Roles of minimally invasive techniques in the management of epithelial ovarian cancer (Review)

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Abstract. Epithelial ovarian cancer (EOC) is a leading cause of mortality among gynecological malignancies, predominantly due to late-stage diagnoses and complex management challenges. Traditional treatment strategies, primarily centered on extensive cytoreductive surgery and platinum-based chemotherapy, have seen notable improvements through the integration of laparoscopy and robotic-assisted procedures. The safety and efficacy of minimally invasive techniques (MITs) have been demonstrated in early-stage EOC, although their applicability in advanced stages requires further investigation. Additionally, molecular-based and immunotherapies, including poly(ADP-ribose) polymerase inhibitors, angiogenesis inhibitors and RNA-based treatments, offer promising adjuncts to MITs by targeting cancer-specific pathways with precision. Despite these innovations, patient selection, surgical expertise and adherence to oncological safety standards remain key factors in determining the efficacy and safety of MITs in EOC management. Future directions emphasize the need for standardized protocols, enhanced imaging techniques and real-time molecular monitoring, which aim to transition EOC management toward a minimally invasive, patient-centered approach. The present review discussed the advancements in MITs and their role in the management of EOC, with a focus on their impact on surgical outcomes, survival rates and patient quality of life.

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1. Introduction

Epithelial ovarian cancer (EOC) is the primary cause of mortality from gynecological malignancies and the sixth most common cause of cancer-related fatalities overall in the Western world. Women face a 1 in 70 to 80 a lifetime risk of developing EOC and a chance of 1 in 90 to 100 of succumbing to this illness (1). Currently, estimates indicate that ~90% of these neoplasms originate from the ovary, while 5-7% originate from the fallopian tubes. Non-epithelial ovarian tumors, developed from stromal or germ cell neoplasms, make up the remaining 3-5% (2). Ovarian cancer is a complex illness shaped by genetic, hormonal and environmental influences. Principal risk factors encompass BRCA mutations, nulliparity, early menarche, late menopause, hormone replacement treatment, obesity and lifestyle choices (1) (Fig. 1). Although several studies indicated that dietary and environmental exposures may serve a role in illness development, causal associations remain ambiguous (3-8). The clinical management of EOC presents considerable hurdles, as the majority of cases are discovered at an advanced stage, hence restricting therapy choices. Surgical intervention is fundamental to therapy, with cytoreductive surgery markedly enhancing survival rates. However, reconciling oncological results with minimally invasive techniques (MITs) continues to be a topic of ongoing research, especially in advanced-stage illness when optimum cytoreduction is more challenging to attain (9). Innovations in surgical methodologies seek to reduce patient stress while maintaining oncological safety; nonetheless, the long-term advantages of minimally invasive surgery (MIS) in EOC necessitate further research (10,11).

A multimodal approach is used to treat EOC, which includes surgery and chemotherapy, with the specifics changing based

on the stage of the disease and the type of tissue involved. The principal intervention is cytoreductive surgery, as achieving a low residual tumor burden markedly associates with improved progression-free and overall survival rates. In early-stage cancer, surgery succeeded by platinum-based chemotherapy yields marked results, whereas in advanced-stage disease, surgical cytoreduction in conjunction with systemic treatment is the standard of care (12,13).

Chemotherapy, primarily with platinum-taxane regimens, continues to be the cornerstone of systemic treatment (3,14). Novel targeted medicines, such as poly(ADP-ribose) polymerase (PARP) inhibitors for BRCA-mutated cancer types and angiogenesis inhibitors such as bevacizumab, have broadened treatment alternatives; yet, therapeutic resistance remains a notable concern (15,16). Radiotherapy is infrequently employed in cases of EOC outside of palliative care, given that its toxicity frequently surpasses its advantages due to the low radiosensitivity of EOC. Current research seeks to enhance therapy approaches by incorporating innovative medicines and enhancing patient selection to increase treatment effectiveness while reducing unwanted effects.

The present review was conducted as a narrative review, with the aim of synthesizing recent advances in minimally invasive surgical techniques and their integration with systemic therapies in the management of EOC. A comprehensive literature search was performed across the PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/) and Web of Science (https://www.webofscience.com/) databases. The search focused on English-language peer-reviewed publications from January 2009 to April 2024. The inclusion criteria encompassed randomized controlled trials (RCTs), prospective and retrospective clinical studies, large cohort analyses, meta-analyses and relevant consensus guidelines associated with surgical management, systemic therapies and their integration in EOC. Studies focusing on non-surgical interventions, preclinical or animal models or other types of gynecological cancer were excluded. Titles and abstracts of 114 article were screened and full texts of relevant articles were reviewed to ensure alignment with the scope of the present review. The Scale for the Assessment of Narrative Review Articles guidelines were followed to enhance the methodological rigor and transparency of the present narrative synthesis (17).

2. Surgical techniques in minimally invasive management

The notion of MIS cancer cytoreduction was first presented through the evaluation of two non-randomized studies that indicated the non-inferiority of laparoscopy regarding progression-free survival (PFS). A randomized phase III trial was subsequently reported, which did not demonstrate non-inferiority in overall survival for patients who had debulking by the minimally invasive surgical strategy compared with open surgery (18,19). Retrospective studies have reported an absence of drawbacks for the MIS approach in terms of PFS and the finding of decreased postoperative pain and tolerance to chemotherapy (20-22).

There are differences in study design and execution between two major prospective randomized phase III trials that investigated the MIS approach, such as operative duration and center experience (19). The different results have been attributed to various factors, such as the longer duration and bleeding that come with laparoscopy and that almost all of the participating centers have only performed a few procedures each year, indicating less experience with the procedure, which could negatively impact the outcomes. Regarding the International Federation of Gynecology and Obstetrics (FIGO) stage IA disease (23), the concept of keeping the uterus stable during minimal surgical changes makes the MIS approach more likely to be used. This could facilitate more straightforward and standardized minimally invasive procedures for complex surgeries. Further recommendations for patient selection criteria, standardized surgical protocols and intraoperative safety measures may emerge from analyses performed by skilled surgical teams (24).

Laparoscopy. Imaging methods often cannot differentiate between the different kinds of adnexal masses on their own, when it comes to functional and benign variants. Accurately predicting the presence of ovarian cancer and the need for surgery can both be improved with laparoscopy. This method also helps in making a correct diagnosis before surgery. Laparoscopy is an improved technique as it helps reduce the need for individuals to undergo unnecessary surgery to treat functional and benign ovarian cysts (25,26). A histology examination of the tumor and its implants typically offer additional diagnostic insights, along with information regarding the stage of disease. Laparoscopy facilitates the sampling of purulent peritoneal effusion for culture testing, which aids in the identification of any accompanying infection and in determining the appropriate surgical approach (20).

In the context of malignant diseases, prioritizing the complete removal of the primary tumor is key in ovarian cancer as well. The primary objective of oncologists and gynecologists is to ensure the safety of the patient; therefore, it is essential to maintain a pathway for the potential conversion of laparoscopy to laparotomy at any given time. Furthermore, depending on the experience of the surgical oncologist, MITs such as laparoscopy can provide patients with adnexal masses of unclear origin the same diagnostic and therapeutic surgical staging benefits as laparotomy (21). Furthermore, the prevention of notable surgical procedures and complications can lead to a more efficient recovery process for the patient. These factors enhance the quality of life (QoL) and potentially the self-esteem of patients while reducing their costs (21,27,28).

Robot-assisted surgery. In EOC surgery, the robotic system enhances precision and dexterity of the surgeon, enabling fine dissection and removal of primary tumors, targeted omentectomy and systematic lymphadenectomy through small ports with three-dimensional magnified visualization (29). Robotic-assisted surgery is particularly crucial for patients with cardiovascular, hepatic, renal or pulmonary comorbidities, as it minimizes physiological stress by reducing intraoperative blood loss, shortening operative time and maintaining stable intra-abdominal pressures, thereby lowering cardiopulmonary complication rates. In women aged 18-40 years who desire fertility preservation, combining laparoscopy with robotic precision enables accurate tumor resection, targeted omentectomy and unilateral salpingo-oophorectomy while sparing

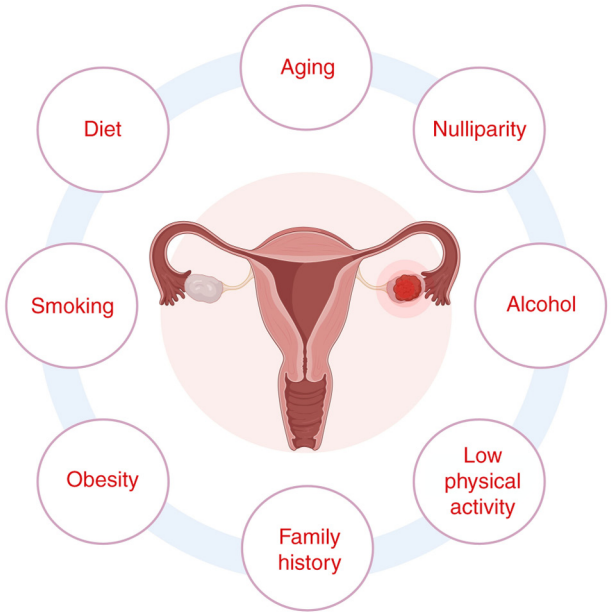

Figure 1. Risk factors associated with the development of epithelial ovarian cancer.

the contralateral ovary (29). Multiple retrospective series have demonstrated that robotic cytoreduction reduces hospital stays to an average of 2-3 days and decreases 90-day morbidity compared with open surgery, driving its increasing adoption among gynecological oncologists (21,28,30,31).

A 2-year retrospective observational study was conducted, analyzing data on women diagnosed with ovarian cancer and compared outcomes according to their surgical methods (29,30). Robot-assisted surgery enables precise pelvic and para-aortic lymphadenectomy, including dissection of nodal stations enriched with hematopoietic progenitor cell niches, thereby improving staging accuracy while minimizing collateral tissue trauma. This allows the provision of gonadotoxic treatments to these patients, which protects their ability to have children. The robot-assisted surgical approach has been employed to perform systematic pelvic and para-aortic lymphadenectomy, enabling accurate staging of ovarian cancer and facilitating evaluation of the therapeutic impact of varying lymph node harvests (31). Robotic surgery methods may help identify high-risk patients who can have a full lymphadenectomy and still receive fertility-preserving treatment. The growing adoption of MITs in ovarian cancer surgery highlights various benefits, including enhanced patient satisfaction and potential cost savings associated with these approaches.

3. Molecular-based therapies in conjunction with MITs

The clinical management of ovarian carcinoma poses significant challenges for oncology professionals due to the typically late-stage presentation of the disease, the high propensity for peritoneal dissemination and the complexity in achieving complete cytoreduction. According to the National Comprehensive Cancer Network guidelines for ovarian cancer, optimal management of advanced-stage EOC requires maximal cytoreductive surgery, preferably achieving no macroscopic residual disease, followed by platinum- and taxane-based chemotherapy, with consideration of neoadjuvant chemotherapy (NACT) and interval debulking in selected patients. Minimally invasive surgical techniques in EOC allow optimal cytoreduction with outcomes comparable to open surgery, while significantly reducing perioperative morbidity and accelerating recovery. This faster recovery enables earlier initiation of adjuvant therapy, so patients can promptly receive novel systemic treatments that improve disease control (27). This faster recovery enables earlier initiation of adjuvant therapy, so patients can promptly receive novel systemic treatments that improve disease control (32). Additionally, integrating immunotherapy (for example, checkpoint inhibitors) is an emerging strategy, combination approaches, such as a PARP inhibitor plus programmed cell death protein (PD)-1 blockade, have demonstrated higher response rates in refractory ovarian cancer compared with either modality alone (33). In current practice, the combination of MIS and these targeted therapies translates into improved clinical outcomes: Patients experience shorter hospital stays, improved treatment responses and extended remissions, which demonstrate that surgical innovation complements systemic advances without compromising oncological efficacy (32).

In EOC, combining MIS with novel systemic therapies (PARP inhibitors or anti-angiogenic agents such as bevacizumab and emerging immunotherapies) is shaping a more effective, multimodal treatment paradigm. MIS (for example, laparoscopic or robotic debulking) offers well-documented perioperative advantages over open surgery, including shorter hospital stays, reduced blood loss and fewer complications, which translate into faster recovery and allows patients to proceed more swiftly to adjuvant systemic therapy. This expedited post-surgery recovery means maintenance treatments such as PARP inhibitor therapy or anti-angiogenic agents can be initiated without undue delay, which maximizes their impact (21,27,32,34,35). By contrast, systemic therapies can shrink or control tumor burden (for instance, NACT is often combined with bevacizumab in trials), which thereby increases the likelihood that a subsequent cytoreduction can be successfully performed via MIS. This bidirectional synergy ensures each modality enhances the other: Effective preoperative systemic therapy can render disease more resectable for minimally invasive surgeons, while the lower surgical morbidity of MIS preserves patient performance status for the continuation of systemic treatments (27,36). Clinical studies and outcomes underscore the value of this integrated approach. The ongoing phase III Laparoscopic Cytoreduction After Neoadjuvant Chemotherapy (LANCE) trial is directly evaluating MIS vs. open laparotomy after NACT in advanced EOC, reflecting the effort to confirm that a less invasive surgical approach can achieve equivalent oncological outcomes (32,35)(Fig. 2).

The benefit of coupling surgery with targeted post-operative therapy has also been reported, for example, in the PAOLA-1 trial, patients who received standard surgery and chemotherapy followed by maintenance olaparib (a PARP inhibitor) plus bevacizumab had markedly prolonged PFS (22.1 months vs. 16.6 months with bevacizumab alone). This finding led to regulatory approval of the olaparib-bevacizumab combination and illustrates how surgery complemented by novel agents can improve patient outcomes (35). Immunotherapy is also being explored in combination with these modalities;

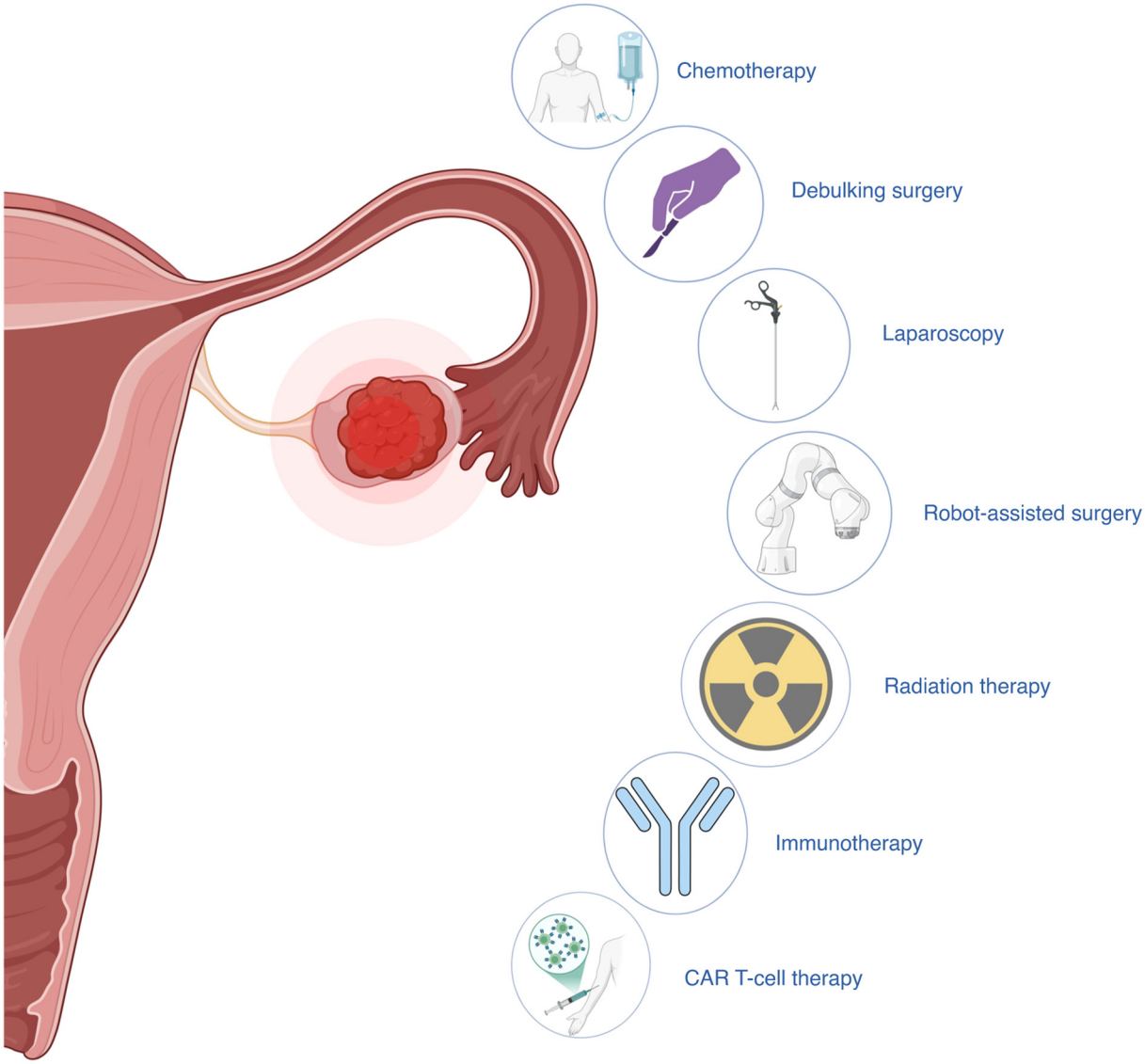

Figure 2. Schematic illustration of management methods for epithelial ovarian cancer. CAR, chimeric antigen receptor.

although checkpoint inhibitors alone have demonstrated limited efficacy in EOC, integrating them with other treatments may unlock synergistic effects. Preclinical evidence suggested that debulking surgery can enhance the impact of immunotherapy by reducing immunosuppressive tumor burden (for example, decreasing myeloid suppressor cells and improving T-cell trafficking) (36) and early-phase studies indicated that PARP inhibitors combined with PD-1/PD-ligand 1 (L1) checkpoint blockade yield additive antitumor activity in ovarian cancer (37). Clinical guidelines now advocate an integrated, individualized approach to EOC management. The National Comprehensive Cancer Network recommends offering minimally invasive surgery for surgical staging in early-stage disease (FIGO I-IIA) or for interval cytoreduction following neoadjuvant platinum-taxane chemotherapy when key criteria are met: i) Disease confined to the pelvis or superficial peritoneum without extensive diaphragmatic, mesenteric, hepatic or splenic involvement; ii) at least a 50% reduction in tumor volume on imaging to facilitate complete gross resection via laparoscopy or robotics; iii) confirmation by preoperative imaging or diagnostic laparoscopy that R0 cytoreduction is achievable without multiorgan resections; and iv) patient performance status of ECOG 0-1 with well-controlled comorbidities and anatomy suitable for minimally invasive access (38,39). Concurrently, American Society of Clinical Oncology/European Society for Medical Oncology consensus guidelines endorse maintenance targeted therapy in patients with advanced (FIGO III-IV) ovarian cancer who respond to first-line platinum-taxane chemotherapy, specifying olaparib maintenance in BRCA-mutated patients based on SOLO-1, niraparib maintenance in BRCA wild-type or homologous recombination deficiency (HRD)-positive patients per PRIMA, and the combination of olaparib plus bevacizumab maintenance in HRD-positive cases according to PAOLA-1 (27,35,40-42). Together, these strategies create a cohesive treatment plan: Maximal tumor reduction through surgery (increasingly via MIS to minimize patient burden) followed by tailored systemic therapy to eradicate microscopic disease and suppress recurrence. This holistic approach has a compounding positive effect on patient outcomes, which

yields longer remissions and potentially improved survival, while also improving QoL by reducing surgical trauma and leveraging more precise, effective medications (27,32,35). In summary, MIS and novel systemic therapies are not competing alternatives but complementary approaches in the treatment of ovarian cancer, as each reinforces the efficacy of the other, which results in a synergistic improvement in clinical results for patients with EOC.

Targeted therapies. Targeted therapies are fundamental in ovarian cancer management as they are designed to interfere with specific molecular pathways that cancer cells rely on for growth, survival and proliferation, distinguishing them from traditional chemotherapy agents such as carboplatin, paclitaxel and doxorubicin, which broadly target all rapidly dividing cells. Unlike conventional chemotherapy, which causes damage to both malignant and normal cells leading to significant side effects such as neutropenia, alopecia, mucositis and fatigue, targeted therapies such as PARP inhibitors (including olaparib and rucaparib), anti-angiogenic agents (including bevacizumab) and folate receptor α inhibitors (including mirvetuximab), specifically attack pathways activated only in cancer cells, resulting in fewer off-target effects. These therapies work by inducing apoptosis through disruption of cancer-specific signaling pathways, including homologous recombination repair pathways and tumor angiogenesis processes, which suppress tumor growth and promote cancer cell death. Furthermore, predictive biomarkers such as BRCA mutations and HRD status enable clinicians to identify patients who are most likely to benefit from these targeted treatments, providing a personalized approach that enhances efficacy (35,43-45).

Nonetheless, the emergence of drug resistance presents a notable limitation. A potentially more effective strategy may involve a combination therapy utilizing ≥2 targeted agents or integrating chemotherapy with hormone therapy alongside a targeted agent to enhance sensitivities (46). The foundation of these approaches relies on current understanding of the molecular pathways that serve a role in the development and progression of cancer. In the past decade, research on EOC has highlighted mutations or amplifications in specific genes that indicate the involvement of pathways associated with DNA damage repair, apoptosis, cell cycle control and anti-angiogenesis. The present review underscores the necessity for innovative pharmaceuticals and the initiation of clinical trials to explore therapeutic alternatives.

PARP inhibitors. In recent years, PARP inhibitors have emerged as a prominent class of targeted therapies in EOC (32,33,47). These agents act by disrupting the DNA repair process, specifically, the repair of single-strand DNA breaks. When PARP is inhibited, these breaks evolve into double-strand DNA damage, which cannot be effectively repaired in cancer cells harboring BRCA1/2 mutations, which leads to cell death via synthetic lethality (37,46,48). Currently, three PARP inhibitors, olaparib, rucaparib and niraparib, are approved by the Food and Drug Administration for ovarian cancer treatment, based on a number of pivotal trials (40,41,49).

For instance, the SOLO-1 trial demonstrated a notable increase in PFS from 13.8 to 56 months in newly diagnosed patients with BRCA-mutated EOC receiving olaparib as maintenance therapy [Hazard ratio (HR), 0.30; P<0.001] (40). The PRIMA trial extended this benefit to a broader population, which demonstrated improved PFS from 8.2 to 13.8 months with niraparib in both BRCA and non-BRCA advanced cases (HR, 0.62; P<0.001) (41). In recurrent BRCA-mutated EOC, the ARIEL3 trial confirmed the efficacy of rucaparib, with PFS increasing from 5.4 to 10.8 months (HR, 0.36; P<0.0001) (49). The VELIA trial assessed veliparib added to first-line chemotherapy and as maintenance, which reported an increase in PFS from 17.3 to 23.5 months (HR, 0.68; P<0.001), which supports the role of PARP inhibitors in newly diagnosed EOC (50). Notably, the PAOLA-1 trial evaluated the combination of olaparib with bevacizumab in HRD-positive patients, which demonstrated improved PFS from 16.6 to 22.1 months (HR, 0.59; P<0.001), which suggested potential synergy between DNA repair inhibition and anti-angiogenic therapy (35). Together, these trials establish the clinical efficacy of PARP inhibitors across different settings: BRCA-mutated, HRD-positive and BRCA wild-type subpopulations. While resistance mechanisms and optimal combinations remain areas of active research, ongoing research continues to explore the role of PARP inhibitors in frontline and maintenance therapy (Table I). These results have firmly established PARP inhibitors, particularly olaparib and niraparib, as standard of care in maintenance therapy for EOC.

Angiogenesis inhibitors. Angiogenesis serves a key role in ovarian cancer progression, which supports tumor growth and metastasis by establishing a dedicated blood supply. Targeting this pathway has yielded promising therapeutic strategies, particularly with bevacizumab, a monoclonal antibody against VEGF and pazopanib, a multi-targeted angiogenesis inhibitor (16,51).

In the GOG-0218 trial, bevacizumab added to standard first-line chemotherapy extended PFS from 10.3 to 14.1 months (HR, 0.717; P<0.001), which highlighted its benefit in newly diagnosed advanced ovarian cancer (16). Similarly, the ICON7 trial demonstrated a modest but notable improvement in PFS (17.3-19 months) in patients receiving bevacizumab with chemotherapy (HR, 0.81; P=0.004) (52). In the recurrent setting, the OCEANS trial confirmed the benefit of bevacizumab in platinum-sensitive relapse, with PFS rising from 8.4 to 12.4 months (HR, 0.484; P<0.0001) (53). For maintenance therapy, the AGO-OVAR16 study evaluated pazopanib and observed a PFS extension from 12.3 to 17.9 months in advanced ovarian cancer (HR, 0.77; P=0.0021) (51).

In recurrent settings, the OCEANS trial demonstrated that adding bevacizumab to chemotherapy improved PFS from 8.4 to 12.4 months (HR, 0.484; P<0.0001) in platinum-sensitive relapses. Similarly, the AGO-OV/AR16 study demonstrated that pazopanib maintenance extended PFS from 12.3 to 17.9 months in advanced ovarian cancer (HR, 0.77; P=0.0021). Despite these positive results, resistance to anti-angiogenic therapy remains a challenge and future directions may involve biomarker-guided patient selection or combination regimens with immunotherapy or PARP inhibitors (Table I). While bevacizumab is incorporated into standard regimens based on GOG-0218 and ICON7, other agents such as pazopanib warrant further investigation.

Table I. Efficacy of targeted therapies in improving PFS across patient populations with ovarian cancer.

A, PARP inhibitors

First author, year	Clinical trial	Drug	NCT no.	Clinical trial subject/design	Control to treatment PFS improvement, months	HR (95% CI)	P-value	(Ref.)
Moore *et al*, 2018	SOLO-1	Olaparib	NCT01844986	Newly diagnosed BRCA-mutated EOC	13.8-56	0.3 (0.2-0.4)	<0.001	(40)
Psomiadou *et al*, 2021	PRIMA	Niraparib	NCT02655016	Advanced ovarian cancer (BRCA and non-BRCA)	8.2-13.8	0.6 (0.5-0.7)	<0.001	(29)
Abitbol *et al*, 2019	ARIEL3	Rucaparib	NCT01968213	Recurrent BRCA-mutated EOC	5.4-10.8	0.3 (0.3-0.4)	<0.0001	(30)
Chen *et al*, 2023	VELIA	Veliparib	NCT02470585	Newly diagnosed EOC	17.3-23.5	0.6 (0.5-0.8)	<0.001	(31)
Baum *et al*, 2022	PAOLA-1	Olaparib + bevacizumab	NCT02477644	HRD-positive ovarian cancer	16.6-22.1	0.6 (0.6-0.7)	<0.001	(24)

B, Angiogenesis inhibitors

First author, year	Clinical trial	Drug	NCT no.	Clinical trial subject/design	Control to treatment PFS improvement, months	HR (95% CI)	P-value	(Ref.)
Rauh-Hain *et al*, 2024	GOG-0218	Bevacizumab	NCT00262847	Advanced ovarian cancer (first-line)	10.3-14.1	0.7 (0.6-0.8)	<0.001	(9)
Ray-Coquard *et al*, 2023	ICON7	Bevacizumab	NCT00483782	Newly diagnosed advanced ovarian cancer	17.3-19	0.8 (0.7-0.9)	0.004	(32)
Zhao *et al*, 2024	OCEANS	Bevacizumab	NCT00434642	Platinum-sensitive recurrent ovarian cancer	8.4-12.4	0.5 (0.4-0.6)	<0.0001	(33)
Nezhat *et al*, 2024	AGO-OVAR16	Pazopanib	NCT00484442	Advanced ovarian cancer (maintenance)	12.3-17.9	0.8 (0.6-0.9)	0.0021	(34)

C, Tyrosine kinase inhibitors

First author, year	Clinical trial	Drug	NCT no.	Clinical trial subject/design	Median PFS	Median follow-up duration, months (95% CI)	P-value	(Ref.)
Ray-Coquard *et al*, 2019	ALTER-GO-010	Anlotinib	NCT02773524	Newly diagnosed advanced ovarian cancer: A phase II, single-arm	6 months, 100%; 9 months, 100%	5.3 (3.7-8)	Final median PFS not yet reached due to ongoing follow-up	(35)

Table I. Continued.

C, Tyrosine kinase inhibitors

First author, year	Clinical trial	Drug	NCT no.	Clinical trial subject/design	Median PFS	Median follow-up duration, months (95% CI)	P-value	(Ref.)
Predina *et al*, 2012	MITO 11	Pazopanib + Paclitaxel	NCT01335226	Platinum-resistant/ refractory advanced ovarian cancer	3.5-6.3	0.4 (0.2-0.7)	0.0002	(36)
Xiao *et al*, 2024	NCT03367741	Cabozantinib + Nivolumab		Recurrent endometrial cancer	1.9-5.3	0.6 (90% CI, 0.3-1)	0.09	(37)

PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; HRD, homologous recombination deficiency; HR, hazard ratio; EOC, epithelial ovarian cancer.

Tyrosine kinase inhibitors (TKIs). TKIs represent a diverse class of targeted agents designed to interfere with signaling pathways that mediate tumor cell proliferation, survival, angiogenesis and invasion (54-56). TKIs block multiple oncogenic signaling cascades that contribute to ovarian cancer growth and spread. By inhibiting the VEGFR and platelet-derived growth factor receptor, TKIs disrupt angiogenesis and stromal support for tumor proliferation, while blockade of fibroblast growth factor receptor signaling further impairs neovascularization and cell survival. In addition, inhibition of the hepatocyte growth factor/c-MET axis reduces tumor cell motility and invasion, and targeting other kinases such as AXL and RET overcome resistance mechanisms and attenuates survival pathways in cancer cells (57-59). Several TKIs have been investigated in ovarian and endometrial cancer types, with growing evidence supporting their utility, especially in combination strategies. For example, anlotinib, a multi-targeted TKI assessed in the ALTER-GO-010 phase II trial for newly diagnosed advanced ovarian cancer. This single-arm study reported a 100% PFS at both 6 and 9 months, with a median PFS of 5.36 months (95% CI, 3.68-7.98), although final PFS was not yet reached due to ongoing follow-up (54,60). The MITO 11 study, while primarily assessing anti-angiogenesis, also demonstrated the efficacy of pazopanib, which possesses TKI activity. Pazopanib combination with paclitaxel yielded notable improvements in PFS in a platinum-resistant/refractory cohort (55). A novel combination of a TKI and immunotherapy was explored in trial NCT03367741, which evaluated cabozantinib plus nivolumab in recurrent endometrial cancer. Patients receiving the combination had a PFS of 5.3 vs. 1.9 months with nivolumab alone (HR, 0.59; P=0.09) (56). Although these trials focused on endometrial compared with ovarian cancer, these findings highlight the expanding landscape of TKI-based combinations in gynecological oncology.

Furthermore, in the NCT03367741 study, the combination of cabozantinib and nivolumab was investigated in recurrent endometrial cancer, which indicated a PFS improvement from 1.9 to 5.3 months (HR, 0.59), which suggests potential synergy between TKIs and immune checkpoint inhibitors, although these findings remain preliminary and warrant further exploration in ovarian cancer (56). Overall, while TKIs alone have demonstrated modest efficacy, their integration into combinatorial regimens, especially with immune checkpoint inhibitors, may offer enhanced therapeutic outcomes. Ongoing trials continue to assess the optimal positioning of TKIs in ovarian cancer treatment, including in front-line, maintenance and recurrent settings (Table I). TKI-based combinations, such as those explored in ALTER-GO-010 and NCT03367741, remain investigational and require validation through larger trials.

4. Immunotherapeutic strategies in EOC

Vaccines. Several types of vaccines have been investigated in EOC, most containing proteins or peptides that are associated with ovarian cancer. Examples of tumor-associated antigens targeted in ovarian cancer vaccines include MUC1, cancer-testis antigen NY-ESO-1, WT1, folate receptor α and mesothelin (61). Numerous studies have seen T-cell responses or longer disease stability in patients who are getting treatment; however, not all of these studies demonstrated the

same benefits (62-64). The initial vaccine evaluated in EOC and the only vaccine assessed in a randomized phase III trial was canvaxin. Autologous tumor cell lysates were changed to add a novel glycosylation site to the mucin 1 protein, which is a known antigen located in ovarian tumors. The vaccine generated antibody responses in 88% of vaccinated patients and seemed to improve tolerance compared with the chemotherapy recommended by the physician in a selected group of women. Eventually, this trial had to be discontinued because the tumors were not under control (65-67). However, canvaxin was still investigated in other studies as an adjuvant, with and without chemotherapy, specifically in patients with EOC (68,69). Several recent clinical trials have evaluated novel antigen-targeted vaccines in EOC (61). The phase I study of folate receptor-α peptide vaccine in patients with advanced ovarian cancer demonstrated induction of FRα-specific $CD8^+$ T-cell responses in 90% of participants and disease stabilization in 40% at 6 months. A multicenter phase II trial of the MUC1-liposomal vaccine tecemotide added to neoadjuvant platinum-taxane chemotherapy reported enhanced MUC1-specific $CD4^+$ and $CD8^+$ T-cell responses in 75% of patients, with a 12-month PFS of 65% compared with 50% historical controls. These treatments demonstrate the potential to prepare women for subsequent therapy with immune checkpoint inhibitors (61,67).

Cell-based interventions. Adoptive transfer of tumor-infiltrating lymphocytes and engineered CAR-T cells targeting mesothelin, HER2 or folate receptor α have demonstrated potent antigen-specific cytotoxicity and clinical activity in early-phase trials of EOC, especially for antibody-coated T cells, chimeric antigen receptor T cells (CAR-T), specifically chosen tumor-infiltrating lymphocytes or those that have been engineered to express a tumor-specific T-cell receptor (70-72). By using genetic engineering to change the T cells of a patient, CAR-T therapies make it possible for these cells to express specific receptors that help find and kill cancer cells. CAR molecules have an antigen-binding domain that is outside of cells, a transmembrane domain and an intracellular signaling domain that activates more co-stimulatory receptors after interacting with the target epitope (73,74). Therefore, CAR-Ts demonstrate specificity for a certain antigen while also being less dependent on HLA expression. CAR-T therapies have evolved in recent years and gaining attention in the field. The anti-CD19 therapy has demonstrated potential in treating patients with B-cell malignancies (75). Concerning EOC, CAR-T-based approaches have been created to target different antigens associated with tumors, such as mesothelin, HER2 and folate receptor α. These treatment approaches have demonstrated potential in early-stage clinical trials (76-79).

Immune checkpoint inhibitors. Immune checkpoint inhibitors have transformed the treatment landscape for multiple malignancies, including metastatic melanoma, non-small cell lung cancer and renal cell carcinoma. By blocking receptors such as PD-1 on T cells or ligands like PD-L1 on tumor cells, these agents prevent inhibitory signaling that normally dampens T-cell activation. Specifically, PD-1/PD-L1 blockade restores T-cell receptor signaling, leading to increased proliferation of effector T cells, enhanced cytokine production and sustained antitumor cytotoxicity. The goal of anti-PD-1/PD-L1 therapies was to revive lymphocytes that had been eliminated by advanced tumors. Anti-PD-1/PD-L1 therapies demonstrated efficacy for several types of cancer that exhibited HLA-antigen presentation; therefore, the demonstrating potential for these types of drugs to help treat EOC. The effectiveness of these drugs could be increased by combining them with other treatments, such as VEGF inhibitors, PARP inhibitors or platinum-based chemotherapy (64,80). The efficacy of both anti-PD-1 and anti-PD-L1 antibodies have been assessed in patients with EOC. Anti-PD-1/PD-L1 monotherapy in EOC has produced modest clinical benefits. In the phase II trial of nivolumab in platinum-resistant ovarian cancer, the objective response rate was 15% and the disease control rate (responses plus stable disease ≥6 months) was 45%, with a median PFS of 3.5 months. Similarly, pembrolizumab in the KEYNOTE-100 study achieved an ORR of 8% and a DCR of 34%, with a median PFS of 2.1 months, indicating that while a subset of patients experiences prolonged stabilization, the overall impact on disease control remains limited (81,82). As a stand-alone treatment, PD-L1 blockade has had response rates of <15%. This suggests that blocking the PD-L1/PD-1 interaction may not be enough to activate and grow T cells, unlike what has been reported with anti-CTLA-4 therapies. Consequently, further immunotherapy approaches are currently being investigated (64,80).

Combining targeted therapies with immunotherapy or chemotherapy holds notable potential in improving outcomes for patients with EOC. PARP inhibitors, when combined with immune checkpoint inhibitors, may enhance antitumor immunity by increasing the tumor neoantigen load and modulating the tumor microenvironment (37,83). Similarly, combining anti-angiogenic agents with immunotherapy can normalize tumor vasculature, promoting enhanced immune cell infiltration. However, these combinations present challenges, including increased risk of overlapping toxicities, optimal treatment schedule, dosing strategies and patient selection. Optimal sequencing refers to the strategic order and timing of administering each therapy to maximize synergistic efficacy and minimize cumulative toxicity. In EOC combinations: For PARP inhibitor + ICI: Sequencing may involve giving the PARP inhibitor first to induce DNA damage and neoantigen release, then administering PD-1/PD-L1 blockade at the peak of antigen presentation to reinvigorate T cells. For anti-angiogenic + ICI: VEGF inhibition is often delivered prior to checkpoint blockade to normalize abnormal tumor vasculature and improve effector T-cell infiltration, followed by PD-1/PD-L1 antibodies to sustain the immune response (37,84,85). Furthermore, identifying reliable biomarkers to predict response remains an unmet need (86). Ongoing trials are actively exploring these strategies and future research will be key to refining combination approaches and determining their place in clinical practice (37).

5. Clinical outcomes and efficacy of MITs

Over the past few decades, MITs such as laparoscopy and robotic-assisted surgery have increasingly been incorporated into the surgical management of EOC. Originally introduced for early-stage disease, these approaches have expanded into

selected cases of advanced-stage (FIGO III-IV) cancer (9,87). Previous studies have demonstrated that, in appropriately selected patients with EOC, MITs can reduce blood loss, shorten hospital stays and accelerate postoperative recovery, all while maintaining long-term oncological outcomes comparable to open laparotomy (27,88). Furthermore, the enhanced visualization of retroperitoneal spaces during MIS may support more accurate staging and surgical precision.

However, outcomes associated with MIS depend heavily on surgeon expertise, institutional experience and careful patient selection. Integrating MIS into oncological practice requires gynecological oncologists to master advanced laparoscopic techniques, particularly when pursuing complete cytoreduction in high-risk patients. Standardization of surgical protocols, including safe tumor handling and use of containment systems, remains essential to minimize the risk of intraoperative tumor spread. The clinical efficacy of MIS in advanced EOC has been summarized from cohort studies, meta-analyses and emerging randomized trial data; the residual disease rates, survival outcomes, recurrence patterns and real-world implementation across high-volume centers were also assessed (Table II).

Residual disease rates. Achieving minimal or no gross residual disease (R0) is critical in advanced ovarian cancer. Recent studies indicate that MIS can attain similar optimal cytoreduction rates as open surgery in selected patients. A 2024 meta-analysis stratified by surgery timing reported no notable difference in optimal debulking rates between MIS and laparotomy for both primary debulking surgery (PDS) and interval debulking surgery (IDS). In interval debulking after NACT, the pooled risk ratio for achieving optimal cytoreduction with MIS was ~1.03 relative to open surgery (95% CI, 0.96-1.11; P=0.05), essentially indicating equivalent success rates. Similarly, the rate of complete gross resection (no macroscopic disease) did not differ between MIS and open approaches (risk ratio, ~1.01; 95% CI, 0.97-1.07) (34). These findings have been similarly reported by other studies (34,42,89); a 2022 systematic review reported no notable disparity in R0 (complete debulking) or R1 (≤1 cm residual) rates between laparoscopic/robotic IDS and open IDS (89).

Individual cohort studies reinforce that well-selected MIS cases can achieve high R0 rates. In the multi-center MISSION trial (2019), which evaluated 127 patients undergoing MIS IDS, 96.1% of patients had no gross residual disease at surgery. The conversion to laparotomy in that series was only ~3.9%, which implied that nearly all intended MIS procedures could be completed with optimal resection (42). Certain single-center studies have reported slightly lower complete resection rates with MIS, but these differences appear to reflect case selection. For example, Pereira *et al* (90) observed a higher R0 rate in their laparotomy group compared with MIS groups, potentially because surgeons attempted MIS only in cases with smaller tumor burden. Across numerous reports, when MIS was chosen for patients with limited disease distribution or marked chemotherapy response, residual disease outcomes were comparable with to open surgery (34,89).

Overall survival. Long-term survival outcomes (overall survival and PFS) have been a central concern when comparing MIS to open debulking in advanced ovarian cancer. Notably, no RCT has yet reported survival comparisons, although the phase III LANCE trial is currently evaluating MIS vs. open laparotomy in this setting (9,27,91). However, multiple large observational studies and meta-analyses in the last 5 years consistently reported no OS disadvantage with MIS and some even suggest non-inferiority or parity in survival (34,88,89).

A comprehensive 2023 analysis of nearly 7,900 patients from the U.S. National Cancer Database (https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/) demonstrated no notable difference in overall survival between MIS and open surgery for interval debulking after NACT. After propensity score matching, the median OS was ~46.7 months with MIS vs. 41.0 months with laparotomy (HR, 0.86; 95% CI, 0.79-0.94); 5-year survival probabilities were essentially equivalent (38.3% MIS vs. 34.8% open; P<0.01 in favor of MIS. This apparent advantage may have been influenced by differences in patient selection). There was no detriment to survival with MIS, if anything, MIS reported a slight survival benefit in this weighted analysis (27). This aligns with a Japanese Gynecologic Oncology Committee meta-analysis (2024) which reported no notable OS differences between MIS and open approaches in advanced-stage disease, whether for PDS or IDS. For instance, in advanced primary debulking cases, the pooled odds of survival were similar (OR, ~0.66; 95% CI, 0.36-1.22; P>0.05), and likewise no OS disadvantage was seen for MIS IDS (OR, ~0.93; CI 0.25-3.44) (88).

PFS has also been reported to be equivalent between minimally invasive and open surgery approaches. Numerous studies found no notable PFS difference between MIS and open surgery groups (20). In a meta-analysis of 6 studies (3,528 patients) focusing on IDS after NACT, MIS was associated with a trend toward improved PFS but no OS difference (89). Specifically, patients in the MIS group had slightly improved PFS in some cohorts, possibly due to selection of improved responders, but on the whole PFS is equivalent when accounting for confounders. For example, Alletti *et al* (92) reported median PFS of 18 months with laparoscopy vs. 12 months with open in a single-center IDS series, but no difference in 5-year OS. In the pooled analysis of six studies (3,528 patients) after NACT, MIS was associated with a median PFS of 15.8-18.0 months vs. 12.0-14.2 months with open surgery, translating into an absolute PFS gain of 1.6-3.8 months. From meta-analysis data, the pooled hazard ratio for progression was 0.85 (95% CI, 0.73-0.99; P=0.04), indicating a 15% lower risk of progression with MIS, even though overall survival did not differ between the groups (89).

Several individual center studies and registry analyses further support OS parity. A study by Pereira *et al* (90) reported that 5-year survival rates were comparable with MIS. In their analysis, 47.5% of patients with MIS IDS were alive at 5 years vs. 30% of patients with open IDS (41 vs. 28% for MIS vs. open PDS). While such differences reflect selection factors, MIS did not compromise long-term survival in appropriate candidates. Additionally, a recent conference report including >2,400 interval debulking cases with R0 resection reported median OS ~51 months MIS vs. 46 months open, a difference that was not statistically significant (HR, ~1.1; P=0.17) (92). Taken together, current evidence indicated that overall survival with MIS in advanced ovarian cancer is comparable to open

Table II. Summary of key comparative studies on minimally invasive vs. open cytoreductive surgery in advanced-stage EOC.

First author, year	Design	Country	Setting	No. of patients (stage)	Intervention vs. control	Key findings	(Ref.)
Jorgensen *et al*, 2023	NCDB retrospective cohort (multi-center).	USA	Interval debulking after NACT (2013-2018)	7,897 (stage III-IV). MIS, 2,021; Open, 5,876 (after matching)	MIS IDS vs. open IDS (propensity-matched)	OS: Median 46.7 months MIS vs. 41.0 months open (HR, 0.86; 95% CI, 0.79-0.94; no detriment). 5-year OS: ~38 vs. 35% (ns). Residual disease: R0 achieved in 76% MIS vs. 73% open (MIS had slightly lower residual rates). Morbidity: 90-day mortality 1.4 vs. 2.5% (P<0.01); shorter LOS (~3 vs. 5 days). MIS usage rose to ~29% by 2018; cases had less extensive disease (fewer multi-organ resections).	(27)
Alletti *et al*, 2016	Single-institution case-control	Italy	Interval debulking (after NACT)	46 (stage III). MIS, 23; open, 23 (matched on chemotherapy response)	Laparoscopic IDS vs. open IDS	OS/PFS: No significant difference in 5-year OS or PFS between groups (matched selection). One analysis demonstrated median PFS 18 MIS vs. 12 months open (P<0.05), attributed to selection. Residual disease: 100% R0 in both groups (all patients optimally debulked). Perioperative: MIS had less blood loss and shorter hospital stay. Demonstrated feasibility of complete laparoscopy in responders.	(92)
Feuer *et al*, 2013	Single-center retrospective	Israel	Mixed PDS/IDS cases (stage III-IV)	89 (advanced EOC). MIS, 63; open, 26 (open included conversions)	Robotic-assisted MIS vs. open (mixed timing)	OS/PFS: No differences in PFS or OS between robotic MIS and open laparotomy. Residual disease: Comparable R0 rates. All cases were R0 by inclusion (complete gross resection achieved). More patients in MIS group had received NACT (52 vs. 15% in open), which indicates selection of responders for MIS. Demonstrated safety of robotic debulking with similar outcomes.	(21)

Table II. Continued.

First author, year	Design	Country	Setting	No. of patients (stage)	Intervention vs. control	Key findings	(Ref.)
Magrina *et al*, 2011	Multi-center retrospective	Spain and USA	Mixed PDS and IDS (primary or secondary cytoreduction)	171 (stage III-IV). Robot, 25; lap, 27; open, 119	Robotic MIS vs. conventional laparoscopy vs. open	OS: No OS differences among the three groups. Residual disease: R0 was achieved more often in open surgery (data from one center demonstrated higher complete resection in laparotomy), but all groups had high optimal debulk rates (>90%). PFS: MIS groups had longer PFS compared with open in this series (P<0.05) Perioperative: MIS had longer OR time in robot group, but much lower EBL and shorter LOS. Highlighted that extensive disease cases went open, explaining R0 difference.	(22)
Pereira *et al*, 2022	Dual-center retrospective	Spain and USA	Both PDS and IDS analyzed (2012-2013)	89 (stage IIIC-IV unresectable at diagnosis). IDS, 59 after NACT; PDS, 30 upfront. Subgroups, MIS vs. open	MIS vs. open at IDS; also some MIS vs. open PDS	OS: At last follow-up, survival favored MIS (47.5 MIS vs. 30% open alive in IDS cohort), although groups differed. No statistically significant OS disadvantage for MIS in either PDS or IDS. Recurrence: No difference in recurrence rate between MIS and open. Findings: MIS was viable for IDS in selected patients without compromising survival. Significantly shorter hospital stays with MIS (2 days vs. 8 days) and fewer bowel resections at IDS.	(90)
Hayek, 2024	NCDB analysis subseta; multi-center	USA	Interval R0 cases only	2,412 (stage III-IV IDS with complete gross resection). MIS, 25.9%; open, 74.1%	MIS vs. open Interval R0 (real-world subset)	OS: No difference in OS for MIS vs. open R0 debulking (median OS ~51 vs. 46 months; HR, 1.10; 95% CI, 0.94-1.26; P=0.17). Achieving R0 negated route as a factor in survival. Morbidity: MIS had shorter hospital stays. 30/90-day mortality and	(93)

Table II. Continued.

First author, year	Design	Country	Setting	No. of patients (stage)	Intervention vs. control	Key findings	(Ref.)
						readmission were low and similar between groups. Other: MIS use increased from ~12% in 2010 to 36.5% in 2019. Open surgery group had more 'extensive' procedures (53% vs. 41%; P<0.001). Real-world data from community centers mirrored high-volume outcomes.	

[a]SGO conference abstract. OS, overall survival; PFS, progression-free survival; HR, hazard ratio; MIS, minimally invasive surgery; IDS, interval debulking surgery; ns, not significant; R0, no macroscopic residual disease after surgery; PDS, primary debulking surgery; EOC, epithelial ovarian cancer; NACT, neoadjuvant chemotherapy; EBL, epithelial borderline lesion; LOS, low-grade serous; NCDB, National Cancer Database; SGO, Society of Gynecological Oncology.

surgery, provided patients are selected for achievable complete cytoreduction (88,93).

Recurrence patterns. Beyond survival duration, the pattern and timing of disease recurrence are important considerations. Thus far, studies have not identified any unique or worse recurrence patterns associated with minimally invasive debulking. Recurrence rates appear similar between MIS and open approaches in advanced-stage patients. For patients with advanced-stage (FIGO III-IV) EOC undergoing interval debulking after NACT, Zeng *et al* (89) performed a meta-analysis of six studies encompassing 3,528 patients and found no significant difference in recurrence rates between minimally invasive surgery and open laparotomy groups. In a dual-center retrospective cohort of 89 patients with stage IIIC-IV EOC (59 MIS vs. 30 open IDS), Pereira *et al* (90) reported equivalent recurrence frequencies in both approaches. Similarly, Alletti *et al* (92) evaluated 46 patients with stage III EOC (23 MIS vs. 23 open IDS) and observed no increase in early or atypical recurrences with minimally invasive techniques. A single-center comparison of robotic vs. open cytoreduction reported that the recurrence-free survival was longer in the MIS cohort (potentially reflecting case-specific factors such as patient selection bias, tumor stage distribution, preoperative disease burden, performance status or differences in adjuvant therapy protocols), but recurrence frequency was similar across groups. No study to date has demonstrated a higher risk of recurrence solely due to the minimally invasive technique when surgical completeness is equivalent (34).

A specific concern with MIS is the risk of port-site metastases (tumor seeding at trocar sites). Port-site metastases have been documented in advanced ovarian cancer after diagnostic laparoscopy, with rates of 5-17% reported when no precautions were taken. However, these metastases are usually detected at the time of subsequent surgery or during chemotherapy and are resected or sterilized by treatment. Furthermore, long-term follow-up has indicated no adverse impact on prognosis from port-site implants if patients receive standard therapy (94). In a novel published series of MIS IDS (from 2015 onwards), port-site recurrences were rare (>1-2% of cases) and have not been reported as a notable pattern of failure compared to the overall recurrence rates in ovarian cancer (89,95). The majority of recurrences after either MIS or open debulking occur in typical intra-abdominal locations (peritoneum and retroperitoneum account for 75-80% of recurrence sites), with remaining recurrences distributed among distant sites (liver, brain and lungs), reflecting the biology of ovarian cancer compared with the surgical route (42,94). Overall, current evidence suggests no difference in recurrence patterns between MIS and open surgery; the key determinant is whether complete cytoreduction is achieved, not the incision type (89). Notably, no increase in distant or early recurrence has been observed with MIS, unlike early-stage cervical cancer MIS trials (95). Ongoing studies will continue to monitor for any subtle differences in recurrence dynamics with MIS.

Patient selection criteria. Patient selection is a key factor in the success of minimally invasive cytoreductive surgery. Several previous studies emphasize that MIS in advanced ovarian cancer should be reserved for patients with a limited

disease burden that can be addressed with standard cytoreductive techniques not requiring extensive multiorgan resections. Common selection criteria include: Notable response to NACT (for interval cases) with substantial tumor shrinkage; disease distribution confined to areas amenable to laparoscopic resection (for example, superficial peritoneal implants, easily accessible pelvic/abdominal disease, omental caking that can be removed *en bloc*); absence of extensive diaphragmatic or mesenteric disease requiring large incisions; and patient factors such as body habitus and comorbidities that favor a minimally invasive approach (42,94). In practice, surgeons often perform a thorough preoperative imaging assessment and may even use diagnostic laparoscopy to confirm that complete resection may be feasible via MIS ports (89).

Previous studies demonstrated that when these selection principles are applied, patients with MIS tend to have lower initial tumor load. For example, in the National Cancer Database (NCDB; https://www.facs.org/quality-programs/cancer/ncdb/) study, MIS cases had significantly fewer 'additional cytoreductive procedures' (for example, bowel or spleen resections) compared with open cases (59.3 vs. 70.8%; P<0.01). This suggests surgeons selected MIS for patients with less disseminated disease, hence needing fewer organ resections. In the same dataset, the rate of any gross residual disease was slightly lower in patients with MIS (23.9 vs. 26.7% in open; corresponding to higher complete resection rates) (27), which suggested that surgeons attempted MIS primarily in cases where they anticipated achieving R0. Another analysis noted patients with MIS were less likely to require 'extensive' surgery compared with open patients (41 vs. 53%; P<0.001). All of this reflects a selection bias: Candidates for MIS are typically those with resectable disease of low complexity (42,93). A multi-center consensus concluded that MIS is appropriate when surgery can be limited to standard cytoreductive procedures without major complexity (42).

Beyond tumor factors, patient factors serve a role; a previous study reported that patients with MIS were on average older compared with those undergoing open surgery (93), possibly because surgeons chose MIS to minimize morbidity in older patients (≥65 years) who had adequate response to chemotherapy. Other selection considerations include performance status and surgeon experience. High-volume centers with advanced MIS skills are more likely to attempt laparoscopy/robotics on borderline cases, whereas less experienced centers might opt for laparotomy for the same patient. In summary, ideal candidates for MIS PDS/IDS are those with regionally confined disease, notable response to therapy and no need for large *en bloc* resections, as determined by imaging or laparoscopic assessment. These selection criteria underlie the similar outcomes seen, and differences in the characteristics of the patient groups, such as age, comorbidities, response to chemotherapy and extent of disease, rather than the surgical approach itself, may account for any modest benefits observed in the MIS cohorts (27,89).

Data limitations and ongoing studies. Although outcomes thus far are encouraging, it is important to acknowledge the limitations of existing data. Selection bias is the foremost limitation, as all comparative studies to date are non-randomized and patients with MIS inevitably had more favorable disease characteristics. Propensity score matching and multivariable adjustments, as performed in the NCDB analyses (27), help mitigate but cannot eliminate this bias. Thus, it remains possible that equivalent patients with extensive disease would fare differently with MIS compared with open surgery. High-level evidence from randomized trials to confirm oncological safety.

To date, no RCT has published definitive results comparing MIS vs. open debulking in advanced ovarian cancer (34). However, the first such trial is presently underway. The international LANCE trial is a phase III multicenter RCT designed to evaluate non-inferiority of MIS vs. laparotomy for IDS in advanced-stage ovarian cancer after 3-4 cycles of NACT (95). The pilot phase of the trial demonstrated feasibility and acceptable conversion rates, enabling full accrual. The outcome of the trial (disease-free survival as primary endpoint) will provide level I evidence on the oncological efficacy of MIS in this setting (9,95). Therefore, until the LANCE trial results are reported, the present review relied on observational data.

Another limitation is that most studies have been conducted in specialized centers or databases from developed healthcare systems, which may not reflect all practice settings globally. There is a paucity of data on MIS outcomes in resource-limited regions or low-volume centers. Additionally, follow-up duration in previous MIS series was still short, as several studies reported a median follow-up of 3-4 years, so long-term survival equivalence and patterns of late recurrence require continued investigation (42). Data on recurrence patterns specifically (for example whether MIS might lead to different metastatic spread) are limited. To date, no concerning safety issues or unexpected complications have been reported. Numerous analyses (for example, NCDB) lack specific details such as exact residual tumor size or QoL outcomes. QoL and recovery metrics may favor MIS (due to faster recovery), but robust prospective data on patient-reported outcomes are needed.

In summary, although current evidence supports MIS as an acceptable approach in advanced ovarian cancer, it is still largely retrospective. Results must be interpreted with caution given the non-randomized nature of published studies and potential confounders (34). The ongoing LANCE RCT and other prospective studies will be key to conclusively establish whether MIS is comparable with open surgery in all oncological outcomes or if differences may emerge when selection bias is removed. To date, the National Comprehensive Cancer Network (NCCN) and the European Society of Gynecological Oncology (96) guidelines emphasize that MIS for advanced ovarian cancer should be offered only in highly selected patients by experienced surgeons, preferably in the context of clinical trials or protocols (38,89). Furthermore, current evidence is largely derived from retrospective studies with inherent selection biases. While several cohort analyses indicate non-inferior outcomes for MIT compared with open surgery, the lack of level I evidence from completed RCTs mandates cautious interpretation. The ongoing LANCE trial is expected to address this gap.

Real-world outcomes in high-volume centers. Real-world data from high-volume gynecological oncology centers have consistently reported that in appropriately selected patients, MIS can safely replicate the oncological outcomes of open

cytoreduction. For instance, the NCDB analyses demonstrated that between 2013 and 2019, MIS usage in IDS increased significantly in the USA, with comparable overall survival (OS) and even lower perioperative mortality compared with open surgery (90-day mortality; 1.4 vs. 2.5%; P<0.01) (27). Similar findings were reported by the MISSION study in Europe and South America (42) and by multi-center registries from including a 2022 meta-analysis (89). These studies confirmed equivalent 5-year OS rates and high R0 rates with MIS when performed by experienced teams (90,92). MIS has also been associated with faster recovery, shorter hospital stays and earlier initiation of postoperative chemotherapy in some cohorts (93). Collectively, these real-world data suggest the feasibility and safety of MIS for advanced ovarian cancer and support its broader implementation when patient selection and surgical expertise are appropriate.

However, comprehensive data specifically addressing QoL in advanced-stage EOC are limited. While some retrospective analyses and small prospective series suggest potential QoL benefits, large, well-powered studies are needed to establish definitive conclusions. Furthermore, while some studies have utilized validated patient-reported outcome instruments such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ)-Core 30 and QLQ-Ovarian Cancer Module 28 to assess postoperative QoL in patients with EOC, robust PRO data specific to advanced-stage disease remain sparse and warrant further prospective investigation (97).

6. Challenges and limitations of MITs

MIS has the potential to improve the outcomes of EOC surgery. However, the implementation of MIS must be accompanied by high adherence to oncological principles, which will consequently push the envelope in technically challenging cases. These are the cases in which the use of conventional laparoscopy or robotic-assisted laparoscopy can be limited, which leads to an increased incompletion of surgery and residual disease. In low-volume centers, adnexal masses may be misdiagnosed and thereby given a less conservative approach, which can lead to stage upstaging and incomplete surgery (42,87,98). Therefore, preoperative and intraoperative protocols and criteria, surgical expertise and the correct allocation of resources, that is, ensuring that surgical expertise is available at several tertiary reference centers as possible.

Previous studies have highlighted that hepatobiliary involvement in ovarian cancer is associated with increased tumor burden, necessitating more complex surgical approaches and specialized expertise (42,87,98). Findings by Di Donato *et al* (98) further confirmed that achieving complete cytoreduction in such cases significantly impacted patient survival outcomes. In the future, the use of novel imaging techniques that can further assess tumor spread and the molecular characteristics of cancer will contribute to patient selection, allowing, whenever possible, an optimal MIS approach to be selected for EOC surgery.

While MITs offer several advantages, they are not free of risks; a key concern is the increased likelihood of intraoperative complications, particularly in advanced-stage ovarian cancer cases where optimal cytoreduction is technically challenging. Additionally, suboptimal staging may lead to higher recurrence rates due to the incomplete assessment of peritoneal spread and lymph node involvement (34). Further studies are needed to determine standardized protocols that minimize these risks and ensure oncological safety.

Patient selection. Currently, there is a lack of consensus in the field of gynecological oncology on the definition of 'early stage' ovarian cancer and its management. Typically, gynecological oncologists identify most EOC types at an advanced stage and the standard surgical intervention involves primary cytoreduction, followed by discrimination (12,13). However, two distinct cohorts of patients with apparently early-stage disease (those with Stage I disease on imaging who are ultimately found to have advanced disease at surgery and those with localized Stage I disease) may potentially gain from varying management approaches. In the early stages of the disease, surgery could lead to the diagnosis of Stage IIIB serous carcinoma, which may cause the disease stage to progress (12,13).

The NCCN guidelines currently advocate conducting the standard staging of surgical procedures for tumors classified as small stage I diseases (99). An alternative biological perspective suggested evaluating an early suspicious pelvic and/or para-aortic stage from a clinical standpoint. It is possible for these rare conditions to be caused by nodal endometriosis or dermoids or these conditions may be associated with a slow progression of hematogenous lymphangiomatosis, which usually occurs when endometriosis stays the same (38,57,92,100). Currently, research on the origins of these small, less aggressive atypical nodular forms of cancer is being conducted. The surgical techniques should vary when executed in a gynecology unit focused on these distinct procedures. Only certain patients qualify as suitable candidates for MIS in cases of advanced stage disease: i) Patients with documented major response to NACT, defined by imaging or laparoscopic assessment showing >80% reduction in tumor volume and confinement of residual disease to easily accessible pelvic and omental sites; ii) individuals whose disease distribution is limited to superficial peritoneal implants, minor omental caking that can be removed *en bloc* and absence of extensive diaphragmatic or mesenteric involvement; iii) cases without bulky upper abdominal disease or large bowel, splenic or hepatic surface metastases, such that no multiorgan resections are anticipated; iv) patients with Charlson comorbidity index <2 and adequate performance status (ECOG 0-1), minimizing anesthesia risk and facilitating rapid postoperative recovery; v) selected older patients (aged ≥65 years) with limited tumor burden who stand to benefit most from reduced perioperative morbidity and shorter hospital stays; and vi) selected older patients (aged ≥65 years) with limited tumor burden who stand to benefit most from reduced perioperative morbidity and shorter hospital stays.

The feasibility and safety of MIS in selected patients has been demonstrated in the MISSION study, where 96% achieved no gross residual disease via MIS after NACT and conversion to laparotomy occurred in only 3.9% of cases (57,92). It could be suggested that patients should have: i) Imaging after clinical evaluation by the multidisciplinary team with radiological diagnosis; ii) FIGO stage IIIC or less; iii) Charlson

comorbidity index <2 (100); iv) pauci-symptomatic small disease; v) imaging with pre-operative diagnostic laparoscopy; and vi) no notable protein anemia. As for the patients with carcinoma *in situ* (CIS), strong de-swelling surgical procedures should be avoided; albumin and hemoglobin must be normal; albumin and creatinine must be normal; fitness status and adequate psycho-physiological support; no overfeeding of the pathology or performance status; and ovarian clear cell carcinoma and CIS, against serous papillary histotype required.

Proper patient selection is key to achieve favorable outcomes in MIS. While early-stage disease, lower histological aggressiveness and a lower Charlson comorbidity index favor the feasibility of this approach, further research is required to validate these selection criteria across diverse patient populations and advanced-stage cases.

Training and expertise. The role of MIS in the management of ovarian cancer has been well documented in the form of low invasive techniques such as laparoscopic, robotic or single port surgery. Consequently, the approach has been associated with favorable reports in terms of blood loss, time, length of stay, wound complications and recovery time. However, despite favorable outcomes for recurrence, mortality and overall survival for patients receiving MIS, favorable surgical results are only associated with centers that have extensive experience in MIS.

The viability of hepatobiliary cytoreduction is markedly influenced by the skill level of the surgeon and the available resources at the institution. Previous studies have demonstrated that high-volume centers tend to achieve superior oncological outcomes compared with lower-volume centers (42,89,98). Di Donato *et al* (98) demonstrated that complete cytoreduction can be achieved in patients with hepatobiliary metastases when conducted in specialized centers with a multidisciplinary approach. In this situation, procedures such as sentinel node mapping and the removal of lymph nodes using minimally invasive methods have been recognized as important (42,89,98). However, these procedures should only be performed by surgeons with documented expertise in minimally invasive debulking surgery, following established institutional guidelines and quality standards to ensure patient safety and adequate disease management.

7. Future directions

Novel technology brings novel challenges in training and implementing these technologies in clinical practice. The implementation of robotic surgery, for instance, is associated with a steep learning curve. The effectiveness of different training models remains to be elucidated. Furthermore, not all departments can afford to start a robotics program directly. Specifically, in resource-limited healthcare systems, a multimillion investment could endanger other goals. In the development of both robotic and laparoscopic surgical techniques, training in simulations is key. Since there are several types and complexities of intraoperative complications, *in vivo* training combined with mentored procedures before leading a procedure might be beneficial.

It will be important to choose patients who are in medically fit before surgery, have few comorbidities (such as hypertension without end-organ damage, diet-controlled diabetes, mild COPD with preserved lung function or stable thyroid disease), have early-stage EOC and have a low risk of complications, as not every patient with stage I-IV EOC will gain advantages from a minimally invasive approach. Prospective trials and retrospective cohort studies may combine to create and assess these algorithms. Furthermore, the formulation of these guidelines is essential, grounded in real data compared with relying on automated training databases. Among promising innovations in EOC management, liquid biopsy and advanced imaging techniques are poised to serve transformative roles, yet several hurdles must be addressed before widespread clinical adoption. Liquid biopsy approaches, such as circulating tumor DNA, circulating tumor cells and exosomal RNA analyses, offer non-invasive means for early detection, monitoring of minimal residual disease and treatment stratification (101,102). However, the sensitivity and specificity of these assays remain variable and standardization across platforms is still evolving. Regulatory approvals are currently limited and liquid biopsy is notably viewed as a complementary adjunct compared with a replacement for traditional imaging and tissue biopsy (101,102). Similarly, advanced imaging modalities, including diffusion-weighted MRI, PET/CT with novel tracers and AI-enhanced imaging, hold potential to improve the detection of small-volume peritoneal disease and informing surgical planning (103,104). Nevertheless, variability in imaging sensitivity, the need for specialized infrastructure and the lack of established cost-effectiveness data pose notable barriers to routine clinical integration. As ongoing prospective studies refine the performance and clinical utility of these technologies, their eventual incorporation into multimodal EOC management strategies will require careful consideration of regulatory, logistical and economic factors.

8. Conclusion

MITs and molecular-based therapies have reshaped the management of EOC, particularly in selected cases of advanced-stage disease. The current evidence, including large cohort studies and recent meta-analyses, demonstrated that in appropriately chosen patients, MIS can achieve comparable oncological outcomes to open surgery, with the added benefits of reduced perioperative morbidity, faster recovery and earlier initiation of adjuvant treatment. These surgical innovations, when aligned with novel systemic therapies such as PARP inhibitors, anti-angiogenic agents and immune checkpoint inhibitors, offer an integrated approach that enhances survival and maintains QoL.

For practicing gynecological oncologists, these findings underscore the importance of individualized treatment planning based on disease burden, response to neoadjuvant therapy and institutional expertise. However, the adoption of these strategies must be guided by rigorous criteria for patient selection, as well as multidisciplinary coordination. Despite these advances, several gaps remain. Long-term survival data from RCTs comparing MIS with laparotomy in advanced

EOC are still pending. Additionally, real-world outcomes in low-volume or resource-limited settings require further validation. QoL metrics and cost-effectiveness analyses also need to be integrated into future research to further inform clinical decision-making.

Currently, several studies support the use of MITs for staging and interval debulking following NACT in carefully selected patients with advanced-stage EOC, when performed by experienced surgeons (27,42,90). For systemic therapy, PARP inhibitors have become standard of care for maintenance treatment in BRCA-mutated and HRD-positive EOC, based on high-level evidence from pivotal trials such as SOLO-1 and PRIMA. By contrast, immunotherapy remains investigational in this setting, with ongoing trials evaluating optimal combinations. Key gaps include the need for level I data validating the long-term oncological safety of MITs in advanced-stage EOC, improved strategies for the integration of systemic therapies and robust patient-reported outcome data to guide treatment decisions. Addressing these questions will be key for the translation of evolving innovations into clinical practice and to optimize the personalized management of EOC.

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RY, JG, YC, CL and JL conceptualized and designed the present review. RY and JG prepared the original draft. YC and CL wrote, edited and reviewed the manuscript. JL provided supervision, conducted the analyses and revised the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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