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Original Article

Evaluation of non-completion of intraperitoneal chemotherapy in patients with advanced epithelial ovarian cancer

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Presentation
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ABSTRACT

Objective: To identify factors associated with non-completion of intraperitoneal with intravenous chemotherapy [IP/IV] in women with epithelial ovarian cancer (EOC).
Methods: This was an Institutional Review Board approved, retrospective cohort study in women with stage III EOC following optimal cytoreductive surgery (CRS) (<1 cm) followed by IP/IV chemotherapy from 2000–2016. Demographic, surgical, and oncologic variables were collected. Pearson χ^2 test and 2 sample t-test evaluated for variables associated with IP/IV chemotherapy completion. Kaplan-Meier survival analysis was performed for progression-free survival (PFS) and overall survival (OS).
Results: Of 96 women, 71.9% (n=69) completed 6 cycles of IP/IV chemotherapy. The majority had high grade serous histology (n=82; 85.4%) and stage IIIC disease (n=83; 86.5%). Common reasons for IP/IV chemotherapy discontinuation were grade 3–4 gastrointestinal (n=10; 37.0%), neurologic (n=6; 22.2%), hematologic (n=3; 11.1%), renal toxicities (n=3; 11.1%) and port infections (n=3; 11.1%). Incidence of IP port complications was 20.8% (n=20). Port complications (48.0% vs. 11.6%; p<0.001) and hospitalization during chemotherapy (29.6% vs. 2.9%; p<0.001) were more frequent in patients who discontinued IP/IV chemotherapy. Patients who completed IP/IV chemotherapy had higher rates of home discharge following CRS (92.2% vs. 72.0%; p<0.01) and lower Eastern Cooperative Oncology Group (ECOG) score (0 vs. 1.0; p=0.04). There was no significant difference in PFS (p=0.51) nor OS (p=0.38) between the cohorts.
Conclusion: In this series, the rate of IP/IV chemotherapy completion is high. Non-home discharge and higher ECOG status following CRS are associated with IP/IV chemotherapy non-completion and should be considered in treatment planning.

Keywords: Ovarian Cancer; Adjuvant Chemotherapy; Intraperitoneal Infusion

INTRODUCTION

Epithelial ovarian cancer (EOC) is a leading cause of gynecologic cancer related death [1]. The 5-year overall survival (OS) for patients is poor, ranging from 30%–40% with the majority of patients presenting with advanced stage disease [2]. The standard treatment for

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No potential conflict of interest relevant to this article was reported.

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advanced EOC is a combination of cytoreductive surgery (CRS) and adjuvant chemotherapy with platinum and taxane. The route of administration remains controversial despite randomized evidence demonstrating a survival advantage with use of intraperitoneal with intravenous (IP/IV) chemotherapy when compared with IV chemotherapy alone in patients with optimally cytoreduced advanced EOC [3-5]. In the Gynecologic Oncology Group (GOG) 172 study, a significant improvement in both progression-free survival (PFS) and OS was observed in patients receiving IP/IV compared to IV chemotherapy [5]. Based on these findings, the National Cancer Institute (NCI) issued a statement recommending the use of IP/IV chemotherapy for patients with optimally cytoreduced advanced-stage EOC [6]. Several subsequent trials have identified a survival advantage for IP/IV chemotherapy, which was summarized in a meta-analysis of 2,119 patients with advanced EOC [4]. This study concluded that women who received at least some component of IP/IV chemotherapy were less likely to die and had longer disease-free intervals compared to those who received IV chemotherapy alone [4].

Despite the well-demonstrated survival benefit, IP/IV chemotherapy is not routinely offered by many gynecologic oncology providers and cancer care centers. A survey of gynecologic oncologists revealed that concerns regarding toxicity, port associated complications, and the complexities preclude administering IP/IV chemotherapy [7]. Concerns regarding increased toxicity of IP/IV chemotherapy are well found. Patients enrolled in the GOG172 randomized trial who received IP/IV chemotherapy treatment arm reported increased incidence of grade 3 or 4 pain, fatigue, hematologic, gastrointestinal, and neurologic effects compared to patients who received IV chemotherapy [5]. Patients receiving IP/IV chemotherapy also reported a worse quality of life prior to cycle 4, and for 3–6 weeks following treatment with only 42% of patients completed all 6 cycles of IP/IV chemotherapy. Despite the poor completion rate, OS and PFS were significantly improved for those receiving IP/IV chemotherapy to IV chemotherapy alone. Since this study, there have been a number of small retrospective studies focused on rates of patient completion and overall toxicity with IP/IV chemotherapy. Data from these investigations supports improved tolerance of IP/IV chemotherapy, with completion rates reported up to 80% [5,8-10]. In a recent study of 41 patients receiving IP/IV chemotherapy after CRS for EOC, over 80% of patients completed at least 6 cycles of therapy. Among patients who did not complete therapy, the biggest risk factors for early cessation of treatment remained catheter related complications, disease progression, and drug related toxicities [10].

As we move toward more individualized cancer treatment strategies, identification of patients who are more likely to complete IP/IV chemotherapy therapy can help in pre-treatment planning and counseling, and may lead to reduced individual treatment toxicities. The objective of this study was to identify patient, surgical, and oncologic variables associated with completion of IP/IV chemotherapy and to determine if non-completion of a planned IP/IV chemotherapy course impacts PFS or OS.

MATERIALS AND METHODS

1. Study design

This was an Institutional Review Board approved retrospective, single institution cohort study performed in patients with a diagnosis of advanced stage (IIIA–IIIC) epithelial ovarian, peritoneal or fallopian tube carcinoma (EOC). Women who were diagnosed with epithelial

ovarian, peritoneal, or fallopian tube carcinoma from 2000 to 2016 were extracted from the electronic medical record via International Classification of Diseases, 9th revision (ICD-9) codes (183.0, 183.2, 183.8, 183.9). Patients were included if they had undergone CRS followed adjuvant chemotherapy with at least one cycle of IP/IV chemotherapy. Patients were excluded if they received surgery and/or any part of their chemotherapy at an outside institution. Additionally, patients were excluded if surgery was considered suboptimal, with greater than 1 cm of residual disease remaining as dictated in the operative report. Patients with low grade, borderline or tumors of low malignant potential were excluded. All patients included in the study were planned to receive 6 cycles of adjuvant IP/IV chemotherapy at their post-operative visit with their gynecologic oncologist. Patients were divided into 2 separate cohorts: first, those who had completed the planned treatment course of IP/IV chemotherapy and, second, those who were unable to complete the planned course of IP/IV chemotherapy and either completed no further chemotherapy or received subsequent IV chemotherapy alone. No patients received IP/IV chemotherapy following interval cytoreduction.

2. Data collection

All data was collected and stored securely within a password protected, secure, online database (REDCap) [11]. Data collection for patient demographics included age at the time of surgery, body mass index (BMI), race, American Society of Anesthesiologists (ASA) classification, genetic carrier status, Eastern Cooperative Oncology Group (ECOG) status at first chemotherapy, Charlson comorbidity index, smoking and medical comorbidities. Surgical variables that were collected included pre-operative laboratory testing, operative time, surgical procedures performed, estimated blood loss (mL) and remaining residual disease following completion of CRS (complete, optimal <1 cm, optimal <0.5 cm) as dictated in the operative report. Operative time was defined as time from skin incision to closure. Intra-operative complications were defined as injury to bowel, bladder, ureters or major vascular structures. Data was collected for post-operative complications (re-operation, venous thromboembolism, myocardial infarction, cuff dehiscence, sepsis, respiratory failure, anastomotic leak and death) and minor complications (ileus, pneumonia, superficial wound infection, readmission, blood transfusion and unplanned intensive care unit [ICU] admission) within thirty days of surgery. Date of discharge was recorded and whether patients were discharged to home without needs, home with home health services, skilled nursing facility or long-term acute care facilities. Cancer histology, stage and largest tumor dimension was recorded from the final pathology report. Laboratory studies prior to chemotherapy were recorded. Physician and advanced practice provider (nurse practitioners, physician assistant) documentation was reviewed for each chemotherapy encounter to determine chemotherapy medications given and the route of administration, cycle number and if there were any changes in the planned treatment course. Specific chemotherapy regimen and dosing schedule of IP/IV and IV chemotherapy was noted. If patients were enrolled on clinical trials, trial number and treatment arm were recorded. Number of cycles of both IP/IV chemotherapy and IV chemotherapy were recorded. Date of IP port placement was documented as well as the volume of chemotherapy infused through the port. All ports were single lumen and 9.6 French in size (Bard, Salt Lake City, UT, USA). The electronic medical record was reviewed for any IP port complication including infection, infusion difficulty, leakage or patient reported symptoms. Date of removal of IP port and the reason for removal was noted. If IP/IV chemotherapy was stopped, reason(s) for discontinuation were noted. Hospitalizations during chemotherapy related directly to chemotherapy or otherwise were reported. Chemotherapy related complications were recorded according to Common Terminology for Adverse Events (CTCAE) v5.0 [12].

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3. Statistical analysis

For statistical analysis, categorical factors were summarized using frequencies and percentages, while continuous measures summaries were reported as medians and interquartile ranges. Patients were divided into 2 groups: those who completed the planned course of IP/IV chemotherapy and those who discontinued the planned course of IP chemotherapy and finished a course of IV chemotherapy. To evaluate risk factors for IP/IV chemotherapy discontinuation, Pearson χ^2 tests and 2 sample t-tests were used. Risk estimates were provided as odds ratios with 95% confidence limits for early outcomes, and hazard ratios with 95% confidence limits for time to recurrence. Analysis was performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). Kaplan-Meier estimates and Cox proportional hazards were used to evaluate differences in time to recurrence or survival.

RESULTS

1. Patient demographics

In total, 96 patients with Stage IIIA–IIIC EOC who had undergone optimal CRS with <1 cm of residual disease were prescribed adjuvant IP/IV chemotherapy post-operatively from 2000–2016 and were included in the final analysis. **Table 1** displays the patient demographic data for all patients. The median age was 59.8 years (55.4, 68.7) and the median BMI was 27.8 kg/m^2 (23.7, 30.9). The majority of patients (n=89; 92.7%) had a pre-chemotherapy ECOG status of 0 or 1, serous histology (n=82; 86.3%) and had stage IIIC disease (n=83; 86.5%). The median cancer antigen 125 (CA125) for the entire cohort was 352.0 (76.7, 814.0). The rate of known hereditary cancer syndromes, including BRCA1/2 mutations and Lynch Syndrome was 13.5% (n=13).

All patients underwent hysterectomy with or without unilateral or bilateral salpingo-oophorectomy (n=96; 100%). Pelvic and para-aortic lymphadenectomy was performed in 43.8% (n=42) and 38.5% (n=37), respectively. Large bowel surgery was performed in 36.5% (n=35), small bowel surgery in 6.3% (n=6) and upper abdominal surgery in 27.1% (n=26). IP ports were placed at the time of CRS in 79.2% (n=76). All patients had resection of disease to less than one centimeter of residual disease; over half of patients had complete resection to no gross residual (n=55; 57.3%). The majority of patients began chemotherapy within 6 weeks of surgery (n=74; 77.1%).

2. IP/IV chemotherapy completion

In total, 69 patients (71.9%) completed the intended course of IP/IV chemotherapy. Details of chemotherapy regimens are described in **Table 1**. The majority of patients received IV Paclitaxel 135 mg/m^2 D1, IP Cisplatin 75 mg D2, IP Paclitaxel 60 mg/m^2 D8 q21 days (modified GOG172 regimen) (n=39; 40.6%) or Carboplatin area under the curve (AUC) 4–6 D1, Taxol 135 mg/m^2 D1 (n=32; 33.3%). Bevacizumab was given with IP/IV chemotherapy in 20.8%.

Table 2 displays the reason for discontinuation of IP/IV chemotherapy. Among the 28.1% (n=27) of patients who did not complete IP/IV chemotherapy, the most common reasons for discontinuation were grade 3–4 gastrointestinal symptoms (n=10; 37.0%), neurologic (n=6; 22.2%), hematologic (n=3; 11.1%) and renal toxicities (n=3; 11.1%) and port site infections (n=3; 11,1%). Less common reasons for discontinuation of IP/IV chemotherapy were vaginoperitoneal fistula (n=1; 3.7%) and bowel perforation due to the IP port (n=1; 3.7%). No patients died during chemotherapy.

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Table 1. Demographic, surgical and oncologic characteristics in women with advanced EOC assigned to receive IP/IV chemotherapy following primary CRS

Variable	Value
Age	59.8 (55.4, 68.7)
BMI	27.8 (23.7, 30.9)
Medical comorbidities	
Obesity (BMI >30)	20 (20.8)
Hypertension	36 (37.5)
Diabetes mellitus	9 (9.4)
CAD	4 (4.2)
PVD	2 (2.1)
Renal disease	2 (2.1)
Prior VTE	5 (5.2)
ASA	
I	0 (0.0)
II	36 (37.5)
III	60 (62.5)
IV	0 (0.0)
Current smoking	5 (5.2)
Known hereditary CA syndrome	
BRCA1	3 (5.3)
BRCA2	9 (8.8)
Lynch syndrome	1 (0.9)
Pre-op CA125	352.0 (76.7, 814.0)
Surgical procedure	
Hysterectomy+U/BSO	96 (100.0)
Pelvic LND	42 (43.8)
Para-aortic LND	37 (38.5)
Omentectomy	96 (100.0)
Appendectomy	32 (33.3)
Small bowel surgery	6 (6.3)
Large bowel surgery	35 (36.5)
IP port placement	76 (79.2)
Upper ABD surgery	26 (27.1)
Residual disease	
Complete	55 (57.3)
Optimal (<0.5 cm)	20 (21.9)
Optimal (<1 cm)	21 (20.8)
Tumor size (cm)	8.0 (3.7, 12.0)
FIGO stage	
IIIA	5 (5.2)
IIIB	8 (8.3)
IIIC	83 (86.5)
Histology	
High grade serous	82 (85.4)
Endometrioid	3 (3.2)
Clear cell	6 (6.3)
Carcinosarcoma	1 (1.1)
Mucinous	1 (1.1)
ECOG status	
0	51 (53.1)
1	38 (40.0)
2	4 (4.2)
3	2 (2.1)
Time to treatment (wk)	
<4	16 (16.8)
4–6	58 (61.1)
6–8	18 (18.9)
>8	3 (3.2)

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Table 1. (Continued) Demographic, surgical and oncologic characteristics in women with advanced EOC assigned to receive IP/IV chemotherapy following primary CRS

Variable	Value
IP/IV chemotherapy regimen	
Paclitaxel 80 mg/m² IV D1,8,15, Carboplatin AUC 6 IP D1, Bevacizumab 15 mg/kg D1 starting cycle 2 q21 days (GOG252 Arm 2)	12 (12.5)
Paclitaxel 135 mg/m² IV D1, Cisplatin 75 mg/m² D2, Bevacizumab 15 mg/kg D1 starting cycle 2 q21 days (GOG252 Arm 3)	8 (8.3)
Carboplatin AUC 4–6 D1, Taxol 135 mg/m² D1	32 (33.3)
IV Paclitaxel 135 mg/m² D1, IP Cisplatin 75 mg D2, IP Paclitaxel 60 mg/m² D8 q21 days (modified GOG172)	39 (40.6)
IV Paclitaxel 135 mg/m² D1 over 24 hours, IP Cisplatin 100 mg/m² D2, IV Paclitaxel 60 mg/m² D8 (GOG172, IP arm)	5 (5.2)
Bevacizumab administration	20 (20.8)

Statistics presented as median (interquartile range: 25%, 75%) or number (%).
ASA, American Society of Anesthesiologists; AUC, area under the curve; BMI, body mass index; CA, cancer antigen; CAD, coronary artery disease; CRS, cytoreductive surgery; ECOG, Eastern Cooperative Oncology Group; EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; GOG, Gynecologic Oncology Group; IP, intraperitoneal; IV, intravenous; LND, lymph node dissection; PVD, peripheral vascular disease; U/BSO, unilateral or bilateral salpingo-oophorectomy; upper ABD surgery, diaphragm stripping or resection, liver resection, splenectomy, pancreatectomy; VTE, venous thromboembolism.

Table 2. Reasons for discontinuation of IP/IV chemotherapy in women with advanced EOC

Reason for discontinuation	No. (%)
Grade 3 or 4 gastrointestinal symptoms	10 (37.0)
Grade 3 or 4 neurologic toxicity	6 (22.2)
Grade 3 or 4 hematologic toxicity	3 (11.1)
Grade 3 or 4 nephrotoxicity	3 (11.1)
Port site infection	3 (11.1)
Vaginoperitoneal fistula	1 (3.7)
Bowel perforation	1 (3.7)

EOC, epithelial ovarian cancer; IP, intraperitoneal; IV, intravenous.

3. IP/IV chemotherapy discontinuation and associated factors

Table 3 displays the individual patient, peri-operative and oncologic variables for women with advanced EOC who did and did not complete IP/IV chemotherapy. There were no significant differences in the median age (60.4 vs. 59.2 years; p=0.97), ASA score (p=0.35), Charlson comorbidity index (p=0.37) or median BMI (27.6 vs. 28.3; p=0.24) for those who completed IP/IV chemotherapy compared to those who did not. Similarly, there were no significant differences between ethnicity (p=0.62) or medical comorbidities including obesity (15.9% vs. 33.3%; p=0.09), hypertension (37.7% vs. 37.0%; p=0.99) or diabetes mellitus (8.7% vs. 11.1%; p=0.71) among patients who finished IP/IV chemotherapy compared to those who did not.

There were no significant differences in the median estimated blood loss (mL) (400.0 vs. 400.0; p=0.75) nor operative time (minutes) (216.0 vs. 202.0; p=0.99) between the 2 groups. There were no significant differences in the procedures underwent by the patients who completed IP/IV chemotherapy compared to those who did not, including hysterectomy (85.5% vs. 96.3%; p=0.17), small bowel surgery (7.3% vs. 3.7%; p=0.99), large bowel surgery (39.1% vs. 29.6%; p=0.33) and upper abdominal surgery (17.4% vs. 14.8%; p=0.99). There was no significant difference in IP/IV chemotherapy completion among patients undergoing IP port placement at a later date compared to at the time of original surgery (82.1% vs. 84.0%; p=0.83).

No significant differences in the incidence of adverse post-operative complications including re-operation within 30 days (2.9% vs. 3.7%; p=0.99), venous thromboembolism (2.9% vs. 0.0%; p=0.99), surgical site infection (4.4% vs. 11.1%; p=0.34), hospital re-admission (4.6%

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Table 3. Patient, surgical and oncologic variables in women with advanced EOC who did complete IP/IV chemotherapy compared to those not completing IP/IV chemotherapy

Variable	Completed IP/IV chemotherapy (n=69)	Did not complete IP/IV chemotherapy (n=27)	p-value
Patient factors			
Age	60.4 (55.3, 69.7)	59.2 (56.5, 67.3)	0.97
BMI	27.6 (23.8, 29.9)	28.3 (22.6, 34.3)	0.24
ASA			0.35
I	0 (0.0)	0 (0.0)	
II	28 (40.6)	8 (29.6)	
III	41 (59.4)	19 (70.4)	
IV	0 (0.0)	0 (0.0)	
Charlson comorbidity index	7.0 (5.0, 8.0)	7.0 (4.0, 9.0)	0.37
Ethnicity			0.62
White	63 (95.5)	24 (92.3)	
African American	3 (4.6)	2 (7.7)	
Medical comorbidities			
Obesity (BMI >30)	11 (15.9)	9 (33.3)	0.09
Hypertension	26 (37.7)	10 (37.0)	0.99
Diabetes mellitus	6 (8.7)	3 (11.1)	0.71
Peri-operative factors			
Estimated blood loss (mL)	400.0 (225.0, 825.0)	400.0 (200.0, 725.0)	0.75
Operative time (min)	216.0 (182.8, 259.3)	202.0 (163.3, 272.3)	0.99
Surgical procedures			
Hysterectomy	59 (85.5)	26 (96.3)	0.17
Pelvic lymphadenectomy	31 (44.9)	11 (40.7)	0.82
Para-aortic lymphadenectomy	25 (36.2)	12 (44.4)	0.49
Omentectomy	62 (89.9)	23 (85.9)	0.50
Small bowel surgery	5 (7.3)	1 (3.7)	0.99
Large bowel surgery	27 (39.1)	8 (29.6)	0.48
Colonic/small bowel diversion procedure	1 (1.5)	0 (0.0)	0.99
Upper abdominal surgery	12 (17.4)	4 (14.8)	0.99
Post-operative complications			
Re-operation in 30 days	2 (2.9)	1 (3.7)	0.99
VTE	2 (2.9)	0 (0.0)	0.99
Surgical site infection	3 (4.4)	3 (11.1)	0.34
Readmission	3 (4.6)	1 (3.7)	0.99
ICU admission	1 (1.5)	1 (3.7)	0.49
Bowel leak	0 (0.0)	0 (0.0)	0.99
Pelvic abscess	2 (2.9)	0 (0.0)	0.51
Post-operative discharge after CRS			**0.007**
Home without needs	59 (92.2)	18 (72.0)	
Home with home-health care	5 (7.8)	4 (16.0)	
Skilled nursing facility	0 (0.0)	3 (12.0)	
Chemotherapy factors			
ECOG status	0 (0.0, 1.0)	1.0 (0.0, 1.0)	**0.03**
HGB (g/dL) prior to chemotherapy	11.4 (11.0, 12.3)	11.5 (10.8, 12.3)	0.96
HCT (%) prior to chemotherapy	35.6 (33.8, 37.7)	36.4 (33.8, 38.5)	0.65
Platelets (k/uL) prior to chemotherapy	358.0 (239.0, 525.0)	300.5 (249.5, 368.3)	0.09
Albumin prior to chemotherapy (g/dL)	4.0 (3.8, 4.3)	3.9 (3.7, 4.3)	0.43
CA125 prior to chemotherapy (U/mL)	57.0 (25.0, 109.8)	51.5 (23.0, 118.8)	0.38
Creatinine (mg/dL) before chemotherapy	0.7 (0.6, 0.9)	0.7 (0.6, 0.9)	0.80
Time to chemotherapy initiation (wk)			0.64
<4	13 (19.1)	3 (11.1)	
4–6	39 (57.4)	19 (70.4)	
6–8	14 (20.6)	4 (14.8)	
>8	2 (2.9)	1 (3.7)	
No. of cycles IP given	6.0 (6.0, 6.0)	3.0 (2.0, 4.0)	<0.001
No. of cycles IV given	0.0 (0.0, 0.0)	2.0 (1.0, 4.0)	<0.001

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Table 3. (Continued) Patient, surgical and oncologic variables in women with advanced EOC who did complete IP/IV chemotherapy compared to those not completing IP/IV chemotherapy

Variable	Completed IP/IV chemotherapy (n=69)	Did not complete IP/IV chemotherapy (n=27)	p-value
IP port placement			0.83
Original surgery	55 (82.1)	21 (84.0)	
Later date via laparoscopy	12 (17.9)	4 (16.0)	
Volume of IP/IV therapy (mL)	2,000.0 (2,000.0, 2,000.0)	2,000.0 (2,000.0, 2,000.0)	0.57
IP/IV regimen			0.55
Paclitaxel 80 mg/m^2 IV D1,8,15, Carboplatin AUC 6 IP D1, Bevacizumab 15 mg/kg D1 starting cycle 2 q21 days (GOG252 Arm 2)	8 (11.6)	4 (14.8)	
Paclitaxel 135 mg/m^2 IV D1, Cisplatin 75 mg/m^2 D2, Bevacizumab 15 mg/kg D1 starting cycle 2 q21 days (GOG252 Arm 3)	7 (10.1)	1 (3.7)	
Carboplatin AUC 4–6 D1, Taxol 135 mg/m^2 D1	22 (31.9)	10 (37.0)	
IV Paclitaxel 135 mg/m^2 D1, IP Cisplatin 75 mg D2, IP Paclitaxel 60 mg/m^2 D8 q21 days (modified GOG172)	29 (42.0)	10 (37.0)	
IV Paclitaxel 135 mg/m^2 D1 over 24 hours, IP Cisplatin 100 mg/m^2 D2, IV Paclitaxel 60 mg/m^2 D8 (GOG172, IP arm)	3 (4.4)	1 (3.7)	
Bevacizumab co-administration	15 (21.7)	5 (18.5)	0.82
IP port complications	8 (11.6)	12 (48.0)	**<0.001**
Hospitalization during chemotherapy	2 (2.9)	8 (29.6)	**<0.001**

Statistics presented as median (interquartile range: 25%, 75%) or number (%). Bold word indicates statistical significance.
ASA, American Society of Anesthesiologists; AUC, area under the curve; BMI, body mass index; CA125, cancer antigen 125; CRS, cytoreductive surgery; ECOG, Eastern Cooperative Oncology Group; EOC, epithelial ovarian cancer; GOG, Gynecologic Oncology Group; HCT, hematocrit; HGB, hemoglobin; ICU, intensive care unit; IP, intraperitoneal; IV, intravenous; VTE, venous thromboembolism.

vs. 3.7%; p=0.99) or ICU admission (1.5% vs. 3.7%; p=0.49) between those who did and did not complete IP/IV chemotherapy, respectively. The rate of discharge to home after CRS compared to discharge with home health or to skilled nursing facilities was significantly higher among those who completed IP/IV chemotherapy (92.2% vs. 72.0%; p<0.01).

Port complications (48.0% vs. 11.6%; p<0.001) and hospitalization during chemotherapy (29.6% vs. 2.9%; p<0.001) were significantly higher among patients who discontinued IP/IV chemotherapy. There was no difference in chemotherapy completion based upon pre-chemotherapy hemoglobin (p=0.96), hematocrit (p=0.65), platelets (p=0.09) and albumin (p=0.43). The majority of patients initiated chemotherapy within 6 weeks of surgery; there was no difference in timing of chemotherapy initiation among those who completed IP/IV chemotherapy compared to those who did not (p=0.64). Finally, there was no difference in IP/IV chemotherapy completion based upon regimen given (p=0.55) or bevacizumab administration (21.7% vs. 18.5%; p=0.82).

4. IP port complications

The total incidence of IP port complications was 20.8% (n=20) (**Table 4**). IP port complications included inability to access port or initiate an infusion (n=6; 30.0%), chemotherapy extravasation/leakage (n=4; 20.0%), intolerable pain from port (n=5; 25.0%), port site infection (n=4; 20.0%) and bowel perforation (n=1; 5.0%). Among the patients who did not complete IP/IV chemotherapy, the incidence of port complications was significantly higher with 48.0% (n=12) experiencing at least one complication (p<0.001) compared to a rate of 11.6% (n=8) in those who did finish the prescribed course of IP/IV chemotherapy.

5. Recurrence and survival

There was no difference in PFS among patients who completed IP/IV chemotherapy compared to those who did not (40.1 vs. 43.1 months; p=0.76) Similarly, no differences in

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Table 4. IP port complications in women receiving IP/IV chemotherapy for advanced EOC

Port site complication	No. (%)
Inability to access port or initiate an infusion	6 (30.0)
Leakage or extravasation of chemotherapy	4 (20.0)
Intolerable pain	5 (25.0)
Port site infection	4 (20.0)
Bowel perforation	1 (5.0)

EOC, epithelial ovarian cancer; IP, intraperitoneal; IV, intravenous.

OS was observed in women who completed IP/IV chemotherapy compared to those who did not (79.2 vs. 76.8 months; p=0.28) Kaplan-Meier curves for PFS and OS for patients who completed IP/IV chemotherapy compared to those who did not are displayed in **Fig. 1**.

DISCUSSION

Large randomized studies have demonstrated that IP/IV chemotherapy is associated with improved survival in patients with advanced optimally debulked EOC compared to IV chemotherapy alone [3-5]. While GOG172 demonstrated improved OS of 65.6 months in the IP/IV arm compared to 49.7 months in women in the IV only arm, only 42% of patients were able to complete the IP/IV chemotherapy regimen [5]. While more recent studies have demonstrated reduced toxicity and patient-reported symptoms, port complications and logistics of administration remain unfortunate barriers to successful delivery of IP/IV chemotherapy [7-10].

In this retrospective cohort of 96 women with advanced EOC, the rate of completion of IP/IV chemotherapy was high at 71.9%. Our study analyzed several patients, surgical and oncologic variables to identify factors association with non-completion of IP/IV chemotherapy. We demonstrated that patient factors, including age, BMI, ethnicity and medical comorbidities including hypertension and diabetes, did not differ significantly among patients who completed IP/IV chemotherapy compared to those who did not. This is similar to prior studies, which have not shown worse morbidity and mortality in patients with increasing age and BMI undergoing IP/IV chemotherapy [13-15]. Of note, no operative variables, including

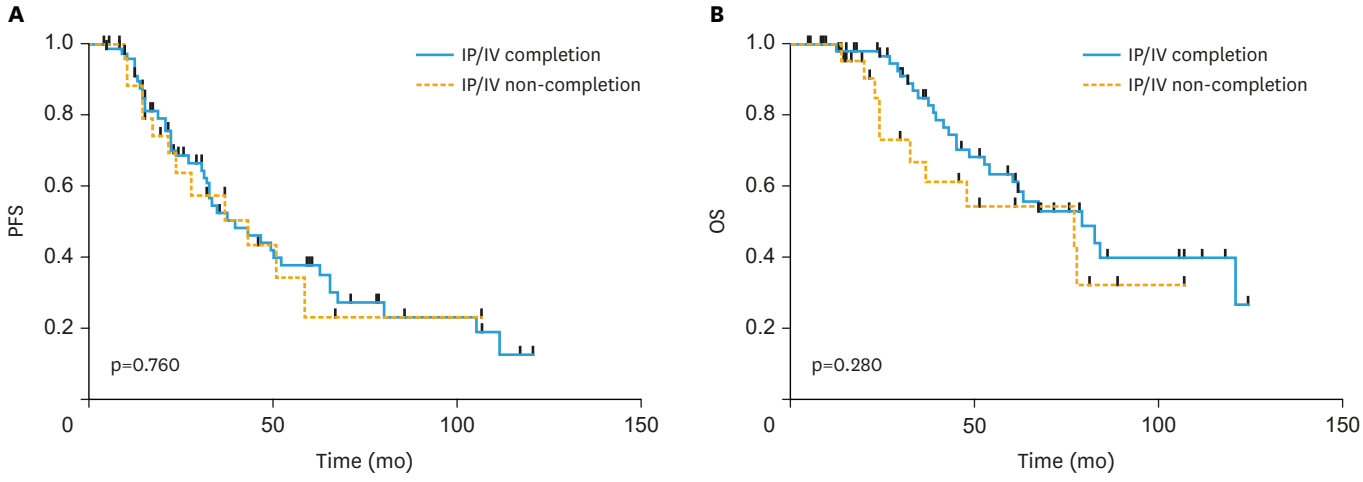

Fig. 1. (A) PFS and (B) OS for patients with advanced EOC who completed IP/IV chemotherapy compared to those who did not.
EOC, epithelial ovarian cancer; OS, overall survival; IP, intraperitoneal; IV, intravenous; PFS, progression-free survival.

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post-operative complications and bowel surgery were associated with non-completion of IP/IV chemotherapy.

Our results identified that patients who completed IP/IV chemotherapy had significantly higher rates of home discharge following CRS versus discharge with home health services or to skilled nursing facilities. In addition, patients with lower pre-chemotherapy ECOG scores were significantly more likely to complete IP/IV chemotherapy. Non-home discharge has been previously correlated with medical frailty and poorer performance status [16,17]. In a retrospective cohort of 587 women with advanced EOC who underwent CRS at the Mayo Clinic, patients with advanced age, advancing ECOG status, greater ASA status and higher CA125 were less likely to be discharged home [16]. Both non-home discharge and higher pre-chemotherapy ECOG status have been demonstrated as markers of worse performance status. This suggests that patients with IP/IV chemotherapy completion may be lower in patients with lower performance status following CRS. Both non-home discharge and ECOG status combine several patients, surgical and demographic variables together and may function as helpful assessment tools for both treatment planning and chemotherapy management, including anticipation of patient tolerance and side effects and patient counseling.

Among women who discontinued IP/IV chemotherapy, the most frequently reported complications were gastrointestinal symptoms including intolerable pain, discomfort and bloating and neurologic, hematologic or renal toxicities. Gastrointestinal symptoms are more common and severe with IP/IV chemotherapy compared to IV chemotherapy alone due to stretching and distention of nerves, abdominopelvic viscera and adhesions [18-20]. Prior studies have shown that volume reduction of chemotherapy being instilled may improve symptoms [5,18-20]. In contrast, our results did not identify any difference in IP/IV chemotherapy discontinuation based upon volume of chemotherapy administered into the peritoneal cavity. Toxicities reported in our study are consistent with GOG172 where nephrotoxicity, neurotoxicity and abdominal pain were significantly worse compared to IV chemotherapy [5,21]. Furthermore, IP/IV treatment resulted in significantly worse neurotoxicity shortly after completion of chemotherapy and at one year later [5,21]. It is important to note that despite the high incidence of adverse side effects and worse quality of life during and immediately after IP/IV chemotherapy compared to IV, there was no difference between quality of life at 12 months after completion of treatment in patients enrolled on GOG172 [21]. Patients must be well-counselled regarding the increased toxicity profile of IP/IV chemotherapy relative to the demonstrated improved survival benefits [5].

Catheter complications during IP/IV chemotherapy have been well-described in the literature [18,19,22,23]. The incidence of port complications in this study was comparable to prior studies [18,19,23]. Although the majority of port issues were minor (difficulty with access, leaking), it is important to note that port complications were significantly higher in those discontinuing IP/IV chemotherapy. In this study, all IP ports were silicone single-lumen Bardport® peritoneal catheters, which have been associated with lower rates of complication compared to fenestrated catheters [18,19,22,23]. In an analysis of patients enrolled in GOG172, 34% of patients discontinued IP/IV chemotherapy due to catheter related complications which included infection, leaking, blockage or access problems [19]. Additionally, Walker et al. [19] reported that placement of IP catheters at the time of large bowel resection may be associated with increased risk for port complications. In a series from Memorial Sloan Kettering of 301 patients undergoing IP/IV chemotherapy, a low rate of catheter-related complications was reported (10%); however, the majority of catheters were

inserted via laparoscopy and avoided concurrent bowel surgery [22]. There is still much to be learned regarding IP/IV chemotherapy administration and IP port complications as these remain a significant barrier to successful administration of IP/IV therapy despite advances in port technology.

Although not powered for PFS or OS, our study identified no difference in survival or recurrence among those who completed 6 cycles IP/IV chemotherapy versus those who did not, and instead completed their adjuvant treatment with IV chemotherapy. Prior data suggests that receipt of any IP/IV chemotherapy may portend a survival advantage, even in patients not completing a total of 6 cycles. In a retrospective analysis of randomized trials GOG114 and 172, improved survival was noted with increasing number of IP/IV cycles with benefit extending over ten years [24]. This was further demonstrated in a retrospective study by Suidan et al. [25] of patients with advanced EOC undergoing IP/IV chemotherapy, where no improvement in PFS or OS was identified when stratified by the number of IP/IV cycles received. Our findings reflect a defined cohort of women who received at least one cycle of IP/IV chemotherapy. Within these women, we did not identify any oncologic benefit (PFS, OS) to IP/IV completion versus non-completion. However, these findings are consistent with prior data suggesting that receipt of any IP/IV chemotherapy may confer a survival benefit and these data are limited overall by a small sample size and lack of IV only comparison group. At this time, available evidence from clinical trials supports use of IP/IV chemotherapy in women with advanced stage EOC following optimal cytoreduction, but translation of this data into clinical practice have been difficult. Successful administration of IP/IV chemotherapy requires a dedicated, knowledgeable oncologic team committed to treating patients, while maintaining a careful balance between patient symptoms, toxicity and supportive care.

Limitations of this study include the retrospective data collection and the inherent associated biases of such a study design, including surgical practices and disease biology. In addition, this study contains a relatively small sample size of patients receiving IP/IV chemotherapy at a single high-volume referral center for gynecologic oncology. Therefore, this experience with IP/IV chemotherapy may not be generalizable to all centers, especially at low volume institutions. An additional limitation is that we were unable to control for provider bias upon patient selection for IP/IV chemotherapy. Our findings demonstrate that patients who completed IP/IV chemotherapy had significantly higher rates of home discharge after surgery and lower ECOG performance status. However, it is important to note that 90% of patients in this study were classified as ECOG 0 or 1 and therefore these findings may not be fully generalizable to all women with advanced EOC. These results may reflect a bias towards provider selection of patients with higher performance status for IP/IV chemotherapy and may under-represent patients with a poorer performance status. These findings should be further studied in a more heterogenous patient group.

In this retrospective cohort study of women with advanced EOC undergoing adjuvant treatment with IP/IV chemotherapy at a high-volume center, the rate of completion was high. While IP port complications were overall high, the incidence approached 50% among those who discontinued IP/IV chemotherapy. Non-home discharge after CRS may be predictive of IP/IV chemotherapy non-completion and may be considered in treatment planning. Patients should be considered for IP/IV chemotherapy despite age, BMI and medical comorbidities. Further studies should focus on reduction of IP port adverse events as this remains a significant barrier to successfully administering IP/IV chemotherapy.

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