Feasibility and safety of minimally invasive technology for interval cytoreductive surgery during advanced ovarian cancer after neoadjuvant chemotherapy

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Abstract
Ovarian cancer (OV) is usually diagnosed in its advanced stages (stages III or IV), minimally invasive surgery (MIS) is increasingly being used to treat advanced OV due to several advantages over laparotomy. MIS represents a novel but controversial treatment approach for interval debulking surgery (IDS). The objective of this review was to clarify the feasibility and safety of MIS for IDS. WanFang database, Chinese National Knowledge Infrastructure (CNKI) databases, Embase, PubMed, Cochrane, Clinicaltrials.gov and Web of Science were searched up to June 2022, Clinical studies based on humans, including randomized controlled trials, quasi-RCTs, non-randomized trials, case-control studies, cohort studies and retrospective observational studies, were included without time restriction. 14 original articles published between 2015 and 2022 were included. In total, there were 13,788 patients enrolled, 2318 (16.8%) were treated with MIS. The pooled rate of laparotomy-conversion was 17.9% (112/711), the pooled rate of optimal cytoreduction was 84.0% (628/748) during MIS group compared with 77.3% (2204/2850) during laparotomy (LAP) group (p < 0.0001), and the pooled rate of perioperative complication was 8.85% (79/893) during MIS versus 4.6% (211/4586) during LAP group (p < 0.0001). We found no significant difference in mean progression-free survival (PFS) and mean overall survival (OS) between two groups. Based on the available retrospective studies, minimally invasive debulking surgery after NACT seemed to have similar perioperative, oncological and prognostic outcomes with laparotomy debulking surgery. MIS seemed to be feasible and safe in carefully selected patients who had good response to NACT, lower preoperative level of CA12-5 and lower tumor burden. However, existed clinical evidence should be viewed with caution and objectivity. MIS for IDS should be cautiously suggested until the observed results are confirmed in the LANCE trial and other larger prospective trials.

Keywords
Minimally invasive surgery; Interval debulking surgery; Advanced ovarian cancer; Laparoscopic surgery; Robotic-assistant surgery

1. Introduction
Ovarian cancer was the most deadly disease among gynecological malignancies. The world health organization (WHO) estimated a total of 295,400 new cases and 184,800 deaths of ovarian cancer worldwide in 2021 [1]. Most ovarian cancer patients are diagnosed when the cancer has reached its advanced stages (stages III or IV) because of the lack of effective early screening method, leading to poor survival rates (5-years survival rate <30%) [2]. Optimal cytoreduction was key point of treatment and prognosis [3]. However, extensive super-radical surgical procedures to achieve minimal residual tumor burden were closely associated with perioperative complication and mortality. Some randomized clinical trials (RCTs) [4–6] demonstrated that patients with optimal cytoreduction after neoadjuvant chemotherapy had lower perioperative complication, meanwhile approximately similar survival prognosis with PDS. Current authoritative guidelines [7] recommend NACT followed by IDS for those preoperatively identified as not suitable for PDS, including stage IV, involvement of vital organs, high tumor burden, significant contradictions or poor performance status, to increase the chances for optimal cytoreduction.

In the early 1990s, pioneers [8] attempted to adopt laparoscopic techniques to diagnose and evaluate OV, including advanced and recurrent diseases. After that, the application of MIS in gynecologic oncology has continuously expanded. Benefit from advancement of laparoscopic techniques and instruments, extensive surgical procedures seem feasible, such as cytoreductive surgery for advanced OV. However, the role
of MIS in ovarian cancer has frequently been controversial [9–11]. Laparoscopy has inherent limitations, including lack of depth perception, non-wristed instrumentation, limited moving range and so on. The critical procedure for cytoreduction in OV is careful exploration of the entire pelvic and peritoneal cavity to avoid missing resectable tumor lesions, including the mesenteric root, lesser sac, and other spaces difficult to access during MIS. It remains skeptical whether MIS could reach the same outcome of cytoreduction, missed small areas of disease may lead to incomplete resection, may impair the prognosis. Patients with diagnostic laparoscopy for advanced-stage OV were shown to have higher rates of port-site recurrence [12] and intraoperative spillage. It was found that intraoperative and preoperative spillage were associated with a worse prognosis [13]. A recent survey [14] on current viewpoint and clinical practice of the German Society for Gynecologic Endoscopy (AGE) members indicated that laparoscopic treatment for early OV and borderline tumors was feasible, thereby the role of MIS during advanced-stage OV needed further evaluation.

However, MIS has various advantages over laparotomy in terms of enhanced recovery after surgery (ERAS), including less postoperative pain, shorter hospital stay, lower incisional hernia rates, lower perioperative complication, lower wound infection, and so on [15–17]. Moreover, optical magnification of anatomical structures, together with modern advanced surgical devices, were shown to increase the feasibility of MIS procedures. MIS was associated with reduced degree of adhesion and easier access to the spatio retroperitoneale [18, 19]. Furthermore, adjuvant chemotherapy could be started sooner because smaller incisions often can help patients recover quicker, and might be beneficial for prognosis. The purpose of NACT is to shrink tumors to improve the possibility of optimal cytoreduction and lowered perioperative complications [20]. A large number of studies evaluated the significance of NACT and its modalities in advanced OV with complete or partial response to NACT and found that the complexity, morbidity and mortality of debulking surgery were significantly reduced, might be a suitable candidate for MIS.

In 1975, Rosenoff et al. [21] reported the diagnostic effect of peritoneoscopy for ovarian cancer for the first time. Since then, MIS was progressively introduced in the management of advanced OV to evaluate probability of optimal cytoreduction, to identify reactivity to chemotherapy or to perform PDS/IDS in selected patients [22]. However, the role of MIS during IDS was not widely recognized, and MIS during IDS remains a controversial treatment approach for advanced OV. The purpose of this review was to summarize existing clinical literature and to comprehensively analyze features of existed clinical studies to clarify the feasibility and safety of MIS during selected advanced OC treated with NACT. We also comprehensively and systematically evaluated the detail of existed research, that might overcome the selected bias of a single study, might provide more convincing evidence for clinical practice.

2. Methods

Literature in all languages were searched. The electronic databases of WanFang database, Chinese National Knowledge Infrastructure (CNKI) databases, Embase, PubMed, Cochrane, Clinicaltrials.gov and Web of Science were searched up to June 2022. Related articles of enrolled literature and Google search were used to avoid omitting newly published and internet resources.

The search was performed using the following key terms: ovar* and (tumor* or tumour* or malignant* or cancer* or carcinoma* or neoplas*) and (minimally invasive or laparoscopic or robotic) and (interval cytoreductive or interval debulking or neoadjuvant chemotherapy). For comprehensiveness, we searched for relevant case-control studies, prospective and retrospective cohort studies, randomized controlled trials (RCTs), quasi-RCTs and non-randomized trials, while case reports and case series were excluded. The flow chart is shown in Fig. 1.

We comprehensively analyzed all original descriptive and comparable studies with respect to perioperative, oncological and survival outcomes of advanced OV patients who had interval debulking surgery by MIS or conventional laparotomy. References of the included literature were also searched to avoid omitting other relevant studies. Studies were excluded if they were duplicated publications, abstracts, letters, case reports, case series, comments and reviews which did not contain primordial data, studies with patients <5 and studies included recurrent patients. Additionally, we excluded studies that included borderline and non-epithelial ovarian tumors, considering that their biological behavior and tumor prognosis differed significantly from ovarian cancer. We extracted baseline demographic data, surgical details, perioperative morbidity, oncology outcomes, and prognostic outcomes in included studies. Prognostic outcomes included overall survival (OS), progression-free survival (PFS), recurrence-free survival (RFS). Oncological outcomes included the rate of optimal cytoreduction, port-site recurrence, intraoperative spillage and perioperative morbidity. Baseline demographic data included Federation Internationale of Gynecologie and Obstetrique (FIGO) Stage, cycles of NACT, reponse to NACT, carbohydrate antigen (CA) 125, radiology assessment and LAP assessment. Surgical details included mean operative time (OT), length of stay (LOS), laparotomy-conversion rate, estimated blood loss (EBL), perioperative complication rate and long-term complication rate.

3. Results

All retrieved titles and abstracts were imported to Endnote software for further analysis, after removed duplicate studies, the remaining literature were examined by two authors (HY and YZ). Studies that did not meet the inclusion criteria were excluded, and full text of potential suitable references were obtained. The eligibility of the retrieved studies was independently assessed by two authors (YW and HO).

After screening, 14 original articles published between 2015 and 2022 were found eligible for this study, comprising 3 one-arm observational studies and 11 comparative studies. Of them, 12 were retrospective cohorts, 1 was a phase II clinical trial, and 1 was a prospective international multicenter RCT still in enrolling stage. The frequency of laparotomy conversion, optimal cytoreduction, perioperative complication, as well as prognostic outcomes were independently extracted.
from the retrieved studies by two authors (PD and HN). Any differences were resolved by mutual discussion or by consulting with a third author when necessary (HY). The main perioperative outcomes are summarized in Supplementary Table 1, the main prognostic outcomes are summarized in Supplementary Table 2, to provide some references to select suitable candidates for MIS, we summarized the main clinicopathological features of patients enrolled in MIS group in Supplementary Table 3.

In total, 14 eligible studies comprised 13,788 patients, of whom 2318 (16.8%) were treated with MIS were enrolled. The results showed that the pooled laparotomy-conversion rate during MIS group was 17.9% (112/711), pooled rate of optimal cytoreduction and perioperative complication were 84.0% (628/748) and 8.85% (79/893) respectively. In 3 retrospective comparative studies (Favero et al. [23] 2015, Gueli Allettiet et al. [24] 2016 and Brown et al. [25] 2018), the mean operation time (OT) was found to be statistically longer in the MIS group. One retrospective comparative study (Molly Morton et al. [26] 2020) found no statistical difference in mean OT. Almost all comparative studies reported less EBL and shorter length of stay in the MIS group compared with the LAP group.

Five original articles (Favero et al. [23] 2015, Gueli Allettiet et al. [24] 2016, Brown et al. [25] 2018, Zhang et al. [27] 2021 and Lecointre et al. [28] 2022) compared the mean progression-free survival (PFS), 4 original articles (Brown et al. [25] 2018, Matsuo et al. [29] 2020, Zhang et al. [27] 2021 and Lecointre et al. [28] 2022) compared the mean overall survival (OS) between the MIS group and LAP group. Only one article (Melamed et al. [30] 2017) compared the 3-year survival, and 1 descriptive one-arm study (Fagotti et al. [31] 2018) reported the 5-year survival in the MIS group. Our assessment found no significant difference in prognosis except in one study (Favero et al. [23] 2015) reported that the cancer-related mortality was higher (20 vs. 0%; p = 0.086) and the mean time to chemotherapy (TTC) as significantly shorter in the MIS group (13.3 vs. 20.5 months; p = 0.288), although the difference did not reach statistical significance.

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**FIGURE 1. Flow diagram for the assessment of studies identified in the literature review.**

<table>
<thead>
<tr>
<th>Records identified through database searching (n= 257)</th>
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<tbody>
<tr>
<td>Records screened (n= 231)</td>
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<tr>
<td>Full-text articles assessed for eligibility (n= 58)</td>
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<tr>
<td>Records included for review (n= 14)</td>
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<tr>
<td>Duplicated records excluded (n= 26)</td>
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<tr>
<td>Records excluded in titles and abstracts screening (n= 173)</td>
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<tr>
<td>Full-text articles excluded for wite reason: Full-text not available (n=4) Conference abstract (n=2) Meta-Analysis and Systematic Review (n=6) Incomplete information (n=4) Narrative review (n=5) With other intervention(n=15) case report and case series (n=8)</td>
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4. Discussion

Ovarian cancer is the most lethal cancer during female genital tract, with its incidence and mortality significantly increased worldwide in recent years [32], thus, making OV a major health care problem. Most patients have already reached its advanced stages (stage III or IV) when initial treatment due to poor detectability on screening. Cytoreductive surgery is the cornerstone of these patients, the aim is to achieve optimal cytoreduction without macroscopic residual tumor. No matter during PDS or IDS, suboptimal debulking (residual tumor >1 cm) was a strong predictor of poor prognosis factor [33–35]. Due to its unique biological behavior and spread pattern, advanced OV always involves multiple organs. Thus, cytoreductive surgery is suitable for these patients as it can resect multiple pelvic and abdominal organs invaded by tumors. Due to the magnitude of disease dissemination, PDS is technically possible in only 20–50% of advanced OV [36]. Meanwhile, extensive super-radical surgical procedures to achieve minimal residual tumor burden were closely associated with perioperative complication and mortality, leading to the proposal of alternative treatment strategies such as NACT, which was then shown to be more beneficial to the patients due to higher rates of adequate resection. Some randomized clinical trials (RCTs) [4–6] demonstrated that patients with optimal IDS had lower perioperative complication, meanwhile approximately similar survival prognoses with PDS. Current authoritative guidelines [7] recommend NACT followed by IDS for those preoperatively identified as not suitable for PDS, including stage IV, Involvement of vital organs, high tumor burden, significant contradictions or poor general health, to increase the chances for optimal cytoreduction.

With the continuous advancement in laparoscopic techniques and instruments, MIS (laparoscopy with or without robotic assistance) has emerged as a feasible alternative to conventional laparotomy in gynecologic oncology. Robotic surgery overcomes the disadvantages of standard laparoscopy in several aspects: simultaneously allowing three-dimensional (3D) vision, shorter learning curves, and improved dexterity. In addition, motion stability software and wristed instruments can simulate the motion of the human hand, making the surgery easier to maneuver [37–40] and particularly useful in the precise and composite surgical procedures. In recent decades, we have observed a considerable progress in the management of OV. The utility of MIS has been introduced into surgery for OV as well, which was strictly limited to the treatment for early-stage disease, diagnosis and biopsy of advanced disease at first [41–43].

With the accumulation of experience from diagnostic and staging laparoscopy, increasing number of scholars have tried MIS during difficult and complex operations, such as debulking surgery in advanced and recurrent ovarian cancer. Optimal debulking surgery required removing the maximum number of visible tumors, sometimes needed to remove multiple pelvic and abdominal organs invaded by the tumors, and required a multidisciplinary team collaboration for optimal individualized treatment management. The widespread metastasis of cancer cells and involvement of multiple visceral organs overrated surgeons to perform minimally invasive debulking surgery. Early attempts found that the mean OT was significantly longer, the frequency of perioperative complications was higher, and the frequency of optimal debulking was lower during MIS compared to LAP [44–46]. However, for those who demonstrated good response to NACT, especially during complete response patients, the complexity, morbidity and mortality associated with debulking surgery were significantly reduced, might be suitable candidates who benefitted most from MIS.

In 2015, Favero et al. [23] published a retrospective descriptive study to evaluate the perioperative details of laparoscopic cytoreductive surgery in 50 cases of advanced OV treated with NACT. The mean chemotherapy-free interval was shorter (13.3 vs. 20.5 months; \( p = 0.288 \)) in MIS than in LAP, however, the observed cancer-related mortality was found to be higher (20% vs. 0%; \( p = 0.086 \)) in MIS than in LAP, although a statistical difference was not reached, the result was discouraged. Thus, the authors suggested the role of laparoscopic interval cytoreduction should be prudently viewed until prospective randomized trials confirm its safety. This led to an urgent need to evaluate and pool relevant data to provide more robust evidence. Based on the limitations of current literature, the main objective of this review was to summarize and comprehensively analyze existing evidences to evaluate the feasibility and safety of MIS during IDS.

4.1 Feasibility of minimally invasive interval cytoreductive surgery

Laparotomy, including PDS and IDS, is the standard surgical approach for advanced OV [46]. In the last decades, MIS was proposed as a possible tool for cytoreductive surgery in advanced ovarian cancer after NACT, with the benefits of superior surgical outcomes and fast recovery. To determine whether alternative technology could replace conventional technology, we evaluated the short-term efficacy of the alternative technology to determine whether it was superior or at least not inferior to standard techniques. When we evaluated the feasibility of MIS for IDS, it was necessary to compare the perioperative outcomes between MIS and LAP. According to inclusion and exclusion criteria, 14 original articles published between 2015 and 2022 were eligible for this study. Three were one-arm observational studies and 11 were comparable studies. Among them, 12 were retrospective cohort studies, one was a prospective phase II clinical trial, and one was an international multicenter RCT that was still in its enrolling stage. In total, there were 13,788 patients, including 2318 (16.8%) treated with MIS. The pooled laparotomy-success rate was found to be 17.9% (112/711), while the pooled rate of optimal cytoresection was 62.8/748 (84.0%), and pooled rate of perioperative complication was 8.85% (79/893) in the MIS group. Three retrospective comparative studies (Favero et al. [23] 2015, Gueli Allettiet al. [24] 2016 and Brown et al. [25] 2018) found that the mean OT was statistically longer in the MIS group, but in the retrospective study by Morton et al. [26], no statistical difference was observed. Almost all comparative studies showed less EBL and a shorter length of stay in MIS group compared with LAP group. The main perioperative outcomes are summarized in Supplementary Table 1.
The retrospective study performed by Corrado et al. [47] aimed to analyze perioperative outcomes of MIS in 30 advanced OV patients from January 2010 to December 2014. After three cycles of NACT, all women received optimal cytoreductive surgery with no macroscopic residual tumor, the outcome of operation and perioperative features were satisfactory, the median OT was 152 minutes, median EBL was 70 mL. There was 1 (3.3%) case of intraoperative complication and 2 (6.6%) postoperative short-term complications. The median length of hospital stay was 4 days. Thus, the results showed that laparoscopic cytoreduction was feasible in advanced OV whose had good clinical response to NACT. However, the study did not analyze critical clinical factors of enrolled patients such as tumor burden, FIGO stage and location of metastatic sites, which might be key factors when deciding whether a patient would be a suitable candidate for MIS.

The pilot observational study performed by Favero et al. [23] aimed to study the perioperative features of IDS during initially unresectable OV from January 2011 to March 2014. Twenty-one patients were enrolled, after 6 cycles of carboplatin and paclitaxel chemotherapy, 10 underwent MIS and 11 underwent LAP. No intraoperative complications, surgery-related death or conversion to laparotomy were founded in MIS group. The mean OT was 292 min and mean length of hospital stay was 3.6 days in MIS group. MIS for IDS during unresectable advanced OV seemed feasible and effective for selected patient. The major limits of this study were selection bias of pilot study and the limited cases enrolled.

In 2015, a prospective multicenter trial (named MISSION trial) performed by Gueli Allettiet al. [52] enrolled 52 advanced OV patients with complete clinical response to NACT. After evaluated the surgical complexity via diagnostic laparoscopy, 30 patients received planned treatment of MIS for IDS, median OT was 285 min and median EBL was 100 mL. In addition, 29 patients (96.6%) underwent complete debulking surgery with no residual disease and most of the patients were discharged on postoperative day 2. No short-term postoperative complications occurred. The median time to chemotherapy (TTC) was 20 days, and all patients successfully completed the planned chemotherapy cycles. Thus, MIS seemed to be feasible for IDS in terms of perioperative outcomes. However, the study only enrolled superior patients with complete response to NACT, limiting the clinical extrapolation of research conclusions.

The retrospective case-control study performed by Gueli Allettiet al. [24] in 2016 aimed to investigate the role of MIS in advanced OV who underwent IDS. 30 patients were enrolled in the MIS group and 65 in the LAP group. Their results showed no statistical differences in terms of surgical procedures and residual tumors between two groups. The median OT was significantly longer in MIS, however, the median length of stay, EBL and TTC were more favorable in MIS. No statistical differences were founded in terms of postoperative short-term complications. MIS might represent a considerable alternative surgery to perform IDS in a specific subgroup of patients. However, the study’s major limitations were its retrospective nature and the limited cases enrolled.

The population based cohort study performed by Melamed et al. [30] in 2017 aimed to investigate the role of MIS in OV with stage IIIc and IV between 2010 and 2012 who underwent NACT and IDS during the national cancer database. 3071 women were enrolled in total, of whom 450 (15%) underwent laparoscopic surgery and reported that the mean postoperative hospitalization of was slightly shorter (4 days in MIS group versus 5 days in LAP group, p < 0.001). Frequency of readmission (5.3% vs. 3.7%; p = 0.26), death within 90 days of surgery (2.8% vs. 2.9%, p = 0.93), and suboptimal debulking (20.6% vs. 22.6%, p = 0.29) were no significant difference between the MIS group and LAP group. Laparoscopic IDS was associated with a significant shorter postoperative hospitalization, whereas similar readmission rates and risk of perioperative death with LAP groups. Large sample size might make the results more credible, but important factors and features of patients selected for laparoscopy were not measured, thus, their conclusion should be taken with caution in light of such limitations.

The retrospective cohort study performed by Brown et al. [25] in 2018 aimed to compare the outcomes between MIS and LAP for advanced OV who had IDS after NACT, 157 patients were enrolled in total, of whom 53 (33.8%) underwent laparoscopic surgery and 104 (66.2%) patients through laparotomy. The frequency of laparotomy conversion was 17%, during 44 patients without laparotomy conversion, 20 patients required a hand port and/or mini-laparotomy. In addition, optimal resections were achieved in 96.3% of patients who underwent MIS, compared with 82.7% of patients who underwent laparotomy (p = 0.02). MIS group had longer mean OT (171 vs. 150 minutes, p = 0.007), lower EBL (156 vs. 278 mL, p < 0.001), fewer intraoperative transfusions (2% vs. 17%, p = 0.006) and shorter hospital stay (3.0 vs. 5.7 days, p < 0.001) than LAP group, while the frequency of perioperative complications, intensive care unit (ICU) stay and readmission were similar between two groups. Thus, MIS seemed feasible and effective for IDS. The main limitations of this study were its retrospective nature and related potential bias in patient selection.

The retrospective multi-institutional study performed by Davidson et al. [48] in 2018 aimed to evaluate the role of surgical complexity scores and MIS in IDS. Of the 282 patients initially identified, 51 patients underwent laparoscopic IDS, 24 (47%) patients were converted to laparotomy, which resulted in optimal cytoreduction without macroscopic residual tumor achieved in 21 patients (87.5%), while in 25 patients who underwent laparoscopic surgery all the way, 19 patients (76.0%) had optimal R0 cytoreduction. Thus, MIS appeared to be safe and feasible with acceptable frequency of optimal cytoreduction. However, the frequency of laparotomy conversion was higher than previous literature reports, which might be because of different practice patterns between institutions and inherent bias associated with the retrospective study and patient enrollment.

The retrospective multicenter study performed by Fagotti et al. [31] in 2018 aimed to investigate the safety, feasibility and outcomes of MIS for IDS across 5 gynecological cancer centers in Italy. 127 patients were included in total, and all of them achieved optimal cytoreduction. 122 (96.1%) patients had optimal R0 cytoreduction, the results were satisfactory, median OT was 225 min, median EBL was 100 mL, median
time to discharge was 2 days, estimated median TTC was 20 days. The frequency of intraoperative complications was 4.7%, of whom one experienced serious complications (simultaneous intestine and bladder injury). Further, 6 (4.7%) patients experienced short-term postoperative complications, and 3 had severe complications. The frequency of laparotomy conversion was 3.9%. Their study indicated that MIS might be considered for IDS when surgery was limited to low-complexity procedures. However, heterogeneity in patients and management in terms of surgery and chemotherapy were the potential limitations of the study.

The population-based retrospective study performed by Matsuo et al. in 2020 aimed to investigate the role of MIS in advanced OV during the national inpatient database from 1/2012 to 9/2015. A total of 1820 patients with metastatic OV who had previous chemotherapy were enrolled, of whom 75 (4.1%) patients underwent MIS, 50 (66.7%) patients were performed using robotic assisted laparoscopy. The frequency of lymphadenectomy was similar between two groups (MIS versus laparotomy: 26.7% vs. 28.4%, p = 0.795), but the frequency of gastrointestinal or hepatic resection was significant lower in MIS group (0% vs. 22.3%, p < 0.001), the frequency of peritoneectomy was also lower in MIS group (86.7% vs. 94.3%, p = 0.013). Among those without gastrointestinal or hepatic resection (n = 1430), patients in the MIS group were found to have a lower perioperative complication rate (20.0% vs. 31.0%, p = 0.044). Multivariable analyses showed that the MIS approach was a favorable factor associated with decreased perioperative complications. These results suggested that MIS was feasible and safe in low-complexity gynecologic surgery without additional cytoreductive procedures. However, data on tumor burden after NACT were not available reported, and thus information about tumor resectability of MIS remains unknown in the study.

The retrospective cohort study performed by Morton et al. in 2020 aimed to determine the perioperative outcomes in women with advanced OV who underwent IDS with hyperthermic intraperitoneal chemotherapy (HIPEC) via MIS or LAP. 50 eligible women were included in total, 10 (20.0%) patients underwent MIS + HIPEC and 40 (80.0%) underwent LAP + HIPEC. The results showed no significant difference in frequency of R0 resection, ICU admission, EBL, OT, use of vasopressors, 30-day adverse events and TTC between two groups, but patients in the MIS group had a comparatively shorter length of stay (3 vs. 4 days, p = 0.016). MIS with HIPEC for IDS after NACT seemed feasible. However, the main limitations of this study were its retrospective nature, small sample size and potential selection bias.

The retrospective cohort study performed by Zhang et al. in 2021 aimed to compare the effect of patients with advanced OV undergoing IDS with either robotic surgery (R-IDS) or open approach (O-IDS). 93 patients were enrolled in total, 43 underwent R-IDS and 50 underwent O-IDS. They found that 91% of the whole cohort were optimally cytoreduced, 57% with no macroscopic residual tumor, the R0 resection was similar between O-IDS and R-IDS (52% vs. 63%, p = 0.4), indicated robotic surgery did not affect debulking success during IDS. The limitations of the study were inherent potential bias associated with the retrospective design of the study and patient selection.

The retrospective propensity-score-matched cohort study performed by Lecointre et al. in 2022 aimed to compare the outcomes between laparoscopic IDS and laparotomy. 37 patients were included in MIS group and 40 in LAP group. Their results showed that MIS was associated with significantly lower short-term postoperative complications (6 vs. 17, p = 0.01) and shorter hospital stay (7.6 vs. 12.1 days, p < 0.001), MIS seemed a safe alternative to LAP for IDS after NACT in carefully-selected patients. However, the study did not anatomize critical clinical factors of enrolled patients such as tumor burden, FIGO stage and location of metastatic sites, which might be key factors when deciding whether a patient would be a suitable candidate for MIS.

The recent population-based retrospective observational study performed by Persenaire et al. enrolled 8085 women from the national cancer database from 2010–2016, aimed to evaluate overall survival (OS) of women with advanced OV after NACT. 6173 (83%) women underwent LAP and 1372 (17%) underwent MIS during IDS. Their results showed mean length of stay was shorter in MIS group (3 vs. 5 days, p < 0.01), however the frequency of postoperative readmission was similar between two groups. The proportion of patients undergoing MIS after NACT increased from 2% in 2010 to 11% in 2016, indicating a nearly 6-fold increase. Thus, MIS seemed feasible and effective for IDS. The study might have benefit from a larger sample size. However, important factors and features of patients selected for laparoscopy were not measured; thus, the results should be interpreted in light of these limitations.

Although the retrieved studies were retrospective and mostly carried a high risk for selection bias and inherent limitation, the overwhelming consistency of the outcomes suggest the potential effectiveness of MIS in carefully-selected patients with advanced OV after NACT, highlight the need for high-quality data to determine the feasibility and safety of MIS during IDS. In this regard, Nitecki et al. initiated an international multicenter prospective randomized trial (named LANCE trial) in 2020 to examine whether MIS was non-inferior to laparotomy in women with advanced OV that completely or partial responded to three or four cycles of NACT, and their study results are eagerly awaited to provide more convincing evidence about the feasibility of MIS in advanced OV.

### 4.2 Safety of minimally invasive interval cytoreductive surgery

The most important index for evaluating cancer management is prognosis. Ovarian cancer was the most deadly disease among gynecological malignancies. The expected long-term survival of advanced OV were only approximately 20% [51]. The standard interval debulking approach was laparotomy. In recent decades, MIS has been increasingly used for IDS in advanced ovarian cancer, prognosis and safety of MIS were evaluated based on indicators such as PFS, OS, recurrence-free survival (RFS) and rate of recurrence (RR). In the 14 original articles included in this review, 5 original articles (Favero
et al. [23] 2015, Gueli Allettiet et al. [24] 2016, Brown et al. [25] 2018, Zhang et al. [27] 2021 and Lecointre et al. [28] 2022 compared the mean progression-free survival (PFS), 4 original articles (Brown et al. [25] 2018, Matsuo et al. [29] 2020, Zhang et al. [27] 2021 and Lecointre et al. [28] 2022) compared the mean overall survival (OS) between MIS group and LAP group, only 1 article (Melamed et al. [30] 2017) compared the 3-year survival and 1 descriptive one-arm study (Fagotti et al. [31] 2018) reported 5-year survival. The results showed no significant difference except in 1 study (Favero et al. [23] 2015) which reported that the cancer-related mortality was significantly higher (20% vs. 0%; p = 0.086), and the mean chemotherapy-free interval was significantly shorter in the MIS group (13.3 vs. 20.5 months; p = 0.288); however, the difference did not reach statistical significance. The main prognostic outcomes are summarized in Supplementary Table 2.

In the prospective multicenter study performed by Gueli Allettiet al. [52], the authors reported 5 peritoneal and 2 lymph nodal recurrences for a median follow-up of 10.5 months. All patients were still alive by the time of the last follow-up. However, because it was a single-arm study, we could not conclude the superiority between MIS and laparotomy in the study.

The retrospective study performed by Favero et al. [23] reported similar recurrence rates after a mean follow-up of 20 months (MIS group vs. LAP group, 80% vs. 88%). although the mean chemotherapy-free interval was significantly shorter in the MIS group (13.3 vs. 20.5 months; p = 0.288), the cancer-related mortality was significantly higher in MIS group (20% vs. 0%; p = 0.086), indicating MIS might be associated with inferior oncologic results.

The retrospective study performed by Gueli Allettiet al. [24] found that patients from the MIS group had a 6-month longer PFS than LAP group. However, multivariate analyses identified only the administration of bevacizumab and shorter TTC were associated with decreased PFS and OS.

The retrospective multicenter study performed by Melamed et al. [30] showed no difference in the 3-year survival between MIS group (47.5%) and LAP group (52.6%, p = 0.12) and death within 90 days postoperation (2.8% in MIS group vs. LAP group, p = 0.93). The oncologic outcomes with MIS seemed not inferior to LAP.

The retrospective cohort study performed by Brown et al. [25] reported similar median PFS (27 vs. 29 months, p = 0.45) and median OS (37 vs. 35 months, p = 0.74) between MIS group and LAP group. The survival seemed not affected by surgical approach.

In the retrospective multicenter study performed by Fagotti et al. [31], the authors found 58.3% (74/127) patients recurred and 31 (24.4%) patients died after a median follow-up time of 37 months (range 7–86), demonstrating a median PFS of 23 months and a 52% (95% CI: 35–67) 5-years overall survival. However, due to the limitation of a single-arm study design, we cannot conclude the inferiority of MIS compared with laparotomy.

The population-based retrospective observational study from the national inpatient database performed by Matsuo et al. [29] also reported a similar median OS (36.5 vs. 35.2 months, HR: 0.94, 95% CI: 0.86–1.04) between patients from the MIS and LAP groups.

The retrospective mono-centric study performed by Morton et al. [26] suggested no difference in RFS between the MIS group and the LAP group (median RFS, 15.0 vs. 17.2 months, p = 0.30) after a median follow-up of 15.1 months. They also reported that the MIS approach was not limited by HIPEC.

The retrospective study performed by Zhang et al. [27] also found similar PFS and OS between patients undergoing MIS and LAP (PFS 15.4 vs. 16.7 months, p = 0.7; OS 38.2 vs. 35.6 months, p = 0.7). R0 cytoreduction improved PFS and OS during both groups, not affected by surgical approach. Subgroup analysis showed that cycles of NACT was closely related with prognosis, >6 total cycles of chemotherapy was associated with shorter PFS and OS. The results suggested MIS did not affect the oncologic prognosis. could be concluded that receiving >6 total cycles of chemotherapy before IDS was associated with decreased PFS and OS in patients undergoing IDS.

The recent retrospective international study performed by Lecointre et al. [28] also suggested no significant difference in terms of median OS (23.1 months vs. 26.3 months, p = 0.17) and median PFS (14.8 months vs. 12 months, p = 0.057) between laparoscopy and laparotomy. Thus, complete laparoscopic interval debulking surgery had similar survival outcomes with laparotomy, MIS might be a safe alternative to LAP for IDS after NACT in selected advanced OV.

These available evidences seem to support the safety of MIS for IDS in selected patients with advanced OV, however, almost all studies were retrospective analyses and carried a high risk for bias and limitations. Existed clinical evidence should be viewed with caution and objectivity, the results of the LANCE trial are eagerly awaited to provide more convincing evidence to evaluate the safety of MIS for IDS.

### 4.3 Candidates for minimally invasive interval cytoreductive surgery

Although the safety and effectiveness of MIS for IDS are yet to be confirmed via high-level evidence, patient selection is important issue still. Currently, there was no relevant criterion to determine whether MIS was suitable. According to the newly-diagnosed advanced ovarian cancer evaluation method, imaging evaluation and diagnostic laparoscopy might be considered. In this review, we summarized the clinical factors of the MIS group from existed clinical studies, including the FIGO stage, cycles of NACT, NACT effects, CA12-5 levels, imaging findings and so on (Supplementary Table 3).

These results might provide some references to select suitable candidates, but because most of the details about clinical pathological characteristics were not comprehensively reported, we could not draw a definite conclusion from these studies. In addition, almost all of the existed clinical research reported the patients were assessed for MIS based on imaging and/or diagnostic laparoscopy prior to IDS. The inclusion criteria of some studies contained good responses (mostly complete responses) for NACT and low levels of CA12-5. According to the limited available evidence, we speculated that the response to NACT, level of CA12-5, tumor burden and surgical skills
of surgeons might be important considerations for selecting appropriate candidates to perform minimally invasive interval debulking surgery.

5. Conclusions

The use of MIS in ovarian cancer has been frequently viewed with skepticism. Based on the findings from available retrospective studies, minimally invasive debulking surgery after NACT seemed to have similar perioperative, oncological and prognostic outcomes with laparotomy debulking surgery. MIS seemed to be feasible and safe in carefully selected patients. However, existing clinical evidence should be viewed with caution and objectivity. Further, MIS for IDS should be cautiously suggested until the results are confirmed by the LANCE and other larger prospective trials.

AUTHOR CONTRIBUTIONS

HY and YZ—were major contributor in writing the manuscript, YW and HN—were in charge of the final approval of the version to be published. PD and HO—searched the literature. All authors read and approved the final manuscript. All authors analyzed the literature review.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1603264897417658388/attachment/Supplementary%20material.docx.

REFERENCES


