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The impact of inter-cycle treatment delays on overall survival in patients with advanced-stage ovarian cancer

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Abstract

Introduction: Chemotherapy forms the cornerstone of systemic treatment for advanced ovarian cancer, extending overall survival; however, drug-related toxicity can lead to treatment delays, potentially diminishing treatment efficacy. This study evaluated the impact of treatment delays on all-cause mortality of patients with ovarian cancer, to better inform decisions on patient management.

Methods: This retrospective, population-based cohort study included 1517 women with advanced-stage ovarian cancer, receiving first-line adjuvant or neoadjuvant chemotherapy in 2014 and 2015. The frequency of inter-cycle delays >7 days was calculated using drug administration dates. Kaplan-Meier estimates were used to compare 2-year overall survival (OS) between patients who were delayed and those treated to schedule. Cox proportional hazards regression was used to investigate the impact of treatment delay on all-cause mortality. Inverse probability of treatment weighting propensity scores were used to adjust for confounding variables.

Results: Delays >7 days occurred in 35.3% of patients. Two-year OS probability was 62.7% in patients who experienced treatment delays >7 days (95% CI, 58.7-66.9) compared to 69.1% in those treated to schedule (95% CI, 66.2-72.0). Delays were not significantly associated with all-cause mortality when adjusted for confounders (HR 1.00 95% CI, 0.83-1.20, *P* = .9).

Conclusions: Delays to chemotherapy treatment were not significantly associated with worsened survival in patients with advanced-stage ovarian cancer. These results can inform clinical decision making that prioritize toxicity management and quality of life for those treated with chemotherapy.

Key words: cancer; ovarian; chemotherapy; treatment; delay; survival.

> ### Implications for practice
> Delays between chemotherapy cycles occur frequently in patients with advanced ovarian cancer. However, prior to our work there was a lack of evidence on the association with these delays and overall survival. This research found no significant association (HR 1.00, 95% CI, 0.83, 1.20) that will reassure both clinicians and patients wishing to employ delays to manage toxicity.

Introduction

Ovarian cancer is highly prevalent on a global scale, with an estimated 313,000 new cases recorded in 2022[1] and around 7400 women diagnosed annually in the UK.[2] Currently, no reliable screening test exists for ovarian cancer, and consequently most women are diagnosed at advanced stages (FIGO stages 3 or 4) after becoming symptomatic from their disease.[3]

Survival outcomes are poor in patients with advanced-stage ovarian cancer, with 2-year survival rates of around 41% for stage 3 patients, and 31% for stage 4 patients in the UK.[4]

Standard treatment for advanced-stage ovarian cancer involves cytoreductive (debulking) surgery followed by treatment with adjuvant or neoadjuvant systemic anti-cancer therapy (SACT) using platinum-based chemotherapy followed by interval debulking surgery.[5] Treatment delays (between

chemotherapy treatments) are often used to allow time for the patient to recover from toxicity and to maintain an acceptable quality of life (QoL). In advanced stages of disease, when survival outcomes are poor, there is a trade-off between increasing length of life through systemic treatment and maintaining QoL through minimizing drug toxicity. Treatments that are too aggressive can increase toxicity and the likelihood of additional hospital attendances, further increasing the burden of chemotherapy treatment for patients.[6] Toxicity can be managed proactively by improving clinical monitoring and access to specialist clinics to address drug-related problems early in the course of an adverse-event, so that fewer patients require hospital admission for management of symptoms.[7] Treatment delays will however be required for many patients to allow time for recovery from adverse- events.

Reports of the frequency of treatment delays in patients with ovarian cancer range widely, from 14.6% to 43.4% of treatments given during a standard chemotherapy regimen.[8,9] The impact of delays on survival outcomes is, however, poorly understood, with some evidence suggesting that treatment delays can reduce survival through impaired dose intensity.[10] Characterizing the impact of delays between chemotherapy cycles is essential to allow clinicians to make informed decisions about patient management, and to communicate with patients about the risks and benefits of delaying chemotherapy treatment. Several studies investigating the impact of delays in ovarian cancer have used small sample sizes or specific subgroups, such as elderly patients, however this question has not yet been addressed in a large, population-based cohort.[11-13]

Further investigation into the association of delays with survival outcomes in advanced-stage ovarian cancer patients is warranted. This work aims to provide evidence that can inform approaches to optimize both chemotherapy treatment benefit and QoL for advanced stage ovarian cancer patients.

Methods

This retrospective cohort study used population-based observational data from a large cohort of patients with advanced-stage ovarian cancer, in England, to quantify the frequency of inter-cycle delays occurring between chemotherapy cycles, and to investigate whether treatment delays were associated with overall survival outcomes.

Data source

English registries that contained patient information for all patients with cancer treated with systemic treatment were available to conduct this study. The National Cancer Registration and Analysis Service (NCRAS) register all patients treated for cancer in NHS hospitals, providing information on surgery, diagnosis, age at initiation of chemotherapy, demographic information such as ethnicity socioeconomic status. These registrations were linked to the SACT dataset, also collected by NCRAS, which provides details on systemic treatment. These datasets were used to identify the patient cohort of interest using International Classification of Disease (ICD) codes specifying a diagnosis ovarian, fallopian tube, or primary peritoneal cancer of gynecological origin were included (ICD codes C48, C56, and C57).

Study population

Data on adult patients with advanced-stage ovarian, fallopian tube, and primary peritoneal cancer of gynecological origin, receiving first-line adjuvant or neoadjuvant chemotherapy between Janaury 01, 2014 and December 12, 2015 in England were provided in the data request. Fallopian tube and primary peritoneal cancers were grouped with ovarian cancer based similar presentation and management. These cancers are collectively referred to here as "ovarian cancer."

Eligibility criteria and data handling

Patients with a diagnosis of stages 3 or 4 ovarian cancer were included. During the study period, standard of care for advanced ovarian cancer was 6 cycles of carboplatin and paclitaxel doublet treatment. Less fit patients may have received carboplatin single-agent according to British Gynecological Cancer Society guidelines, and therefore these patients were included in the study.[11,14] Patients were excluded as follows: did not receive platinum-based chemotherapy, chemotherapy given within a clinical trial, treatment for synchronous cancer, missing drug administration data, treatment outside study period, missing death date information, surgery >1 year before start of chemotherapy treatment, diagnosis >6 months before chemotherapy treatment, patient received less than 6 cycles of chemotherapy. Cancer stages were grouped based on clinical guidance as "stage 3A/B, "stage 3C," "stage 4." Patients with incomplete staging data, listed as "stage 3" only (without further description) could not be assigned to 3A/B or 3C groups and were labeled as "stage 3." Region and hospital type (local or academic) were assigned using NHS organization codes.

Calculating delays to chemotherapy treatment

Delays to chemotherapy treatment were calculated using time between dates of drug administrations. Treatments were considered delayed when given >7 days later than expected based on standard drug regimen schedules.[12] The definition of >7 day delay was chosen based on other studies of this kind[13,15,16] that used this length of delay, as this period of treatment delay occurs commonly in patients receiving chemotherapy. Dates for interval debulking surgery (IDS) were used to exclude any delays resultant of surgery and associated recovery. Delays in bevacizumab administration were not classified as delays where this was used within a treatment regimen.

Defining surgical status

Surgical status was categorized as primary debulking surgery (PDS) if they underwent surgery and started chemotherapy within 1 year. Patient whose surgery was performed up to 180 days after cycle one of neoadjuvant chemotherapy were identified as receiving interval debulking surgery (IDS).[17] Patients who did not receive surgery were included in the study, as these patients represent an important subgroup that was recently highlighted in the Ovarian Cancer Audit of access to surgery in advanced ovarian cancer patients in England.[18] Surgical status was incorporated into survival analysis as a covariate to account for these different treatment strategies.

Statistical analysis

The outcome of interest was 2-year overall survival (OS). The outcome of 2-year OS was chosen as the primary outcome in concordance with other investigations of survival in advanced ovarian cancer[19] with all-cause mortality being the outcome metric. Kaplan-Meier (KM) survivor functions compared survival between patients who experienced

treatment delays and those who were treated to schedule. In this patient cohort, breaks in chemotherapy treatment following surgery are inevitable to allow for recovery from toxicity. To test whether there were disparities between English regions in this type of delay, descriptive statistics were used to compare time from surgery to next chemotherapy between regions.

Multivariable Cox proportional hazards regression was used to investigate the relationship between treatment delay and other covariates with OS. Inverse probability of treatment weighting (IPTW) propensity scores were applied to adjust for covariate differences treatment delay and treated to schedule patient groups.[20] Covariates of interest were: age at start of treatment, cancer stage at diagnosis, body mass index (BMI), bevacizumab administration, chemotherapy regimen, surgical modality, Charlson comorbidity index (an index score of comorbidity based on ICD-10 codes), index of multiple deprivation, ethnicity and region, after a preliminary literature review identified these as variables of interest. Univariate linear and logistic regressions were used to test for associations between covariates and survival outcomes before incorporation into the Cox regression model. All data available were used, and a post-hoc sample size calculation was performed to confirm the sample size was sufficiently large to achieve 95% statistical confidence.

Comparison of time for surgery break between regions

Time from debulking surgery to next chemotherapy treatment was calculated for each patient and compared between regions in England. Descriptive statistics were used to describe median time in days for each region to assess whether any regional differences exist in time to start or resume chemotherapy after debulking surgery.

Missing data

Data were incomplete for some variables and labelled as "Unknown" where missing values could not be inferred from other available data. Height and weight values that were recorded erroneously were assigned a value of 0 and the patient's BMI was labelled as "Unknown." Multiple Imputation by Chained Equations (MICE) approach was used to impute estimated BMI values for patients where data were missing. Missingness of data is described in results.

Results

Description of cohort

A total of 1517 patients met inclusion criteria. Exclusions made are shown as a flowchart in Figure 1. Baseline characteristics of the study cohort are given in Table 1, showing overall characteristics of the entire cohort and a comparison of characteristics between patients experiencing treatment delay and those completing treatment to schedule. The median age was 66 years (range 18-91), with median age in the delayed group of 68 years compared to 66 in those treated to schedule. Supplementary Table S1 describes the study cohort stratified by surgical modality.

BMI was calculated for 1334 patients (87.9%) where height and weight data were available; for 183 patients (12.1%), missing height or weight values did not allow BMI to be calculated and were imputed using MICE.

Frequency of treatment delays

Of the 1517 patients, 536 (35.3%) of patients experienced at least 1 delay to treatment of >7 days between chemotherapy cycles, excluding for breaks for IDS. Of all treatments given (n = 10 194), 9% (917) of all treatments given (n = 10 194) were delayed >7 days. Median length of delay was 15 days for 3-weekly regimens and 14 days for weekly regimens. In PDS patients, delays occurred in 30% of patients (n = 176), compared to 33% (n = 152) of IDS patients. In those who underwent debulking surgery, 44% (n = 208) of patients experienced treatment delays between either adjuvant or neoadjuvant chemotherapy cycles, accounting for breaks for surgery.

Kaplan-Meier survival analysis

In total 1517 patients were included in KM survival estimates. Median follow-up time was 35.4 months. Two-year OS probability was 62.7% in patients who experienced treatment delays >7 days (95% CI, 58.7-66.9) compared to 69.1% in those treated to schedule (95% CI, 66.3-72.0), log-rank test *P* < .01. The KM curve comparing survival between groups is shown in Figure 2. Patients were censored at the timepoint of 2 years from initiation of chemotherapy if the event of all-cause mortality did not occur. Two patients had an unknown survival status at the end of the study period and were censored at the 2-year timepoint. Median OS was not reached and therefore not reported.

Figure 3 shows 2-year OS time by length of treatment delay. There were no significant differences in 2-year OS between patients who experienced <2 weeks, 2-4 week, 4-6 week, or > 6 week delay.

Cox proportional hazards regression analysis

Table 2 describes the results of Cox proportional hazards regression analysis. A hazard ratio of 1.00 (95% CI, 0.83-1.20, *P* = .99) was calculated for the association of inter-cycle delays>7 days with the OS, adjusting for covariates using IPTW propensity scores. Covariates were well balanced between delayed and treated to schedule groups with all standardized mean difference (SMD) values within the 0.1 threshold, shown as a love plot in Supplementary Figure S1.

Time from surgery to next chemotherapy treatment

Supplementary Table S2 shows median time from surgery to next chemotherapy by English region. Figure 4 shows time to next chemotherapy as a histogram, stratified into PDS and IDS cohorts. Time from surgery to next chemotherapy was comparable between regions for IDS patients (range 48-56 days). For patients undergoing PDS, time from surgery was markedly higher in the South East (91 days, IQR 70-143).

Discussion

This retrospective study was the first study of its kind performed in a large, population-based cohort, finding no significant association of treatment delay with 2-year overall survival in advanced-stage, newly diagnosed ovarian cancer patients treated with platinum-based chemotherapy. This finding is a first indication that delaying chemotherapy treatment between treatment cycles is not detrimental to survival outcomes in this patient cohort and should reassure the clinical community.
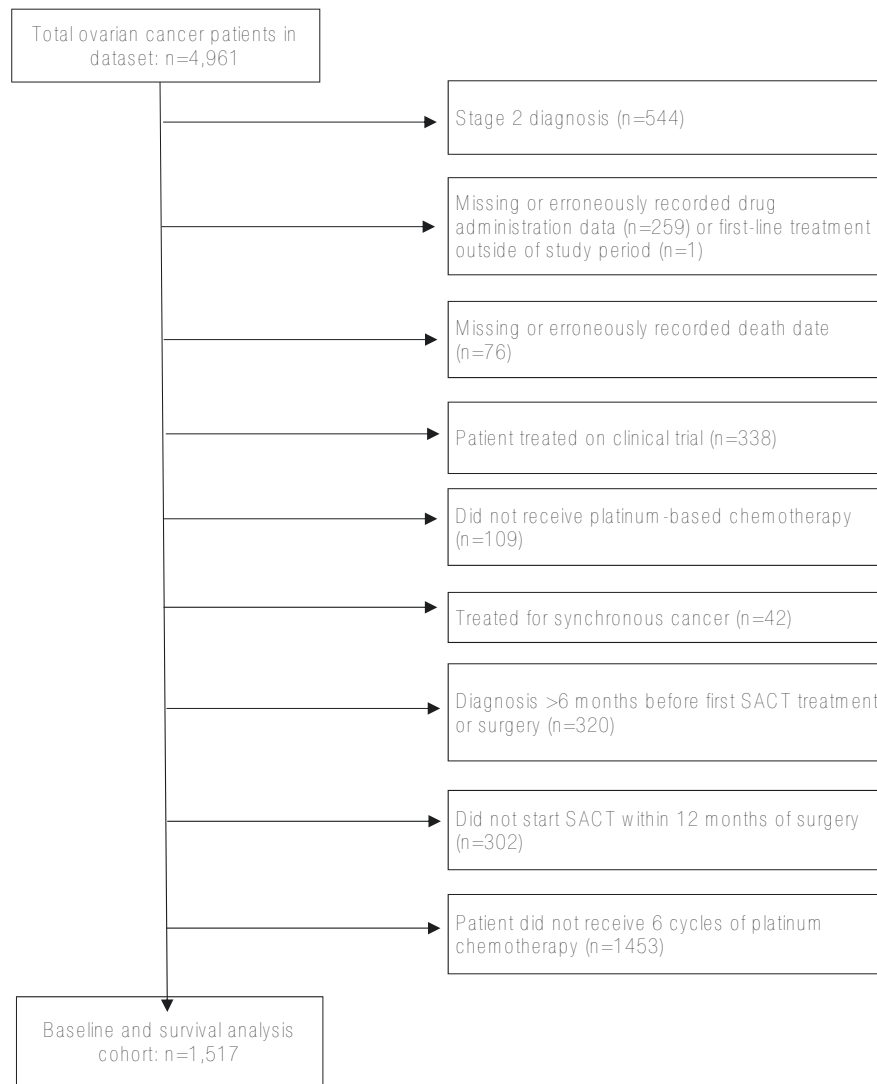
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┌─────────────────────┐
│ Total ovarian cancer │
│ patients in          │          ┌──────────────────────────────────┐
│ dataset: n=4,961     │─────────▶│ Stage 2 diagnosis (n=544)        │
└─────────────────────┘          └──────────────────────────────────┘

                                  ┌──────────────────────────────────┐
                                 ▶│ Missing or erroneously recorded   │
                                  │ drug administration data (n=259) │
                                  │ or first-line treatment outside  │
                                  │ of study period (n=1)            │
                                  └──────────────────────────────────┘

                                  ┌──────────────────────────────────┐
                                 ▶│ Missing or erroneously recorded   │
                                  │ death date (n=76)                │
                                  └──────────────────────────────────┘

                                  ┌──────────────────────────────────┐
                                 ▶│ Patient treated on clinical trial │
                                  │ (n=338)                          │
                                  └──────────────────────────────────┘

                                  ┌──────────────────────────────────┐
                                 ▶│ Did not receive platinum-based    │
                                  │ chemotherapy (n=109)             │
                                  └──────────────────────────────────┘

                                  ┌──────────────────────────────────┐
                                 ▶│ Treated for synchronous cancer    │
                                  │ (n=42)                           │
                                  └──────────────────────────────────┘

                                  ┌──────────────────────────────────┐
                                 ▶│ Diagnosis >6 months before first  │
                                  │ SACT treatment or surgery (n=320)│
                                  └──────────────────────────────────┘

                                  ┌──────────────────────────────────┐
                                 ▶│ Did not start SACT within 12      │
                                  │ months of surgery (n=302)        │
                                  └──────────────────────────────────┘

                                  ┌──────────────────────────────────┐
                                 ▶│ Patient did not receive 6 cycles  │
                                  │ of platinum chemotherapy (n=1453)│
                                  └──────────────────────────────────┘
┌─────────────────────┐
│ Baseline and survival│
│ analysis cohort:     │
│ n=1,517              │
└─────────────────────┘
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Figure 1. Exclusions made to extracted data.

In this study, on average 35.3% of patients experienced delays to chemotherapy. This frequency of delay is comparable to reports from other authors of 27%, 56%, and 28%-58%.[21-23] The frequency of treatment delay during adjuvant and neoadjuvant chemotherapy was comparable between patients who underwent primary or interval cytoreductive surgery, but for patients treated with chemotherapy alone (without surgery), treatment delays occurred more frequently. This finding may be indicative of higher toxicity burden in this group, where surgery was not offered due to older age or poorer fitness. Median age of patients who did not receive surgery was 7 years greater than those who underwent PDS or IDS, which is concordant with reports of reduced offering of surgery to older ovarian cancer patients.[24]

The hazard ratio of 1.0 and CI of 0.83-1.20 suggests that treatment delay was not associated with survival after adjustment for covariates. These findings are concordant with evidence presented by others who have reported no significant differences in progression-free or overall survival between ovarian cancer patients who experience treatment delays and those completing chemotherapy regimens to schedule.[21] Significant associations of treatment delay with poorer survival were not however reported in another study including

only 184 patients (HR 1.75, 95% CI, 1.09-2.82, $P < .05$).[25]; Moreover, the authors reported a higher frequency of treatment delay (45.8%), than in this study, likely accounted for by inclusion of elderly patients aged 65 and over. Results presented here, using a large cohort of patients of all ages treated over a 2-year period in England, do not support this finding.

Other studies have investigated the impact of delay from diagnosis to initiation of treatment in patients with ovarian cancer, reporting small but significant associations of 1-2 month delay (HR 1.06, 95% CI, 1.01-1.11).[26] A similar study, however, did not find a significant difference in survival between patients who started treatment immediately and those who had a >2 week delay before initiation of chemotherapy.[27] As many ovarian cancer patients with ovarian cancer present at advanced stages of disease, prognosis is usually poor, with reports of median progression-free survival of 16-21 months and overall survival of 46 months.[24,28] Toxicity management should therefore prioritize maintenance of acceptable QoL, as these results demonstrate that treatment delays >7 days were not significantly associated with survival.

Comparing time from surgery to next chemotherapy treatment showed that the surgical break period was comparable between regions of England for IDS patients. For PDS

Table 1. Baseline characteristics of study cohort, showing total cohort and treated-to-schedule vs delayed cohorts (n = 1517)

Characteristic	Total (*n* = 1517)	Treated to schedule (*n* = 981)[1]	Delayed > 7 days (*n* = 536)[1]	SMD[2]
Regimen				
Carboplatin + paclitaxel (3-weekly)	985 (69%)	682 (69.2%)	303 (30.8%)	-0.008
Carboplatin + paclitaxel (weekly)	67 (4.4%)	30 (44.8%)	37 (55.2%)	0.003
Carboplatin (3-weekly)	460 (30%)	266 (57.8%)	194 (42.2%)	-0.002
Carboplatin (weekly)	5 (0.3%)	3 (60%)	2 (40%)	-0.001
Age at first treatment (IQR)	66 (58,73)	66 (57, 73)	68 (59, 75)	0.013
Stage at diagnosis				
3	95 (6.3%)	54 (56.8%)	41 (33.2%)	0.001
3A/B	204 (13%)	152 (74.5%)	52 (25.5%)	-0.015
3C	784 (52%)	511 (65.2%)	273 (34.8%)	-0.011
4	434 (29%)	264 (60.8%)	170 (29.2%)	0.022
Surgery				
Primary debulking surgery	499 (33%)	347 (69.5%)	152 (30.5%)	-0.016
Interval debulking surgery	540 (36%)	364 (67.4%)	176 (32.6%)	0.004
No surgery	478 (32%)	270 (56.5%)	208 (43.5%)	0.012
Survival status				
Alive	328 (22.8%)	228 (23.2%)	100 (18.7%)	-
Dead	1,187 (78.2%)	751 (76.8%)	436 (81.3%)	-
Unknown	2 (0.1%)	2 (0.2%)		
Ethnicity				
Asian	55 (3.6%)	34 (58.2%)	21 (41.8%)	0.016
Black	21 (1.4%)	14 (66.6%)	7 (33.3%)	0.003
Chinese	3 (0.2%)	3 (100%)	0	-0.051
Mixed race	5 (0.3%)	4 (80%)	1 (20%)	0.011
Not stated	28 (1.8%)	20 (71.4%)	8 (28.6%)	0.021
Other	17 (1.1%)	9 (52.9%)	8 (47.1%)	0.007
Unknown	5 (0.3%)	3 (60%)	2 (40%)	0.004
White	1,383 (91%)	894 (64.6%)	489 (35.4%)	-0.01
Charlson comorbidity index				0.014
0	1,357 (89.5%)	880 (64.8%)	477 (35.2%)	-
1	102 (6.7%)	61 (59.8%)	41 (40.2%)	-
2	34 (2.2%)	23 (67.6%)	11 (32.4%)	-
3	17 (1.1%)	11 (64.7%)	6 (35.3%)	-
4	7 (0.5%)	6 (86%)	1 (14%)	-
Index of multiple deprivation				
1—least deprived	336 (22%)	224 (66.6%)	112 (33.3%)	-0.005
2	356 (23%)	221(62.1%)	135 (37.9%)	-0.004
3	330 (22%)	225 (68.2%)	105 (31.8%)	0.006
4	283 (19%)	182 (64.3%)	101 (35.7%)	0.008
5—most deprived	212 (14%)	129 (60.8%)	83 (39.2%)	-0.005
Bevacizumab treatment	203 (13%)	131 (64.5%)	72 (35.5%)	-0.007
Body mass index (IQR)	25.5 (22.3, 29.4)	25.6 (22.3, 29.7)	25.4 (22.3, 28.8)	-0.013
Unknown	203 (13.4%)	113 (7.4%)	70 (4.6%)	

[1]*n* (%); Median (IQR).
[2]Abbreviation: SMD, standardised mean difference of effect size between treated to schedule and delayed groups.

patients, hospitals in the Southeast region of England showed a slightly longer time for patients to receive chemotherapy after surgery. This finding warrants further investigation of causes related to increased waiting times for patients in this area. The impact of surgical break on survival outcomes was not investigated as part of this study as the exposure of interest was chemotherapy treatment delay.

Delays to chemotherapy can occur for many reasons, such as allowing time to recover from toxicity, hospital scheduling, and capacity issues and patient preference.[29] The high
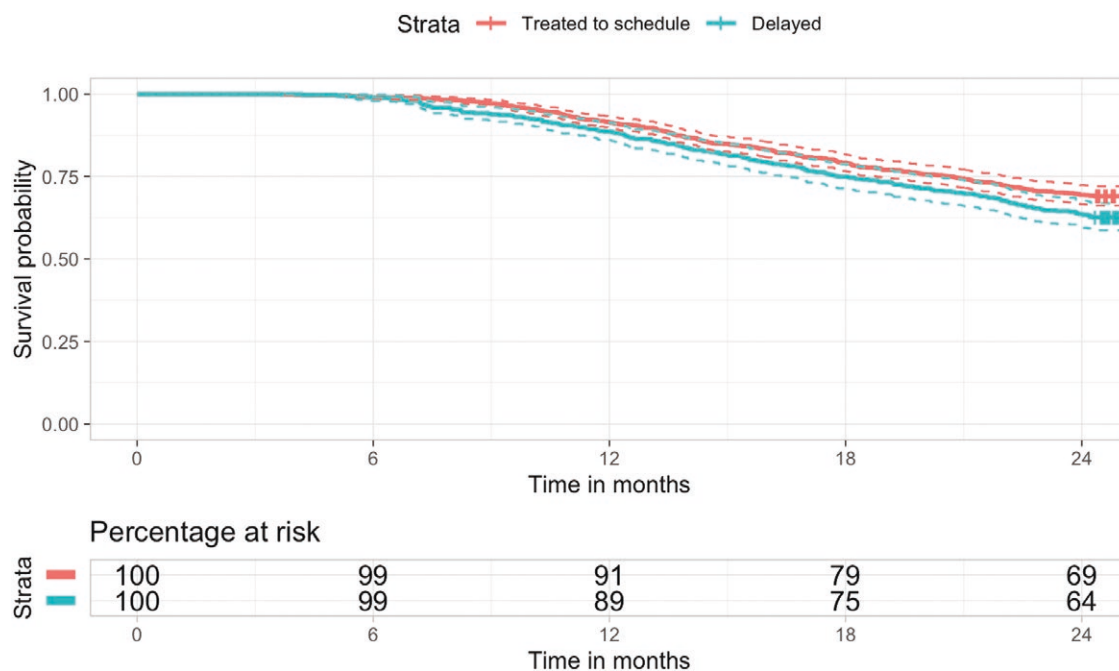
Figure 2. Kaplan-Meier survival curve comparing 2-year overall survival between patients who experienced inter-cycle delays > 7 days and those who were treated to schedule.
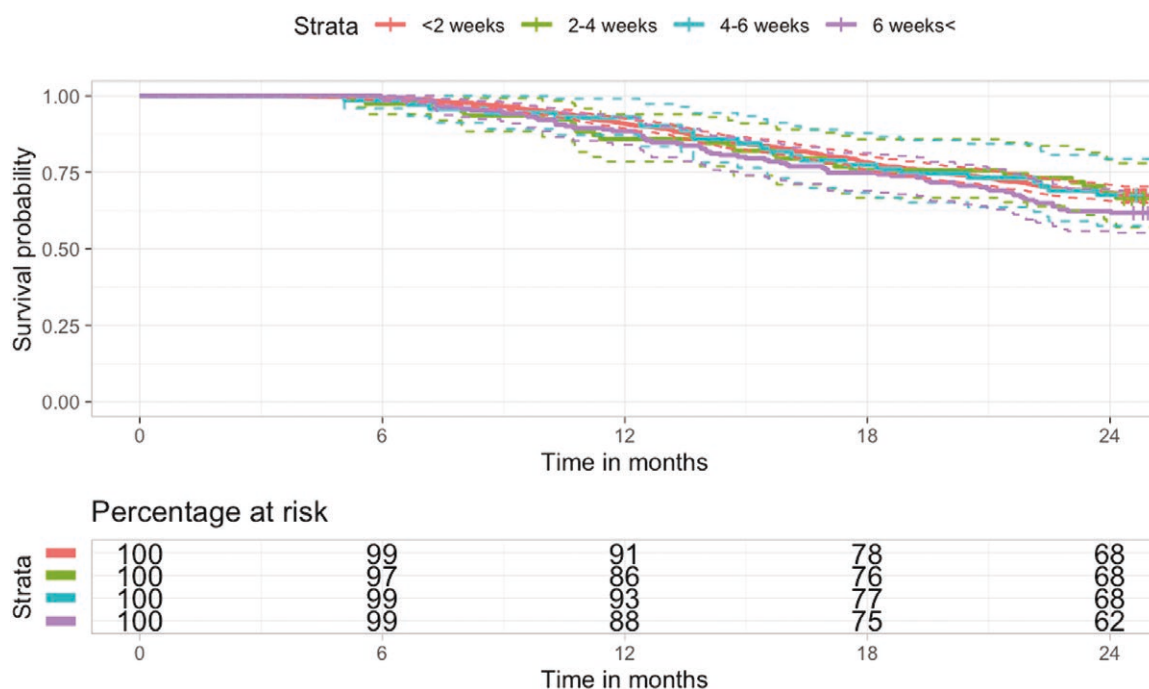

Figure 3. Kaplan Meier survival curve comparing 2-year overall survival between patients experiencing different lengths of treatment delay.

Table 2. Cox proportional hazards regression analysis.

Characteristic	HR[1]	95% CI[1]	*P*-value
Treatment delay > 7 days	1.00	0.83, 1.20	0.99

[1] CI, confidence interval; HR = hazard ratio.

frequency of treatment delays in this study, and reported by other authors, suggests that toxicity burden is high in patients with advanced-stage ovarian cancer. Findings from this study can support clinicians to prioritize toxicity management and QoL in patients with advanced-stage ovarian cancer being treated with platinum-based chemotherapy. Improved toxicity management strategies such as the use of Electronic Patient Reported Outcome Measures (EPROMS) may be applicable in patients with advanced-stage ovarian cancer, so that
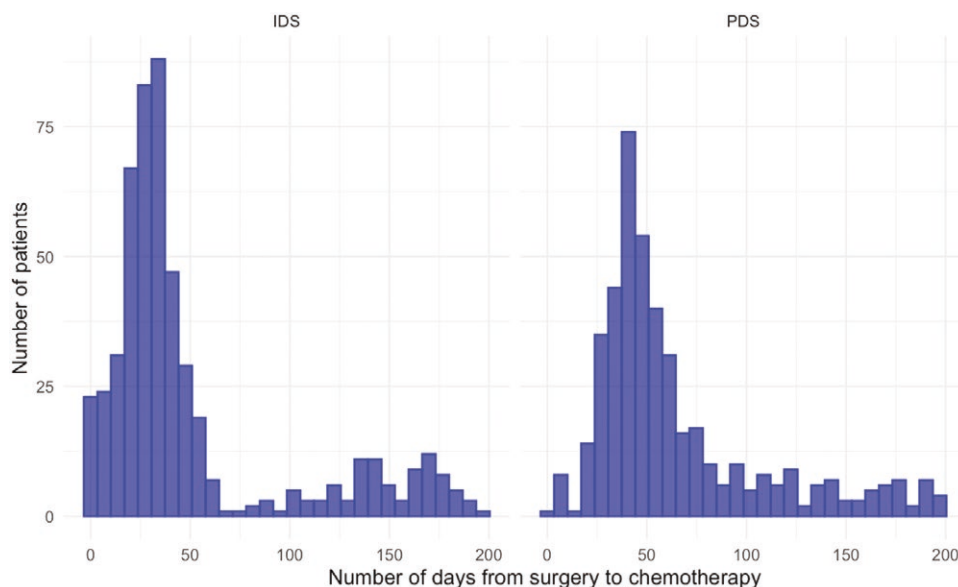
Figure 4. Histogram showing time from surgery date to date of next chemotherapy for patients receiving primary debulking surgery (PDS) or interval debulking surgery (IDS).

treatment-related toxicity can be managed at earlier stages to prevent escalation, requiring clinical intervention, or hospital admission.[30] The time cost, financial burden and opportunity costs of undergoing chemotherapy treatment should also be considered within this context of poor survival outcomes.

The study period preceded the introduction of PARP-inhibitors as standard of care treatment, which were therefore not considered as part of this study. As the exposure of interest was platinum-based chemotherapy, this limitation does not impact the validity of findings presented. Histology and residual disease status following surgery are known to be important prognostic factors for survival in ovarian cancer,[31,32] however these data were not available in the dataset and could not be included as covariates in survival analyses. Similarly, dose reduction and relative dose intensity could not be calculated as creatinine values were not available. Despite these limitations, this study benefits from the large cohort size and the availability of national population data, representing wide coverage of cancer treating hospitals in England.

Conclusions

Our study demonstrated that inter-cycle delays days in standard first-line chemotherapy regimens were not significantly associated with 2-year overall survival outcomes in patients with advanced-stage ovarian cancer. Findings from this study can support clinicians to prioritize toxicity management and quality of life in ovarian cancer patients treated with platinum-based chemotherapy, rather than prioritizing completion of treatment to schedule despite high toxicity burden.

Author contributions

Luke Steventon, Pinkie Chambers Shibani Nicum, Samixa Shah, Kenneth K.C. Man, Rowan Miller, Martin D. Forster conceptualized the study. Ofran Almossawi, Shira Hasson, Kenneth K.C. Man, Luke Steventon, and Pinkie Chambers conducted the statistical analysis. Luke Steventon wrote the first draft of the manuscript under the supervision of Pinkie Chambers and Kenneth K.C. Man. All authors were involved in interpreting, drafting, and revising the manuscript.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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Conflicts of interest

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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