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# Factors influencing clinical trial enrollment among ovarian cancer patients☆

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## HIGHLIGHTS

- Older patients are less likely to enroll on ovarian cancer clinical trials.
- Mode of chemotherapy administration differed based on trial enrollment.
- Patients treated on trial lived longer than those who did not.

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## ABSTRACT

*Objective.* To characterize patients who did not enroll on a clinical trial and identify barriers that may limit enrollment among patients with advanced epithelial ovarian cancer (EOC) presenting for first-line chemotherapy.

*Methods.* We conducted a retrospective review of patients diagnosed with stage II-IV EOC from 10/2009–4/2013, a time period during which multiple trials were available to all EOC patients, including optimally debulked, suboptimally debulked, or undergoing neoadjuvant chemotherapy. Enrollment status, demographics, tumor characteristics, and treatment details were recorded. SAS version 9.3 was used for all analyses.

*Results.* 144 patients met study criteria; 67% were enrolled on a trial. Enrolled patients were significantly younger (median 61 vs 68 years, $p = 0.002$). Stage ($p = 0.30$), race ($p = 0.75$), and performance status ($p = 0.38$) were similar between enrolled and non-enrolled patients. Distance did not impact enrollment, as nearly half of patients in both groups lived >50 miles from the treatment center (39.0% vs 47.8%, $p = 0.36$). Mode of chemotherapy administration significantly differed based on participation (all $p < 0.05$). Despite similar residual disease status ($p = 1.00$) and number of chemotherapy regimens received ($p = 0.59$), patients treated on trial had a higher 3-year survival rate (70.7% vs 51.7%, $p = 0.031$). The difference in median progression-free survival approached significance (20.2 vs 9.2 months, $p = 0.091$).

*Conclusion.* In an institution where the culture is to offer clinical trials to all eligible patients, 33% of front-line EOC patients did not participate. Increasing age was associated with non-participation. Modifiable barriers must be overcome so that trial enrollment can better reflect true EOC demographics.



## 1. Introduction

In the United States, epithelial ovarian cancer (EOC) affects approximately 22,280 women each year and remains the most fatal gynecologic cancer [1]. The lethality is owed to the predilection of advanced stage disease at diagnosis and the lack of curative therapies. Due to provocative clinical trial findings, when a woman is diagnosed with EOC, she may now be offered intraperitoneal chemotherapy [2] or dose dense intravenous (IV) paclitaxel [3] as options, in addition to standard IV paclitaxel and carboplatin chemotherapy every 21 days [4], depending on the patient's disease characteristics. Unfortunately, the vast majority of women will recur and enter years of subsequent therapies without

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hope for cure. We are in an era of exciting novel therapeutic options for oncology patients, many of which may have relevance to the treatment of EOC either as primary therapy or for recurrent disease. Answering important questions regarding these therapies requires expert clinical trial design and robust accrual to clinical trials to help improve treatment options and survival rates. Although tremendous variability exists between centers and providers, only 3–5% of adult cancer patients receive treatment on a clinical trial [5,6]. Factors which influence clinical trial participation include the physician's ability to comfortably discuss protocols and a strong commitment from both the physician and the institution to develop and maintain a clinical trials portfolio and program [7].

In addition to the physician's role in clinical trial enrollment, certain non-modifiable factors may also play a role. Older patient age has consistently been associated with lower likelihood of cooperative group oncology trial enrollment. This might be explained by an increased number of co-morbidities in the older population and therefore, a decrease in the number of eligible patients. A patient's perception of poor health may influence her commitment to clinical trial protocols or willingness to treat. Furthermore, physician bias may also play a role when counseling older patients about enrollment due to age alone [8,9]. Race is another factor that may influence trial enrollment. Several authors have reported that racial minority status is negatively associated with clinical trial enrollment for cancer treatment. In gynecologic cancer, this data is mixed. Scalici et al. reviewed 170 GOG publications that provided racial breakdown and found that black women were less likely to enroll in cooperative group trials for gynecologic cancer treatment (83% white, 8% black and 9% other). They also found a decline in the proportion of black patients enrolled on study when comparing the years 1994–2002 (16% enrollment) to 2009–2013 (6% enrollment) [10]. However, NRG/GOG 247, which evaluated modifiable characteristics associated with clinical trial enrollment in women with cervical and endometrial cancer, found greater odds of participation by non-white patients, with 45% of white women enrolling on a trial compared to 83% black, 78% Asian, and 75% Native American women. They postulated that this might be due to concerns about inadequate treatment and quality of care if minority patients declined participation [11].

At our institution, there is abundant clinical trial access across all tumor types, ubiquitous agreement among providers that the optimal way to care for cancer patients is on clinical trial, and a strong institutional culture of trial enrollment. Despite this, some patients are not enrolled on a clinical trial for their treatment. This study aimed to characterize patients who did not enroll on a clinical trial and to identify potential modifiable barriers that may limit enrollment among patients with advanced EOC presenting for front-line chemotherapy.

## 2. Methods

After obtaining Institutional Review Board approval, (study #3600) a retrospective chart review was performed encompassing patients diagnosed with stage II-IV EOC at The University of Oklahoma Health Sciences Center from October 2009 to April 2013. This time period is significant and was deliberately selected because clinical trials including cooperative group, pharmaceutical, and investigator initiated, were open and available to all EOC patients presenting for front line therapy, including optimally debulked, suboptimally debulked (defined as >1 cm), or those undergoing neoadjuvant chemotherapy. Trial enrollment status, demographics, and tumor characteristics were recorded. Treatment details including primary treatment, chemotherapeutic agents, and number of cycles were documented. Treatment groups were divided into patients who received primary chemotherapy with no plan for surgery, surgery followed by adjuvant chemotherapy, neoadjuvant chemotherapy with surgery, and no treatment. The distance patients lived from the hospital were categorized into three separate groups, including patients who lived <25 miles, 25 to 50 miles, or >50 miles from the cancer center. Distance traveled was calculated by using an internet search for zip code from hospital to zip code of patient residence. Progression free survival (PFS) was defined as time from completion of primary treatment to time of recurrence and was censored at the time of last follow up if no recurrence. Overall survival (OS) was defined as time from date of diagnosis to date of death. If death did not occur within the study period, OS was censored at the date of last follow up. Descriptive statistics (median, range, count, and percent) were reported. Comparisons between groups were performed using Wilcoxon rank-sum or two-sample *t*-test for continuous variables and Chi-square test for categorical variables. PFS and OS data were summarized by Kaplan-Meier method and compared between groups with Log-rank test. Multivariate analyses of survival outcomes were performed using the Cox model. A two-sided *p*-value of $<0.05$ defines statistical significance. SAS version 9.3 was used for all analyses.

## 3. Results

During the study period, 144 patients were diagnosed with stage II-IV EOC and treated at our center. Of these women, 97 (67.4%) were enrolled on a clinical trial. Demographics for the study population are shown in Table 1. The median age of patients on clinical trial was 61 years, and the median age for patients not treated on trial was 68 years ($p = 0.002$). In both groups, most patients were Caucasian, had stage III disease, underwent primary debulking surgery followed by adjuvant chemotherapy, and had high grade serous histology. Stage ($p = 0.30$), race ($p = 0.75$), and performance status ($p = 0.38$) were similar between the groups. The distance a patient lived from the cancer center did not impact trial enrollment, as nearly half of all patients in both groups lived >50 miles from the treatment center (39.0% vs 47.8%, $p = 0.36$). The majority of patients in each group had Medicare/private insurance (87.6% vs 91.5%, $p = 0.09$) and had a performance status of 0 (91.6% vs 86.7%, $p = 0.38$).

Histology distribution differed with fewer high grade serous patients treated on trial (76.3% vs 89.4%), although statistical significance was not reached ($p = 0.07$; Table 2). Table 3 shows the treatments received by each group. Although time to initiate treatment was similar (0.95 versus 1.02 months, $p = 0.91$), trial patients received less neoadjuvant chemotherapy (6.2% vs 31.9%), but they received more primary chemotherapy without surgery (8.3% vs 0%, $p < 0.0001$), intraperitoneal

**Table 1**
Baseline patient characteristics by trial enrollment status.

| | Enrolled on a clinical trial, $N = 97$ | Not enrolled on a clinical trial, $N = 47$ | *p*-Value |
|---|---|---|---|
| Median age (range) | 61 (26–81) | 68 (48–85) | **0.002** |
| Race | | | 0.75 |
| White | 88 (90.7%) | 44 (93.6%) | |
| Black | 2 (2.1%) | 1 (2.1%) | |
| American Indian | 4 (4.1%) | 1 (2.1%) | |
| Hispanic | 3 (3.1%) | 1 (2.1%) | |
| Asian | 0 (0%) | 0 (0%) | |
| Other | 0 (0%) | 0 (0%) | |
| Insurance status | | | 0.09 |
| Medicare | 26 (26.8%) | 22 (46.8%) | |
| Medicaid | 9 (9.3%) | 2 (4.3%) | |
| Private | 59 (60.8%) | 21 (44.7%) | |
| No insurance | 3 (3.1%) | 2 (4.3%) | |
| Distance lived from cancer center | | | 0.36 |
| <25 miles | 48 (50.5%) | 22 (47.8%) | |
| 25–50 miles | 10 (10.5%) | 2 (4.4%) | |
| >50 miles | 37 (39.0%) | 22 (47.8%) | |
| Performance status | | | 0.38 |
| 0 | 87 (91.6%) | 39 (86.7%) | |
| 1 | 7 (7.4%) | 5 (11.1%) | |
| 2 | 1 (1.1%) | 1 (2.2%) | |
| 3 | 0 (0%) | 0 (0%) | |
| 4 | 0 (0%) | 0 (0%) | |
| Unknown | 0 (0%) | 0 (0%) | |

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