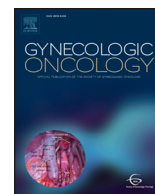




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# Assessing feasibility and perioperative outcomes with minimally invasive surgery compared with laparotomy for interval debulking surgery with hyperthermic intraperitoneal chemotherapy for advanced epithelial ovarian cancer

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## HIGHLIGHTS

- When comparing MIS and LAP at time of HIPEC, no differences are observed in adverse perioperative outcomes.
- MIS was associated with shorter hospitalization and with no significant difference in the rate of R0 resections.
- Patient candidacy for an MIS IDS should not prevent surgeons from utilizing HIPEC in appropriate candidates.

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## ABSTRACT

**Objective.** To determine peri-operative outcomes in women with advanced epithelial ovarian cancer (EOC) undergoing interval debulking surgery (IDS) with hyperthermic intraperitoneal chemotherapy (HIPEC) via minimally invasive interval debulking surgery (MIS) or laparotomy (LAP).

**Methods.** A single institution, retrospective cohort study was performed in women with EOC who underwent IDS with HIPEC from 2017 to 2019 via MIS or LAP. Peri-operative outcomes were compared using univariate analysis.

**Results.** In total, 50 eligible women were identified; ten (20.0%) underwent MIS + HIPEC and 40 (80.0%) LAP + HIPEC. The median age of patients in the MIS group was 71.1 vs. 64.2 years in LAP ( $p = 0.031$ ). There was no significant difference in pre-operative complete radiographic response following NACT ( $p = 0.18$ ). Notably, there was no difference in the rate of R0 resection (70.0% vs. 77.5%;  $p = 0.39$ ). There was no significant difference in ICU admission, estimated blood loss, operative time, or use of vasopressors between the cohorts. Similarly, there was no difference in 30-day adverse events for MIS vs. LAP, but length of stay was decreased for those who underwent minimally invasive procedures (3 vs. 4 days,  $p = 0.016$ ). Time to initiation of chemotherapy following surgery was not significantly different between groups (26.2 days vs 32.0 days,  $p = 0.090$ ). With median follow-up of 15.1 months, there was no difference in recurrence free survival (median 15.0 vs 17.2 months log-rank,  $p = 0.30$ ) for MIS vs. LAP.

**Conclusions.** In this retrospective cohort study, we demonstrate that in women with advanced EOC, HIPEC with MIS at the time of IDS following NACT is feasible. Our institutional experience demonstrates similar rates of R0 cytoreduction, compared to LAP. An MIS approach should not prevent surgeons from utilizing HIPEC where indicated for management of advanced EOC.

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## 1. Introduction

Epithelial ovarian cancer (EOC) is a leading cause of gynecologic cancer death [1]. The five-year overall survival is poor, as the majority of

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patients are diagnosed with advanced disease [2]. The standard treatment for advanced EOC is a combination of cytoreductive surgery followed by platinum and taxane chemotherapy. However, neoadjuvant chemotherapy (NACT) prior to interval debulking surgery (IDS) is an acceptable alternative, with no detriment to overall survival (OS) or recurrence free survival (RFS) demonstrated in randomized trials [3–7]. NACT has been shown to reduce perioperative morbidity and mortality and may increase likelihood of optimal cytoreduction at IDS [2,4,5,8].

In efforts to improve oncologic and perioperative outcomes for women with advanced EOC, researchers have sought to optimize delivery of NACT and IDS. Recent studies have established a role for hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of IDS in women with EOC [7,9]. In a randomized clinical trial of patients with Stage III EOC undergoing IDS following NACT, the addition of HIPEC was associated with improved RFS and OS, without an increase in grade 3 or 4 toxicity [7]. Similarly, minimally invasive surgical (MIS) approaches to IDS have been evaluated. Utilizing MIS for IDS has shown comparable short-term OS and improved perioperative outcomes, including shorter hospital stay, decreased blood loss and return to chemotherapy [6,10–12]. However, feasibility and perioperative outcomes following MIS with HIPEC at the time of IDS are yet to be described in women with advanced EOC, compared to LAP. To this end, the objective of this study was to compare perioperative outcomes in women with advanced EOC undergoing IDS with HIPEC via MIS or LAP approaches.

## 2. Methods

### 2.1. Study design

This study is an Institutional Review Board approved, single institution retrospective cohort study of women with high-grade stage III or IV epithelial ovarian, fallopian tube, and primary peritoneal carcinomas treated at Cleveland Clinic from 2017 to 2019 contained within a prospectively maintained HIPEC registry. Eligible patients had undergone IDS with HIPEC following neoadjuvant chemotherapy via either LAP or MIS. Low grade carcinomas and borderline histologies were excluded. Patients were pre-operatively selected for MIS or LAP at the discretion of the primary surgeon based on patient characteristics, including BMI and performance status, and oncologic characteristics, such as extent and location of residual disease on post-treatment imaging. There was no randomization strategy employed for treatment with MIS or LAP.

### 2.2. Surgical procedure

At our institution, interval CRS is tentatively planned following at least a partial response to 3–4 cycles of NACT with carboplatin and paclitaxel, in accordance with National Comprehensive Cancer Network (NCCN) guidelines<sup>13</sup>. Decision to proceed with NACT and IDS, versus primary cytoreductive surgery, was at the discretion of primary gynecologic oncologist. All patients were treated with carboplatin and paclitaxel given on either a standard (q21 day) or dose dense schedule, at the discretion of the provider. All patients chosen for a MIS approach were counseled on the limitations of the procedure, and potential risks including conversion to open procedure. MIS procedures were performed via either single port laparoscopy starting with manual palpation through an incision, approximately 7 cm in size (GelPoint, Applied Medical), robotic-assisted laparoscopy or traditional laparoscopy.

Following optimal cytoreduction, large bore catheters are placed through the abdominal incision and connected to the HIPEC pump. Following this, the abdominal incision is closed to ensure a water-tight fashion. A closed approach to HIPEC administration was utilized in all cases. In multi-port or robotic-assisted laparoscopy, the umbilical incision is extended to accommodate the tubing. The inflow catheter is placed within the pelvis and an outflow catheter is placed on the superior aspect of the liver, after transection of the falciform ligament. Both

catheters are connected to temperature probes that monitor temperature of the perfusate. Cisplatin (80–100 mg/m<sup>2</sup>) with or without paclitaxel (135–175 mg/m<sup>2</sup>) were administered in a perfusate of normal saline at a goal temperature of 41–43C degrees for a total treatment time of 90 min. Please see Fig. 1 for a depiction of this process.

Following HIPEC, all infusion catheters were removed and the abdomen was copiously irrigated. Patients were monitored closely throughout the procedure for hemodynamic instability or laboratory abnormalities, including electrolyte derangements, acidosis and hyperglycemia. Patients were admitted to the ICU after the procedure if persistent lactic acidosis or hemodynamic instability precluding extubation, hyperglycemia requiring insulin drip with a titration nomogram or at the discretion of anesthesia and surgical teams. All patients received the same pre-operative and post-operative care, including pre-operative antibiotic prophylaxis, with appropriate re-dosing.

### 2.3. Data collection

Patients were identified from a prospectively maintained database, which contains all patients who have undergone HIPEC procedures within the gynecologic oncology department at Cleveland Clinic from 2009 to 2020. Patient demographics were collected, including age, ethnicity, BMI, American Society of Anesthesiologists (ASA) score, medical comorbidities, and surgical history. Oncologic variables included stage, histology, NACT regimen (agent(s)/cycles), response to NACT (RECIST v1.1 criteria), CA 125 at diagnosis, and preoperative CA125 [14]. Seven attending physicians performed the surgical procedures at a single institution with assistance of fellow and resident trainees. The primary surgeon determined the HIPEC protocol, including chemotherapy regimen, after optimal cytoreduction was achieved. Intra-operative data was collected, including residual disease, operative time, estimated blood loss, cytotoxic agents, intra-operative procedures, and intra-operative vasopressor support. Post-operative outcomes were analyzed including ICU admission, 30-day post-operative complications [17], length of hospital stay, disposition on discharge, and overall interval to adjuvant chemotherapy. Adjuvant treatment decisions were made based on NCCN guidelines [13] with or without the guidance of an institutional tumor board. All data points were collected and stored within a secure, password protected RedCap database [15,16].

### 2.4. Statistical analysis

Age and BMI were summarized using means and standard deviations and compared using two-sample *t*-tests. Other continuous measures and ordinal measures were summarized using medians and quartiles and compared using Wilcoxon rank sum tests. Categorical factors were summarized using frequencies and percentages and were compared using Fisher's exact tests. For recurrence free survival (RFS), time to recurrence was defined as month difference from day of HIPEC to day of recurrence; month was defined as 30 days. Log-rank test was performed for RFS between groups. A *p* value of <0.05 was considered statistically significant. Statistical analysis was performed using SAS software version 9.4 (SAS Institute Inc., Cary NC).

## 3. Results

### 3.1. Patient demographics and oncologic characteristics

In total, 50 eligible women who underwent IDS with HIPEC were identified from 2017 to 2019, with 10 (20%) patients undergoing MIS and 40 (80%) patients undergoing LAP. MIS procedures were performed via single port (*n* = 8; 80%), robotic-assisted (*n* = 1; 10%) or multi-port laparoscopy (*n* = 1; 10%). While patients undergoing MIS were significantly older compared to LAP (mean 71.1 vs 64.2 years, *p* = 0.031), but similar in race (*p* = 0.61), body mass index (mean 25.4 vs 28.3 kg/m<sup>2</sup>, *p* = 0.19), ASA class III or IV (60% vs. 75%; *p* = 0.44) or medical

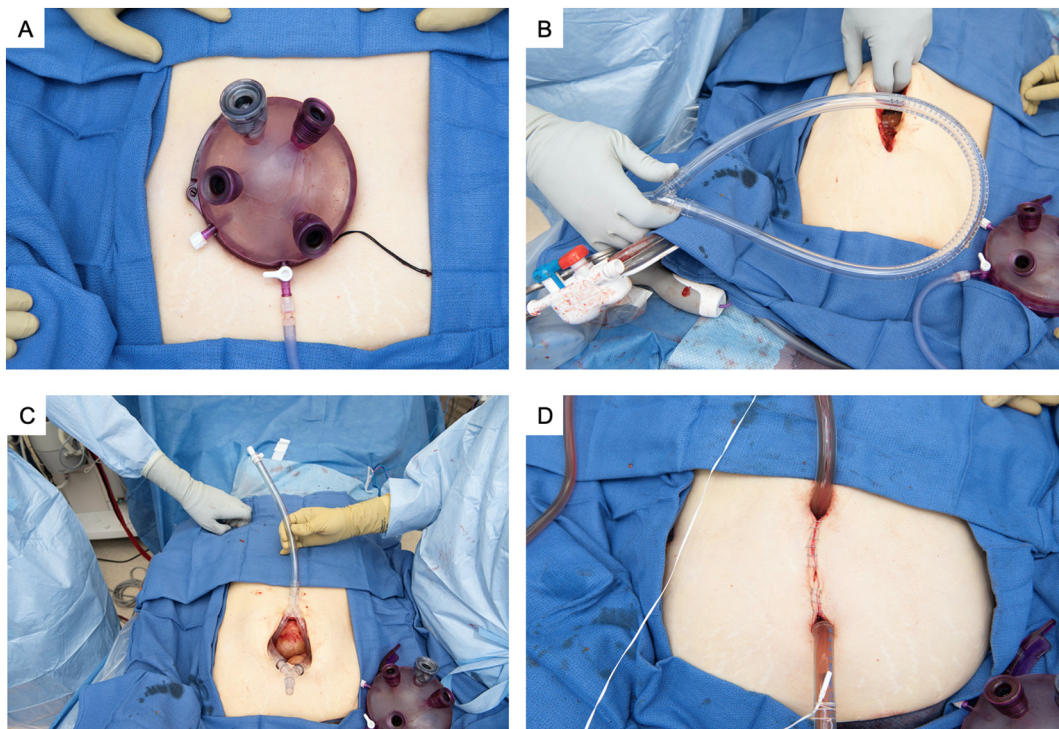


Fig. 1. Hyperthermic intraperitoneal chemotherapy procedural steps.

comorbidities (all  $p > 0.05$ ) between the groups (Table 1). The majority of the patients had stage III disease (80.0% vs. 75.0%;  $p = 0.99$ ) and serous histology (100% vs. 95.0%,  $p = 0.99$ ) for both MIS and LAP, respectively (Table 2). The preoperative hemoglobin or hematocrit was not significantly different between groups (10.9 vs 11.0,  $p = 0.23$ , 33.2 vs

34.5,  $p = 0.14$  respectively). Patients in each group received a similar number of cycles of neoadjuvant chemotherapy. All patients received carboplatin and paclitaxel, with the majority dosed on a weekly schedule for both MIS and LAP, respectively (70% vs. 58%). There was no significant difference in pre-treatment CA125 between groups (mean 494 vs 581  $p = 0.65$ ). While the median pre-operative CA125 was significantly lower among those who underwent MIS compared to LAP (median 18.8 vs. 43.5;  $p = 0.03$ ), the median percentage reduction in CA125 from diagnosis to before surgery between groups was not significantly different (97.0% vs 90.0%;  $p = 0.19$ ). Pre-operative complete radiographic response by RECIST criteria<sup>14</sup> following NACT was observed in 20.0% ( $n = 2$ ) of those who received MIS compared to 5.1% ( $n = 2$ ) of those who underwent LAP ( $p = 0.18$ ). There was no difference in days since last administration of NACT prior to HIPEC between groups ( $p = 0.22$ ) (Table 2).

**Table 1**  
Patient demographics.

Variable	MIS ( $n = 10$ )	LAP ( $N = 40$ )	$p$ -value
Age at HIPEC	71.1 ± 7.0	64.2 ± 9.1	0.031*
Race**			0.61
White	9 (90.0)	36 (92.3)	
Black	1 (10.0)	2 (5.1)	
Others	0 (0.0)	1 (2.6)	
BMI at diagnosis	25.4 ± 5.0	28.3 ± 6.5	0.19
ASA Score			0.44
0–2	4 (40.0)	10 (25.0)	
3–4	6 (60.0)	30 (75.0)	
Medical History			
Obesity	1 (10.0)	9 (22.5)	0.66
Hypertension	4 (40.0)	25 (62.5)	0.29
Diabetes	1 (10.0)	4 (10.0)	0.99
Venous Thromboembolism	1 (10.0)	2 (5.0)	0.50
Coronary Artery Disease	2 (20.0)	2 (5.0)	0.17
Peripheral Vascular disease	0 (0.0)	2 (5.0)	0.99
Immunosuppression	0 (0.0)	0 (0.0)	0.99
Pulmonary disease	1 (10.0)	5 (12.5)	0.99
Renal disease	0 (0.0)	1 (2.5)	0.99
CHF	1 (10.0)	1 (2.5)	0.99
Hypothyroidism	1 (10.0)	7 (17.5)	0.99
Hyperlipidemia	3 (30.0)	6 (15.0)	0.36
Psychiatric	1 (10.0)	6 (15.0)	0.99
Breast Cancer	1 (10.0)	3 (7.5)	0.99
Other	2 (20.0)	15 (37.5)	0.46

Statistics presented as Mean ± SD, Median [P25, P75], N (column %). HIPEC – Hyperthermic intraperitoneal chemotherapy, BMI – Body Mass Index ASA – American Society of Anesthesiologists, CHF – Congestive heart failure.

\* Statistically significant.

\*\* One missing value in laparotomy group.

### 3.2. Surgical characteristics

Two patients with intended minimally invasive surgical procedures were converted to laparotomy (4%), one for adhesive disease and the other per patient request from discussion prior to surgery. There were no significant differences between intra-operative procedures performed, including hysterectomy (90% vs. 72.5%;  $p = 0.42$ ), small bowel resection (0.0% vs. 2.5%;  $p = 0.99$ ), large bowel resection (0.0% vs. 25.0%;  $p = 0.18$ ), splenectomy (0.0% vs. 12.5%;  $p = 0.57$ ) and omentectomy (100.0% vs. 87.5%;  $p = 0.57$ ) in women who underwent IDS with HIPEC and either MIS or LAP, respectively. Furthermore, there were no significant differences in estimated blood loss (median 100 vs. 225 cc,  $p = 0.072$ ) or operative time (median 5.4 vs. 5.6 h,  $p = 0.93$ ) between patients who underwent either MIS or LAP, respectively. The majority of women who underwent MIS received HIPEC with cisplatin alone ( $n = 8$ ; 80.0%) compared to the LAP cohort where most received cisplatin with paclitaxel (60%;  $n = 24$ ) ( $p = 0.035$ ). There were similar rates for those who underwent MIS or LAP for intra-operative blood transfusion (50.0% vs. 55.0%,  $p = 0.99$ ), vasopressor use (80.0% vs. 87.5%,  $p = 0.62$ ), hyponatremia (<132 mg/dL) (10.0% vs. 0.0%,

**Table 2**

Oncologic information for patients undergoing interval debulking surgery with HIPEC via minimally invasive surgery or laparotomy.

Factor	MIS (n = 10)	LAP (N = 40)	p-value
<b>Oncologic factors</b>			
Stage			0.99
II	1 (2.0)	0 (0.0)	
III	8 (80.0)	20 (75.0)	
IV	2 (20.0)	9 (22.5)	
Histology			0.99
Serous	10 (100.0)	38 (95.0)	
Endometrioid	0 (0.0)	1 (2.5)	
Clear Cell	0 (0.0)	1 (2.5)	
BRCA status**			0.64
BRCA1	1 (10.0)	1 (2.5)	
BRCA2	0 (0.0)	3 (7.5)	
Somatic BRCA	0 (0.0)	1 (2.5)	
None	5 (50.0)	21 (52.5)	
Unknown	4 (40.0)	14 (35.0)	
Pre-operative disease burden			
Pelvic	9 (90.0)	25 (62.5)	0.14
Extra-pelvic	7 (70.0)	31 (77.5)	0.69
Extra-abdominal	0 (0.0)	1 (2.5)	0.99
Cycles of Neoadjuvant	3 [3.0, 5.0]	3 [3.0, 4.0]	0.99
Response to Neoadjuvant**			0.18
Complete	2 (20.0)	2 (5.1)	
Partial	7 (70.0)	37 (94.9)	
CA125 Pre-treatment	494 [231,767]	581 [125,2505]	0.65
CA125 Pre-op	18.8 [12.0, 28.1]	43.5 [19.0, 149.0]	0.030*
Change in CA125	−0.97 [−0.98, −0.86]	−0.90 [−0.94, −0.81]	0.19
Days from last Chemo to HIPEC	26.0 [23.0, 32.0]	30.0 [26.0, 34.0]	0.22

Statistics presented as Mean ± SD, Median (P25, P75), N (column %).

HIPEC – Hyperthermic intraperitoneal chemotherapy.

\* Statistically significant.

\*\* One missing value from laparotomy group.

$p = 0.20$ ), hypomagnesemia ( $<1.7$  mg/dL) (10.0% vs. 32.5%;  $p = 0.25$ ) or hypokalemia ( $<3.5$  mg/dL) (50.0% vs. 70.0%,  $p = 0.28$ ). All patients ( $n = 50$ ) had optimal cytoreduction at the time of IDS. There was no significant difference in rates of cytoreduction to no gross residual disease (RO) for women who had MIS compared to LAP (70.0% vs. 77.5%;  $p = 0.39$ ) (Table 3).

### 3.3. Perioperative outcomes

Perioperative outcomes and adverse events are displayed in Table 4. Postoperatively, there were no differences in ICU admission (20.0% vs. 17.5%,  $p = 0.65$ ) or post-operative complications using the Accordion scale<sup>17</sup> ( $p = 0.64$ ) between women who underwent IDS with HIPEC via MIS or LAP, respectively. For minor complications specifically, there were similar rates of post-operative ileus (10.0% vs. 12.5%,  $p = 0.99$ ), superficial incisional surgical site infection (10.0% vs. 5.0%,  $p = 0.50$ ) or readmission (10.0% vs. 10.0%,  $p = 0.99$ ) for MIS vs. LAP, respectively. Similarly, there were no significant differences among major complications including re-operation (0.0% vs. 7.5%;  $p = 0.99$ ), respiratory failure (0.0% vs. 0.0%,  $p = 0.99$ ), venous thromboembolism (0.0% vs. 5.0%;  $p = 0.99$ ) or mortality (0.0% vs. 2.5%;  $p = 0.99$ ) for MIS vs. LAP, respectively. Overall length of stay was significantly lower for MIS compared to the LAP group (median 3.0 vs 4.0 days,  $p = 0.016$ ). There was no difference in post-discharge needs between the groups, with the majority of patients discharged home in both MIS and LAP cohorts (80.0% vs. 64.1%,  $p = 0.93$ ). There were no significant differences in the time to chemotherapy following surgery between groups (median 26.0 vs. 32.0 days;  $p = 0.090$ ). At a median follow-up of 15.1 months (range 1.4–50.4 months), there was no significant difference in recurrence free survival (15.0 vs. 17.2 months; log-rank  $p = 0.30$ ) for MIS vs. LAP (Figure 2).

**Table 3**

Peri-operative details for patients undergoing interval debulking surgery with HIPEC via minimally invasive surgery or laparotomy.

<b>Operative factors</b>			
Factor	MIS (n = 10)	LAP (N = 40)	p-value
Estimated blood loss	100.0 [100.0, 200.0]	225.0 [125.0, 500.0]	0.072
Operative Time (hr)	5.4 [4.8, 6.5]	5.6 [4.8, 7.1]	0.93
Residual Disease			0.39
Optimal NOS	0 (0.0)	1 (2.5)	
Optimal >5 mm	0 (0.0)	4 (10.0)	
Optimal 1–5 mm	3 (30.0)	4 (10.0)	
Optimal R0	7 (70.0)	31 (77.5)	
IntraOp Transfusion	5 (50.0)	22 (55.0)	0.99
Vasopressor	8 (80.0)	35 (87.5)	0.62
HIPEC Agent			0.035*
Cisplatin/Paclitaxel	2 (20.0)	24 (60.0)	
Cisplatin	8 (80.0)	16 (40.0)	
Intraoperative Electrolytes			
Acidosis (LA > 2)	6 (60.0)	34 (85.0)	0.097
Hyponatremia (Na <132)	1 (10.0)	0 (0.0)	0.20
Hypernatremia (Na > 144)	0 (0.0)	0 (0.0)	
Hypokalemia (K < 3.5)	5 (50.0)	28 (70.0)	0.28
Hypomagnesemia (Mg < 1.7)	1 (10.0)	13 (32.5)	0.25
Other electrolyte	1 (10.0)	3 (7.5)	0.99
Procedures Completed			
Hysterectomy	9 (90.0)	29 (72.5)	0.42
Small bowel surgery	0 (0.0)	1 (2.5)	0.99
Large bowel surgery	0 (0.0)	10 (25.0)	0.18
Omentectomy	10 (100.0)	35 (82.5)	0.57
Splenectomy	0 (0.0)	5 (12.5)	0.62

Statistics presented as Mean ± SD, Median [P25, P75], N (column %).

NOS – Not otherwise specified, R0 – no gross residual disease, HIPEC – hyperthermic intraperitoneal chemotherapy, LA – lactic acid.

\* Statistically significant.

## 4. Discussion

In recent years there has been an impetus to improve surgical care and oncologic outcomes in women who are not optimal candidates for primary cytoreductive surgery, and then undergo NACT followed by IDS [6,7,10,12,18,19]. Recent studies have demonstrated that MIS IDS may be considered as an alternative to LAP in carefully selected patients [6,10–12,18–21]. In addition, in a randomized phase 3 trial, HIPEC at the time of IDS for stage III EOC was associated with an OS benefit of 11.8 months, compared to IDS alone [7]. While both HIPEC and MIS represent promising strategies to improve care for women with EOC, at present, data is limited regarding the feasibility of combining MIS IDS with HIPEC and outcomes compared to LAP. In this single institution retrospective study in women with advanced EOC utilizing a prospectively maintained registry, we demonstrate that HIPEC at the time of MIS IDS is feasible, and in our experience safe with low rates of post-operative adverse events compared to LAP.

MIS has become increasingly utilized to care for patients with gynecologic cancer, including women undergoing IDS for EOC [6,10–12,18,19]. In retrospective study by Brown et al., 53 patients who had MIS IDS experienced decreased blood loss, shorter hospital stay, and comparable rates of perioperative adverse events compared to 104 women who underwent LAP [10]. Regarding oncologic outcomes, multiple non-randomized studies have demonstrated comparable rates of optimal cytoreduction, RFS and OS for IDS with MIS compared to LAP [6,10,12,18,19]. In a study of the National Cancer Database by Melamed et al., 3071 women with advanced EOC underwent IDS, with 450 undergoing MIS. They identified no difference in rate of suboptimal resection or three year overall survival for patients who underwent MIS procedures compared to LAP [18]. These studies led to amendment of the NCCN EOC guidelines to include MIS IDS as an option for women who can undergo optimal debulking following NACT [13].

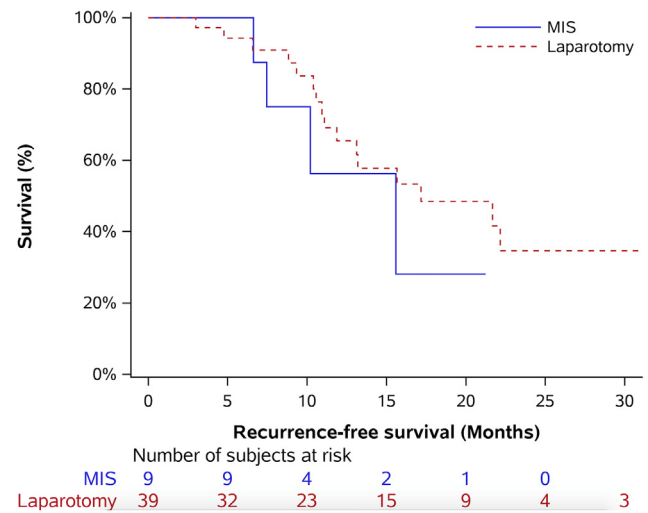
**Table 4**  
Post-operative outcomes for women undergoing interval debulking surgery with HIPEC via minimally invasive surgery or laparotomy.

Factor	MIS (n = 10)	LAPS (N = 40)	p-value
ICU admission	2 (20.0)	7 (17.5)	0.65
Length of hospital stay**	3.0 [2.0, 4.0]	4.0 [4.0, 7.0]	0.016*
Discharge disposition <sup>^</sup>			0.93
Home	8 (80.0)	25 (64.1)	
Home w/home health	1 (10.0)	7 (17.9)	
Home with PT	0 (0.0)	3 (7.7)	
Nursing Facility	1 (10.0)	4 (10.3)	
Days to Chemotherapy <sup>+</sup>	26.0 [25.0, 29.0]	32.0 [27.0, 42.0]	0.090
Accordion Postoperative Severity Classification			0.64
None	6 (60.0)	16 (40.0)	
Mild	2 (20.0)	14 (35.0)	
Moderate	2 (20.0)	5 (12.5)	
Severe	0 (0.0)	4 (10.0)	
Death	0 (0.0)	1 (2.5)	
Minor Complications			
Ileus	1 (10.0)	5 (12.5)	0.99
Pneumonia	0 (0.0)	0 (0.0)	
Superficial incision SSI	1 (10.0)	2 (5.0)	0.50
Pelvic Abscess	0 (0.0)	1 (2.5)	0.99
Readmission	1 (10.0)	4 (10.0)	0.99
Post-operative fever	0 (0.0)	2 (5.0)	0.99
Other	0 (0.0)	11 (27.5)	0.092
Major Complications			
Re-operation	0 (0.0)	3 (7.5)	0.99
VTE	0 (0.0)	2 (5.0)	0.99
MI	0 (0.0)	0 (0.0)	
CVA	0 (0.0)	0 (0.0)	
Vaginal cuff dehiscence	0 (0.0)	0 (0.0)	
Fascial Dehiscence	0 (0.0)	0 (0.0)	
Sepsis	0 (0.0)	3 (7.5)	0.99
Respiratory Failure	0 (0.0)	0 (0.0)	
Bowel leak	0 (0.0)	1 (2.5)	0.99
Urine leak	0 (0.0)	0 (0.0)	
Deep space infection	0 (0.0)	0 (0.0)	
Death	0 (0.0)	1 (2.5)	0.99
Other	0 (0.0)	0 (0.0)	

Statistics presented as Mean ± SD, Median [P25, P75], N (column %).  
 ICU – intensive care unit, PT-physical therapy, SSI – surgical site infection, VTE – venous thromboembolic event, MI – myocardial infarction, CVA – cerebrovascular event.  
 \* Statistically significant.  
 \*\* Four missing values from laparotomy group.  
 ^ One missing value from laparotomy group.  
 + One missing value from MIS group and three missing values from laparotomy group.

However, it is important to note the absence of randomized data to demonstrate MIS as a non-inferior option to open surgery for patients with advanced ovarian carcinoma and patients should be counseled as such.

Prior studies have demonstrated that HIPEC at the time of MIS for other peritoneal based malignancies is feasible. In a retrospective series of patients with peritoneal based malignancies by Rodriguez-Ortiz et al., outcomes were compared among 60 patients who underwent cytoreduction and HIPEC via an open (n = 42) or MIS (n = 17) approach. Comparable to our findings, the patients who underwent HIPEC with MIS had decreased length of stay, similar surgical time and comparable rates of post-operative complications and need for blood transfusion. In addition, MIS cytoreductive surgery combined with HIPEC was associated with reduced interval to chemotherapy [22]. In addition, similar to our results, in a retrospective study of 14 patients with EOC who underwent MIS HIPEC following NACT, no post-operative complications occurred and the majority of patients (71.4%) had R0 resection [23]. Our data builds on these prior studies supporting that in women with advanced EOC, HIPEC at the time of MIS IDS is feasible and with low rates of post-operative complications.



**Fig. 2.** Recurrence Free Survival following Interval Debulking Surgery for Advanced Epithelial Ovarian Cancer via MIS or LAP.

There are several limitations to this study. Primarily, the sample size of patients included within the MIS HIPEC cohort was small. Additionally, the patients were not randomized to treatment groups and decisional planning for surgical approach (MIS or LAP) was at the discretion of the primary gynecologic oncologist, and therefore, the possibility of selection bias cannot be ignored. In addition, the patients who underwent MIS likely represent a cohort with lower residual disease, as they had significantly lower preoperative CA125 and less complex surgery, with no MIS patients undergoing bowel resections or splenectomy. In addition, this study occurred at a high-volume institution, and therefore, these findings may not be generalizable to all centers and surgeon skill-sets. A relatively high rate of transfusion was noted in both groups despite similar preoperative hemoglobin and relatively low estimated blood loss. This may be a reflection of underestimation of blood loss or liberal transfusion practices at our institution. This may also reflect dilutional intraoperative anemia secondary to the large volumes of IV fluid hydration given during the HIPEC portion of the case. This may be better defined if a larger sample of MIS patients were available.

An additional consideration is that a significantly greater proportion of patients in the laparotomy group who received cisplatin with paclitaxel, compared to cisplatin alone. While randomized data currently supports the use of single agent HIPEC with cisplatin in women with advanced EOC, paclitaxel has been increasingly combined with cisplatin at our institution, with preliminary data demonstrating no difference in adverse outcomes or toxicity [7,24]. However, the short follow up duration limits our ability to draw conclusions regarding oncologic outcomes for these patients, and additional investigation is underway to this end. In women who are candidates for MIS IDS following NACT, it is essential that patients are counseled on lack of prospective data for oncologic outcomes and the potential risks of an MIS approach. Despite these limitations, our study provides important evidence regarding perioperative and short-term oncologic outcomes with MIS and LAP IDS with HIPEC following NACT in patients with advanced EOC. Based on this data, it is reasonable in patients who have a favorable response to NACT and are candidates for IDS via a MIS, to consider addition of HIPEC with cisplatin at the time of the procedure.

In conclusion, in this single institution retrospective cohort study of women with advanced EOC undergoing NACT followed by IDS, HIPEC at the time of MIS is feasible, with similar incidence of adverse perioperative outcomes, and rates of complete cytoreduction. Patient candidacy for an MIS IDS should not prevent surgeons from utilizing HIPEC,

where indicated, for the management of properly selected women with advanced EOC.

## Disclosure

The authors have no financial disclosures.

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## Declaration of Competing Interest

All authors have no relevant conflicts of interest to disclose.

## References

- [1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2019, *CA Cancer J. Clin.* 69 (1) (2019) 7–34, <https://doi.org/10.3322/caac.21551>.
- [2] A.A. Wright, K. Bohlke, D.K. Armstrong, et al., Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of clinical oncology clinical practice guideline, *J. Clin. Oncol.* 34 (28) (2016) 3460–3473, <https://doi.org/10.1200/JCO.2016.68.6907>.
- [3] I. Vergote, C.G. Tropé, F. Amant, et al., Neoadjuvant chemotherapy or primary surgery in stage IIIc or IV ovarian cancer, *N. Engl. J. Med.* 363 (10) (2010) 943–953, <https://doi.org/10.1056/NEJMoa0908806>.
- [4] S. Kehoe, J. Hook, M. Nankivell, et al., Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial, *Lancet* 386 (9990) (2015) 249–257, [https://doi.org/10.1016/S0140-6736\(14\)62223-6](https://doi.org/10.1016/S0140-6736(14)62223-6).
- [5] A. Fagotti, G. Ferrandina, G. Vizzielli, et al., Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): final analysis of peri-operative outcome, *Eur. J. Cancer* 59 (2016) 22–33, <https://doi.org/10.1016/j.ejca.2016.01.017>.
- [6] K. Matsuo, M. Klar, R.S. Mandelbaum, et al., Minimally Invasive Interval Debulking Surgery After Neoadjuvant Chemotherapy for Metastatic Ovarian Cancer: A National Study in the United States. 301, 2020 863–866, <https://doi.org/10.1007/s00404-020-05442-4>.
- [7] W.J. van Driel, S.N. Koole, K. Sikorska, et al., Hyperthermic intraperitoneal chemotherapy in ovarian cancer, *N. Engl. J. Med.* 378 (3) (2018) 230–240, <https://doi.org/10.1056/NEJMoa1708618>.
- [8] D.K. Armstrong, B. Bundy, L. Wenzel, et al., Intraperitoneal cisplatin and paclitaxel in ovarian cancer, *N. Engl. J. Med.* 354 (1) (2006) 34–43, <https://doi.org/10.1056/NEJMoa052985>.
- [9] M. C. A. V. G. M, et al., Effect of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy on relapse pattern in primary epithelial ovarian cancer: a propensity score based case-control study, *J. Gynecol. Oncol.* 29 (3) (2018) <https://doi.org/10.3802/JGO.2018.29.E53>.
- [10] J. Brown, L. Drury, E.K. Crane, et al., When less is more: minimally invasive surgery compared with laparotomy for interval debulking after neoadjuvant chemotherapy in women with advanced ovarian cancer, *J. Minim. Invasive Gynecol.* 26 (2019) 902–909, <https://doi.org/10.1016/j.jmig.2018.09.765>.
- [11] A. F. S. GA, G. C, et al., The international mission study: minimally invasive surgery in ovarian neoplasms after neoadjuvant chemotherapy, *Int. J. Gynecol. Cancer* 29 (1) (2019) <https://doi.org/10.1136/IJGC-2018-000012>.
- [12] S. Gueli Alletti, C. Bottoni, F. Fanfani, et al., Minimally invasive interval debulking surgery in ovarian neoplasm (MISSION trial-NCT02324595): a feasibility study, *Am. J. Obstet. Gynecol.* 214 (4) (2016) <https://doi.org/10.1016/j.ajog.2015.10.922> 503.e1–503.e6.
- [13] D.K. Armstrong, R.D. Alvarez, J.N. Bakkum-Gamez, et al., NCCN clinical practice guideline in oncology: ovarian cancer including fallopian tube cancer and primary peritoneal cancer. version 2, 2019.
- [14] P. Therasse, S.G. Arbuck, E.A. Eisenhauer, et al., New Guidelines to Evaluate the Response to Treatment in Solid Tumors, <https://ctep.cancer.gov/protocolDevelopment/docs/therassecrcstjnci.pdf> 2020.
- [15] P.A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, J.G. Conde, Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support, *J. Biomed. Inform.* 42 (2) (2009) 377–381, <https://doi.org/10.1016/j.jbi.2008.08.010>.
- [16] P.A. Harris, R. Taylor, B.L. Minor, et al., The REDCap consortium: Building an international community of software platform partners, *J. Biomed. Inform.* 95 (2019) 103208, <https://doi.org/10.1016/j.jbi.2019.103208>.
- [17] S.M. Strasberg, D.C. Linehan, W.G. Hawkins, The accordion severity grading system of surgical complications, *Ann. Surg.* 250 (2) (2009) 177–186, <https://doi.org/10.1097/SLA.0b013e3181afde41>.
- [18] A. Melamed, R. Nitecki, D.M. Boruta, et al., Laparoscopy compared with laparotomy for debulking ovarian cancer after neoadjuvant chemotherapy, *Obstet. Gynecol.* 129 (5) (2017) 861–869, <https://doi.org/10.1097/AOG.0000000000001851>.
- [19] J. Abitbol, W. Gotlieb, Z. Zeng, et al., Incorporating robotic surgery into the management of ovarian cancer after neoadjuvant chemotherapy, *Int. J. Gynecol. Cancer* 29 (9) (2019) 1341–1347, <https://doi.org/10.1136/ijgc-2019-000413>.
- [20] J.L. Walker, M.R. Piedmonte, N.M. Spirtos, et al., Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: gynecologic oncology group LAP2 study, *J. Clin. Oncol.* 30 (7) (2012) 695–700, <https://doi.org/10.1200/JCO.2011.38.8645>.
- [21] A. Melamed, J.A. Rauh-Hain, Minimally invasive interval cytoreductive surgery: it's time for a randomized trial, *Int. J. Gynecol. Cancer* 29 (9) (2019) 1339–1340, <https://doi.org/10.1136/ijgc-2019-000971>.
- [22] Rodríguez-Ortiz L, Arjona-Sánchez A, Ibañez-Rubio M, et al. Laparoscopic cytoreductive surgery and HIPEC: a comparative matched analysis. 1:3. doi: <https://doi.org/10.1007/s00464-020-07572-x>
- [23] T. Gao, X. Huang, W. Wang, M. Wu, Z. Lin, J. Li, Feasibility and safety of neoadjuvant laparoscopic hyperthermic intraperitoneal chemotherapy in patients with advanced stage ovarian cancer: a single-center experience, *Cancer Manag. Res.* 11 (2019) 6931–6940, <https://doi.org/10.2147/CMAR.S213882>.
- [24] M.P. Horowitz, L. Chambers, M. Gruner, A.B. Costales, M. Morton, A.M. Chichura, P.G. Rose, C.M. Michener, R. Debernardo, Comparison of outcomes with utilization of hyperthermic cheotherapy with paclitaxel and cisplatin versus cisplatin alone at interval debulking surgery in women with epithelial ovarian cancer, Presented virtually at the Society of Gynecologic Oncology 51st Annual Meeting on Women's Cancer, May 2020.