Disparities in Ovarian Cancer Survival at the only NCI-designated Cancer Center in Kansas

By

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Abstract

Ovarian cancer is the fifth most deadly cancer among women and the deadliest gynecologic cancer in the United States. Although it is a relatively rare form of cancer, its toll on morbidity and mortality is not equally distributed. In Maryland, women who reside at distance extremes (< 10 miles and > 50 miles) to an urban NCI-designated cancer center (NCI-CC) are less likely to complete treatment for gynecologic malignancies. In California, women with low socioeconomic status and those who live more than 50 miles from an NCI-CC are less likely to receive guideline-adherent care and have worse ovarian cancer survival. Our objective was to examine the impact of residential distance and socioeconomic status on survival outcomes for patients receiving treatment for ovarian cancer at a frontier-state NCI-CC.

Patients who were treated for ovarian cancer at a single institution from 2010-2015 were identified. Age at diagnosis, insurance status, and distance from the patient's home to the institution were abstracted. Median income was estimated using 2013 American Census Survey. Clinical data including stage at diagnosis, surgical status, chemotherapy cycles, Charlson comorbidity index, dates of diagnosis, recurrence, and death were obtained. Patients treated at other institutions and those with non-epithelial pathology were excluded. Overall survival (OS) and progression free survival (PFS) were analyzed by Kaplan Meier survival curves and cox proportional hazard models using SAS v9.4.

A total of 329 patients were identified, 227 patients completed all care at the institution and 102 patients completed partial care. Among patients who received all their care at the NCI-CC, survival analysis based on distance demonstrated that patients who lived less than 10 miles from the institution had worse survival (p=0.0137). 5-year survival was 37% for patients who lived less than 10 miles from the institution and 57% for those who lived greater than 10 miles away. Lower median income (<$55,268) regardless of distance to institution was also associated with worse survival, p = 0.0210. Among patients who received partial care at the institution, greater than 80% received NCCN guideline adherent care. There was no survival disparity between patients who received all vs partial care at our NCI-CC.

Among patients who received all care for ovarian cancer at our institution, stage at diagnosis, presence of comorbidities, lower median income and residential distance less than 10 was associated with worse overall survival. We report high rates of NCCN guideline adherent care regardless of if all vs partial care was received at our institution.

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Chapter 1: Introduction

Ovarian cancer is the most lethal gynecologic cancer in the United States (US). In 2020, it is estimated that there will be 21,750 new cases of ovarian cancer and 13,940 ovarian cancer deaths [1]. Although, ovarian cancer comprises 2.5% of all cancers diagnosed in women, it is responsible for 5% of female deaths attributed to cancer, making it the fifth leading cause of cancer death in the US [2]. Outcomes from this deadly cancer are not equal across racial/ethnic groups or geographic populations. African American/non-Hispanic Black (NHB) women have the second highest mortality rates (6.6 deaths per 100,000 women) despite relatively low incidence rates (9.4 per 100,000) [2]. Caucasian/non-Hispanic White (NHW) women have the highest rate of ovarian cancer incidence (12.0 per 100,000) and mortality (7.9 deaths per 100,000) [2]. Lower rates of survival in NHB women can be attributed in part to late stage of diagnosis, a lower likelihood of receiving optimal treatment, and the presence of more comorbidities compared with other women [2-7]. National Comprehensive Cancer Network (NCCN) guideline non-adherent care is an independent predictor of inferior overall survival [6]. Median income less than $35,000 is also negatively associated with survival [6]. The three strongest predictors of poor survival outcomes after controlling for non-NCCN guideline adherent care, are NHB race, Medicaid payer status and non-insured status; each accounting for a 30% increased risk of death [6].

Geographic disparities in ovarian cancer survival also exist but are not as well studied as racial/ethnic disparities**.** A recent study has shown that women who reside in the southern US have worse outcomes regardless of race [8]. In California, receipt of NCCN guideline adherent care was independently associated with geographic proximity to a high-volume hospital[9]. NHB race, low socioeconomic status, and geographic location ≥ 50 mi from a

high-volume hospital were independently associated with an increased risk of non-adherent care [9]. Geographic distance from treatment facility has been shown to contribute to disparities in completion of gynecologic cancer treatment [10]. This smaller study (n= 150) at an urban NCI-designated cancer center (NCI-CC) in Baltimore, determined that distance extremes (<10 miles and >50 miles), increased travel time and medical comorbidities were associated with a lower likelihood of treatment completion for gynecologic malignancies [10].

The primary objective of this study is to determine if geographic distance from a single NCI-CC, with a large catchment area that spans the entire state of Kansas and western Missouri, is associated with differences in survival. The secondary objective is to determine rates of NCCN guideline adherent care among patients who received partial care at the NCI-CC.

Chapter 2: Literature Review

Racial disparities in ovarian cancer survival has long been established. The largest study to date, used findings from the CONCORD-2 study and covered 80% of the US population [11]. To analyze ovarian cancer survival by state and race between 2001-2009, data from the Center for Disease Control and Prevention's National Program of Cancer Registries (NPCR) and National Cancer Institutes' Surveillance, Epidemiology and End Results (SEER) Program were used [11]. This study found that ovarian cancer survival was worse for NHB women and did not improve over time in most of the 37 states included [11]. Of the 172,849 women included in this population-based study, none were from the state of Kansas.

Another study completed by Bristow et al used a population-based analysis of National Cancer Data Base (NCDB) records for primary ovarian cancer diagnosed between 1998 to 2002 [6]. Main outcome measures were differences in adherence to NCCN guidelines and overall survival by race and socioeconomic status. Non-NCCN guideline adherent care was an independent predictor of inferior overall survival. Median income less than $35,000 was also negatively associated with survival [6]. The three strongest predictors of poor survival outcomes after controlling for non-NCCN guideline adherent care, were NHB race, Medicaid payer status and non-insured status; each accounting for a 30% increased risk of death [6]. Although this study used a large validated database of over 45,000 patients, information including the specifics of surgical outcome (i.e. residual disease - a predictor of survival), type of number of chemotherapy cycles administered and medical comorbidities were not available. Our proposed research involves patients treated solely at our cancer center; thus, we have access to their entire treatment history

allowing us to better account for differences in surgical outcome, chemotherapy and medical comorbidities.

Geographic disparities in ovarian cancer survival also exist but are not as well studied as racial/ethnic disparities. A recent study has also shown that women who reside in the southern US have worse outcomes regardless of race [8]. In California, receipt of NCCN guidelines adherent care was independently associated with geographic proximity to a high-volume hospital [9]. In this large study of over 11,000 patients diagnosed from 1996-2006, only 45.5% received NCCN guideline adherent care. NHB race, low socioeconomic status, and geographic location ≥ 50 mi from a high-volume hospital were independently associated with an increased risk of non-adherent care [9]. Although this study used the validated California Cancer Registry, medical comorbidity information was not available and the census block of residence for each subject was used rather than exact residence due to de-identification. Additionally, the California Cancer Registry did not capture physician volume or physician specialty. These potential confounders are not be present in our study because we have access to the identified information of all patients in the study and the specialties of treating physicians. Geographic distance from treatment facility has been shown to contribute to disparities in completion of gynecologic cancer treatment [10]. In this smaller study (n = 150) describing incident gynecologic cancer diagnoses between 2009-2011 at an urban NCI-designated cancer center (NCI-CC) in Baltimore, distance extremes (<10 miles and >50 miles), increased travel time and medical comorbidities were associated with a lower likelihood of treatment completion for gynecologic malignancies [10]. This study was of all

gynecologic cancers, not specifically ovarian cancer and did not examine survival outcomes.

NHB women and those who live farther away from an NCI-CC have been shown to have worse ovarian cancer outcomes. Social determinants of health, including community and social contextual factors have also been shown to affect cancer outcomes. A secondary analysis of data from an ovarian cancer clinical trial sought to correlate health-related quality of life with social determinants of health [12]. This study of over 900 patients found no correlation between race, distance traveled and community socioeconomic status to physical well-being, functional well-being, ovarian-specific well-being, and trial outcome index [12]. However, higher health-related quality of life was associated with private insurance. This study had limitations; it did not evaluate survival outcomes and was completed using secondary data from ovarian cancer patients enrolled in a clinical trial, which introduces selection bias and likely represents a homogenous group. The authors report the study population was 90% NHW with relatively little variability in zip code characteristics. Our catchment area spans several counties and zip codes; thus, we expect to have a heterogenous group of patients to better evaluate the association between socioeconomic status and survival.

2.1 Population

The University of Kansas Cancer Center (KUCC) is the only NCI-CC in the state of Kansas and serves a large catchment area. KUCC's catchment area includes the entire state of Kansas (105 counties) and 18 counties in Western Missouri. Of the 123 counties, 96 are either rural or frontier counties, and include significantly underserved communities,

largely elderly rural NHWs, Native Americans, and immigrant Asia populations. Yet, KUCC is in the urban core of Kansas City that includes an established urban NHB and a rapidly growing Hispanic population. KUCC is between 190 and 594 miles from the nearest 6 current NCI-CCs. Therefore, patients travel long distances to seek care at this tertiary NCI-CC.

In the state of Kansas, the incidence of ovarian cancer is similar to the national average at 11.4 per 100,000 and the mortality is rate is 7.1 per 100,000 [13] However, there is a gap in knowledge regarding the impact of racial/ethnic and geographic classifications on ovarian cancer survival in Kansas. Additionally, rates of the receipt of NCCN guideline adherent care is also unknown. At KUCC, we are uniquely positioned to investigate both racial/ethnic and geographic disparities in ovarian cancer because of the broad urban, rural and frontier populations we serve. The primary objective of this study is to determine the impact of race and geographic classification in women treated for ovarian cancer at KUCC over a 5-year period (2010-2015). We will also determine the rate of NCCN-guideline adherent care for patients who received all vs partial care at KUCC.

Chapter 3: Study Design

3.1 Methods

Institutional Review Board approval for the study was obtained through the University of Kansas Medical Center. Using an innovative search discovery tool “HERON” (Healthcare Enterprise Repository for Ontological Narration) patients with a diagnosis of ovarian, fallopian tube and primary peritoneal cancer (using ICD-9 and ICD-10 codes) between 2010-2015 were identified. Additionally, the “C3OD” Curated Clinical Cancer Outcomes database, the institution’s cancer registry, was also queried for ICD-O-3 codes pertaining to ovarian, fallopian tube and primary peritoneal cancers between 2010-2015. After patients in both datasets were identified, chart review was used to exclude patients with recurrent disease, non-epithelial histology, synchronous tumors and patients who did not receive any care at the institution (i.e. presented for second opinion), appendix A. Patients who received only chemotherapy, had reoperation for staging or primary surgical staging then additional care (ie. adjuvant chemotherapy) at an outside institution were categorized as receiving partial care at KUCC.

Manual chart review was completed to abstract clinical characteristics including, age, stage at diagnosis, date of diagnosis, type of chemotherapy and number of cycles, presence of comorbidities at diagnosis, dates of recurrence (if any), and death (if deceased) of patients who met criteria. Platinum resistance was defined as recurrence less than 6 months following the end of chemotherapy. Operative reports were reviewed to determine surgical debulking status of 1) no residual disease, 2) optimal debulking (< 1cm of residual disease) or 3) suboptimal debulking (>1cm of residual disease). Baseline comorbidity score was computed using Charlson Comorbidity Index (CCI) to account for baseline health conditions, scores for metastatic cancer was excluded since all patients

in the study have cancer. Receipt of stage-specific NCCN-guideline adherent care was determined according to the guidelines of 2008 [14]. NCCN-guideline adherent surgical care for advanced stage disease includes 1) laparotomy/total abdominal hysterectomy, removal of bilateral ovaries and fallopian tubes with comprehensive staging or 2) unilateral removal of ovary and fallopian tube for clinical stage 1A-1C with comprehensive staging if patient desires fertility 3) cytoreductive surgery if clinical stage II, III or IV or 3) interval cytoreduction for patients with bulky stage III/IV disease who are not surgical candidates. NCCN-guideline adherent chemotherapy treatment includes completion of 6 cycles of multiagent chemotherapy including intravenous taxane and platinum agent for stage II-IV. For stage IA or IB, grade 1 observation was considered guideline adherent. For stage IA or IB, grade 2 observation or 3-6 cycles IV taxane/platinum chemotherapy was considered guideline adherent. For stage IA or IB grade 3 and stage IC any grade, 3-6 cycles of intravenous taxane/platinum chemotherapy was guideline adherent.

To evaluate the impact of racial/ethnic and geographic classification on survival outcomes among patients who received all their treatment for ovarian cancer at the institution, we collected demographic information including self-reported race and geographic distance to KUCC (miles). Patients were stratified by <10 miles to KUCC, 10-50 miles and greater than 50 miles to the institution based on previous literature [10]. Due to sample size and concerns for survival curve proportionality assumptions (survival curves were not parallel), patients were recategorized into greater than and less than 10 miles to the institution. To evaluate possible confounders, insurance status was obtained, Medicaid and Medicare were categorized as public insurance. Median income was estimated using the 2013 American Census Survey tables by matching on state, county, tract and block

group (or zip code if the address is a P.O. Box). Primary outcomes were overall survival (time from diagnosis to death) and progression free survival (time from treatment completion to recurrence). For patients who were known to be alive at the time of data collection (10/2019), time to outcome was censored at date of last clinical encounter. Date of death was obtained through manual chart review using our electronic health record system with access to integrated electronic medical records of other institutions (Epic Care Everywhere). Additionally, HERON and C3OD databases are integrated with the social security death index to provide date of death for patients who died outside of our health system and integrated records system.

3.2 Statistical Methods

Descriptive statistics were used for patient demographics (including age, race and geographic classification) and clinical characteristics. Chi-squared or Fisher's exact test were used to assess differences between categorical variables. Survival curves for overall survival and progression free survival were generated using the Kaplan-Meier estimate of survival probability and analyzed using the log rank test. Survival proportionality assumptions were examined. We conducted stratified analyses by geographic classification, and median income to evaluate the individual effect on mortality. Cox proportional hazards model were fitted for covariates and known predictors of poor survival including stage at diagnosis, age and cytoreductive status. Statistical significance was set to a p-value <0.05.

Chapter 4: Results: All care

4.1 Demographic and Clinical Factors

A total of 329 patient met study criteria, 227 received all care for ovarian cancer at KUCC and 102 patients received partial care at KUCC. Of the 227 patients who received all their care at the institution, 51 patients lived within 10 miles and 176 lived greater than 10 miles from the institution (Table 1). Approximately 88% of patients were white with an estimated median income of $55,268. Mean age and age group distribution was similar between both groups. More non-white patients lived within 10 miles than greater than 10 miles from the institution, p =0.0007. Most patients presented with papillary serous histology (%) and stage III disease (%) at diagnosis. The vast majority of patients received NCCN guideline adherent care (84%) and underwent optimal cytoreductive surgery (80%). However, more patients who lived greater than 10 miles away received optimal cytoreductive therapy than those who lived less than 10 miles away, 83.5% vs. 67%, p=0.0324. When stratified by race, non-white patients had lower rates of optimal cytoreduction and higher rates of not receiving surgery (Table 2). There were no other demographic and clinical differences by race noted. There was no difference in receipt of NCCN guideline adherent care by distance to the institution. However, there was a difference in receipt of NCCN guideline adherent care by stage (Table 3).

4.2 Decreased overall survival among patients who live less than 10 miles to institution.

Among patients who received all their ovarian cancer care at KUCC, median progression free survival was 26 months and median overall survival was 64 months. There was no difference in progression free survival by distance to the institution (Figure 1). Patients who lived less than 10 miles to the institution had worse overall survival than those that lived greater than 10 miles away, p = 0.0137 (Figure 2). There was a 1.67 increased risk

of death among patients who lived less than 10 miles to the institution, 95% CI 1.10-2.52, p= 0.0153. There was no difference in progression free survival by distance to the institution. The 5-year survival rate was 37% for patients who lived less than 10 miles to the institution and 57% for those who lived greater than 10 miles away.

4.3 Comorbidities and lower estimated median income associated with increased risk of death in ovarian cancer patients.

Patients with lower estimated median income had worse overall survival than patients with higher median income, p=0.0210 (Figure 3). There was no difference in survival by insurance status, data not shown. After controlling for age, non-white race, late stage disease at diagnosis, Charlson Comorbidity Index (CCI), lower estimate median income and suboptimal cytoreduction, distance less than 10 miles was not associated with an increased risk of death (Table 4). CCI was associated with a 1.20 increased risk of death, 95% CI (1.021 – 1.418), p =0.0274. There was no difference in survival when stratified by CCI, data not shown. Estimated median income of less than $55,268 was also associated with a 1.52 increased risk of death, 95% CI (1.005 – 2.292), p = 0.0473. Non-white race and age at diagnosis was not associated with an increased risk of death in this cohort.

Table 1. Demographic and clinical factors by distance.

	Overall (%) n = 227	<10 miles (%) n = 51	>10 miles (%) n = 176	p-value
Age in years (mean) ± SD	60.6 ± 11.0	60.6 ± 11.1	60.6 ± 11.0	0.9999
Age in years				0.9497
< 65	137 (60)	31 (61)	106 (60)	
65-75	65 (29)	15 (29)	50 (28.5)	
>75	25 (11)	5 (10)	20 (11.5)	
Race				**0.0007**
White	200 (88)	38 (75)	162 (92)	
Non-white	27 (12)	13 (25)	14 (8)	
Insurance status				0.2881
Private	94 (41)	18 (35)	76 (43)	
Public (Medicaid, Medicare)	127 (56)	32 (63)	95 (54)	
Unknown	6 (3)	1 (2)	5 (3)	
Median Income				0.2306
Less than $55,268	112 (49)	28 (55)	84 (47)	
More than $55,268	109 (48)	20 (39)	89 (51)	
Unknown	6 (3)	3 (6)	3 (2)	
FIGO Stage				0.5591
I	47 (21)	8 (16)	39 (22)	
II	15 (7)	2 (4)	13 (8)	
III	132 (58)	33 (64)	99 (56)	
IV	33 (14)	8 (16)	25 (14)	
Histology				0.8686[#]
Papillary Serous	168 (74)	41 (80)	127 (72)	
Endometrioid	21 (9)	4 (8)	17 (10)	
Clear Cell	14 (6)	3 (6)	11 (6)	
Mucinous	13 (6)	1 (2)	12 (7)	
Carcinosarcoma	2 (1)	0 (0)	2 (1)	
Undifferentiated	7 (3)	2 (4)	5 (3)	
Mixed cell	2 (1)	0 (0)	2 (1)	
Charlson Comorbidity Index				0.6250
0	27 (12)	6 (12)	21 (12)	
1	47 (21)	13 (25)	34 (19)	
2+	153 (67)	32 (63)	121 (69)	
Cytoreduction Status				**0.0324**[#]
Optimal (<1cm)	181 (80)	34 (67)	147 (83.5)	
Suboptimal (>1cm)	34 (15)	13 (25)	21 (12)	
Unknown	1 (0.5)	0 (0)	1 (0.5)	
No surgery	11 (5)	4 (8)	7 (4)	
Neoadjuvant Chemotherapy				0.3633
Yes	36 (16)	6 (12)	30 (17)	
No	191 (84)	45 (88)	146 (83)	
NCCN* guideline adherent care				0.6914
Yes	191 (84)	42 (82)	149 (85)	
No	36 (16)	9 (18)	27 (15)	

*National Comprehensive Cancer Network (NCCN)

[#]Fisher's exact test used due to small sample size; chi-square test used otherwise.

Table 2. Demographic and clinical factors by race.

	Overall (%) n = 227	White Race (%) n = 200	Non-white race[#] (%) n = 27	p-value
Age in years (mean) ± SD	60.6 ± 11.0	60.9 ± 10.9	57.7 ± 10.9	0.1495
Age in years				0.3501
< 65	137 (60)	117 (58.5)	20 (74)	
65-75	65 (29)	60 (30)	5 (19)	
>75	25 (11)	23 (10.5)	2 (7)	
Insurance status				0.3094
Private	94 (41)	81 (40.5)	13 (48)	
Public (Medicaid, Medicare)	127 (56)	115 (57.5)	12 (44)	
Unknown	6 (3)	4 (2)	2 (7)	
Median Income				0.0971
Less than $55,268	112 (49)	96 (48)	16 (59)	
More than $55,268	109 (48)	101 (50.5)	8 (30)	
Unknown	6 (3)	3 (1.5)	3 (11)	
FIGO Stage				0.1442
I	47 (21)	42 (21.5)	4 (15)	
II	15 (7)	14 (7)	1 (4)	
III	132 (58)	118 (59)	14 (52)	
IV	33 (14)	25 (12.5)	8 (30)	
Histology				0.9738
Papillary Serous	168 (74)	148 (72.5)	23 (85)	
Endometrioid	21 (9)	19 (9.5)	2 (7)	
Clear Cell	14 (6)	13 (6.5)	1 (4)	
Mucinous	13 (6)	12 (6)	1 (4)	
Carcinosarcoma	2 (1)	2 (1)	0 (0)	
Undifferentiated	7 (3)	7 (3.5)	0 (0)	
Mixed cell	2 (1)	2 (1)	0 (0)	
Charlson Comorbidity Index				0.1872
0	27 (12)	21 (10.5)	6 (22)	
1	47 (21)	43 (21.5)	4 (15)	
2+	153 (67)	136 (68)	17 (63)	
Cytoreduction Status				**0.0137**
Optimal (<1cm)	181 (80)	163 (81.5)	18 (67)	
Suboptimal (>1cm)	34 (15)	30 (15)	4 (15)	
Unknown	1 (0.5)	1 (0.5)	0 (0)	
No surgery	11 (5)	6 (3)	5 (19)	
Neoadjuvant Chemotherapy				0.1572
Yes	36 (16)	29 (14.5)	7 (26)	
No	191 (84)	171 (85.5)	20 (74)	
NCCN* guideline adherent care				0.3972
Yes	191 (84)	170 (85)	21 (78)	
No	36 (16)	30 (15)	6 (22)	

*National Comprehensive Cancer Network (NCCN)
[#]Non-white race: 18 Black, 5 Asian, 8 Latina and 6 'other'
Fisher's exact test used due to small sample size.

Table 3. NCCN guideline adherent care received by stage.

	NCCN adherent (%) n = 191	NCCN non-adherent* (%) n =36	p- value[#]
FIGO Stage			0.0015
I	45 (24)	2 (6)	
II	14 (7)	1 (3)	
III	111 (58)	21 (58)	
IV	21 (11)	12 (33)	

*Includes 19 patients that died prior to completion of treatment.
[#]Fisher's exact test.

Table 4. Adjusted all-cause mortality.

Variables	Hazard Ratio*	95% CI	p-value
< 10 miles to NCI-CC	1.19	0.751 – 1.902	0.4511
Age at diagnosis	0.99	0.968 – 1.017	0.5458
Non-white race	0.80	0.406 – 1.559	0.5048
Late Stage (III/IV)	5.43	2.577 – 11.437	**<0.001**
Charlson Comorbidity Index (CCI)	1.20	1.021 – 1.418	**0.0274**
Lower Median Income <$55,268	1.52	1.005 – 2.292	**0.0473**
Suboptimal cytoreduction	1.99	1.246 – 3.198	**0.0040**

*Age and CCI are continuous variables, all others categorical.

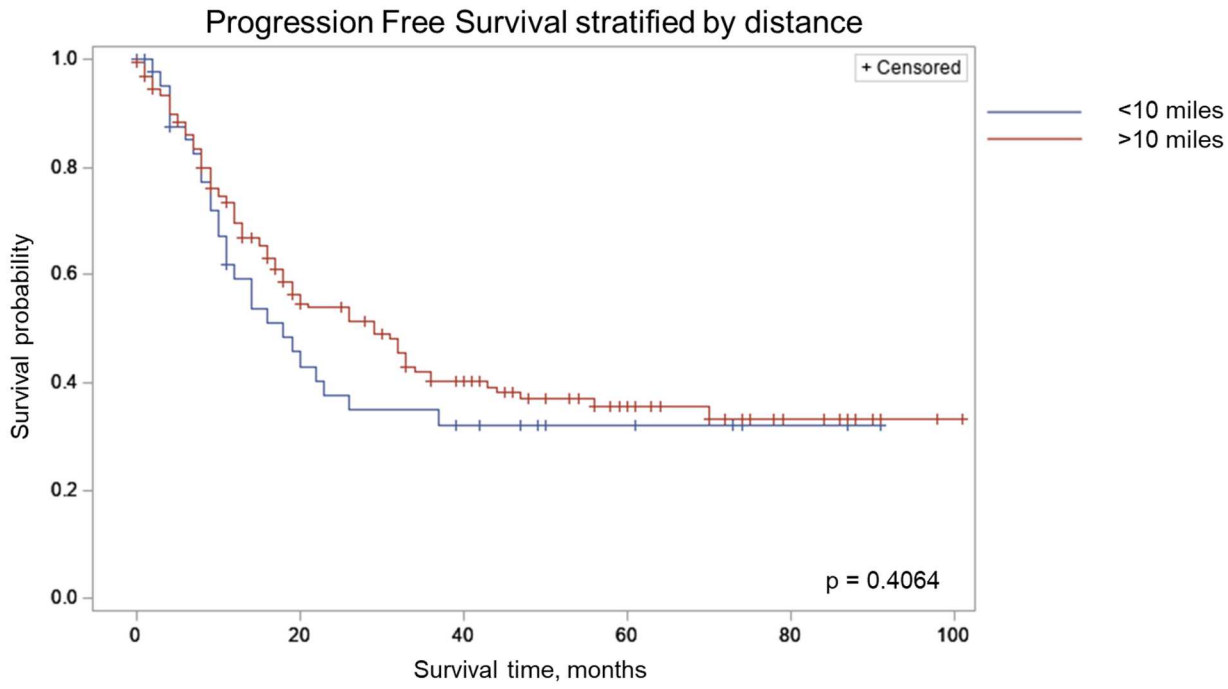

Figure 1. Progression free survival by geographic distance.

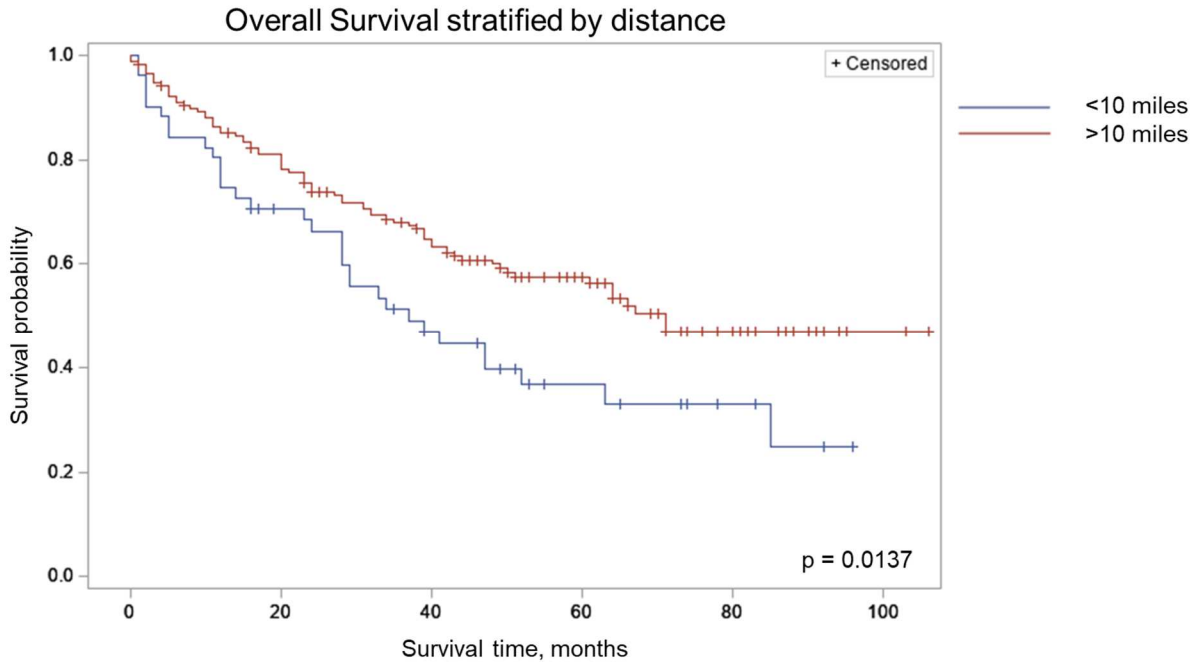

Figure 2. Overall survival by geographic distance.

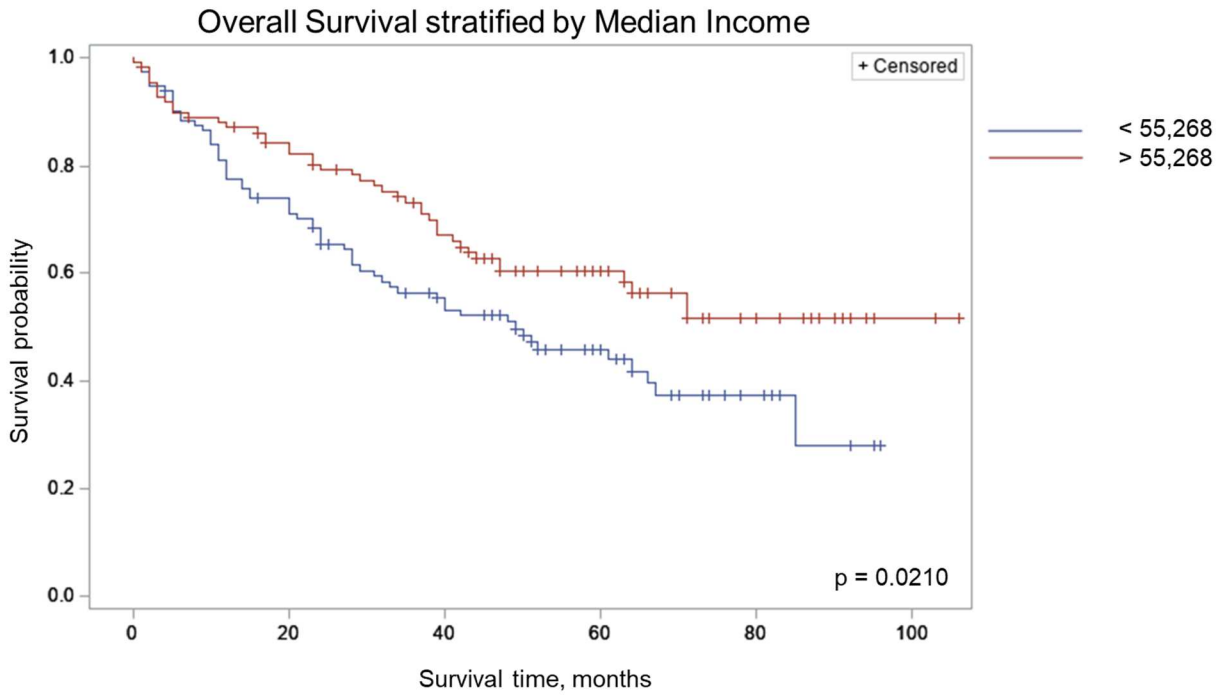

Figure 3. Overall survival by estimated median income.

Chapter 5: Results: Partial care

5.1 Demographic and Clinical Factors

Of the 102 patients who received partial care at the institution, 17 (17%) received chemotherapy alone, 11 (11%) had reoperation for staging surgery and 75 (74%) had primary staging surgery alone at the institution. Like the all care cohort, 90% of patients were white with an estimated median income of $51,667 (Table 5). The majority of patients presented with papillary serous histology (70%) and late stage ovarian cancer (67%). 74% of patients underwent optimal cytoreductive surgery and only 9% received neoadjuvant chemotherapy. More than half (55%) of patients had a CCI of greater than 2.

5.2 Older age, higher CCI and advanced stage disease more likely to receive non-NCCN guideline adherent care.

Among patients who received partial ovarian cancer care at KUCC, median overall survival was 57 months. Most patients (81%) received NCCN guideline adherent care. Patients who received non-NCCN guideline adherent care were older (age >75), had higher CCI values and advanced stage disease at diagnosis as compared to patients who received NCCN guideline adherent care (Table 5). There was no difference in race, insurance status, histology, median income, cytoreduction status or receipt of neoadjuvant therapy by NCCN guideline adherent status. There was no difference in survival based on distance to NCI-CC among patients who received partial care (data not shown).

4.3 No difference in overall survival among patients who received all or partial care at NCI-CC.

There was no difference in race, estimated median income and insurance status of patients who received all vs partial care at NCI-CC. However, patients who received partial care were more likely to live greater than 10 miles away 95% v. 78%, $p < 0.0001$. Patients who received all care at KUCC had higher CCI and were more likely not to have had surgery (Table 6). Of the 11 patients who did not receive surgery, 4 had neoadjuvant chemotherapy and died prior to planned surgery, 2 had progression of disease on neoadjuvant chemotherapy and 7 had chemotherapy only without plan for surgery due to patient preference or patient being deemed not a surgical candidate. However, there was no difference in receipt of NCCN guideline adherent care between groups. There was no difference in all-cause overall survival among patients who received all or partial care at KUCC, $p=0.3144$ (Figure 4).

Table 5. Demographic and clinical factors by NCCN guideline adherence.

	Overall (%) n = 102	NCCN* Adherent n = 83	NCCN non-adherent n = 19	p-value
Age in years (mean) ± SD	61.7 ± 11.9	60.3 ± 11.6	67.9 ± 11.4	**0.0159**
Age in years				**0.0173**
< 65	66 (65)	58 (70)	8 (42)	
65-75	23 (22)	18 (22)	5 (26)	
>75	13 (13)	7 (8)	6 (32)	
Race				0.6834
White	92 (90)	74 (89)	18 (95)	
Non-white	10 (10)	9 (11)	1 (5)	
Insurance status				0.1324
Private	44 (45)	37 (49)	7 (32)	
Public (Medicaid, Medicare)	43 (44)	30 (39)	13 (59)	
Unknown	11 (11)	9 (12)	2 (9)	
Median Income				0.1902
Less than $51,667	48 (47)	36 (43)	12 (63)	
More than $51,667	47 (46)	41 (49)	6 (32)	
Unknown	7 (7)	6 (7)	1 (5)	
FIGO Stage				**0.0124**
I	26 (25)	25 (30)	1 (5)	
II	8 (8)	7 (9)	1 (5)	
III	52 (51)	36 (43)	16 (85)	
IV	16 (16)	15 (18)	1 (5)	
Histology				0.9859
Papillary Serous	72 (70)	57 (69)	15 (79)	
Endometrioid	10 (10)	9 (11)	1 (5)	
Clear Cell	7 (7)	6 (7)	1 (5)	
Mucinous	5 (5)	4 (5)	1 (5)	
Carcinosarcoma	6 (6)	5 (6)	1 (5)	
Undifferentiated	0 (0)	0 (0)	0 (0)	
Mixed cell	2 (2)	2 (2)	0 (0)	
Charlson Comorbidity Index				**0.0451**
0	23 (22.5)	20 (24)	3 (16)	
1	23 (22.5)	22 (27)	1 (5)	
2+	56 (55)	41 (49)	15 (79)	
Cytoreduction Status				0.9038
Optimal (<1cm)	76 (74)	62 (75)	14 (74)	
Suboptimal (>1cm)	19 (19)	15 (18)	4 (21)	
Unknown	7 (7)	6 (7)	1 (5)	
Neoadjuvant Chemotherapy				0.2031
Yes	9 (9)	9 (11)	0 (0)	
No	93 (91)	74 (89)	19 (100)	

*National Comprehensive Cancer Network (NCCN)
Fisher's exact test used due to small sample size.

Table 6. Demographic and clinical factors by care received at NCI-CC.

	Overall (%) n = 329	All Care n = 227	Partial Care n = 102	p-value
Age in years (mean) ± SD	62.6 ± 11.7	62.6 ± 11.7	61.7 ± 11.9	0.5364
Age in years				0.5033
< 65	203 (62)	137 (60)	66 (65)	
65-75	88 (27)	65 (29)	23 (22)	
>75	38 (11)	25 (11)	13 (13)	
Race				0.5789
White	292 (89)	200 (88)	92 (90)	
Non-white	37 (11)	27 (12)	10 (10)	
Insurance status				0.1415
Private	171 (52)	127 (56)	44 (43)	
Public (Medicaid, Medicare)	141 (43)	94 (41)	47 (46)	
Unknown	17 (5)	6 (3)	11 (11)	
Median Income				0.5396
Less than $54,778	158 (48)	108 (48)	50 (49)	
More than $54,778	158 (48)	113 (49)	45 (44)	
Unknown	13 (4)	6 (3)	7 (7)	
Distance to NCI-CC				**<0.0001**
< 10 miles	56 (17)	51 (22)	5 (5)	
> 10 miles	273 (83)	176 (78)	97 (95)	
FIGO Stage				0.6619
I	73 (22)	47 (21)	26 (25)	
II	23 (7)	15 (7)	8 (8)	
III	184 (56)	132 (58)	52 (51)	
IV	49 (15)	33 (14.5)	16 (16)	
Histology				0.0793[#]
Papillary Serous	240 (73)	168 (74)	72 (70.5)	
Endometrioid	31 (9)	9 (21)	10 (10)	
Clear Cell	21 (6)	14 (6)	7 (7)	
Mucinous	18 (5)	13 (6)	5 (5)	
Carcinosarcoma	8 (2)	2 (0.5)	6 (6)	
Undifferentiated	7 (2)	7 (3)	0 (0)	
Mixed cell	4 (1)	2 (0.5)	2 (2)	
Charlson Comorbidity Index				**0.0287**
0	50 (15)	27 (12)	23 (23)	
1	70 (21)	47 (21)	23 (23)	
2+	209 (64)	153 (67)	56 (55)	
Cytoreduction Status				**0.0004[#]**
Optimal (<1cm)	257 (78)	181 (80)	76 (75)	
Suboptimal (>1cm)	53 (16)	34 (15)	19 (19)	
Unknown	8 (2)	1 (0.5)	7 (7)	
No surgery	11 (3)	11 (5)	0 (0)	
Neoadjuvant Chemotherapy				0.0859
Yes	45 (14)	36 (16)	9 (9)	
No	284 (86)	191 (84)	93 (91)	
NCCN* adherent care				0.5337
Yes	274 (83)	191 (84)	83 (81)	
No	55 (17)	36 (16)	19 (19)	

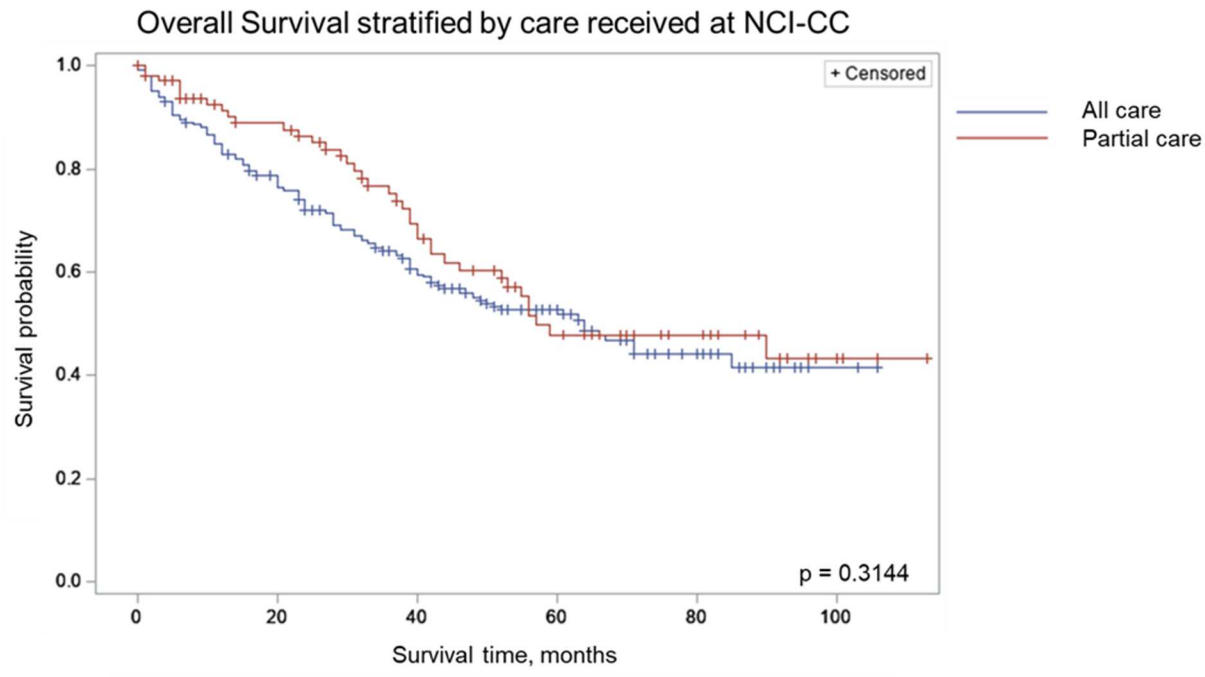

Figure 4. Overall survival by care received from NCI-CC.

Chapter 6: Discussion

Patients with newly diagnosed ovarian cancer often travel long distances to receive care. KUCC is between 190 and 594 miles from the nearest 6 NCI-CCs and our catchment area spans the entire state of Kansas and western Missouri. Thus, patients often travel long distances to receive care at our institution. Unlike other studies that demonstrate residential distance greater than 50 miles to be associated with worse outcomes, our study has shown that geographic proximity (<10 miles) is associated with worse overall survival for patients who receive all their care at our institution.

Our NCI-CC is located in Wyandotte county, Kansas, which has the worst health outcomes in the state of Kansas, including the highest risk of premature death, low birthweight, obesity and physical inactivity [15]. Wyandotte county Kansas also has the highest number of uninsured residents and income inequality in the state. In prior studies, geographic disparities in ovarian cancer were also associated with lower socioeconomic status and NHB race [6]. Consistent with this finding, our study has shown that lower median income is associated with decreased overall survival and is a risk factor for mortality.

Although race was not associated with worse overall survival, compared with white women, non-white women were more likely to live closer to the institution and had lower rates of optimal debulking. It is likely that the small percentage of non-white patients (12%) was not adequate to detect a difference in survival based on race. Despite this, it is notable that non-white patients and those who lived within 10 miles had lower rates of optimal debulking and higher rates of not receiving any surgical care. This result provides a window into potential disparities in our patients and is consistent with a previous study in Southern Alabama where NHB patients had lower rates of optimal debulking [16].

Multiple prior studies have shown that NHB race is associated with inequity in treatment, including delays in chemotherapy initiation and decreased rates of surgical staging [3, 6, 7, 17, 18]. Recently, Dilley et al. showed that NHB race was also associated with higher medical comorbidities and lower rates of optimal cytoreduction [19]. In that study, after controlling for age, stage, CCI and suboptimal cytoreduction, NHB was still associated with worse survival, however, they did not account for socioeconomic status. In our study, there was no difference in presence of comorbidities by distance to the institution or by race.

After controlling for age at diagnosis, non-white race, late stage at diagnosis, presence of comorbidities, median income and suboptimal cytoreduction; geographic distance was not an independent predictor of worse overall survival. Still, given the association between geographic distance, median income and race, geographic distance may be a surrogate measure for neighborhood socioeconomic status in this cohort. A previous study in Cook County, Illinois has shown that neighborhood disadvantage, characterized by lack of economic resources, education, employment and health care, is significantly associated with worse ovarian cancer survival [20]. In that study, adjusting for clinical factors attenuated but did not completely account survival disparities, however, they did not include adjustments for cytoreduction status or comorbid conditions.

NCCN guideline adherent care for ovarian cancer is a validated measure of quality cancer care and improved survival [21]. Geographic disparities in ovarian cancer survival have been associated with receipt of NCCN guideline adherent care. In California, only 45% of patients received NCCN guideline adherent care. In that study, geographic proximity to high-volume hospitals was associated with receiving NCCN guideline adherent care[9].

We found that receipt of NCCN guideline adherent care was above 80% regardless distance to the institution or care received (all vs partial). Patients who did not receive NCCN guideline adherent care often had more comorbid diseases, were older, presented with late stage disease, were not surgical candidates or declined surgical management.

Our NCI-CC is the only NCI-designated cancer center in the region; thus, patients often present to our institution for partial care and receive the rest of their care at institutions closer to home. This is supported by the finding that 95% of patients who received partial care lived greater than 10 miles from the institution and 75% of our partial care patients had primary staging surgery at our institution then chemotherapy at outside institutions. Although patients received partial care at our NCI-CC, our fellowship-trained gynecologic oncologists often direct cancer care in coordination with the local medical oncologist. This is not uncommon since greater than 70% of gynecologic oncologist practice in urban settings [22]. When surveyed about solutions to overcome barriers to care for patients who live outside of urban centers, gynecologic oncologists believed that the best solution was to coordinate local and centralized services [22]. For instance, patients would travel for high complexity components of care, such as surgery, with routine chemotherapy or radiation treatments being coordinated locally. Our study is the first to our knowledge to report that patients receive NCCN guideline adherent care at similar rates regardless of whether they received all or partial ovarian cancer care at an NCI-CC. Similarly, we found no difference in survival among patients who received all vs partial care at our institution.

In summary, we report high rates of NCCN guideline adherent care for ovarian cancer and reports no difference in survival based on care (all vs partial) received at a single NCI-CC that serves a large catchment area. Patients who live in geographic proximity to

the institution have an increased risk of death associated with lower socioeconomic status and lower rates of optimal cytoreduction. Consistent with prior studies, advanced stage at diagnosis, presence of comorbidities and suboptimal cytoreduction is associated with an increased risk of death in this cohort. This study highlights the importance of mitigating disparities in survival outcomes and has potentially identified an actionable disparity in rates of optimal debulking.

Strengths.

To our knowledge, this is the first study to describe ovarian cancer survival outcomes and NCCN guideline adherence among women in Kansas. A strength of our analysis is that it was performed at a single NCI-CC with a catchment area that encompasses an entire understudied population—the state of Kansas which is not represented in national databases (i.e. SEER). This study leverages two independent databases, HERON and C3OD, to ensure a complete cohort of patients treated during the study period. Complete chart review also allowed us to include detailed variables such as tumor cytoreduction status, patient comorbid conditions, physician volume, physician specialty that were often lacking in prior studies.

Limitations.

This is a retrospective study that has inherent potential for errors in reporting. The retrospective nature of this study also makes it impossible to control for unknown potential confounders or variables. Additionally, due to low numbers of non-white patients, NHB, Asian and Latina women were grouped into one group (non-), which does not adequately address racial heterogeneity.

To estimate median income, we used the census data from the block group of the patient's residence not their actual income data. This might lead to an over or underestimation of median income for subjects in the study. However, there is no other practical way to generate income data for this type of study.

For patients in the partial care group, we may not have complete data for ovarian cancer recurrence because patients may not return to our institution for treatment but will likely continue to receive treatment from an outside oncologist. Since our databases are integrated with the social security death index, we believe our overall survival rates are as accurate as possible.

Considerations for Future Research.

Our cohort consists of patients who received care at our NCI-CC, thus, it is not possible to determine outcomes for patients without any access to care. To determine the true benefit of receiving care at an NCI-CC and rates of NCCN guideline adherence in the catchment area, it is important to evaluate outcomes for patients who did not receive any care at an NCI-CC. Further studies are warranted to determine ovarian cancer outcomes and rates of NCCN guideline adherent care in Kansas using state-level cancer registry data.

We have described potential disparities in treatment for patients who live less than 10 miles to the institution. Disparities due to social determinants of health of patients who reside in Wyandotte County, Kansas may be better assessed with qualitative studies that can determine barriers to care, economic stability, educational deficits and neighborhood environments.

One actionable factor that may contribute to disparities among our patients is receipt of optimal cytoreduction, it is important to be cognizant of this disparity and make all efforts to ensure patients have the best chance of having an optimal cytoreductive surgery. Dilley et al. reported that in response to finding similar results among their patients, they performed a quality improvement project in which providers utilized a checklist to assess perioperative morbidity to reinforce decisions to pursue neoadjuvant chemotherapy instead of cytoreduction surgery [19]. Following this intervention, they report an increase in their rates of optimal cytoreduction [23]. A similar intervention, following a standard algorithm could be implemented within our practice to mitigate disparities in optimal cytoreduction.

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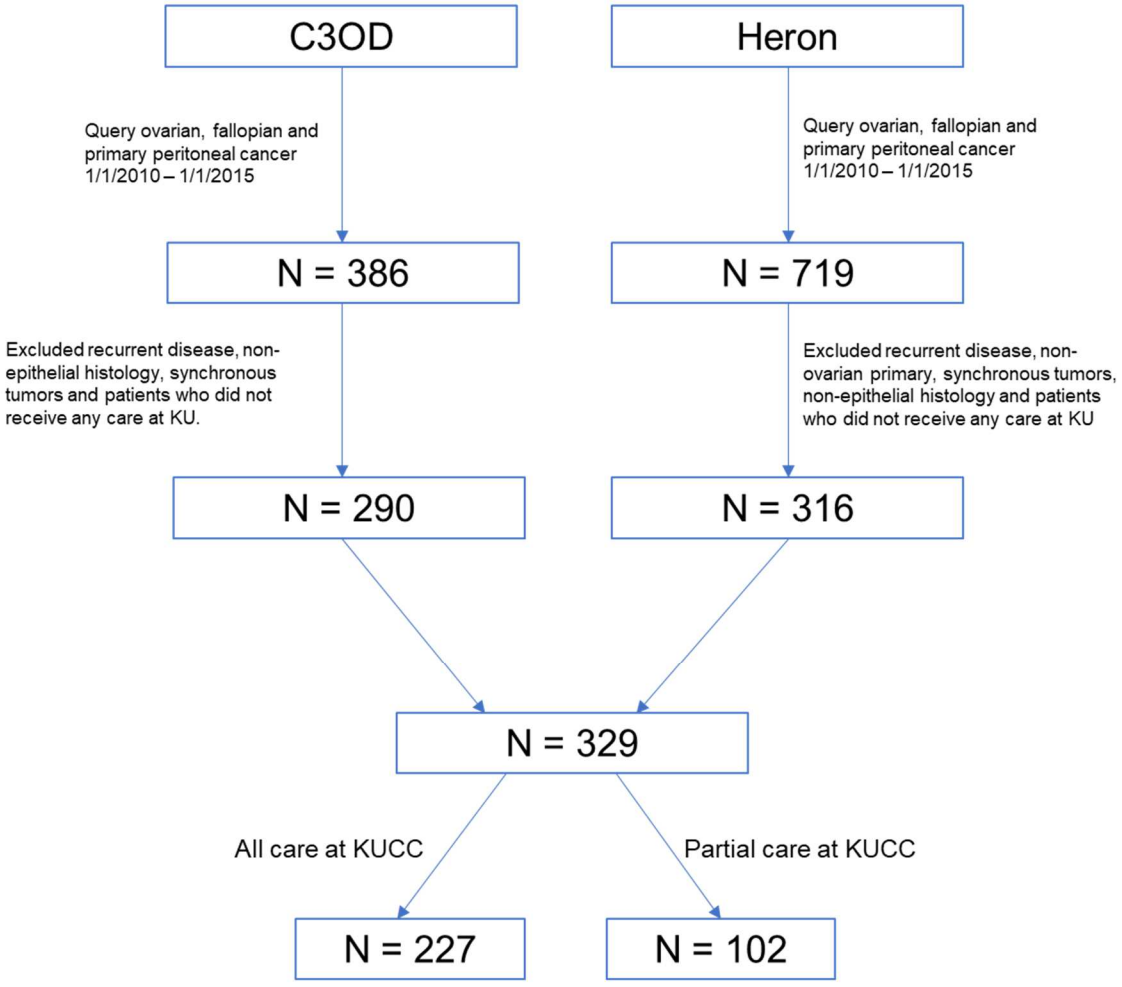
Appendix



Appendix A. Flow diagram of patients screened for inclusion criteria.