



Research Report

Efficacy of hyperthermic intraperitoneal chemotherapy and interval debulking surgery in women with advanced uterine serous carcinoma

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ABSTRACT

Objective(s): To investigate the efficacy and safety of hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of interval debulking surgery (IDS) in women with advanced uterine serous carcinoma (USC) following neoadjuvant chemotherapy (NACT).

Methods: An IRB-approved single-institution prospective registry was queried to identify women with incidentally identified USC at the time of IDS + HIPEC for high-grade serous carcinoma. Patient demographic, oncologic, and surgical outcomes data were recorded. Univariate analysis determined progression-free survival (PFS) and overall survival (OS).

Results: In total, seven patients were found to have advanced USC after undergoing IDS + HIPEC, with a median age of 64.5 years. The majority had stage IV, (n = 6, 85.7%), MMR proficient (n = 5, 71.4%), p53 mutant (n = 6, 85.1%) USC. The median pre-operative CA125 was 24.0U/mL. HIPEC regimen was cisplatin (n = 3, 42.9%) or cisplatin with paclitaxel (n = 4, 57.1%). All patients underwent optimal cytoreduction, with 71.4% (n = 5) having no gross residual disease. Accordion post-operative complications were mild in 14.3% (n = 1), moderate in 57.1% (n = 4) and severe in 14.3% (n = 1); 14.3% (n = 1) had no complications. The median length of stay was 6.5 days (IQR 4–8 days) with a median time to chemotherapy of 33.0 days. The median PFS was 14.0 months (95% CI 3.5–20.8 months), and the median OS was 27.0 months (95% CI 5.1- not reached).

Conclusions: In this small, prospective series, we demonstrate that IDS + HIPEC is well tolerated in patients with USC and is associated with favorable PFS and OS following NACT. Further prospective investigation is needed to validate these promising findings in larger, heterogeneous cohorts of women with advanced USC who are not candidates for primary surgical management.

1. Introduction

Uterine serous carcinoma (USC) accounts for a minority of endometrial cancers (EC), yet this aggressive variant has a poor prognosis and is responsible for a disproportionately high number of EC-related deaths (Siegel et al., 2020; Lortet-Tieulent et al., 2018; Hamilton et al., 2006). USC has a unique propensity for extra-uterine spread and intraperitoneal metastasis found at the time of diagnosis, as well as an increased risk for recurrent disease despite multi-modality therapy

(Holman et al., 2017; Thomas et al., 2007; Bogani et al., 2019; Wilkinson-Ryan et al., 2015; Chambers et al., 2021; Bristow et al., 2001; Rauh-Hain et al., 2010; Goff et al., 1994; Lee et al., 2014). In women diagnosed with advanced USC, primary cytoreductive surgery (PCS) is favored, however, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) may be considered based upon medical comorbidities and disease burden at the time of diagnosis (NCCN, 2021; Bogani et al., 2019; Wilkinson-Ryan et al., 2015; Chambers et al., 2021).

In patients with stage IVB USC, retrospective studies have

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demonstrated comparable oncologic outcomes for PCS compared to NACT and IDS (Bogani et al., 2019; Wilkinson-Ryan et al., 2015; Chambers et al., 2021). In a retrospective study by Bogani and colleagues of 34 patients, there was no significant difference in PFS (12.0 vs. 15.3 months, $p = 0.663$) or OS (16.7 vs. 18.0 months) based upon the initial treatment approach (Bogani et al., 2019). Similarly, in a retrospective study of 10 patients who underwent NACT followed by IDS compared to 34 treated with PCS, there was no difference in median PFS (10.4 vs. 12.0, $p = 0.29$) or median OS (17.3 vs. 20.7 months, $p = 0.23$) (Wilkinson-Ryan et al., 2015).

The poor prognosis of women with advanced USC regardless of treatment paradigm highlights the significant, unmet need to advance therapeutic options (Holman et al., 2017; Thomas et al., 2007; Bogani et al., 2019; Wilkinson-Ryan et al., 2015; Chambers et al., 2021; Bristow et al., 2001; Rauh-Hain et al., 2010; Goff et al., 1994; Lee et al., 2014). HIPEC has been increasingly utilized to manage peritoneal-based malignancies, such as ovarian cancer (OC) (Chambers et al., 2020; Chichura et al., 2021; Chambers et al., 2021; van Driel et al., 2018; Spiliotis et al., 2015; Lei et al., 2020). In a phase III randomized trial by Van Driel et al. of women with advanced OC, IDS with HIPEC significantly improved PFS and OS compared to IDS alone (van Driel et al., 2018). Currently, there is limited retrospective data regarding HIPEC utilization in women with advanced or recurrent EC, including USC (Brind'Amour et al., 2021; Navarro-Barrios et al., 2020; Tempfer et al., 2019; Díaz-Montes et al., 2018; Spiliotis, 2018). Given the propensity for extra-uterine metastasis and peritoneal spread in women with USC, HIPEC at the time of cytoreductive surgery may have biological plausibility. The objective of this study was to report preliminary data for efficacy and safety of HIPEC at the time of IDS in women with advanced USC following NACT in a prospective single institutional registry.

2. Methods

2.1. Study design

This study is an Institutional Review Board approved, single-institution case series using a prospective database including all women with stage III or IV USC who underwent IDS with HIPEC from January 1st 2014 to December 1st 2020 at the Cleveland Clinic. Of note, all patients were believed to have advanced high-grade serous ovarian cancer based upon clinical presentation and/or radiographic findings leading to the decision to perform HIPEC. Patients were selected to receive NACT with carboplatin and paclitaxel followed by IDS at the primary surgeon's discretion, based upon patient and oncologic characteristics, such as performance status, medical comorbidities, and disease burden at diagnosis. While no formal guidelines exist at our institution to define a patient's candidacy for HIPEC, eligible patients must have good performance status, well-controlled medical comorbidities, optimal cytoreduction to <1 cm of residual disease and be hemodynamically stable following IDS. Informed consent was obtained from all participants. Within this cohort, the diagnosis of USC was confirmed on final surgical pathology in patients believed to have a diagnosis of high-grade serous ovarian cancer initially, leading to subsequent mismatch repair (MMR) and HER2 testing. All IDS with HIPEC were performed as previously described (Chambers et al., 2020; Chichura et al., 2021; Chambers et al., 2021). HIPEC chemotherapy regimen was cisplatin (100 mg/m²) with or without paclitaxel (135–175 mg/m²) administered in a normal saline perfusate at a goal temperature of 41–43C degrees for 90 min.

2.2. Data collection

Patient demographics were extracted from the electronic medical record, including age, race, body mass index (kg/m²), American Society of Anesthesiologists (ASA) score at HIPEC, and medical comorbidities. Oncologic variables included stage, histology, MMR status (proficient,

deficient, or unknown), and p53 status (mutant, wild-type, unknown). Surgical variables collected included HIPEC regimen, residual disease following cytoreduction, surgical procedures, operative time, estimated blood loss, and Surgical Complexity Score (Aletti et al., 2007). Major and minor postoperative adverse events were recorded and graded according to the Accordion Severity Grading System (Strasberg et al., 2009). All patient data were collected and stored within a secure, encrypted REDCap database (Harris et al., 2009).

2.3. Statistical analysis

Normally distributed continuous variables were reported as mean and standard deviation. Other continuous and ordinal variables were reported using medians and interquartile range. Categorical factors were described as frequencies and percentages. For PFS and OS, time to recurrence or death was defined as the difference in months from HIPEC date to recurrence date and death date. 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 surgical Characteristics

Seven eligible patients with advanced USC were treated with IDS with HIPEC from January 1st 2014 to December 1st 2020, at the Cleveland Clinic. The median age was 64.5 years (IQR 61.2, 69.9 years). The majority of patients had Stage IV disease ($n = 6$, 85.7%) and pre-operative ASA score of III or IV ($n = 4$, 57.1%). Additionally, the majority of patients had MMR proficient ($n = 5$, 71.4%), p53 mutant ($n = 6$, 85.1%) USC. The median CA125 before surgery was 24.0U/mL (IQR 16.0, 60.0). Patients received HIPEC with either cisplatin alone ($n = 3$, 42.9%) or paclitaxel with cisplatin ($n = 4$, 57.1%). All patients underwent optimal cytoreduction at the time of IDS, with 71.4% ($n = 5$) having no gross residual disease (Table 1).

3.2. Surgical information and perioperative outcomes

Most patients underwent either moderate ($n = 3$, 42.9%) or high ($n = 3$, 42.9%) complexity surgical procedures, based on Surgical Complexity score (Aletti et al., 2007). Hysterectomy was performed in all patients ($n = 7$, 100%), with the majority of patients undergoing large bowel surgery with re-anastomosis ($n = 6$, 85.7%). The median operative time and estimated blood loss were 6.9 h (IQR 6.3, 7.5 h) and 500.0 cc (IQR 350.0, 650.0). In total, the incidence of Accordion post-operative complications were none in 14.3% ($n = 1$), mild in 14.3% ($n = 1$), moderate in 57.1% ($n = 4$) and severe in 14.3% ($n = 1$) (Díaz-Montes et al., 2018 Jul). No patient mortalities occurred. The median length of stay was 6.5 days (IQR 4.0, 8.0 days). The majority of patients were discharged home following surgery ($n = 4$, 57.1%). The median time to chemotherapy was 33.0 days (IQR 26.0, 42.0 days) (Table 2).

3.3. Oncologic outcomes

The median follow-up duration for the cohort was 12.4 months (IQR 7.6, 27.0 months). The median PFS was 14.0 months (95% CI, 3.5–20.8 months) with one year progression survival of 71.4% (95% CI, 38.0, 100.0). Furthermore, the median OS was 27.0 months (95% CI, 5.1–NR) with two-year overall survival of 57.1% (8.3, 100.0) (Fig. 1). Detailed patient information is displayed in Table 3.

4. Discussion

The prognosis of women diagnosed with advanced, initially unresectable USC is poor, with most studies demonstrating OS between 16 and 20 months (Holman et al., 2017; Thomas et al., 2007; Bogani et al.,

Table 1
Patient and oncologic characteristics.

Variable	N = 7
Age (years)	64.5 [61.2, 69.9]
<u>Race</u>	
White	6 (85.7)
Black	1 (14.3)
BMI (kg/m ²)	31.1 [21.8, 33.7]
<u>ASA Score at Surgery</u>	
0–2	3 (42.9)
3–4	4 (57.1)
<u>Medical Comorbidities</u>	
HTN	5 (71.4)
DM	2 (28.6)
VTE	2 (28.6)
CAD	1 (14.3)
Pulmonary Disease	1 (14.3)
Renal Disease	2 (28.6)
CA125 prior to Surgery (U/mL)	24.0 [16.0, 60.0]
<u>Stage</u>	
III	1 (14.3)
IV	6 (85.7)
<u>HIPEC Regimen</u>	
Cisplatin alone	3 (42.9)
Cisplatin/Paclitaxel	4 (57.1)
<u>Residual Disease</u>	
R0 (no gross residual)	5 (71.4)
<1cm residual disease	2 (28.6)
<u>MMR Status</u>	
MMR proficient	5 (71.4)
MMR deficient	2 (28.6)
<u>P53 Status</u>	
Mutant	6 (85.1)
Wild type	1 (14.3)
Cycles of Neoadjuvant Chemotherapy	4.0 [4.0, 6.0]
Distance Travelled (miles)	35.6 [14.8, 102.0]

BMI, body mass index; ASA, American Society of Anesthesiologists; HTN, hypertension; DM, diabetes mellitus; VTE, venous thromboembolic disease; CAD, coronary artery disease; CKD, chronic kidney disease; HIPEC, Hyperthermic intraperitoneal chemotherapy; NACT, neoadjuvant chemotherapy; CRS, cytoreductive surgery; LND, lymph node dissection; NOS, not otherwise specified. Categorical variables are presented as n (%); continuous variables are presented as mean with interquartile range (25, 75).

2019; Wilkinson-Ryan et al., 2015; Chambers et al., 2021; Bristow et al., 2001; Rauh-Hain et al., 2010; Goff et al., 1994; Lee et al., 2014). Despite contemporary advances in therapeutics, there is an unmet need to improve outcomes in this population and develop novel treatment strategies. In recent years, HIPEC has been increasingly studied for the management of advanced ovarian cancer and has been shown to decrease peritoneal-based recurrences (Chambers et al., 2021). In a recent phase III trial by Van Driel et al., HIPEC at IDS improved OS by 11.8 months compared to IDS alone (van Driel et al., 2018). While prior small retrospective studies have evaluated the use of HIPEC in women with advanced or recurrent EC, the role of HIPEC at the time of IDS in women with advanced USC is unknown (Brind'Amour et al., 2021; Navarro-Barrios et al., 2020; Tempfer et al., 2019; Díaz-Montes et al., 2018; Spiliotis, 2018). Given the propensity of USC for extra-uterine disease and peritoneal metastasis at diagnosis and recurrence, HIPEC may be a novel approach for improving outcomes in this population. To this end, in this small, prospective series of women with incidental stage III/IV USC undergoing NACT, we demonstrate that IDS with HIPEC has acceptable toxicity and is associated with favorable PFS and OS compared to historical studies.

In our cohort of women with advanced, unresectable USC who underwent IDS with HIPEC, the median PFS was 14.0 months, and median OS was 27.0 months. Compared to published retrospective studies in women with advanced USC who underwent surgical management, oncologic outcomes in our study were favorable. In a retrospective series by Wilkinson-Ryan et al., there was no difference in PFS (10.4 vs. 12 months, p = 0.19) or OS (17.3 vs. 20.7 months, p = 0.23) for patients

Table 2
Surgical and perioperative characteristics.

Variable	N=7
Intraoperative Pressor Requirements	7 (100.0)
Blood Transfusion	3 (42.9)
<u>Surgical Complexity Score</u>	
Low	1 (14.3)
Moderate	3 (42.9)
High	3 (42.9)
<u>Procedures</u>	
Hysterectomy	7 (100.0)
Pelvic lymphadenectomy	1 (14.3)
Para-aortic lymphadenectomy	1 (14.3)
Omentectomy	7 (100.0)
Large bowel surgery	6 (85.7)
Small bowel surgery	0 (0.0)
Splenectomy	1 (14.3)
Ileostomy/Colostomy	0 (0.0)
<u>Diaphragm Resection</u>	1 (14.3)
Operative time (hours)	6.9 [6.3, 7.5]
Estimated Blood Loss (mL)	500.0 [350.0, 650.0]
ICU admission	4 (57.1)
<u>Accordion Postoperative Severity Classification</u>	
None	1 (14.3)
Mild	1 (14.3)
Moderate	4 (57.1)
Severe	1 (14.3)
<u>Major Complications</u>	
Re-operation	0 (0.0)
Anastomotic Leak	1 (14.3)
Death	0 (0.0)
Venous thromboembolism	0 (0.0)
Respiratory Failure	0 (0.0)
Myocardial Infarction/Stroke	0 (0.0)
<u>Minor Complications</u>	
Surgical site infection	0 (0.0)
Ileus	0 (0.0)
Readmission	1 (14.3)
Acute Kidney Injury	1 (16.7)
Length of Stay (days)	6.5 [4.0, 8.0]
<u>Discharge Disposition</u>	
Home	4 (57.1)
Home with Home Health	1 (14.3)
Skilled Nursing Facility	2 (28.6)
Days to Chemotherapy	33.0 [26.0, 42.0]

Categorical variables are presented as n (%); continuous variables are presented as mean with interquartile range (25, 75). Bold indicates statistically significant with p < 0.05.

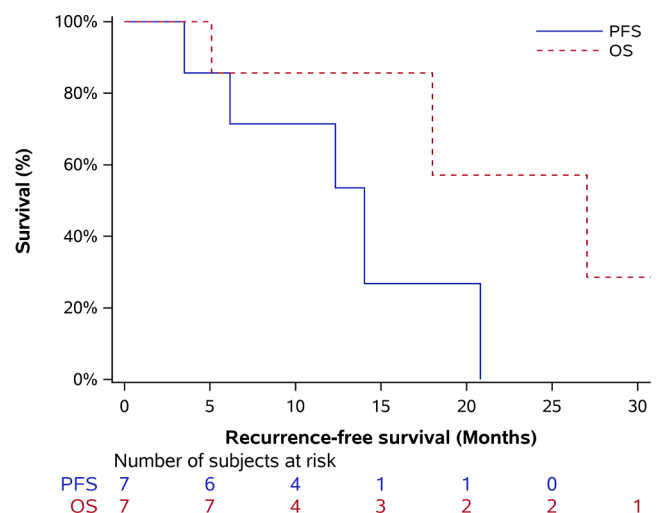


Fig. 1. Progression Free Survival and Overall Survival of Women with Advanced Uterine Serous Carcinoma undergoing Interval Debulking Surgery with HIPEC.

Table 3
Patient details.

Patient	Age and Comorbidities	Oncologic Data	Surgical Procedure	Postoperative Complications	PFS (m)	OS (m)
1	64 year old F, HTN, DM, CKD, HLD	Stage IVB; MMRp, p53 mutant	XL, TAH, BSO, RSR, PPALND, HIPEC with cisplatin and paclitaxel to <1 cm residual disease	Severe -Anastomotic leak managed conservatively with drain, TPN. ICU admission.	3.5	Dead of disease at 5.1 months (Peritoneal based disease)
2	62 year old F, DM and history of VTE	Stage IIIC, MMRd, p53 mutant	XL, TAH, BSO, RSR with primary reanastomosis, HIPEC with cisplatin and paclitaxel to no gross residual disease	Moderate -Readmitted with post-operative symptomatic anemia, received 2 units of packed RBC.	14.1	Dead of disease at 27.1 months (Brain metastasis)
3	30.8 year old F; none	Stage IVB, MMRp, p53 mutant	XL, TAH, BSO, HIPEC with cisplatin to no gross residual disease	None	27.9	Alive with disease at 46 months
4	69.6 year old F, HTN and history of VTE	Stage IVB, MMRp, p53 wildtype	XL, TAH, BSO, RSR with primary reanastomosis, HIPEC with cisplatin and paclitaxel to no gross residual disease	Moderate - <i>C. difficile</i> colitis.	12.4	Dead of disease at 18.0 months (Brain metastasis)
5	61.5 year old F, HTN, CHF, HLD	Stage IVB, MMRp, p53 mutant	XL, TAH, BSO, RSR with primary reanastomosis, partial gastrectomy, splenectomy, HIPEC with cisplatin to no gross residual disease	Mild - post-operative ileus	-	NED at 26.4 months
6	76.5 year old, HTN	Stage IVB, MMRd, p53 mutant	XL, TAH, BSO, RSR with primary reanastomosis, HIPEC with cisplatin and paclitaxel to no gross residual disease	Moderate - ICU admission due to inability to extubate in OR and blood transfusion.	6.2	Alive with disease at 9.9 months
7	63 year old, HTN, pulmonary disease, CKD,	Stage IVB, MMRp, p53 mutant	XL, TAH, BSO, RSR with primary reanastomosis, HIPEC with cisplatin to <1 cm residual disease	Moderate - need for blood transfusion	-	NED at 7.6 months

HTN, Hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; HLD, hyperlipidemia; CHF, congestive heart failure; VTE, venous thromboembolism; MMR, mismatch repair; XL, exploratory laparotomy; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; RSR, rectosigmoid resection; PPALND, pelvic and *para*-aortic lymph node dissection; HIPEC, hyperthermic intraperitoneal chemotherapy; TPN, total parenteral nutrition; RBC, red blood cells; NED, no evidence of disease.

with stage IVB USC treated with NACT/IDS or PCS (Wilkinson-Ryan et al., 2015). Similarly, in a similar retrospective study by Bogani and colleagues, no difference in PFS (12.0 vs. 15.3 months) or OS (16.7 vs. 18.0 months) was observed for NACT compared to PCS (Bogani et al., 2019). Our findings suggest that HIPEC at the time of IDS may benefit women with advanced USC compared to prior historical studies, and further prospective study in larger cohorts is warranted.

Notably, numerous retrospective studies have identified the amount of residual disease following surgical cytoreduction as a strong predictor of survival in women with advanced USC (Holman et al., 2017; Thomas et al., 2007; Bogani et al., 2019; Wilkinson-Ryan et al., 2015; Chambers et al., 2021; Bristow et al., 2001; Rauh-Hain et al., 2010). In a study by Bristow et al. of 31 patients with stage IVB USC undergoing PCS, while the entire cohort's OS was 14.1 months, oncologic outcomes were significantly improved among women following optimal versus suboptimal cytoreduction (26.2 vs. 9.6 months) (Bristow et al., 2001). Similarly, in a retrospective study of 125 women with USC who underwent PCS at the Mayo Clinic, patients with no visible disease after cytoreduction had a significantly better median survival of 51 months, compared to 14 months in those with residual disease (Thomas et al., 2007). Therefore, it is plausible that the superior OS in our study may also be explained by the majority of women undergoing moderate or high complexity surgery with optimal cytoreduction to no gross residual disease. Nonetheless, the favorable PFS and OS with the addition of HIPEC at the time of IDS in this limited sample of women with optimally cytoreduced USC is hypothesis-generating for future prospective investigations.

An important consideration with HIPEC at the time of IDS is patient tolerability and toxicity. Notably, randomized studies in women with OC have not demonstrated an increased risk of grade III or IV adverse events following IDS with HIPEC versus IDS alone (van Driel et al., 2018). Furthermore, recently published retrospective studies have shown acceptable toxicity following CRS with HIPEC in women with advanced OC (Chambers et al., 2020; Chichura et al., 2021; Chambers et al., 2021; van Driel et al., 2018; Spiliotis et al., 2015; Lei et al., 2020; Brind'Amour et al., 2021; Navarro-Barrios et al., 2020; Tempfer et al., 2019; Díaz-Montes et al., 2018; Spiliotis, 2018). Notably, in our series of women with advanced USC, HIPEC was overall well-tolerated with only one

patient experiencing a severe complication, which was anastomotic failure following rectosigmoid resection with primary re-anastomosis. This was managed conservatively with imaged guided drain placement, total parenteral nutrition and antibiotics. Further study is needed to understand whether HIPEC increases postoperative morbidity and mortality compared to IDS alone in women with advanced USC.

There are several significant limitations to consider in the interpretation of our results. Primarily, our findings are limited by the small sample size, including only seven patients with advanced USC, without a control cohort who did not receive HIPEC. Similarly, all treatment decisions, including patient selection for NACT with IDS, were at the primary gynecologic oncologist's discretion. Due to the non-randomized patient selection for IDS with HIPEC, the possibility of selection bias cannot be ignored, potentially favoring the inclusion of patients with a good performance status. Additionally, all patients were believed to have advanced high-grade serous ovarian cancer based upon clinical presentation and/or radiographic findings leading to the decision to perform HIPEC. Notably, HIPEC is not routinely offered at our institution in women with advanced USC undergoing NACT followed by IDS.

Despite these limitations, our study is the first to report the safety and efficacy of IDS with HIPEC in women with advanced USC and contributes relevant, timely information to the literature. Our single institution, prospective data suggest that HIPEC at the time of IDS in women with initially unresected advanced USC is associated with favorable PFS and OS and acceptable postoperative morbidity. Further study is warranted to assess the efficacy of HIPEC in larger, more heterogeneous cohorts of women with advanced USC.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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