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Chemotherapy delay after primary debulking surgery for ovarian cancer

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HIGHLIGHTS

- Nearly 60% of women experience chemotherapy delay >28 days.
- Chemotherapy delay >35 days is associated with a 7% increased hazard of death.
- The evidence-based best surgery to chemotherapy interval is 21–35 days.

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ABSTRACT

Objective. To determine the association of chemotherapy delay with overall survival (OS) and investigate predictors of delay among a population-representative American ovarian cancer cohort.

Methods. An observational retrospective cohort analysis of women with ovarian cancer who received National Comprehensive Cancer Network guideline-consistent care was performed with the 1998–2011 National Cancer Data Base. Chemotherapy delay was defined as initiation of multiagent chemotherapy >28 days from primary debulking surgery. Associations of patient and disease characteristics with chemotherapy delay were tested with multivariate logistic regression. Survival analyses for women diagnosed from 2003 to 2006 approximated a 21-day cycle intravenous platinum-taxane chemotherapy cohort. Overall survival was estimated by Kaplan-Meier analyses and Cox proportional-hazards regressions, with sensitivity analyses using matched cohorts.

Results. 58.1% (26,149/45,001) of women experienced chemotherapy delay. Race, insurance status, cancer center type, and community median income were significantly associated with chemotherapy delay ($P < 0.001$). Odds for chemotherapy delay were higher for older or sicker women, women with endometrioid or mucinous histology, lower stage or grade disease, and uninsured or low-income women ($P < 0.05$). Chemotherapy delay >35 days from surgery was associated with a 7% (95% confidence interval, 2–13%) increased hazard of death ($P = 0.01$). Relative hazard of death was lowest between 25 and 29 days after surgery but was not significantly different within the longer two-week interval from 21 to 35 days.

Conclusion. A survival benefit may be achieved by consistently starting chemotherapy between 21 and 35 days from primary debulking surgery. Women at higher risk for chemotherapy delay may be targeted for close follow-up.

1. Introduction

Over 22,000 cases of ovarian cancer are diagnosed in the United States each year [1]. Despite significant research on early diagnosis and novel therapeutics, the national five-year survival rate has increased only 10% since the 1970s [1]. Health service interventions such as reductions in treatment delays are also needed. The current standard-of-care management of many women with ovarian cancer remains primary debulking surgery (PDS) followed by multiagent chemotherapy [2]. Existing literature is inconclusive as to whether the time interval between PDS and chemotherapy initiation affects overall survival (OS) of women with ovarian cancer. Two studies suggest that chemotherapy delay beyond 25–28 days is associated with decreased survival [3,4]. These studies and other reports either did not find a survival association or reported associations that differ by volume of residual disease after PDS [3–11]. All studies are observational retrospective cohort analyses. Many are of small, international cohorts who may not represent American women with ovarian cancer or reflect the socioeconomic and health services disparities that influence ovarian cancer

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management and survival in America [12–17]. The impact of socioeconomic and demographic determinants of health on chemotherapy delay in the United States is not described.

We used the National Cancer Data Base (NCDB) to determine patient and disease characteristics including socioeconomic and demographic determinants of health that may predict chemotherapy delay. We also performed survival analyses to characterize how chemotherapy delay impacts survival among a large, contemporary population-representative cohort selected to include women who predominantly received standard intravenous platinum-taxane doublet chemotherapy.

2. Methods and materials

2.1. Data source

We performed an observational retrospective cohort analysis of women with ovarian cancer from the 1998–2011 NCDB dataset. The NCDB is a hospital-based national cancer registry created by the American College of Surgeons and American Cancer Society, and includes approximately 70% of all ovarian cancers diagnosed nationally [18]. Individual-level data is prospectively collected by professional registrars and is audited [18]. Local institutional review board approval is not required at Northwestern University for NCDB data analysis.

2.2. Cohort selection

Women with stage I-IV ovarian cancer were selected ($n = 198{,}554$). Women with stage I and grade 1 disease were excluded as some may not require chemotherapy (new $n = 188{,}375$) [2]. Women who received National Comprehensive Cancer Network (NCCN) guideline consistent care defined as surgery including at least oophorectomy and hysterectomy, consistent with possible surgical staging, and multiagent chemotherapy were included (new $n = 87{,}379$). 87.0% (75,994/87,379) of these women were specifically coded as having omentectomy, debulking or exenteration, mostly posterior due to concurrent rectosigmoid resection. Women who received neoadjuvant chemotherapy were excluded (new $n = 77{,}787$). The time in days from PDS to chemotherapy initiation was calculated by subtracting the time from diagnosis to surgery from the time from diagnosis to chemotherapy. Women missing time intervals were excluded (new $n = 45{,}001$). Time intervals were first recorded in 2003. The cohort consisted of women diagnosed from 2003 to 2011 who received PDS followed by multiagent chemotherapy starting at a known time after PDS. For regression models, women with uncommon histologies were excluded by including only women with serous (8010, 8140, 8441, 8460, 8461), clear cell (8310), endometrioid (8380), or mucinous (8480) ICD-O-3 histologies (new $n = 37{,}964$). Regression cohorts are further limited to women with no missing data for any variable included in the regression models. The cohort size for each regression is thus reported separately with the Results. For survival analyses, 19,269 women with clinical follow-up data were diagnosed from 2003 to 2006. Limiting the survival analyses to women diagnosed from 2003 to 2006 presumably ensures that the survival estimates represent predominantly women who received an intravenous platinum-taxane doublet planned every 21 days.

2.3. Covariate selection and definitions

Covariates included age, Charlson/Deyo composite comorbidity score, stage, grade, histology, race, insurance status, distance from residency zip code to hospital, community median household income quartile by zip code, and cancer center type. Cancer centers were classified as community, academic, or other. Race was grouped as white, black, other or unknown for regression analyses. The other group included a large number of specific codes for diverse East and South Asian, Pacific Islander, and Native American races. Low counts for these smaller groups led us to combine these groups into the other category for regression.

From the background literature, an a priori decision of the analysis was that chemotherapy delay was defined as initiation >28 days from PDS [3,4]. Also, for survival analyses we expected to observe that women who received early chemotherapy initiation (<14 days after surgery) would have decreased survival. Presumably this group includes more women with symptomatic or significant residual disease after PDS. NCDB does not describe volume of residual disease. We discretized time to chemotherapy initiation for survival analyses initially at 0–14 days and made additional groups for each 7-day interval after 14 days. We observed that women who received chemotherapy from 0 to 20 days had similarly increased hazard of death. Therefore we redefined the initial group to be 0–20 days. This balanced the counts of women between these groups without losing resolution of survival differences. The reference group for regression was made 21–28 days. After 49 days, the counts of women were decreased in number and so the final group was defined as ≥50 days. NCDB variable definitions are publicly available online at the American College of Surgeons.

2.4. Statistical analyses

Socioeconomic and demographic characteristics were compared between women who did versus did not experience chemotherapy delay using Chi-square or Mann-Whitney *U* tests for categorical or ordinal variables, respectively. A multivariate binomial logistic regression model was built by stepwise selection to determine adjusted odds ratios for chemotherapy delay and initially included covariates age, comorbidity scores, distance to hospital, stage, grade, histology, race, cancer center type, insurance status, and income quartile. Interaction terms between socioeconomic and demographic covariates were tested. Insignificant covariates were removed. The Analysis of Deviance table confirmed that all remaining covariates were significant. Goodness of fit was confirmed with deviance residuals.

Unadjusted median OS and five-year survival proportions were compared using empiric Kaplan-Meier analysis. A stratified, multivariable Cox proportional-hazards model of OS was built by stepwise selection to evaluate time to chemotherapy initiation after PDS as a discretized variable. The proportional-hazards assumption was checked and the model stratified as required. Stratification variables included age categories, stage, grade, and histology. Additional covariates included insurance status, income, race groups, and cancer center type. Interactions between time to chemotherapy initiation, socioeconomic, and demographic covariates were tested and a significant interaction between race and income was modeled. The Analysis of Deviance table confirmed that all remaining covariates were significant. Goodness of fit was confirmed with deviance residuals. To illustrate the nonlinearity of survival response to chemotherapy delay, we plotted relative hazard derived from the stratified, multivariable Cox model with time to chemotherapy included as a continuous variable using restricted cubic splines [3].

To decrease possible selection biases matched cohort analyses were performed. One-to-one nearest-neighbor propensity score matching was performed to generate similar cohorts who started chemotherapy between 21 and 35 days versus ≥36 days after PDS. Cohorts were matched using age, comorbidity score, stage, grade, histology, race, insurance status, income quartile, and cancer center type. Characteristics were compared between matched cohorts with Chi-squared tests for categorical variables and Mann-Whitney *U* tests for ordinal or numeric variables. As a sensitivity analysis of the matching algorithm, exact matching was also performed. Survival of matched cohorts was estimated by Kaplan-Meier analyses. Hazard ratios were calculated from stratified, multivariable Cox proportional-hazards models including the same covariates. All *p*-values are two-tailed. Statistical analyses were

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