NARRATIVE REVIEW

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Precision and progress: minimally invasive surgery in gynecologic cancer treatment

MIS in Gynecologic Oncology

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ABSTRACT

Minimally invasive surgery (MIS), which comprises laparoscopy, robotic surgery, and vaginal transluminal natural endoscopic surgery (vNOTES), has gained notoriety in the setting of many gynecologic diseases, including endometrial, ovarian, and cervical cancers. Over the years, several studies have conducted comparisons between MIS and laparotomic surgery. The predominant aspects of these techniques include less intraoperative bleeding, shorter hospitalization, accelerated postoperative recovery and lower incidence of peri- and postoperative adverse events. However, costs and operative time remain high. Articles comparing different

minimally invasive surgical procedures for the management of gynecologic cancer were reviewed. Although several articles have pointed out that the use of the surgical approach by MIS has not shown substantial differences in survival compared with laparotomy and has manifested excellent peri- and postoperative outcomes for endometrial cancer, the relevance of minimally invasive surgery for cervical and ovarian cancer remains controversial. Incipient indications suggest laparoscopic cytoreduction as an emerging procedure for appropriately selected patients following neoadjuvant chemotherapy treatment. Several scientific evidence have attested to the improved clinical parameters associated with the adoption of a minimally invasive surgical approach compared with open procedures. The preeminent goal of minimally invasive surgery should aim at optimizing oncologic outcomes and improving the health status of patients.

Key words

Minimally invasive surgery (MIS); gynecologic cancer; laparoscopy; robotic surgery; perioperative outcomes.

Introduction

Minimally invasive surgery (MIS), including laparoscopy, robotic surgery, and vaginal natural transluminal endoscopic orifice surgery (vNOTES), has been an increasingly used modality for the management of various gynecologic conditions, including endometrial, ovarian, and cervical cancer. Over the years, several studies have compared MIS with laparotomic surgery showing its characteristics, demonstrating its non-inferiority to open surgery [1–3]. The increased use of MIS is mainly due to its positive aspects: less intraoperative blood loss, reduced hospitalization, faster postoperative recovery and lower incidence of peri and postoperative complications [4,5]. Unfortunately, costs and operating times, mainly for robotic surgery, remain high [6]. However, with the development of new technologies, it seems necessary to submit these methodologies to a critical evaluation to ensure that the oncologic outcomes are superior or at least equivalent to the laparotomic approach, historically considered the standard of care. Furthermore, due to the complex nature of patient populations and tumor processes, these minimally invasive approaches are not free of difficulty and the adoption of minimally invasive methodologies is currently subject to controversy, particularly concerning cervical and ovarian cancers [7–10].

In 2022, gynecological cancers were responsible for 1,473,427 new cases and 680,372 deaths worldwide, exhibiting significant regional disparities in both incidence and mortality rates. In Europe, there were slightly over 270,000 new cases reported, with approximately 100,000 associated deaths [11].

From 2015 to 2021, a total of 246,743 hysterectomies were performed across the United States. Of these, 188,534 procedures (76%) were conducted for benign indications, while 59,209 procedures (24%) were related to gynecologic cancer case [12] A prevalent surgical procedure conducted within the European Union is the hysterectomy. In 2022, the highest incidence of hysterectomies was recorded in Czechia, at a rate of 146.1 per 100,000 inhabitants. In contrast, the incidence across other EU member states varied, with the Netherlands reporting a rate of 45.7 per 100,000 (based on 2021 data) and Lithuania exhibiting a higher rate of 127.4 per 100,000. Romania demonstrating the lowest rate at 7% [13]. In Europe, MIS has revolutionized the approach to gynecologic oncology, providing safe and effective options for the treatment of gynecologic cancers. However, the decision on the optimal surgical approach must be made in a case-by-case situation, considering the specific patient and tumor characteristics. This review aims to explore the current literature about minimally invasive surgery in gynecological cancers, according to the most relevant and novel studies.

Materials and Methods

The search was conducted in March 2024, by different authors independently, on different databases (MEDLINE, EMBASE, Global Health, Cochrane Database and Web of Science) to find all relevant trials. No filter about the year of publication was set. We screened articles including the following keywords: “Endometrial Cancer”, “Ovarian Cancer”, “Cervical Cancer”, “Minimally Invasive Surgery”, “Laparoscopy”, “Robotic Assisted Laparoscopy”, “Gynecologic Surgery”. Key criteria for inclusion were: (i) English articles, (ii) original studies about minimally invasive surgery or gynecologic surgery, (iii) studies comparing different surgeries in gynecological cancer. Letters, editorials and case reports were excluded from this review. All articles were screened using the keywords by independent authors (TGD and EDA). The studies that met the inclusion criteria were further considered, and relevant data were extracted and analyzed for each paper. The full text of these potentially eligible articles was retrieved and assessed for eligibility by other independent review team members (IC and OD). Any disagreement between them over the eligibility of some articles was resolved through discussion with an external collaborator (GB). All the studies screened through the inclusion criteria were examined, and relevant data was extracted for each paper. Two authors (TGD and EDA) independently extracted data from articles about study characteristics and included populations, types of intervention and outcomes. Due to the nature of the findings, we opted for a comprehensive synthesis of the results from selected articles.

Results

Cervical cancer

In Italy, cervical cancer is the fifth most common cancer in women under the age of 50 and accounts for 1.3% of all diagnosed cancers. Worldwide, it is the third most common cancer in terms of incidence and mortality among females with an estimated 604,000 new cases and 342,000 deaths in 2020 [14].

In addition to the well-established causal effect of HPV infection in the etiology of intraepithelial neoplasia and cervical cancer, other factors may be involved as the reactive oxygen species (ROS) and free radicals [15].

Radical hysterectomy is the standard of care for the treatment of early-stage cervical carcinoma (FIGO stage IA2-IB1) [16,17], except for patients who desire to preserve fertility, where fertility-sparing treatment appears to be a valid option [18].

For decades, this procedure has been performed via laparotomy with excellent cure rates. In 2018, this result was validated by the LACC trial where, although similar postoperative quality of life was observed among the treatment groups [19], the 4.5-year disease-free survival (DFS) rate was found to be 86.0% with MIS and 96.5% with open surgery; similarly, a lower overall survival (OS) can be seen in minimally invasive surgery compared with open surgery [20].

In 2020, the SUCCOR study, an international observational European cohort study, analyzed oncologic outcomes in IB1 cervical cancer patients undergoing radical hysterectomy. Of the 1272 patients included in the study, 693 were extracted for analysis, of whom 228 underwent radical hysterectomy by laparoscopic surgery and 63 by robotic surgery. A 4.5-year disease-free survival assessment was performed for both groups. The results indicated twice the risk of recurrence for patients treated with minimally invasive surgery compared with those undergoing open surgery ($p = 0.001$). Similarly, the risk of mortality was 2.42 times higher in the minimally invasive surgery group than in the open surgery group ($p = 0.005$). In addition, it was observed that the use of uterine manipulators would appear to be associated with decreased disease-free survival [21].

Bilal M Sert et al. [22] confirmed the evidence reported in previous investigations. Of the 582 patients included in the study (353 in the laparotomy cohort and 229 in the minimally invasive cohort), twice the risk of recurrence was observed in the group undergoing MIS compared with the open group (HR 2.73, 95% CI: 1.56-4.80). Although MIS does not show favorable results in terms of DFS and OS compared to open surgery, recent data indicate that after radical hysterectomy, MIS has a lower rate of postoperative complications than the open procedure (31.2% vs 19.9%, $p < 0.001$) [23–25].

The comparison of robotic and laparoscopic surgery for the treatment of cervical cancer is a topic of growing interest in the scientific community. Both procedures represent minimally invasive surgery modalities, although they differ in their execution. Scientific studies and literature reviews have aimed to evaluate the outcomes and advantages of the two techniques in dealing with cervical cancer. However, some investigations have found no significant differences in terms of operative duration, blood loss, risk of intra- and postoperative complications, and the number of lymph nodes excised [26–28]. Currently, the choice between open and MIS depends on the surgeon's expertise, available resources, and the complexity of the specific case. Although in some studies [29], the recurrence rate would appear to be higher in laparoscopic surgery, these data are not statistically significant ($p=0.250$).

The robotic-assisted surgical procedure manifests efficacy, safety, and viability in the setting of women with cervical cancer. Although most studies attest to parity in survival outcomes between the robotic approach and laparoscopy, there is a statistically significant reduction in postoperative complications, duration of bladder catheters and drains, and overall length of hospital stay in populations treated with the robotic technique compared to those undergoing laparoscopy ($p < 0.05$) [30]. This equivalence between the two procedures is also found when hysterectomy is combined with pelvic lymphadenectomy [31].

In recent years, single-site robotic radical hysterectomy has been explored, an advanced surgical procedure that employs robotic technology to conduct a complete hysterectomy through a single incision, with the intent of minimizing the surgical impact on the patient. This approach is technically feasible in patients with cervical carcinoma [32], showing little difference from the multiport robotic procedure, except for a lower postoperative hospital discharge and total hospital costs compared with multiport robotics ($p < 0.001$), and a reduced extent of lymph node recovery compared with multiport robotics ($p < 0.001$), as attested by this retrospective study involving 62 patients [33].

Nowadays, the natural orifice transvaginal transluminal endoscopic natural orifice surgery (vNOTES) procedure has been successfully applied in adnexal surgeries, hysterectomies, and lymphadenectomies. Scientific literature regarding this innovative technique is still limited, although studies have been conducted, both with and without the use of gas. At present, it is possible to state that both methodologies are technically feasible and safe in performing hysterectomy in the field of gynecologic oncology [34]. Undoubtedly, scrupulous preoperative patient selection and adaptation of intraoperative techniques are a safe approach to conducting vNOTES procedures [35].

Endometrial cancer

Endometrial cancer (EC) is the most common gynecologic cancer and 6th most common cause of cancer death among women worldwide [36]. Its incidence is increasing year after year in every ethnic population and in 2020 more than 417.000 new EC cases were diagnosed, with nearly 100.000 deaths [37].

Surgery is the most important treatment for endometrial cancer, which includes peritoneal fluid aspiration, total extrafascial hysterectomy combined with bilateral salpingo-oophorectomy, and in selected cases, omentectomy and sentinel lymph node biopsy [38–40], however, a more conservative approach should be considered for women desiring fertility preservation [41]. Etrusco et al. demonstrated how fertility-sparing treatment may represent a feasible and safe option for women of childbearing age diagnosed with Grade 2 endometrial cancer [42].

In the 1990s, the use of minimally invasive surgery was introduced to achieve complete surgical staging of endometrial cancer. The Gynecologic Oncology Group (GOG) conducted a prospective randomized trial to compare laparotomy with laparoscopy (GOG-LAP2 trial). This study involved 2616 patients with endometrial cancer and showed that laparoscopic surgery for uterine cancer is feasible and has a better safety profile than the same procedure performed by laparotomy. The 5-year overall survival was 90% in both groups, but length of hospitalization, pain, postoperative complications, and quality of life were better in the laparoscopic group [43].

Over the years since the conclusion of the LAP2 trial, numerous studies, both randomized and nonrandomized, have been conducted to evaluate and compare the use of MIS with laparotomy surgery in the context of endometrial cancer. Numerous investigations highlight that the surgical approach using MIS not only did not manifest significant differences in survival outcomes compared with laparotomy but showed superior peri- and postoperative outcomes [44,45].

After the introduction of laparoscopy, the evolution of minimally invasive surgery continued with the advent of robotic surgery. Beginning in 2005, robotic surgery for endometrial carcinoma rapidly gained popularity. It has demonstrated comparable oncologic outcomes, with reduced length of hospital stay, fewer complications, and lower conversion rates than laparoscopy. However, it is associated with higher costs than laparoscopy, and numerous scientific investigations confirm its safety and efficacy, especially in obese patients [46–48].

Currently, although there are few randomized trials comparing robotics with laparoscopy and laparotomy, we can say that the conversion rate, blood loss, and length of hospitalization are lower in the robotic group, in contrast to a significantly higher cost and longer operative time [49–51].

Despite the advantageous features of the robotic-assisted surgical procedure compared to laparotomic surgery, some research reveals that the recurrence rate is statistically higher in the group of patients treated by robotic procedure than in those who underwent laparotomic surgery. These conclusions emerge from a retrospective study conducted on a cohort of 135 patients with stage I endometrial carcinoma with intermediate-risk endometrioid features. The analysis significantly demonstrated that the five-year disease-free survival rate was higher in the group of patients who underwent laparotomic surgery (100%) than in those who underwent the robotic procedure (91.8%) ($p=0.005$) [52].

A similar result was found in a further retrospective study involving a cohort of just over 1,000 patients. This study focused on the comparison of two minimally invasive surgical techniques: laparoscopy and robot-assisted surgery. The conclusion from this investigation was that patients who underwent robotic surgery had poorer disease-free survival than those who underwent laparoscopy ($p = 0.04$) [53].

An important consideration in minimally invasive surgery concerns the use of the uterine manipulator. Over the years, concerns have emerged that the use of the uterine manipulator may increase the risk of dissemination of early-stage disease and lead to a higher incidence of recurrence. In 2013, a randomized trial [54] appeared to end this concern, demonstrating in a sample of 110 randomized patients that implementation of uterine manipulation systems did not generate a significant increase in rates of positive peritoneal cytology or lymphovascular space invasion. About 8 years later, a large retrospective study conducted by Pablo Padilla-Iserte et al. [55], involving more than 2,500 patients (1756 undergoing hysterectomy with uterine manipulator

and 905 without), showed that the recurrence rate in endometrial cancer was 11.69% in the group with uterine manipulator and 7.4% in the group without manipulator (P < 0.001). At present, there is still no clear consensus on this issue.

Among the innovations introduced in robotic surgery, in recent years total hysterectomy with bilateral salpingo-oophorectomy and lymphadenectomy has been performed through the "single port" robotic technique [56,57], leaving a scar of slightly more than 2 cm. With a multichannel system consisting of a five-lumen port, access is provided to the instruments to perform the procedure. These studies, although characterized by a limited cohort, have found the feasibility of the surgical procedure in endometrial carcinoma with the consequence of leaving a unique small scar. Using a multichannel system consisting of a five-lumen port, access is provided to the instruments needed to conduct the procedure. These studies, while presenting a limited cohort, have identified the feasibility of this surgical procedure in the context of low-risk endometrial cancer.

In recent years, the vNOTES approach has also gained acceptance for the treatment of early-stage endometrial cancer, proving to be safe and feasible. This method has also been successfully applied in patients undergoing sentinel lymph node biopsy and/or bilateral pelvic lymphadenectomy. Available studies indicate the feasibility of the vNOTES procedure, with the prospect of reduced postoperative hospital stay, more timely recovery, and superior cosmetic results [58,59]. In 2021 Emre Mat et al, although on a limited cohort of 6 patients, highlighted the increased benefits offered by the vNOTES procedure to obese patients when performed by an experienced surgeon [60].

Ovarian cancer

Ovarian cancer affects thousands of women every year and represents the female cancer with the highest mortality rate, with an estimated 13,270 deaths in the US in 2023 [61,62]. Its prevalence is highest in the female cohort over the age of fifty; however, it is likely to occur in any age group. Its high mortality is attributable to early clinical identification, which often occurs in advanced stages, regarding stages III-IV according to the International Federation of Gynecology and Obstetrics (FIGO) classification. Traditionally, ovarian cancer has been managed mainly through a complete staging surgical approach by laparotomy: bilateral salpingo-oophorectomy, abdominal hysterectomy, omentectomy, aortic and pelvic lymphadenectomy, as well as peritoneal biopsies and peritoneal washing. Minimally invasive surgery in the treatment of ovarian cancer has gradually emerged as the predominant therapeutic modality in recent years. This surgical methodology is focused on minimizing the impact on the patient's body. Laparoscopic surgery in early-stage ovarian cancer was first described in the mid-1990s [63]. Since then, several studies have been published evaluating the safety, feasibility, and potential benefits of laparoscopic surgical staging of ovarian tumors [64,65]. Laparoscopy offers multiple advantages with better clinical outcomes in terms of less postoperative pain, less blood loss and shorter hospital stay than laparotomy [66]. In contrast, laparoscopy has disadvantages such as the inability to palpate lymph nodes, rupture of the ovary capsule, and the risk of metastasis at the trocar site [67]. Laparoscopy can also be used to perform complete debulking surgery in patients with ovarian carcinoma or recurrent ovarian carcinoma. This is shown by a retrospective study conducted by Gallotta et al. [68], who demonstrated that in 58 patients with recurrent ovarian carcinoma, complete debulking was documented in all cases. Intraoperative complications had a rate of 6.8%, while early postoperative complications were recorded at 10.3%, with only one grade 3 complication. The median PFS was found to be 28 months, with a second-year PFS of 58.7%. This investigation highlights the feasibility and safety of the laparoscopic approach for optimal cytoreduction in patients with recurrent ovarian cancer. Laparoscopic cytoreduction could be a new procedure for appropriately selected patients following neoadjuvant chemotherapy treatment. Aletti et al. [69]

have shown that minimal invasive interval debulking surgery (MI-IDS) appears to be feasible and safe for patients manifesting a clinically complete response to neoadjuvant therapy. A residual tumor size of 0 cm was achieved in 96.6% of subjects, with no early postoperative complications observed.

Although laparotomy has traditionally been the predominant approach, Pecorino et al. highlighted the efficacy of minimally invasive methods in both staging and fertility-sparing interventions for ovarian borderline tumors [70].

In addition, the application of a psychometric test revealed the presence of moderate distress in the vast majority of patients, thus demonstrating the relevance of psycho-oncological assessments in the context of such surgical procedures. Over time, MIS has progressively consolidated its position, and several scientific investigations attest that MIS does not appear to be inferior to laparotomic surgery for ovarian cancer staging. Moreover, such research highlights peri- and postoperative advantages, positively reflecting on surgical outcomes [71,72]. Over the years, robotic-assisted surgery has also gained relevance in the field of gynecologic oncology. Perioperative results show comparability between conventional laparoscopy and the robotic approach, both in the early stages and in advanced or recurrent disease [73]. The long-term prospects for the clinical outcomes of robot-assisted laparoscopy in patients with ovarian cancer are insufficiently investigated. B Facer's study [74], conducted on a cohort of approximately 1900 patients undergoing MIS, revealed no disparity in overall mortality between the robot-assisted laparoscopic approach and conventional laparoscopy. Although robot-assisted laparoscopy was associated with a lower incidence of conversion to open surgery, no significant divergence in survival was shown between patients undergoing robot-assisted laparoscopy and those undergoing conventional laparoscopy

Discussion

Minimally invasive surgery in gynecology consists of a set of surgical procedures aimed at treating gynecologic conditions using less invasive surgical approaches than traditional open practices to minimize patients' traumatic impact. Over the years, the adoption of MIS has progressively grown. For example, in 2006, only 2 % of radical hysterectomy procedures were performed by laparoscopy, while in 2010, the laparoscopic rate increased to 23 %, with 10 % of procedures performed using robot-assisted surgery. At the same time, the rate of open radical hysterectomies decreased from 98% to 67% [75]. The analysis conducted shows that, especially in large hospitals, there is a greater propensity to adopt minimally invasive surgical approaches.

In this study, we conducted a synthesis of the available evidence regarding the impact of MIS in the management of major ovarian, cervical, and endometrial malignancies. The findings not only reflect the inherent surgical advantages of this modality but also highlight the oncologic benefits. One of the highlights is undoubtedly the cosmetic outcome resulting from this procedure.

Since the introduction of this surgical methodology, the focus has been progressively turned to minimizing the size of scars [76], simultaneously promoting an improvement in patient's quality of life. Furthermore, it can also positively affect the psychological side of patients. This is corroborated by a survey conducted by Gueli Alletti S. et al. [77] which found statistically significant differences in favor of MI-IDS by psychometric evaluation in women with advanced ovarian cancer. In addition, we are currently able to exploit natural anatomical orifices, consequently reducing the scarring footprint in patients' bodies [78], highlighting how minimally invasive procedures induce a reduced level of pain, facilitating faster recovery for patients [79].

Surgeons sometimes prefer a minimally invasive approach to perform lymphadenectomy in gynecologic neoplastic settings; in fact, its positive effect is mainly manifested in surgical

outcomes, with reduced length of hospital stay (11.6 vs 16.9 days, P < 0.001) and lower mean estimated blood loss (220 vs 531 mL, P = 0.002) [80].

The decreased blood losses observed can also be attributed to the utilization of novel electrocautery hemostasis methods [81]. Although the recent electrocautery devices appear as appealing and potentially safer options, there is currently insufficient evidence to declare one vascular sealing technology superior to another.

During minimally invasive procedures, the adoption of new methods, such as the use of indocyanine green, is becoming increasingly common as a support for the surgeon. Recently, to prevent pelvic organ injuries during laparoscopic procedures, the use of indocyanine green has been shown to be effective in identifying the course of the ureters [82].

In addition, minimally invasive methodologies can also be used for more complex procedures, such as eviscerations for malignant neoplastic disease. The investigation by Puntambekar S. et al. documented the feasibility of such a procedure in 10 patients with advanced gynecologic neoplastic disease [83]. Of course, carefully selected patients could achieve a survival benefit by obtaining a residual tumor equal to 0.

Minimally invasive surgery is now employed in almost all procedures related to benign gynaecological pathologies. Contemporary surgical techniques increasingly prioritise minimising invasiveness to reduce patient trauma, mitigate complications and promote faster recovery. Ahmed Elmaasrawy et al. demonstrated that the transvaginal endoscopic approach for the removal of benign adnexal masses has numerous advantages over the traditional transumbilical method [84,85].

Conclusions

Over the past two decades, minimally invasive surgical methodologies have sparked a revolution in the field of gynecologic oncology. Several scientific evidence attested to the improvement in clinical outcomes associated with the adoption of a minimally invasive approach in comparison with open procedures. Both conventional laparoscopy and robotic-assisted surgery manifest significant advantages, and the preference between the two modalities often depends on the surgeon's decisions. It has been widely found that minimally invasive surgery not only results in substantial benefits to the patient but also helps to reduce hospital stay time and perioperative complications. The goal of surgery should materialize in optimizing oncologic outcomes and optimizing patient health, concomitant with rationalization of associated costs. The further and broader adoption of these techniques in clinical practice seems promising for improving surgical outcomes and improving the post-operative experience for patients undergoing surgery for gynecological malignancy.

Implications

The evidence of higher recurrence and mortality rates associated with minimally invasive surgery compared to open surgery in cervical cancer highlights the importance of guidelines and of promoting appropriate training for surgeons. Furthermore, the observation of lower postoperative complications with robotic surgery suggests that, although it may be more expensive, it may be a preferable option for selected patients, especially in settings where rapid recovery is crucial. The increasing incidence of endometrial and ovarian cancer requires an organised response from healthcare systems, including not only the adoption of safer and more effective surgical techniques, but also a multidisciplinary approach that considers the psychological and social aspects of patients. Finally, innovation in surgery, such as vNOTES techniques, opens new

possibilities for less invasive interventions, necessitating continuous critical evaluation and adaptation of clinical practices based on solid evidence.

Compliance with Ethical Standards

Authors contribution: Conception and project administration: A.G., G.B. and V.D.D. Methodology and data collection: O.D. and I.C. Investigation and data curation: A.S.L. and A.E. Visualization, writing – original draft and writing – review & editing: T.G.D. and E.D.A. Supervision: E.V. and D.C. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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