Gynecologic Oncology Reports 40 (2022) 100951

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Research Report

Assessment of travel distance for hyperthermic intraperitoneal chemotherapy in women with ovarian cancer

Laura M. Chambers [a,b,*], Meng Yao [c], Molly Morton [d], Morgan Gruner [d], Anna Chichura [d], Anthony B. Costales [e], Max Horowitz [b], Peter G. Rose [b], Chad M. Michener [b], Robert Debernardo [b]

[a] Division of Gynecologic Oncology, The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute, Columbus, OH, United States
[b] Division of Gynecologic Oncology, Obstetrics, Gynecology, Women's Health Institute, Cleveland Clinic, Desk A81, 9500 Euclid Avenue, Cleveland, OH 44195, United States
[c] Department of Qualitative Health Sciences, Cleveland Clinic, Cleveland, OH 44195, United States
[d] Obstetrics, Gynecology, Women's Health Institute, Cleveland Clinic, Desk A81, 9500 Euclid Avenue, Cleveland, OH 44195, United States
[e] Department of Gynecologic Oncology, Baylor College of Medicine, Houston, TX 77030, United States

ARTICLE INFO

Keywords:
Ovarian cancer
Cytoreductive surgery
Hyperthermic intraperitoneal chemotherapy
Travel distance
Disparities
Perioperative outcomes

ABSTRACT

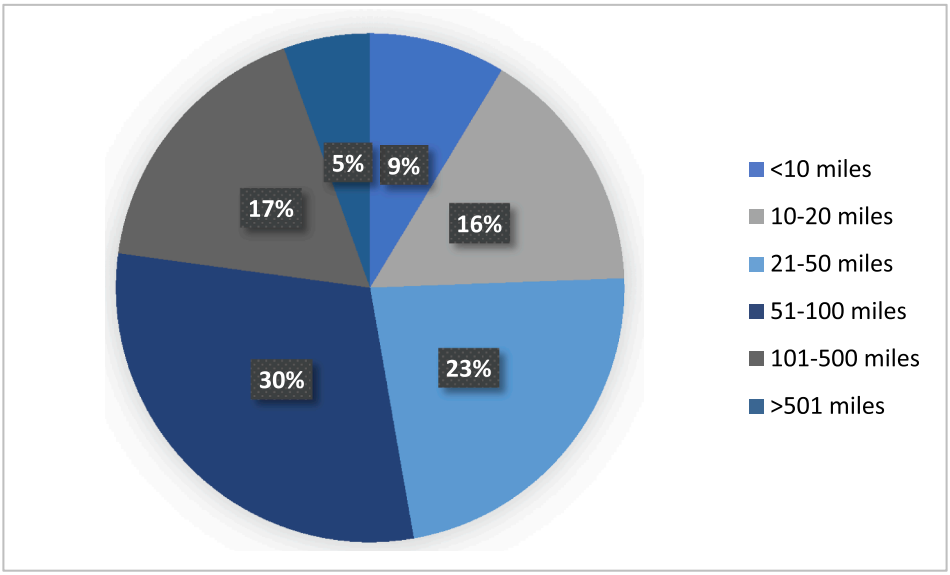
Objective (s): To evaluate travel distance in women with advanced or recurrent epithelial ovarian cancer (OC) undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) and the subsequent impact upon outcomes.
Methods: An IRB-approved single-institution prospective registry was queried for women with OC who underwent HIPEC from 1/1/2009–12/1/2020. Demographic, oncologic, and surgical data were recorded. The patient's home zip code was compared to the institutional zip code to determine travel distance using Google Maps. Patients were divided into three strata for analysis: 1) local: ≤50 miles, 2) regional: 51–99 miles, and 3) distant: ≥100 miles and univariate analysis was performed.
Results: Of 127 women, the median distance travelled was 57.0 miles (IQR: 20.6, 84.6). There were no significant differences in mild (28.3% vs. 26.3 vs. 24.1%), moderate (21.7% vs. 15.8% vs. 17.2%) or severe postoperative complications (11.7% vs. 5.3% vs. 17.2%) ($p = 0.75$) for local, regional and distant patients, respectively. There was no difference in progression-free survival (17.4 vs. 22.2 vs. 12.8 months, $p > 0.05$) or overall survival (57.3 vs. 61.6 vs. 29.2 months, $p > 0.05$) for local, regional or distant patients, respectively.
Conclusions: This study demonstrates that women with OC are willing to travel for HIPEC, with over 50% traveling > 50 miles. Our results suggest that women who travel for HIPEC procedures are not at increased risk for perioperative complications or worse oncologic outcomes than those local to HIPEC centers.

1. Introduction

Epithelial ovarian cancer is a leading cause of gynecologic cancer death in the United States (Siegel et al., 2020). The first-line treatment for advanced ovarian cancer is a combination of cytoreductive surgery and platinum-based chemotherapy (Armstrong et al., 2021; Vergote et al., 2010; Kehoe et al., 2015). In women who are poor surgical candidates or have a low likelihood of optimal cytoreduction, neoadjuvant chemotherapy followed by interval debulking is an acceptable alternative (Vergote et al., 2010; Kehoe et al., 2015). According to National Comprehensive Cancer Network guidelines, hyperthermic intraperitoneal chemotherapy (HIPEC) may be considered at the time of interval debulking surgery in women with ovarian cancer based upon promising data from recent prospective trials (Armstrong et al., 2021; van Driel et al., 2018; Spiliotis et al., 2011; Spiliotis et al., 2015; Cascales-Campos et al., 2014; Bakrin et al., 2013; Lei et al., 2020; Morton et al., 2021; Chambers et al., 2020; Costales et al., 2021). Despite this, HIPEC uptake across the United States is low (Charo et al., 2020). Notably, in a study by Charo et al. of a national claims database from January 2016 – January 2020, only 152 patients with ovarian cancer received HIPEC at the time of surgery at 39 centers, compared to 20,014 women with ovarian cancer who underwent surgery without HIPEC at

* Corresponding author at: Division of Gynecologic Oncology, The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute, Columbus, OH, United States.
E-mail address: laura.chambers@osumc.edu (L.M. Chambers).

https://doi.org/10.1016/j.gore.2022.100951
Received 14 January 2022; Received in revised form 22 February 2022; Accepted 24 February 2022
Available online 28 February 2022



Travel Distance	N (%)
Median Distance Travelled	57.0 [20.6, 84.6]
Distance Group	
<10 miles	11 (8.7)
10-20 miles	20 (15.7)
21-50 miles	29 (22.8)
51-100 miles	38 (29.9)
101-500 miles	22 (17.3)
>500 miles	7 (5.5)

Fig. 1. Travel distance for HIPEC in women with ovarian cancer.

256 hospitals during the same period (Charo et al., 2020).

One of the major benefits of HIPEC is the delivery of chemotherapy in a single administration at the time of surgery (Chambers et al., 2020). Despite historical concerns regarding toxicity and morbidity related to HIPEC, recent studies have demonstrated that HIPEC is well-tolerated with a low rate of adverse events in selected patients treated at experienced centers (van Driel et al., 2018; Bakrin et al., 2013; Lei et al., 2020; Morton et al., 2021; Chambers et al., 2020; Chichura et al., 2021). However, the small number of centers performing HIPEC nationwide may pose a barrier to patients who are eligible candidates and interested in these procedures. Subsequently, patient-centered resources, including websites like HIPECtreatment.com and hashtags such as #SoMe4-Peritoneum, were established to serve as communities for patients to share data, locate HIPEC surgeons, and share testimonials (HIPEC-treatment.com, 2020).

Willingness to travel and the impact of travel distance upon outcomes have been previously evaluated in women with ovarian cancer (Shalowitz et al., 2018; Knisely et al., 2020; Daruvala et al., 2021; Stewart et al., 2014; Bristow et al., 2015; Villanueva et al., 2019). In a study by Knisely et al., including over 50,000 women diagnosed with ovarian cancer from the National Cancer Database, the median travel distance was 14.6 miles (Knisely et al., 2020). However, to date, patterns of travel distance and impact upon perioperative and oncologic outcomes in women with ovarian cancer who undergo surgery with HIPEC across the United States are unknown. This study aims to evaluate travel distance in women with advanced or recurrent ovarian cancer HIPEC and subsequent impact upon outcomes at a high-volume Midwest medical center.

2. Materials and methods

2.1. Study design

We performed an Institutional Review Board approved study using a prospective database that including all women diagnosed with ovarian cancer treated with cytoreductive surgery with HIPEC from January 1st' 2009 to December 1st' 2020, at the Cleveland Clinic. Eligible women received HIPEC at the time of 1) interval cytoreductive surgery following neoadjuvant platinum-based chemotherapy or 2) secondary cytoreductive surgery for the management of recurrent, platinum-sensitive ovarian cancer. The treating gynecologic oncologist was responsible for the surgical decision-making for HIPEC. All HIPEC procedures were performed as previously described (Chambers et al., 2020). Travel distance was determined by comparing the patient's home zip code to the zip code at the Cleveland Clinic Main Campus, where all cytoreductive surgery with HIPEC procedures are performed using Google Maps software (Google Maps, 2021). Travel distance was recorded as the shortest distance in miles between the two locations. Patients were sub-categorized into three distance groups: 1) local: $\leq$50 miles) 2) regional: 51–99 miles and 3) distant: $\geq$100 miles.

2.2. Data collection

Patient demographics were extracted from the electronic medical record, including age, race, body mass index (kg/m^2), American Society of Anesthesiologists score at HIPEC, medical comorbidities, and home zip code. Oncologic variables included stage, histology, and indication for HIPEC (interval or secondary cytoreductive surgery). Surgical

Table 1
Patient and surgical characteristics.

Variable	Local (≤50 miles) (n=60)	Regional (51-99 miles) (n=38)	Distant (≥100 miles) (n=29)	P Value
Patient Demographics				
Median Distance Travelled (miles)	19.6 [12.4, 26.0]	67.8 [60.6, 79.9]	197.0 [125.0, 315.0]	**<0.001**
Age	62.1 ± 11.0	59.9 ± 11.4	60.7 ± 9.4	0.60
Race				0.06
White	54 (90.0)	37 (97.4)	24 (85.7)	
Black	2 (3.3)	1 (2.6)	4 (14.3)	
Other	4 (6.7)	0 (0.0)	0 (0.0)	
BMI	27.7 ± 6.5	28.2 ± 8.2	28.8 ± 7.6	0.79
ASA Score at Surgery				0.80
0-2	13 (22.0)	8 (21.1)	8 (27.6)	
3-4	46 (78.0)	30 (78.9)	21 (72.4)	
Genetic Cancer Syndrome				0.32
BRCA1				
BRCA2	10 (17.2)	4 (11.1)	4 (13.8)	
None	4 (6.9)	2 (5.6)	0 (0.0)	
Unknown	26 (44.8)	25 (69.4)	16 (55.2)	
	1 (1.7)	0 (0.0)	0 (0.0)	
Indication for HIPEC				0.32
Interval CRS	40 (66.7)	20 (52.6)	16 (55.2)	
Recurrent CRS	20 (33.3)	18 (47.4)	13 (44.8)	
Histology				0.76
Serous	52 (86.7)	30 (78.9)	26 (89.7)	
Endometrioid	1 (1.7)	2 (5.3)	0 (0.0)	
Clear Cell	2 (3.3)	2 (5.3)	1 (3.4)	
Carcinosarcoma	0 (0.0)	1 (2.6)	0 (0.0)	
Mucinous	2 (3.3)	(5.3)	1 (3.4)	
Other	3 (5.0)	1 (2.6)	1 (3.4)	
Cycles of NACT	3.0 [3.0, 4.0]	4.0 [3.5, 5.0]	3.0 [3.0, 4.0]	**0.04**
Surgical Details				
HIPEC Regimen				0.30
Cisplatin alone	28 (46.7)	10 (26.3)	12 (41.4)	
Paclitaxel/Cisplatin	27 (45.0)	21 (55.3)	16 (55.2)	
Mitomycin/Cisplatin	2 (3.3)	3 (7.9)	0 (0.0)	
Adriamycin/Cisplatin	3 (5.0)	4 (10.5)	1 (3.4)	
Surgical Procedures				
Hysterectomy	38 (63.3)	16 (42.1)	11 (37.9)	0.17
Small Bowel Surgery	6 (10.0)	6 (15.8)	3 (10.8)	0.68
Large Bowel Surgery	15 (25.0)	8 (21.1)	7 (24.1)	0.90
Ileostomy	2 (3.3)	1 (2.6)	0 (0.0)	0.99
Splenectomy	6 (10.0)	4 (10.5)	8 (27.6)	0.06
Liver resection	1 (1.7)	4 (10.5)	3 (10.3)	0.09
Diaphragm stripping/ resection	8 (13.3)	4 (10.5)	1 (3.4)	0.39
Pelvic LND	5 (8.3)	2 (5.3)	3 (10.3)	0.70
Para-Aortic LND	9 (15.0)	6 (15.8)	5 (17.2)	0.96
Surgical Complexity Score				0.30
Low	39 (65.0)	28 (73.7)	15 (51.7)	
Moderate	15 (25.0)	7 (18.4)	13 (44.8)	
High	6 (10.0)	3 (7.9)	1 (3.4)	
Operative time (hours)	5.6 [4.7, 7.0]	5.2 [4.5, 5.9]	5.7 [4.9, 7.0]	0.19
Estimated Blood Loss (mL)	200.0 [100.0, 425.0]	150.0 [100.0, 200.0]	200.0 [100.0, 400.0]	0.13
Residual Disease				0.25
Optimal (NOS)	1 (1.7)	0 (0.0)	3 (10.3)	
Optimal >6 mm	2 (3.8)	2 (6.7)	0 (0.0)	
Optimal 1-5 mm	9 (17.3)	2 (6.7)	3 (12.0)	
Optimal (R0)	40 (76.9)	26 (86.7)	19 (76.0)	
Minimally Invasive Debulking	9 (10.0)	2 (5.3)	2 (6.9)	0.36

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) or standard deviation. Bold indicates statistically significant with $p < 0.05$.

variables collected included HIPEC chemotherapy regimen, amount of residual disease after cytoreduction, surgical procedures, operative time, estimated blood loss, and Surgical Complexity Score (Aletti et al., 2007). In addition, major and minor postoperative adverse events were recorded through review of inpatient and outpatient encounters 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

For statistical analysis, patients were divided into three groups: 1) local: ≤50 miles 2) regional: 51–99 miles and 3) distant: ≥100 miles. 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. Progression-free survival was defined as the difference in months from HIPEC date to recurrence date. Similarly, overall survival was defined date of HIPEC to the date of death, or censored at the last follow-up. 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

127 women with EOC were treated with CRS with HIPEC from January 1st, 2009, to December 1st, 2020, at the Cleveland Clinic. The median distance traveled was 57.0 miles (IQR 20.6, 84.6 miles). Among these patients, distance traveled was < 10 miles in 8.7% (n = 11), 10–20 miles in 15.7% (n = 20), 21–50 miles in 22.8% (n = 29), 51–100 miles in 29.9% (n = 38), 101–500 miles in 17.3% (n = 22) and > 500 miles in 5.5% (n = 7) (Fig. 1). The geographic representation of distance traveled across the United States is displayed in Supplemental Fig. 1. Patients were divided into three cohorts: 1) local: ≤50 miles) 2) regional: 51–99 miles and 3) distant: ≥100 miles with median distance traveled of 19.6 miles, 67.8 miles, and 196.0 miles, respectively, and demographic information was compared (Table 1). The median distance travelled was compared overtime: 49.3 miles (IQR 20.6, 79.0) in 2016 and prior, 66.2 miles (IQR 33.9, 129.0) in 2017, 57.2 miles (IQR 18.6, 100.0) in 2018, 31.8 miles (IQR 14.3, 125.0) in 2019 and 38.6 miles (IQR 16.0, 69.3) in 2020 (p = 0.25) (Table 2) (see Fig. 2).

The median age for patients was 62.1 ± 11.0, 59.9 ± 11.4, and 60.7 ± 9.4 years, respectively (p < 0.60). There were no significant difference in indication for HIPEC with 66.7%, 52.6% and 55.2% undergoing HIPEC at interval CRS and 33.3%, 47.4% and 44.8% undergoing HIPEC at CRS for recurrent, platinum-sensitive EOC (p = 0.32). There were no differences in white race (90.0% vs. 97.4% vs. 85.7%, p = 0.06), BMI (27.7 ± 6.5 vs. 28.2 ± 8.2 vs. 28.8 ± 7.6, p = 0.79), pre-operative ASA score of III/IV (78.0% vs. 78.9% vs. 72.4%, p = 0.80), serous histology (86.7% vs. 78.9% vs. 89.7%, p = 0.76) and hereditary cancer syndromes (p = 0.32) between the cohorts. Patients who resided within 51–99 miles of our cancer center who underwent HIPEC at the time of interval CRS were more likely to receive a median of 4.0 cycles of NACT, compared to 3.0 cycles for those who lived < 50 miles or ≥100 miles away (p = 0.04) (Table 1).

Surgical details are displayed in Table 1. There were no significant differences in intraoperative HIPEC chemotherapy regimen used, with the majority of patients who were local, regional, or distant to our facility receiving cisplatin alone (46.3% vs. 26.3% vs. 41.4%) or paclitaxel with cisplatin (45.0% vs. 55.3% vs. 55.2%)(p = 0.30). There were no

Table 2
Travel distance by year.

	2009–2016 (n = 26)	2017 (n = 23)	2018 (n = 23)	2019 (n = 25)	2020 (n = 30)	P Value
Travel Distance(miles)	49.3 [20.6, 79.0]	66.2 [33.9, 129.0]	57.2 [18.6, 100.0]	31.8 [14.3, 125.0]	38.6 [16.0, 69.3]	0.25

Continuous variables are presented as median with interquartile range (25, 75) or standard deviation.

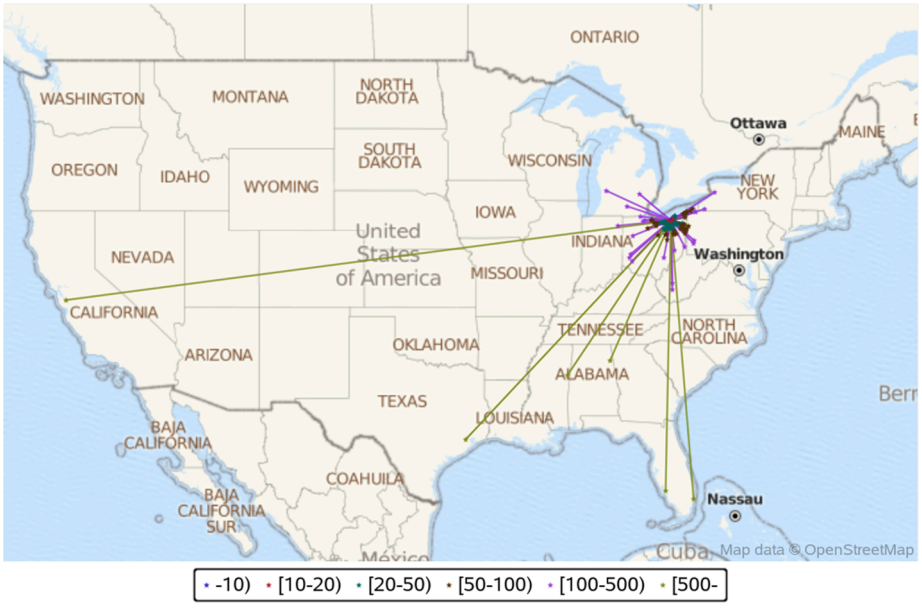


Fig. 2. Geographic distribution of travel distance for HIPEC.

differences in surgical procedures performed ($p > 0.05$) nor Surgical Complexity Score ($p = 0.30$) between the groups. The majority patients underwent optimal cytoreduction to microscopic residual disease (76.9% vs. 86.7% vs. 76.0%, $p = 0.25$).

3.2. Perioperative outcomes

Table 3 displays perioperative outcomes for patients by travel distance. There were no significant differences in the incidence of mild (28.3% vs. 26.3 vs. 24.1%), moderate (21.7% vs. 15.8% vs. 17.2%) and severe complications (11.7% vs. 5.3% vs. 17.2%) ($p = 0.75$) according to the Accordion post-operative scale. Besides a higher incidence of re-operation among patients who traveled ≥ 100 miles compared to <50 or 51–99 miles, (1.7% vs. 0.0%, 10.3%, $p = 0.04$), there were no observed differences in major and minor complications for patients based on travel distance. There were no differences in median length of stay (5.0 vs. 5.0 vs. 5.0 days, $p = 0.71$), median days to chemotherapy (33.0 vs. 34.0 vs. 30.0 days, $p = 0.50$) or discharge to skilled nursing facility (11.9% vs. 7.9% vs. 0.0%, $p = 0.19$) for patients from local, regional or distant locations, respectively.

3.3. Oncologic outcomes

Table 4 demonstrates univariate analysis for PFS and OS. The median follow-up duration was 20.0 months (95% CI, 9.1, 32.7). The median follow-up duration was 18.4 months, 27.3 months, and 15.0 months, respectively, for local, regional, and distant patients ($p = 0.08$). There was no significant difference in PFS between the cohorts, median PFS 17.4 months for local patients, 22.2 months for regional patients (HR 0.72, 95% CI 0.41, 1.27, $p = 0.26$) and 12.8 months (HR 1.30, 95% CI 0.72, 2.37, $p = 0.39$) for distant patients. Similarly, there was no difference in OS, median OS 57.3 months for local patients, 61.6 months (HR 1.17, 95% CI 0.52, 2.65p = 0.71) for regional patients, and 29.2 months for distant patients (Log-rank $p = 0.22$) (Supplemental Fig. 1)

4. Discussion

Over the last decade, there has been increasing evidence for HIPEC utilization in the management of women with recurrent or advanced EOC (Armstrong et al., 2021; van Driel et al., 2018; Spiliotis et al., 2011; Spiliotis et al., 2015; Cascales-Campos et al., 2014; Bakrin et al., 2013; Lei et al., 2020; Morton et al., 2021; Chambers et al., 2020; Costales et al., 2021; Charo et al., 2020). Despite promising data and NCCN inclusion of HIPEC as an option for women with EOC following NACT and IDS, uptake across the United States is limited (Charo et al., 2020). In an analysis of a national claims database from 2016 to 2020, HIPEC was performed in only 0.75% of surgeries for EOC (Charo et al., 2020). Understanding real-world patient behaviors, such as travel distance for HIPEC, will inform our understanding of patients' preferences and how to best serve them during their cancer treatment. Furthermore, data regarding outcomes will allow for improved patient counseling among those who choose to travel for HIPEC procedures.

In this analysis of a prospective registry for women with advanced or recurrent EOC undergoing CRS with HIPEC, we demonstrate that the median travel distance is 57.0 miles, which has been stable over the study period. Additionally, over 20% of patients treated at our institution travelled >100 miles for HIPEC procedures. When perioperative and oncologic outcomes were compared for patients who were local (<50), regional (51–99 miles), or distant (>100 miles), there was no difference in most post-operative complications, length of stay, time to chemotherapy, progression-free survival, or overall survival. Of note, patients who travelled >100 miles had increased rate of re-operation compared to those locally and regionally.

One of the unique, promising aspects of HIPEC for women with advanced or recurrent EOC is the potential for a significant improvement in oncologic outcomes with treatment at a single timepoint. While

Table 3
Perioperative outcomes.

Variable	Local (≤50 miles) (n=60)	Regional (51–99 miles) (n=38)	Distant (≤100 miles) (n=29)	P Value
ICU Admission	7 (11.7)	5 (13.2)	7 (24.1)	0.28
Accordion Post-operative Complications Severity				0.75
None				
Mild	22 (36.7)	20 (52.6)	12 (41.4)	
Moderate	17 (28.3)	10 (26.3)	7 (24.1)	
Severe	13 (21.7)	6 (15.8)	5 (17.2)	
Death	7 (11.7)	2 (5.3)	5 (17.2)	
	1 (1.7)	0 (0.0)	0 (0.0)	
Major Complications				
Re-operation	1 (1.7)	0 (0.0)	3 (10.3)	**0.04**
Anastomotic Leak	2 (3.3)	0 (0.0)	2 (6.9)	0.26
Death	1 (1.7)	0 (0.0)	0 (0.0)	0.99
Venous thromboembolism	1 (1.7)	2 (5.3)	0 (0.0)	0.45
Respiratory Failure	2 (3.3)	1 (2.6)	1 (3.4)	0.99
Myocardial Infarction/ Stroke	0 (0.0)	0 (0.0)	0 (0.0)	–
Minor Complications				
Surgical site infection	4 (6.7)	2 (5.3)	0 (0.0)	0.48
Ileus	5 (8.3)	7 (18.4)	4 (13.8)	0.32
Readmission	7 (11.7)	3 (7.9)	4 (13.8)	0.72
Acute Kidney Injury	7 (11.7)	3 (7.9)	3 (10.3)	0.93
Discharge Disposition				0.19
Home	40 (67.8)	30 (78.9)	26 (89.7)	
Home with Home Health	6 (10.2)	4 (10.5)	3 (10.3)	
Home with Home Physical Therapy	6 (10.2)	1 (2.6)	0 (0.0)	
Skilled Nursing Facility	7 (11.9)	3 (7.9)	0 (0.0)	
Length of Stay	5.0 [4.0, 7.0]	5.0 [3.0, 6.0]	5.0 [4.0, 8.0]	0.71
Time to Chemotherapy	33.0 [28.0, 43.0]	34.0 [29.0, 46.0]	30.0 [27.0, 39.0]	0.50

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 median with interquartile range (25, 75). Bold indicates statistically significant with $p < 0.05$.

a diagnosis of advanced or recurrent EOC portends a poor prognosis, studies have demonstrated that HIPEC at the time of interval CRS is associated with oncologic benefit (van Driel et al., 2018; Spiliotis et al., 2011; Spiliotis et al., 2015; Cascales-Campos et al., 2014; Bakrin et al., 2013; Lei et al., 2020; Morton et al., 2021; Chambers et al., 2020; Costales et al., 2021). In a phase III trial published by Van Driel et al., women with stage III EOC who underwent interval CRS with HIPEC had a survival benefit of 11.8 months compared to those who did not have HIPEC (van Driel et al., 2018). In a recent study of the National Cancer Database of 56,834 women diagnosed with EOC from 2004 to 2016 by Knisely et al., the median travel distance was 14.6 miles (Knisely et al., 2020). In their study, comparable to our findings, travel distance did not impact 30 or 90-day mortality nor long-term oncologic outcomes. In contrast, the median distance traveled by women in our study who received HIPEC was 57.0 miles, which is over three times the median travel distance previously reported for women with EOC (Knisely et al., 2020).

Our findings are consistent with prior studies demonstrating that women with EOC are willing to travel for increased oncologic benefit. In a cross-sectional survey study by Shalowitz et al., 62 women with adnexal masses were queried about their willingness to travel for cancer care if their survival would be positively impacted (Shalowitz et al., 2018). 80% of patients were willing to travel over 50 miles for a survival benefit of 6% (Shalowitz et al., 2018). These results, similar to our own, suggest that women with EOC are willing to seek out and travel for novel treatment strategies that may offer improved survival benefit. This was also demonstrated in women with EOC who enroll in clinical trials at diagnosis (Greenwade et al., 2017). In a study by Greenwade et al., there was no difference in travel distance for women enrolled on trial than those not enrolled on trial, with 39.0% of those traveling over 50 miles (Greenwade et al., 2017). An additional interesting finding is that patients who travelled > 100 miles had increased rate of re-operation compared to patients who travelled shorter distances. While our study did not identify any patient or oncologic factors associated with increased travel distance that may increase risk of complications and need for re-operation, further research is needed to understand socio-economic and psychological reasons that may impact patient decision making for increased travel for cancer treatment and how this impacts post-operative outcomes.

Our study has several limitations. When designing this study, we intentionally did not include a control cohort of women with EOC treated with CRS without HIPEC at our institution. Within the expansive Midwest region that our multi-center hospital network serves, there are numerous treatment facilities for EOC within our institution and numerous excellent hospitals outside of our center. At our facility, in patients undergoing CRS without HIPEC, either due to medical or surgical ineligibility, care may be intentionally coordinated closer to their home. At present, all CRS with HIPEC cases at Cleveland Clinic occur at one centralized location. Notably, the closest facility offering CRS with HIPEC for gynecologic cancer is over 350 miles away, according to HIPECtreatment.com (HIPECtreatment.com, 2020). Therefore, we felt that comparing travel distance for all CRS cases may bias the results, as these patient populations are inherently different. With this in mind, we chose to focus our analysis on the travel distance of women with EOC undergoing CRS with HIPEC and subsequent outcomes. To this end, our study occurred at a high-volume center for women undergoing CRS with HIPEC for advanced or recurrent EOC, and therefore, our surgical and oncologic outcomes may not be reflective of all surgeons and hospital systems.

Due to the nature of utilizing a prospective registry for HIPEC, we are missing important information about patient demographics that may impact travel distance, such as insurance status, familial support systems closer to our institution, and financial considerations, such as income and cost of travel. Additionally, it is possible that post-operative events, including readmissions to outside hospitals, were not fully captured, especially in patients who lived at increased distances from our hospital center. Furthermore, we do not have important qualitative data regarding patient preferences and values for travel distance with use of a

Table 4
Oncologic details.

Variable	PFS				OS			
	Median Months (95% CI)	**1 year** PFS (95% CI)	HR (95% CI)	P Value	Median Months (95% CI)	**3 year** OS (95% CI)	HR (95% CI)	P Value
Local <50 miles	17.4 (10.5–33.0)	58.5 (44.1, 73.0)	–		57.3 (36.0-)	70.8 (52.7–88.9)	–	0.71
Regional 51-99 miles	22.2 (15.6–39.4)	76.1 (61.5, 90.6)	0.72 (0.41, 1.27)	0.26	61.6 (29.2-)	61.9 (42.1, 81.7)	1.17 (0.52, 2.65)	
Distant >100 miles	12.8 (11.6–25.5)	62.2 (42.5, 81.8)	1.30 (0.72, 2.37)	0.39	29.2 (21.7-)	44.6 (17.2, 72.1)		

CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; PFS, progression free survival; OS, overall survival.
P values are displayed as Cox univariate with $p < 0.05$ designating significance. Values with * denotes log-rank P value given sample size and available survival events.

database. Finally, while no statistically different PFS or OS outcomes were determined based on travel distance, the limited follow-up duration of 20.0 months and small sample size impedes our assessment of long-term outcomes, especially OS. Additionally, for the purposes of our analysis and small sample sizes, we intentionally included patients who underwent primary and secondary CRS for PFS and OS analysis, but acknowledge that these cohorts are heterogenous, which may account for the discrepancy in PFS and OS. Additionally, patients who live further from our medical center may be more likely to receive their chemotherapy at outside facilities, including by medical oncologists. In a recent study by Cham and colleagues, fragmentation of care in patients travelling over 50 miles with newly diagnosed ovarian cancer was associated with worse OS. Further study is therefore needed to understand the impact of travel distance and regionalization of care upon oncologic outcomes.

Despite these limitations, our study is the first to evaluate travel distances in women with EOC undergoing HIPEC and contributes important, relevant information to the literature. Our findings demonstrate that women are willing to travel for CRS with HIPEC, with over half of patients traveling at least 50 miles for procedures, which is over three times the travel distance previously reported in large database studies. Importantly, we demonstrate no detriment to perioperative or oncologic outcomes based upon travel distance. We hope our results will inform clinicians in patient counseling for outcomes following HIPEC with CRS in patients who are willing to travel for care. Additionally, we hope these data will guide healthcare institutions in understanding patient demand and willingness to travel for HIPEC procedures.

To conclude, in this analysis of a single-institution prospective registry at a high volume referral center for HIPEC, we demonstrate that women with EOC are traveling for the benefits of HIPEC, with over one-half traveling >50 miles. Our results suggest that women who travel for HIPEC procedures are not at increased risk for perioperative complications or worse oncologic outcomes than those who are local to HIPEC centers. Our findings suggest that women may be willing to seek out and travel for novel therapies for meaningful improvement in overall survival, such as HIPEC, but further research is needed to understand socioeconomic and psychological reasons that may impact patient decision making for increased travel for cancer treatment.

CRediT authorship contribution statement

Laura M. Chambers: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Meng Yao:** Data curation, Writing – original draft, Writing – review & editing. **Molly Morton:** Data curation, Writing – original draft, Writing – review & editing. **Morgan Gruner:** Data curation, Writing – original draft, Writing – review & editing. **Anna Chichura:** Data curation, Writing – original draft, Writing – review & editing. **Anthony B. Costales:** Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Max Horowitz:** Data curation, Writing – original draft, Writing – review & editing. **Peter G. Rose:** Data curation, Writing – original draft, Writing – review & editing. **Chad M. Michener:** Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Project administration, Supervision. **Robert Debernardo:** Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Project administration, Supervision.

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.

References

Aletti, G.D., Dowdy, S.C., Podratz, K.C., Cliby, W.A., 2007. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. Am. J. Obstet. Gynecol. 197 (6), 676.e1–676.e7.

Armstrong, D.K., Alvarez, R.D., Bakkum-Gamez, J.N., et al., 2021. NCCN clinical practice guideline in oncology: ovarian cancer including fallopian tube cancer and primary peritoneal cancer. version 1.

Bakrin, N., et al., 2013. Peritoneal carcinomatosis treated with cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for advanced ovarian carcinoma: A French multicentre retrospective cohort study of 566 patients. Eur. J. Surg. Oncol. 39 (12), 1435–1443.

Bristow, R.E., Chang, J., Ziogas, A., Gillen, D.L., Bai, L., Vieira, V.M., 2015. Spatial analysis of advanced-stage ovarian cancer mortality in California. Am. J. Obstet. Gynecol. 213 (1), 43.e1–43.e8. https://doi.org/10.1016/j.ajog.2015.01.045. Epub 2015 Jan 31.

Cascales-Campos, P.A., et al., 2014. Treatment of microscopic disease with hyperthermic intraoperative intraperitoneal chemotherapy after complete cytoreduction improves disease-free survival in patients with stage IIIC/IV ovarian cancer. Ann. Surg. Oncol. 21 (7), 2383–2389.

Chambers, L.M., Costales, A.B., Crean-Tate, K., Kuznicki, M., Morton, M., Horowitz, M., Jagielo, T., Rose, P.G., Michener, C., Vargas, R., Debernardo, R., 2020. A guide to establishing a hyperthermic intraperitoneal chemotherapy program in gynecologic oncology. Gynecol. Oncol. 158 (3), 794–802.

Charo, L.M., Jou, J., Binder, P., Hohmann, S.F., Saenz, C., McHale, M., Eskander, R.N., Plaxe, S., 2020. Current status of hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer in the United States. Gynecol. Oncol. 159 (3), 681–686.

Chichura, A., Chambers, L.M., Costales, A.B., Yao, M., Gruner, M., Morton, M., Rose, P. G., Vargas, R., Michener, C.M., Debernardo, R., 2021. Impact of intra-operative factors upon perioperative outcomes in women undergoing hyperthermic intraperitoneal chemotherapy for gynecologic cancer. Gynecol. Oncol. S0090-8258 (21)00053-6.

Costales, A.B., Chambers, L., Chichura, A., Rose, P.G., Mahdi, H., Michener, C.M., Yao, M., Debernardo, R., 2021. Effect of platinum sensitivity on the efficacy of hyperthermic intraperitoneal chemotherapy (HIPEC) in recurrent epithelial ovarian cancer. J. Gynecol. Obstet. Hum. Reprod. 50 (5), 101844. https://doi.org/10.1016/j.jogoh.2020.101844.

Daruvala, A., Lucas, F.L., Sammon, J., Darus, C., Bradford, L., 2021. Impact of geography and travel distance on outcomes in epithelial ovarian cancer: a national cancer database analysis. Int. J. Gynecol. Cancer. 31 (2), 209–214.

Google Maps, google.com.

Greenwade, M.M., Moore, K.N., Gillen, J.M., Ding, K., Rowland, M.R., Crim, A.K., Kleis, B., Gunderson, C.C., 2017. Factors influencing clinical trial enrollment among ovarian cancer patients. Gynecol. Oncol. 146 (3), 465–469.

Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J.G., 2009. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J. Biomed. Inform. 42 (2), 377–381.

HIPECtreatment.com, accessed February 2nd, 2020.

Kehoe, S., Hook, J., Nankivell, M., Jayson, G.C., Kitchener, H., Lopes, T., Luesley, D., Perren, T., Bannoo, S., Mascarenhas, M., Dobbs, S., Essapen, S., Twigg, J., Herod, J., McCluggage, G., Parmar, M., Swart, A.-M., 2015. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet (London, England). 386 (9990), 249–257. https://doi.org/10.1016/S0140-6736(14)62223-6.

Knisely, A., Huang, Y., Melamed, A., Tergas, A.I., St. Clair, C.M., Hou, J.Y., Khoury-Collado, F., Ananth, C.V., Neugut, A.I., Hershman, D.L., Wright, J.D., 2020. Travel distance, hospital volume and their association with ovarian cancer short- and long-term outcomes. Gynecol. Oncol. 158 (2), 415–423.

Lei, Z., Wang, Y., Wang, J., Wang, K., Tian, J., Zhao, Y., Chen, L., Wang, J., Luo, J., Jia, M., Tang, H., He, Q., Liao, Q., Yang, X., Guan, T., Wang, L., Cui, S., 2020. Chinese Peritoneal Oncology Study Group (Gynecologic Oncology Study Group). Evaluation of Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy for Stage III Epithelial Ovarian Cancer. JAMA Netw. Open. 3 (8), e2013940.

Morton, M., Chambers, L.M., Costales, A.B., Chichura, A., Gruner, M., Horowitz, M.P., Rose, P.G., Yao, M., Debernardo, R., Michener, C., 2021. 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. Gynecol. Oncol. 160 (1), 45–50.

Shalowitz, D.I., Nivasch, E., Burger, R.A., Schapira, M.M., 2018. Are patients willing to travel for better ovarian cancer care? Gynecol. Oncol. 148 (1), 42–48.

Siegel, R.L., Miller, K.D., Jemal, A., 2020. Cancer statistics. CA Cancer. J. Clin. 70, 7–30.

Spiliotis, J., Vaxevanidou, A., Sergouniotis, F., Lambropoulou, E., Datsis, A., Christopoulou, A., 2011. The role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of recurrent advanced ovarian cancer: a prospective study. J. BUON. 16 (1), 74–79.

Spiliotis, J., Halkia, E., Lianos, E., Kalantzi, N., Grivas, A., Efstathiou, E., Giassas, S., 2015. Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann. Surg. Oncol. 22 (5), 1570–1575.

Stewart, S.L., Cooney, D., Hirsch, S., Westervelt, L., Richards, T.B., Rim, S.H., Thomas, C. C., 2014. The Effect of Gynecologic Oncologist Availability on Ovarian Cancer Mortality. World J. Obstet. Gynecol. 3 (2), 71–77.

Strasberg, S.M., Linehan, D.C., Hawkins, W.G., 2009. The accordion severity grading system of surgical complications. Ann. Surg. 250, 177–186.

van Driel, W.J., Koole, S.N., Sikorska, K., Schagen van Leeuwen, J.H., Schreuder, H.W.R., Hermans, R.H.M., de Hingh, I.H.J.T., van der Velden, J., Arts, H.J., Massuger, L.F.A. G., Aalbers, A.G.J., Verwaal, V.J., Kieffer, J.M., Van de Vijver, K.K., van Tinteren, H., Aaronson, N.K., Sonke, G.S., 2018. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. N Engl. J. Med. 378 (3), 230–240. https://doi.org/10.1056/NEJMoa1708618.

Vergote, I., Tropé, C.G., Amant, F., Kristensen, G.B., Ehlen, T., Johnson, N., Verheijen, R. H.M., van der Burg, M.E.L., Lacave, A.J., Panici, P.B., Kenter, G.G., Casado, A., Mendiola, C., Coens, C., Verleye, L., Stuart, G.C.E., Pecorelli, S., Reed, N.S., 2010. Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIC or IV Ovarian Cancer. N Engl. J. Med. 363 (10), 943–953. https://doi.org/10.1056/NEJMoa0908806.

Villanueva, C., Chang, J., Bartell, S.M., Ziogas, A., Bristow, R., Vieira, V.M., 2019. Contribution of Geographic Location to Disparities in Ovarian Cancer Treatment. J. Natl. Compr. Canc Netw. 17 (11), 1318–1329.