HHS Public Access

Author manuscript

Am J Surg. Author manuscript; available in PMC 2021 April 17.

Published in final edited form as:

Am J Surg. 2021 April ; 221(4): 712–717. doi:10.1016/j.amjsurg.2020.12.009.

Disparities in ovarian cancer survival at the only NCI-designated cancer center in Kansas

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Abstract

Background: This study examined the impact of geographic distance on survival outcomes for patients receiving treatment for ovarian cancer at the only NCI-designated cancer center (NCI-CC) in Kansas.

Methods: We identified ovarian cancer patients treated at the University of Kansas Cancer Center between 2010 and 2015. Demographic factors and clinical characteristics were abstracted. The main outcome measure was overall survival according to geographic distance from the institution. Kaplan Meier survival curves and Cox proportional hazard models were generated using SAS v9.4.

Results: 220 patients were identified. Survival analysis based on distance from the institution demonstrated that patients who lived ≤10 miles from the institution had worse overall survival ($p = 0.0207$) and were more likely to have suboptimal cytoreductive surgery ($p = 0.0276$). Lower estimated median income was also associated with a 1.54 increased risk of death, 95% CI (1.031–2.292), $p = 0.0347$.

Conclusions: We determined that ovarian cancer survival disparities exist in our patient population. Lower rates of optimal cytoreductive surgery has been identified as a possible driver of poor prognosis for patients who lived in proximity to our institution.

Keywords

Ovarian cancer disparities; Suboptimal debulking; Geographic disparities

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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]

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 United States have worse outcomes regardless of race.[8] In California, receipt of National Comprehensive Cancer Network (NCCN) guideline adherent care was independently associated with geographic proximity to a high-volume hospital.[9] In that study, barriers to receipt of NCCN guideline adherent care disproportionately affected racial minorities and women with low socioeconomic status. 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] However, increasing socioeconomic status was inversely associated with distance from a high-volume hospital and NHW patients were more likely to travel to receive care in comparison to NHB. In fact, travel distance ≥20 miles was associated with an independent and protective effect against non-guideline adherent care until a distance of 50 miles was met at which time geographic distance was associated with an increased risk of non-adherent care.[9] While this was a large study of over 11,000 patients from the validated California Cancer Registry, medical comorbidity information was not available. Thus, we do not know how comorbid conditions affected receipt of NCCN guideline adherent care. Other studies have also shown that geographic distance from treatment facility 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] NHB women and those with Medicaid insurance had the shortest travel times to the NCI-CC, and those with the shortest travel times were most likely not to complete therapy. Additionally, women who died prior to completion of therapy traveled the farthest and were more likely to have multiple medical comorbidities.[10]

The primary objective of this study was to determine if geographic distance from a single NCI-CC in Kansas (with a large catchment area that spans the entire state of Kansas and western Missouri) is associated with differences in survival. We predicted that like prior

studies, distance traveled would be negatively associated with receipt of guideline adherent care and survival.

2. 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),[11,12] patients with a diagnosis of ovarian, fallopian tube and primary peritoneal cancer (using ICD-9 and ICD-10 codes) between 2010 and 2015 were identified. HERON combines data from various hospital and medical center sources including but not limited to the electronic medical record, billing system, biospecimen repository and is integrated with the social security death index. Additionally, the "C3OD" Curated Clinical Cancer Outcomes database, the University of Kansas Cancer Center (KUCC) cancer registry, was also queried for ICD-*O*-3 codes pertaining to ovarian, fallopian tube and primary peritoneal cancers between 2010 and 2015. After patients in both datasets were identified, manual chart review was performed 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. Patients who received all treatment at KUCC were included. Those who received chemotherapy or surgical staging at an outside institution were excluded.

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 (<1 cm of residual disease) or 3) suboptimal debulking (>1 cm 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 according to 2008 guidelines was determined.[13] NCCN-guideline adherent surgical care for advanced stage disease includes 1) removal of ovaries, fallopian tubes and/or uterus, 2) debulking or cytoreductive surgery and 3) examination of lymph nodes. NCCN-guideline adherent chemotherapy treatment includes completion of multiagent chemotherapy including a platinum agent.

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 (miles) to KUCC from home address. Patients were stratified by ≤10 miles (n = 49) 11–50 miles (n = 128) and >50 miles (n = 43) to the NCI-designated CC 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 ≤10 miles and >10 miles to KUCC. 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 treatment completion to recurrence). For patients who were known to be alive at the time of data collection, time to outcome was censored at last clinical encounter. HERON is integrated with the social security death index to provide date of death for patients who died outside of our health system.

2.1. 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. Potential confounding was assessed by using a 15% change rule from the crude to adjusted estimate. We evaluated for potential collinearity by examining variance inflation factor (VIF) among the exploratory factors in our model and evaluated for interaction between selected variables. Statistical significance was set to a p-value <0.05.

3. Results

3.1. Demographic and clinical factors

Of the 220 patients who received all their care at KUCC, 49 (22%) patients lived ≤10 miles and 171 (78%) lived > 10 miles from the institution (Table 1). Approximately 88% of patients were white with an estimated median income of $55,008. Mean age and age group distribution was similar between both groups. More non-white patients lived ≤10 miles from the institution, $p = 0.0020$. Most patients presented with papillary serous histology (75%) and stage III disease (60%) at diagnosis. Most patients received NCCN guideline adherent care (84%) and underwent optimal cytoreductive surgery (79%). However, patients who lived >10 miles away were more likely to receive optimal cytoreductive therapy compared to those who lived ≤10 miles away (83% vs. 65%, $p = 0.0276$). When stratified by race, non-white patients had lower rates of optimal cytoreduction and higher rates of not receiving surgery (Table 2). Of the 5 non-white patients who did not receive surgery, all 5 had neoadjuvant chemotherapy, 1 died prior to consideration for interval surgery, 2 were considered non-surgical candidates and 2 had progression of disease on neoadjuvant therapy precluding consideration for surgery. 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.

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

Among patients who received their ovarian cancer care at KUCC, median progression free survival was 26 months and median overall survival was 61 months. There was no difference

in progression free survival by distance to the institution, data not shown. Patients who lived ≤10 miles to the institution had worse overall survival than those that lived >10 miles away, p = 0.0207 (Fig. 1). There was a 1.61 increased risk of death among patients who lived less than 10 miles to the institution, 95% CI 1.07–2.42, p = 0.0229. There was no difference in progression free survival by distance to the institution. The 5-year survival rate was 36% for patients who lived ≤10 miles to the institution and 55% for those who lived >10 miles away.

3.3. Lower estimated median income and suboptimal debulking surgery 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 = 0.0221 (Fig. 2). There was no difference in survival by insurance status, data not shown. After controlling for age at diagnosis, non-white race, late stage disease at diagnosis, Charlson Comorbidity Index (CCI), lower estimate median income and suboptimal cytoreduction, distance ≤10 miles were not associated with an increased risk of death (Table 3). However, suboptimal debulking surgery was associated with a 1.84 increased risk of death, 95% CI (1.167–2.906), p = 0.0086. Estimated median income of less than $55,008 was also associated with a 1.54 increased risk of death, 95% CI (1.031–2.292), p = 0.0347. Non-white race and age at diagnosis was not associated with an increased risk of death in this cohort.

We evaluated for confounding and found less than 15% change in the crude analysis to the adjusted analysis for the variables stage at diagnosis, age, race, median income or Charlson Comorbidity index. After examining VIF for exploratory factors in the model, there was no evidence of collinearity. There were no statistically significant interactions between variables in the model.

4. Discussion

Our study has shown that geographic proximity (≤10 miles) is associated with worse overall ovarian cancer survival for patients who receive care at an NCI-designated CC in Kansas. These results are in contrast to previous studies that have demonstrated geographic distance >50 miles is associated with increased risk for non-adherent care.[9] However, in these prior studies, geographic disparities in ovarian cancer was also associated with lower socioeconomic status and NHB race.[6,9] 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. It is likely that our small percentage of non-white patients (12%) was not adequate to detect a difference in survival based on race/ethnicity.

It is worth mentioning that while KUCC is the only NCI-CC in the state of Kansas and has a catchment area that spans the entire state of Kansas and western Missouri, the cancer center is physically located in Wyandotte County, Kansas. Wyandotte County has the worst health outcomes in the state of Kansas, including the highest risk of premature death, low birthweight, obesity and physical inactivity.[14] Wyandotte County also has the highest number of uninsured residents and highest rate of income inequality in the state. Thus, it may seem plausible that the decreased survival noted among patients who lived within 10 miles of the institution reflects the overall poor health outcomes of the region. Similarly, in

Baltimore, patients who lived closest to the NCI-CC were most likely not to complete treatment for their gynecologic cancer that the authors postulate was likely secondary to unique social stressors due to urban poverty.[10] However, it is notable in our study that non-white patients and those who lived ≤10 miles to the institution, 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.[15] 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.[3,6,7,16,17] Recently, Dilley et al. showed that NHB race was also associated with higher medical comorbidities and lower rates of optimal cytoreduction.[18] In that study, after controlling for age, stage, medical comorbidities and suboptimal cytoreduction, NHB was still associated with worse survival, though they did not account for socioeconomic status. In our study, we saw no differences in the rates of comorbid conditions by race or distance.

In our study, we did not identify a factor responsible for lower rates of optimal debulking of patients closer to our institution. However, known factors associated with suboptimal cytoreductive surgery at the time of primary surgery include age greater than 60, American Association of Anesthesiologists (ASA) class 3–4, diffuse small bowel thickening/adhesions, mesenteric lesions, extensive carcinomatosis, stomach and bowel tumor infiltration.[19] More aggressive tumor biology is also associated with a higher risk for residual disease after surgery for ovarian cancer.[20] 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 higher rates of suboptimal debulking surgery and more aggressive ovarian cancer.[21] Peterson et al. speculate that residents of disadvantaged neighborhoods have higher levels of environmental stress that contributes to immune dysfunction and epigenetic changes, resulting in more aggressive tumors and greater residual lesions.[21]

NCCN guideline-adherent care for ovarian cancer is a validated measure of quality cancer care and improved survival.[22] 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 >80% irrespective of distance to the institution. NCCN guideline adherence is based upon receipt of cytoreductive surgery, not the outcome of the surgery (optimal vs. suboptimal), but optimal debulking cytoreductive surgery is associated with improved ovarian cancer survival.[23]

The main strength of this study is that it was performed at the only NCI-CC in the state of Kansas, which is not represented in national databases (i.e. SEER) and thus, is an understudied population. To our knowledge, this is the first study to describe the impact of geographic distance on ovarian cancer survival outcomes and NCCN guideline adherence among women in Kansas. The main limitation of this study is that it is a retrospective study. Thus, we recognize the inherent potential for errors in reporting and unknown potential

confounders or variables. Also, due to low numbers of non-white patients, NHB, Asian and Latina women were grouped into one group (non-white), which does not adequately address racial and ethnic heterogeneity.

5. Conclusion

Among patients who received care for ovarian cancer at the only NCI-CC in Kansas, after controlling for age at diagnosis, non-white race, late stage at diagnosis, presence of comorbidities, median income and suboptimal cytoreduction, geographic distance alone is not an independent predictor of worse overall survival. However, lower rates of optimal debulking surgery and higher rates of not receiving surgery at all are associated with decreased survival among patients who lived in close proximity (≤10 miles) to the institution. Thus, while geographic distance alone is not the main driver of outcome, it could serve as a proxy for poor social determinants of health and accompanying aggressive tumor biology among patients.

Funding

This work was supported by a CTSA grant from NCATS awarded to the University of Kansas (# TL1TR002368). HERON is funded by CTSA Award #UL1TR002366. The dataset(s) used for the analyses described were obtained from the University of Kansas Medical Center Curated Cancer Clinical Outcomes Database. SP was supported by the Ovarian Cancer Research Alliance Ann and Sol Schreiber Mentored Investigator Award (600245).

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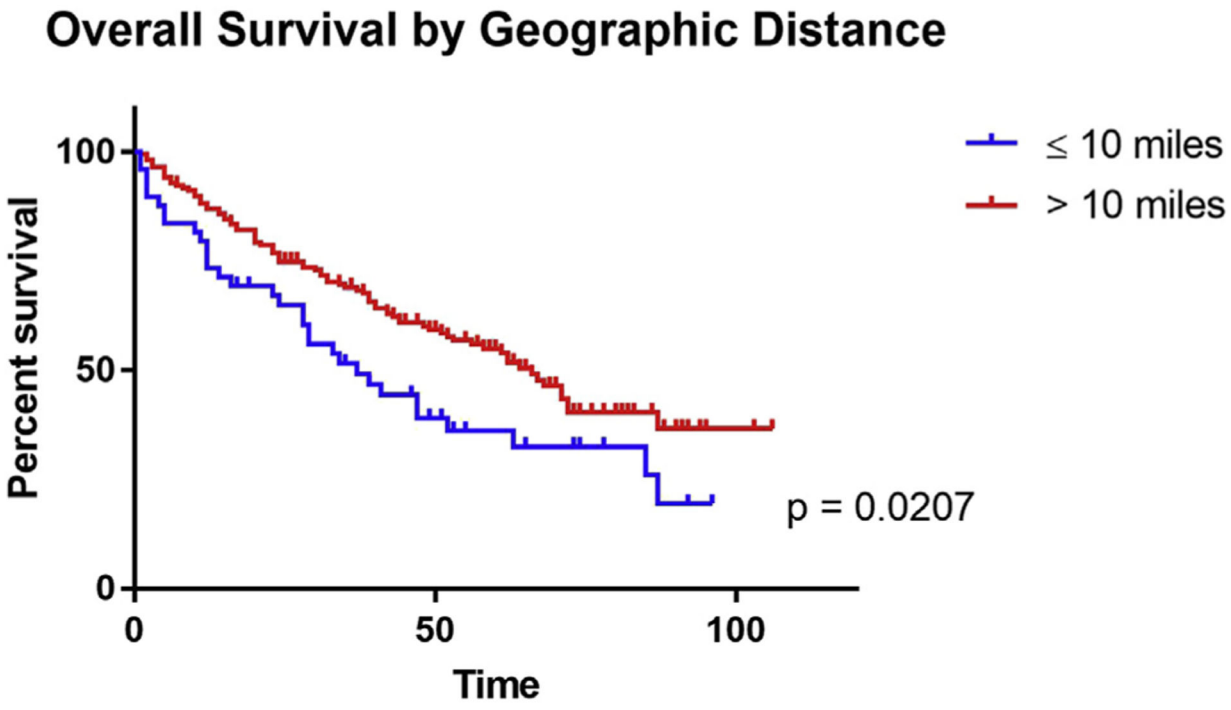

Fig. 1.
Overall survival by geographic distance.

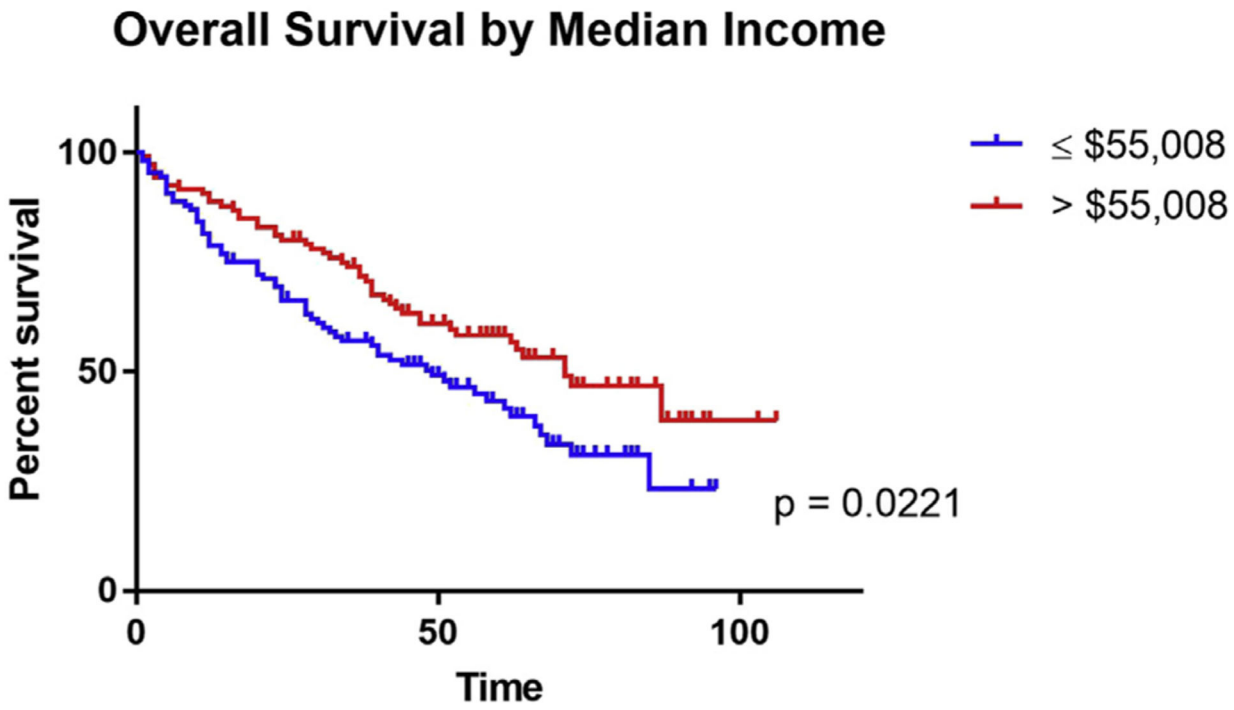

Fig. 2.
Overall survival by estimated median income.

Table 1

Demographic and clinical factors by distance.

	Overall (%) n = 220	**≤10 miles (%) n = 49**	**>10 miles (%) n = 171**	**p-value**
Age in years (mean) ± SD	60.6 ± 11.0	61.0 ± 11.1	60.4 ± 11.0	0.9227
Age in years				0.9652
< 65	133 (60.5)	29 (59)	104 (61)	
65–75	64 (29)	15 (31)	49 (28.5)	
>75	23 (10.5)	5 (10)	18 (10.5)	
Race				**0.0006**
White	193 (88)	36 (73)	157 (92)	
Non-white	27 (12)	13 (27)	14 (8)	
Insurance status				0.3246
Private	89 (40)	17 (35)	72 (42)	
Public (Medicaid, Medicare)	125 (57)	31 (63)	94 (55)	
Unknown	6 (3)	1 (2)	5 (3)	
Median Income				0.2487
Less than $55,008	111 (50.5)	28 (57)	83 (48.5)	
More than $55,008	105 (47.7)	19 (39)	86 (50.3)	
Unknown	4 (1.8)	2 (4)	2 (1.2)	
FIGO Stage				0.4694
I	42 (19)	7 (14)	35 (20)	
II	17 (8)	2 (4)	15 (9)	
III	131 (60)	32 (65)	99 (58)	
IV	30 (14)	8 (16)	22 (13)	
Histology				0.7429[b]
Papillary Serous	164 (75)	40 (82)	124 (72)	
Endometrioid	19 (9)	4 (8)	15 (9)	
Clear Cell	13 (6)	2 (4)	11 (6)	
Mucinous	14 (6)	1 (2)	13 (9)	
Carcinosarcoma	2 (1)	0 (0)	2 (1)	
Undifferentiated	6 (3)	2 (4)	4 (3)	

	Overall (%) n = 220	≤10 miles (%) n = 49	>10 miles (%) n = 171	p-value
Mixed cell	2 (1)	0 (0)	2 (1)	
Charlson Comorbidity Index				0.9096
0	24 (11)	5 (10)	19 (11)	
1	49 (22)	12 (25)	37 (22)	
2+	147 (67)	32 (65)	115 (67)	
Cytoreduction Status				**0.0276**[b]
Optimal (<1 cm)	174 (79)	32 (65)	142 (83)	
Suboptimal (>1 cm)	35 (16)	13 (27)	22 (13)	
Unknown	1 (0.5)	0 (0)	1 (0.5)	
No surgery	10 (4.5)	4 (8)	6 (3.5)	
Neoadjuvant Chemotherapy				0.4264
Yes	35 (16)	6 (12)	29 (17)	
No	185 (84)	43 (88)	142 (83)	
NCCN[a] guideline adherent care				0.3894
Yes	188 (85)	40 (82)	148 (87)	
No	32 (15)	9 (18)	23 (13)	

[a]National Comprehensive Cancer Network (NCCN).

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

Am J Surg. Author manuscript; available in PMC 2021 April 17.

Table 2

Demographic and clinical factors by race.

	Overall (%) n = 220	White Race (%) n = 193	Non-white race[b] (%) n = 27	p-value
Age in years (mean) ± SD	60.6 ± 11.0	60.9 ± 10.9	57.7 ± 10.9	0.1622
Age in years				0.3012
< 65	133 (60.5)	113 (58.5)	20 (74)	
65–75	64 (29)	59 (30.5)	5 (19)	
>75	23 (10.5)	21 (11)	2 (7)	
Insurance status				0.2611
Private	89 (40)	76 (39)	13 (48)	
Public (Medicaid, Medicare)	125 (57)	113 (59)	12 (44)	
Unknown	6 (3)	4 (2)	2 (7)	
Median Income				0.0833
Less than $55,008	108 (49)	92 (47.7)	16 (59)	
More than $55,008	108 (49)	100 (51.8)	8 (30)	
Unknown	4 (2)	1 (0.5)	3 (11)	
FIGO Stage				0.0713
I	42 (19)	38 (20)	4 (15)	
II	17 (8)	16 (8)	1 (4)	
III	131 (69)	117 (61)	14 (52)	
IV	30 (14)	22 (11)	8 (30)	
Histology				0.8667
Papillary Serous	164 (75)	141 (73)	23 (85)	
Endometrioid	19 (9)	17 (9)	2 (7)	
Clear Cell	13 (6)	12 (6)	1 (4)	
Mucinous	14 (6)	13 (7)	1 (4)	
Carcinosarcoma	2 (1)	2 (1)	0 (0)	
Undifferentiated	6 (3)	6 (3)	0 (0)	
Mixed cell	2 (1)	2 (1)	0 (0)	
Charlson Comorbidity Index				0.1082
0	24 (11)	18 (9)	6 (22)	

	Overall (%) n = 220	White Race (%) n = 193	Non-white race[b] (%) n = 27	p-value
1	49 (22)	45 (23)	4 (15)	
2+	147 (67)	130 (68)	17 (63)	
Cytoreduction Status				**0.0029**
Optimal (<1 cm)	171 (80)	156 (81)	18 (67)	
Suboptimal (>1 cm)	35 (15)	31 (16)	4 (15)	
Unknown	1 (0.5)	1 (0.5)	0 (0)	
No surgery	10 (4.5)	5 (2.5)	5 (18)	
Neoadjuvant Chemotherapy				0.1287
Yes	35 (16)	28 (14.5)	7 (26)	
No	185 (84)	165 (85.5)	20 (74)	
NCCN[a] guideline adherent care				0.2271
Yes	188 (85)	167 (87)	21 (78)	
No	32 (15)	26 (13)	6 (22)	

Fisher's exact test used due to small sample size.

[a]National Comprehensive Cancer Network (NCCN).

[b]Non-white race: 18 Black, 5 Asian, 8 Latina and 6 'other'.

Am J Surg. Author manuscript; available in PMC 2021 April 17.

Table 3

Adjusted all-cause mortality.

Variables[a]	Hazard Ratio	95% CI	p-value
≤10 miles to NCI-CC	1.15	0.728–1.802	0.5563
Age at diagnosis	0.98	0.954–1.010	0.2008
Non-white race	0.72	0.369–1.412	0.3411
Late Stage (III/IV)	6.56	3.001–14.354	**<0.001**
Charlson Comorbidity Index (CCI)	1.25	0.0998–1.154	0.0517
Lower Median Income <$55,008	1.58	1.031–2.292	**0.0347**
Suboptimal cytoreduction	1.84	1.167–2.906	**0.0086**

[a]Age and CCI are continuous variables, all others categorical.