accrual.

Another argument was that the choice of type II or type III MIS radical surgery was left to the operating surgeon. There were no protocol guidelines indicating which type of surgery should be performed for which size (25). Even though the LACC trial assessed the MIS approach, only 45 patients [16% of MIS (27)] who underwent robotic surgery were included (25).

Another controversy started from the fact that the control group, OS approach, performed unexpectedly well, with a low result for recurrences (26,28). Given the fact that histological data on tumor size was missing in a third of OS cases, this may be due to the incomplete data presented (26). Another perspective is the characteristics of the cohort. Leitao (28) identified: 92% had stage B1 cervical cancer, 2% had positive vaginal margins and 13% had nodal metastasis compared to the Gynecologic Oncology Group (GOG) trials 109, 92 and 49, the 3- and 5-year progression free survival rate of the LACC trial cohort should have fallen between 80% and 95%.

Carry on, Modify or Adapt?

The scientific community attempted to understand the causes why MIS does not provide a

similar oncological outcome as OS. Taking into consideration the basic principles of oncological surgery, the following weak points were identified as possible causes. The surgical technique of MIS radical hysterectomy is associated with the use of uterine manipulators (29,30). This can condition the spread due to erosion and friction of the tumor, even leading to its perforation (31). Another possible cause was that tumor cells may spread within the peritoneal cavity by circulating carbon dioxide when intraperitoneal colpotomy is performed above the manipulator rim (29-31).

Other possible reason may be the experience of the surgeon, the learning curve, if he has the experience to perform oncological gynecologic MIS (32). This may be translated into the volume of the treatment center of the particular pathology. Gennari et al (33) proved that for early stage cervical cancer the treatment center was associated with the survival and not the surgical approach: those treated in university cancer centers had the overall survival significantly increased that those in non-university centers. Other studies have identified that the proficiency levels of the surgeon may be associated with survival outcomes of cancer patients (34). The influence of the learning curve on the survival of early-stage cervical cancer patients after OS and MIS radical hysterectomy was evaluated by Li et al (35). For OS the learning period was defined as 30 cases and for MIS as 60 cases, after that the surgeons were considered proficient (35). Irrespective of the approach, proficient surgeons had better 5-year disease free survival than those in the learning period after adjusting for risk factors. All patients with tumors less than 2 cm had similar 5-year disease free survival regardless of the operation approach or learning curve (35). Interestingly, MIS presented lower survival rates than OS when tumors where ≥ 2 cm in the proficient surgeon group. The authors concluded that MIS radical hysterectomy required more cases than OS to achieve acceptable 5-year disease free survival (35). Kim et al (36) demonstrated as well that patients included in the early phase of MIS revealed poorer progression-free survival,

surgical proficiency could significantly affect the oncological outcome in MIS.

All things considered, the medical community should not forget the benefits of MIS. Some studies show that the rate of postoperative complications is significantly lower for the MIS16. Li et al.³⁷ performed a meta-analysis demonstrating that MIS is superior to laparotomy with fewer postoperative overall complications (wound infection, pelvic infection and abscess, lymphedema, intestinal obstruction, pulmonary embolism, and urinary tract infection), but is associated with higher risk of intraoperative complications (cystotomy, bowel injury, and subcutaneous emphysema) and postoperative fistula complications. Assessing the postoperative quality of life, Frumovitz et al (38) stated that it is similar between MIS and OS approach at 6 weeks and 3 months after surgery.

Taking into account the technological advantages given by robotic surgery, the scientific community turned the focus on it as a way to overcome the difficulties from laparoscopy. Multiple studies emerged showing that robotic MIS for early-stage cervical cancer was not associated with increased risk of recurrence or reduction in survival outcomes (39,40). There is an international multi-center, open-label randomized controlled trial evaluating the oncological safety of robot-assisted approach to early-stage cervical cancer compared with standard laparotomy that is ongoing with estimated closure date May 2027 (41) that will clear the topic.

In 2020, the SUCCOR study revealed similar results: MIS is associated with increased risk of relapse and death compared to OS (13). Additionally, this study determined that by non-using the uterine manipulator and adopting maneuvers to avoid tumor spread during colpotomy (protective vaginal closure), the MIS patients had similar outcomes as those with OS (13). Kampers et al (42), in a systematic review and meta-analysis, found that disease free survival and overall survival in laparoscopy seem to be depending on the surgical technique (no uterine manipulator with vaginal colpotomy).

Protective operating techniques result in improved survival (42). In the same year, Nica et al (43) did not find the use of an intrauterine manipulator as an independent factor associated with the rate of recurrence after controlling for adverse pathological factors. They identified tumor size as the only factor consistently associated with disease-free survival (43). Li et al (34) identified as well that the tumor size may be an important factor affecting the survival of cervical cancer patients, as Hwang et al (14) showed similar recurrence and overall survival for cervical masses less than 2 cm. Kanno et al (44) also acknowledged that MIS radical hysterectomy with no-touch isolation techniques for stage IA to IB1 is a safe approach, but no significant differences were associated with the tumor diameter over the size of 2 centimeters. Neither Baiocchi et al (20) identified the tumor size as a risk factor.

To address this issue, Köhler et al (29) established a surgical technique that combined the MIS and vaginal approach: laparoscopic radical hysterectomy with transvaginal closure of the vaginal cuff. The retrospective study conducted by Köhler using the same inclusion criteria as Ramirez et al (5) showed similar oncological outcomes (29), but further validation in randomized studies are necessary. These maneuvers have been shown to decrease the relapse rate in retrospective studies (45,46). Multiple surgical techniques were proposed, but they can be grouped as follow: transvaginal approach or intracorporeal approach. For the transvaginal approach, the surgeon creates the vaginal cuff with a purse string suture after approximating the margins with straight Kocher clamps (29) or with simple interrupted stitches reinforced by a purse string (46). Some authors propose to first incise the vaginal mucosa circumferentially and after that the cuff is closed with a running suture (31). The intracorporeal approach implies that the vagina should be clamped with a bulldog or sectioned using a surgical stapler (46). The vaginal cuff length is not associated with local recurrence (47).

In 2003, Höckel et al (48) proposed the total

mesometrial resection (TMR) based on developmentally defined surgical anatomy inspired by the advances made in the surgical treatment of rectal cancer: the introduction of total mesorectal excision based on the same principle (48). He assumed that an incomplete resection of the posterior subperitoneal and retroperitoneal extension of the Mullerian compartment in conventional radical hysterectomy may be the cause of relapse (49). The cervical cancer spreads locally within this compartment for relatively long phases in its natural course and by TMR a complete excision is achieved except for its distal part to preserve a functional vaginal vault (49). After publishing the results, Höckel et al. raised many controversies in terms of feasibility and safety of the surgical technique proposed (50, 51), question marks that can be elucidated only by prospective multicenter studies. The multicenter study No. NCT01819077 may finally show if TMR is efficient in the treatment of cervical cancer, improving oncological outcomes without the necessity of the multimodal treatment (52). In 2019, Höckel et al. (53) reported mature results from a single-center, prospective, observational study: 495 patients with cervical cancer stage IB to IIB had a 5-year disease-specific survival of 89.4% and recurrence-free survival of 83.1%, with no neoadjuvant therapy. This technique was soon translated to robotic surgery with similar results (54).

Case Series Presentation

Taking into consideration the above-mentioned data, the study presents a case series in which we merge both techniques (vaginal cuff closure and total mesometrial excision) in order to perform an oncologically safe minimal invasive procedure for cervical cancer patients.

The first case was a 66-year-old woman with IIIB cervical cancer with neoadjuvant radiotherapy. An exploratory laparoscopy was performed to exclude peritoneal and liver involvement. After that, a total radical hysterectomy with bilateral oophorectomy Höckel

technique with pelvic lymph node dissection with prior vaginal cuff closure was carried out using laparoscopic approach. Early postoperatively, the patient developed cardiac dysrhythmia (paroxysmal atrial fibrillation) which was chemically converted to sinus rhythm. The patient had prolonged postoperative ileus and leukocytosis, thus, a CT scan was performed. A right juxtavesical ureteral fistula was noted. A double J catheter was placed with complete remission of symptoms and discharged on postoperative day 9.

The second case was a 53-year-old woman with IB1 cervical cancer for which neoadjuvant radiotherapy was performed and a total radical hysterectomy with bilateral oophorectomy Höckel technique with pelvic lymph node dissection with prior vaginal cuff closure by laparoscopic approach. Postoperative period was uneventful, with 5 days postoperative hospital stay.

The third case was 34-year-old woman with IB1 cervical cancer with neoadjuvant radiotherapy for which a total radical hysterectomy with bilateral oophorectomy Höckel technique with pelvic lymph node dissection and vaginal cuff closure was performed by laparoscopic approach. The patient was discharged 5 days after surgery with no complaints.

Conclusion

The paradigm shift that took place in 2018 raised the question: does minimally invasive surgery still play a role in cervical cancer treatment? Köhler surgical technique seems to address some of the issues raised by the MIS with good results. Höckel proposes total mesometrial excision to decrease the risk of recurrence. The case series presented showed that it is feasible and safe to merge these techniques. Further prospective studies are needed in order to assess the risk and benefits of these techniques.

Conflict of Interest

The authors declare no conflict of interest.

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Ethics Approval

Informed consent was obtained from all patients who underwent surgery and approval from the local Ethics Review Board of Fundeni Clinical Institute was obtained for the use of the patient data in this study.

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