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Original Article

Prognostic influence of an early time to chemotherapy following primary cytoreductive surgery for advanced epithelial ovarian cancer

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No potential conflict of interest relevant to this article was reported.

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ABSTRACT

Objective: The current investigation analyzes the prognostic role of the time to chemotherapy (TTC) interval following primary cytoreductive surgery for patients with advanced epithelial ovarian cancer.
Methods: Characteristics and outcome data for 509 consecutive patients with stage IIIB–IVB ovarian, fallopian tube, and peritoneal cancer who had primary cytoreductive surgery between January 2000 and December 2019 are utilized. A univariate Cox regression determined the association of categorical variables with progression-free survival (PFS) and overall survival (OS). Significant variables ($p \leq 0.05$) on univariate analysis were applied to Cox proportional hazard regression.
Results: The median TTC was 19 days and overall follow-up was 62.2 months. The PFS and OS were 25.5 months and 78.4 months for the study cohort plus 28.4 months and OS 84.5 months for patients rendered grossly disease-free. An early TTC (7–14 vs. 15–21 vs. 22–28 vs. >28 days) was associated with an improved PFS (41.7 vs. 30.6 vs. 18.9 vs. 17.9 months; $p<0.001$) and OS (132.7 vs. 104.6 vs. 56.5 vs. 48.0 months; $p<0.001$). The performance status, histology, disease distribution, dimension of residual disease, and categorical plus continuous TTC were predictors of PFS and OS. The use of maintenance therapy was also a predictor of PFS, and the route of chemotherapy administration was a predictor of OS.
Conclusions: For advanced epithelial ovarian cancer, a TTC of less than 21-days was observed to independently improve the PFS and OS. A 7–14 days TTC trended towards a further extension of the OS.

Keywords: Ovarian Cancer; Primary Cytoreductive Surgery; TTC

Synopsis
Chemotherapy was administered as early as possible after extensive primary cytoreductive surgery for patients with stage IIIB-IV epithelial ovarian cancer. Early time to chemotherapy improved survival. Complete recovery from surgery before chemotherapy is not essential.

INTRODUCTION

The treatment of advanced-stage epithelial ovarian cancer (EOC) has evolved over decades [1,2]. Cytoreductive surgery resulting in the absence of macroscopic residual disease (R0) is associated with improved progression-free survival (PFS) and overall survival (OS) in primary, neoadjuvant, and recurrent disease settings [3-11]. However, an optimal time to chemotherapy (TTC) interval following primary cytoreductive surgery has not been established. Laboratory investigators have observed a surgically induced, time-limited, increased Gompertzian kinetic growth rate of cancer cells to augment chemosensitivity, most significantly for microscopic disease [12,13]. Inconsistent deductions have been drawn about an association of the TTC with survival following primary and interval cytoreduction in retrospective observational, post-trial singular, and collective studies, plus meta-analyses [14-24]. The primary objective of the current study is to explore the influence of a TTC as early as possible on PFS and OS for advanced-stage EOC relative to prognostic factors in prior TTC investigations and previously limited to primary cytoreductive studies.

MATERIALS AND METHODS

A data set for this study cohort was retrieved for consecutive patients with stage IIIB-IVB (International Federation of Gynecology and Obstetrics; FIGO 2014) epithelial ovarian, fallopian tube, and peritoneal cancers (grouped as EOC) who had primary cytoreductive surgery between January 2000 and December 2019. Demographic, clinical, histologic, operative, chemotherapeutic, and outcome data were prospectively entered into a statistical database. Since the primary author performed cytoreduction and managed all patients in community hospitals with information de-identified for analysis, the study was exempted from Institutional Review Board approval (Pearl Pathways, Indianapolis, IN, USA).

The present study aimed to determine the prognostic impact of a TTC without delay, with an operative objective of R0 and the primary endpoints of PFS and OS. A maximal surgical effort was utilized unless residual disease ≤5 mm was precluded by the distribution of metastatic disease. Previously described procedures utilized in a surgical scoring system to document complexity were employed to achieve R0 (**Table S1**) [4]. Neoadjuvant chemotherapy with interval cytoreduction was utilized for patients with a prohibitive risk of surgical morbidity or metastatic disease that minimizes the probability of achieving R0 per imaging studies [10,11]. Patients with a moderate or severe baseline Charlson comorbidity index required preoperative medical clearance [25,26]. Unresectable hepatic metastases, extra-abdominal metastatic disease, portal vein encasement, or small bowel involvement minimizing the probability of R0 were treated with neoadjuvant chemotherapy. Other decisions about the prospect of R0 based on computed tomography (CT) or magnetic resonance imaging (MRI) findings were individualized. For example, although encasement of the spleen with extension to the lateral pancreas and gastric serosa was resectable, further confluent encasement of the splenic flexure of the colonic mesentery and stomach were contraindications to surgery. While still in-house or shortly after discharge, chemotherapy was intended for patients who met discharge criteria, had stabilization of comorbidities, a grade 0–2 Clavien-Dindo complication, or completed the preliminary phase of therapeutics for a Clavien-Dindo grade 3 complication [27]. For example, the TTC was not delayed for patients requiring wound care or antibiotics. Those who required interventional drainage of an infected collection and IV antibiotics received chemotherapy while treated with subsequent oral antibiotics. A granulocyte colony-stimulating factor was consistently utilized to prevent neutropenia after a ≤21-day TTC.

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Baseline demographic, clinical, pathologic, and therapeutic characteristics were categorized (**Table 1**). The age-adjusted Charlson Comorbidity Index (ACCI) characterized the age with adjustments for comorbidities, and the Eastern Cooperative Oncology Group (ECOG) performance status represented the functional status [25,26,28]. The disease distribution was categorized with both the 2014 FIGO stage (IIIB, IIIC vs. IVA, B) and a modification of the Memorial Sloan Kettering Cancer Center criteria to stratify the extent of upper abdominal disease (UAD) for stage IIIB, IIIC EOC [7]. Metastatic nodularity or confluent disease >1 cm cephalad to the greater omentum was categorized as extensive UAD, modified to include parenchymal hepatic and splenic, pleural, and cardiophrenic nodal metastases. Minimal UAD was limited to ≤1 cm metastatic disease cephalad to the greater omentum. The absence of UAD required the disease to be caudal to the transverse colon. Operations were categorized with a previously described surgical complexity scoring system based on the complexity of procedures and the number performed (**Table S1**) [4]. The TTC was stratified as 7–14, 15–21, 22–28, and >28 days and used as a continuous variable, with the cytoreductive outcome as R0, ≤5, and >5 mm of residual disease. Complications were categorized with the Clavien-Dindo grading system [27].

Table 1. Demographic, pathologic, and operative factors (n=509)

Patient characteristic	7–14 days TTC	15–21 days TTC	22–28 days TTC	>28 days TTC	p-value*
Median days	12	18	26	35	
No. of patients	147 (28.9%)	141 (27.7%)	81 (15.9%)	140 (27.5%)	
Age (yr)					0.474
<62.42	75 (51.0%)	77 (54.6%)	39 (48.1%)	64 (45.7%)	
≥62.42	72 (49.0%)	64 (45.4%)	42 (51.9%)	76 (54.3%)	
Age-ACCI					0.341
0–1	56 (38.1%)	53 (37.6%)	31 (38.3%)	46 (32.9%)	
2–3	80 (54.4%)	74 (52.5%)	37 (45.7%)	73 (52.1%)	
≥4	11 (7.5%)	14 (9.9%)	13 (16.0%)	21 (15.0%)	
Race					0.850
Caucasian	116 (78.9%)	110 (78.0 %)	65 (80.2%)	111 (79.3%)	
Black	3 (2.0%)	2 (1.4%)	1 (2.1%)	3 (1.8%)	
Hispanic	18 (12.2%)	22 (15.6%)	10 (12.3%)	23 (16.4%)	
Asian	9 (6.1%)	7 (5.0%)	5 (6.2%)	3 (2.1%)	
Native American	1 (0.7%)	0	0	0	
ECOG					0.210
0–1	69 (46.9%)	56 (39.7%)	28 (34.6%)	48 (34.3%)	
2	67 (45.6%)	74 (52.2%)	47 (58.0%)	74 (52.9%)	
3	11 (7.5%)	11 (7.8%)	6 (7.4%)	18 (12.9%)	
CA-125					0.094
≤500	61 (41.5%)	43 (30.9%)	19 (23.8%)	36 (25.2%)	
501–1,000	47 (32.0%)	60 (43.2%)	40 (50.0%)	63 (44.1%)	
>1,000	39 (26.5%)	38 (27.0%)	22 (27.7%)	41 (29.3%)	
Histology					0.101
Serous	107 (72.8%)	103 (73.0%)	57 (70.4%)	100 (71.4%)	
Endometroid/Mixed	19 (12.9%)	21 (14.9%)	4 (4.9%)	17 (12.1%)	
Mucinous	4 (2.7%)	4 (2.8%)	4 (4.9%)	6 (4.3%)	
Clear cell	6 (4.1%)	4 (2.8%)	1 (1.2%)	2 (1.4%)	
Anaplastic	11 (7.5%)	9 (6.4%)	15 (18.5%)	15 (10.7%)	
Grade					0.638
1–2	25 (17.0%)	21 (14.9%)	12 (14.8%)	28 (20.0%)	
3	122 (83.0%)	120 (85.1%)	69 (85.2%)	112 (80.0%)	
Stage-FIGO 2014					0.095
IIIB, IIIC	127 (86.4%)	115 (81.6%)	59 (72.8%)	114 (81.4%)	
IVA, IVB	20 (13.6%)	26 (18.4%)	22 (27.2%)	26 (18.6%)	
Volume of ascites (L)					0.041
≤1	60 (40.8%)	38 (27.0%)	18 (22.2%)	43 (30.7%)	
>1	87 (59.2%)	103 (73.0%)	63 (77.8%)	97 (69.3%)	

(continued to the next page)

Table 1. (Continued) Demographic, pathologic, and operative factors (n=509)

Patient characteristic	7–14 days TTC	15–21 days TTC	22–28 days TTC	>28 days TTC	p-value*
Surgical complexity score					0.128
Low (≤3)	25 (17.0%)	22 (15.6%)	10 (12.3%)	22 (15.7%)	
Intermediate (4–7)	75 (51.0%)	64 (45.4%)	28 (34.6%)	65 (46.4%)	
High (≥8)	47 (32.0%)	55 (39.0%)	43 (53.1%)	53 (37.9%)	
Extent of upper abdominal disease					0.002
Absent	49 (33.3%)	37 (26.2%)	8 (9.9%)	33 (23.6%)	
Minimal	37 (25.2%)	29 (20.6%)	31 (38.3%)	39 (27.9%)	
Extensive	61 (41.5%)	75 (53.2%)	42 (51.9%)	68 (48.6%)	
Residual disease (macroscopic)					0.069
R0 (none)	132 (89.8%)	113 (80.1%)	69 (85.2%)	128 (91.4%)	
≤5 mm	14 (9.5%)	23 (16.3%)	10 (12.3%)	8 (5.7%)	
>5 mm	1 (0.7%)	5 (3.5%)	2 (2.5%)	4 (2.9%)	
Clavien-Dindo grade 2–3 complication					0.043
Yes	18 (12.2%)	31 (22.0%)	16 (19.8%)	12 (8.6%)	
No	129 (87.8%)	110 (78.0%)	65 (80.2%)	128 (91.4%)	
Clavien-Dindo grade 2–3 infectious complication					0.573
Yes	20 (13.6%)	15 (10.6%)	8 (9.9%)	12 (8.6%)	
No	127 (86.4%)	126 (89.4%)	73 (90.1%)	128 (89.2%)	
Clavien-Dindo grade 1–2 complications post-chemotherapy infectious†					0.739
Any	9 (6.1%)	7 (5.0%)	3 (3.7%)	5 (3.6%)	
None	138 (93.9%)	134 (95.0%)	78 (96.3%)	135 (96.4%)	
Route of chemotherapy					0.709
Intravenous	140 (95.23%)	133 (94.3%)	77 (95.1%)	136 (96.5%)	
Intraperitoneal	7 (4.8%)	8 (5.7%)	4 (4.9%)	4 (3.5%)	
Maintenance therapy‡					<0.001
Administered	44 (29.9%)	18 (12.8%)	8 (9.9%)	9 (6.4%)	
Not administered	103 (70.1%)	123 (87.2%)	73 (90.1%)	131 (93.6%)	

Values are presented as number of patients (%).
ACCI, adjusted Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.
*χ^2 tests used to compare the distribution of variables between TTC categories. †Clavien-Dindo grade 1–2 complications post-chemotherapy were unrelated to chemotherapy; were due to urinary tract or wound infections. ‡Maintenance therapy includes all bevacizumab and poly adenosine diphosphate-ribose polymerase inhibitors.

The TTC was defined as the time interval from the date of primary cytoreductive surgery to the administration of chemotherapy. PFS was defined as the time interval from cytoreduction to disease progression, recurrence, or the most recent follow-up. The OS was defined as the time interval from cytoreduction to the date of death or the most recent follow-up. A recurrence was diagnosed with a ≥50% rise in CA-125 or HE-4, confirmation or further elevation within 1-2 weeks, and subsequent imaging with a CT scan, MRI, or PET/CT. A solitary lesion of <2 cm was confirmed to be a recurrence with a CT-guided biopsy when possible. Prior studies to determine the influence of primary cytoreductive surgery on survival and those that included cytoreduction in a framework to explore the prognostic impact of a factor other than the TTC were termed cytoreductive settings.

Pearson's χ^2 was used to compare the distribution variables for TTC groups. A univariate Cox proportional hazards regression analysis was performed to identify factors associated with PFS and OS. Linear regression was also used to evaluate the prediction of survival with a daily TTC. Factors significant on univariate analysis were included in a multivariate Cox proportional hazards regression model with a backward conditional method to retain independently significant cofactors. The variance inflation factor (VIF) was determined for cofactors in the multivariate analysis and confirmed to be ≤2.5. Survival curves with PFS and OS percentages were approximated with a Kaplan-Meier estimator using a log-rank test. All statistical analyses were considered significant with a p-value ≤0.05. Statistical analysis was performed with IBM SPSS 26 statistics for Mac OS 11.5 (IBM Corp, Armonk, NY, USA).

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RESULTS

Five hundred and fifty-two consecutive patients with stage IIIB–IVB EOC were identified, of which 509 patients were included in the analysis. Exclusion criteria included a low malignant potential EOC (n=15), neoadjuvant chemotherapy (n=14), chemotherapy refusal (n=2), postoperative mortality without chemotherapy (n=4), relocation (n=3), and unavailable TTC data (n=5). The median TTC was 19 days (range, 7–67], and the median overall follow-up was 62.2 months. R0 was achieved for 442 (86.8%) patients, ≤5 mm residual disease for 55 (10.8%), and >5 mm residual disease for 12 (2.4%). All patients received intravenous or intravenous/intraperitoneal (IV/IP) administration of platinum-based adjunctive therapy. The first cycle of chemotherapy was administered by a Gynecologic Oncologist (author or former associate) for 196 (38.5%) patients and by a Medical Oncologist for 313 (61.5%). Examination of the distributions of characteristics within TTC groups revealed, ascitic volume, extent of UAD, and Clavien-Dindo grading system (grade 2–3; overall) to be associated with different patterns of TTC delay (**Table 1**). Surgical complications post-chemotherapy were limited to urinary tract infections treated with oral antibiotics and wound infections treated with local wound care and antibiotics selectively (**Table 1**).

The overall PFS was 25.5 months, and the OS was 78.4 months. At the time of analysis, 146 (28.6%) patients were progression-free with a median follow-up of 106.6 months, and 226 (44.3%) were alive with a median follow-up of 101.3 months. The PFS was 28.4 months and OS 84.5 months for R0 patients. On univariate Cox regression, a continuous TTC was associated with an overall PFS (hazard ratio [HR]=1.03; confidence interval [CI]=1.02–1.04; p≤0.001) and OS (HR=1.03; CI=1.02–1.05; p<0.001), and for the R0 subgroup; PFS (HR=1.03; CI=1.02–1.04; p<0.001) and OS (HR=1.04; CI=1.03–1.05; p<0.001). Linear regression analysis of an association between a continuous TTC with hazards of disease progression and survival for the study cohort yielded significant linear and cubic models (**Fig. S1**). A categorical TTC (7–14 vs. 15–21 vs. 22–28 vs. >28 days) extension was associated with a declining PFS (41.7 vs. 30.6 vs. 18.9 vs. 17.9 months; p<0.001), and OS (132.7 vs. 104.6 vs. 56.5 vs. 48.0 months; p<0.001) (**Fig. 1A**). A delayed TTC for R0 patients also reduced PFS (45.6 vs. 40.4 vs. 21.0 vs. 18.7 months; p<0.001) and OS (137.3 vs. 121.4 vs. 57.1 vs. 48.7 months; p<0.001) (**Fig. 1B**). The TTC additionally influenced survival for patients with extensive UAD rendered R0; PFS (26.3 vs. 23.7 vs. 22.4 vs. 13.8 months; p=0.008) and OS (95.3 vs. 79.2 vs. 55.8 vs. 30.6 months; p=0.004) (**Fig. 1C**). A univariate Cox regression also associated the median age, ACCI, ECOG, histology, grade, stage ascitic volume, extent of UAD, surgical complexity, and residual disease with PFS and OS (**Tables 2** and **3**). The usage of maintenance therapy was also associated with PFS (**Table 2**). The route of chemotherapy administration was associated with the OS (**Table 3**). Race, CA-125, and an infectious complication did not influence PFS or OS (**Fig. S2**). A multivariate Cox proportional hazards regression confirmed the ECOG, histology, the extent of UAD, residual disease, continuous and categorical TTC, and usage of maintenance therapy to be associated with PFS (**Tables 2** and **4**). The ACCI, ECOG, histology, extent of UAD, residual disease, continuous and categorical TTC, and route of chemotherapy administration were associated with OS (**Tables 3** and **4**).

DISCUSSION

The current study demonstrates an expeditious TTC following primary cytoreductive surgery for advanced stage EOC to be independently associated with an improved PFS and

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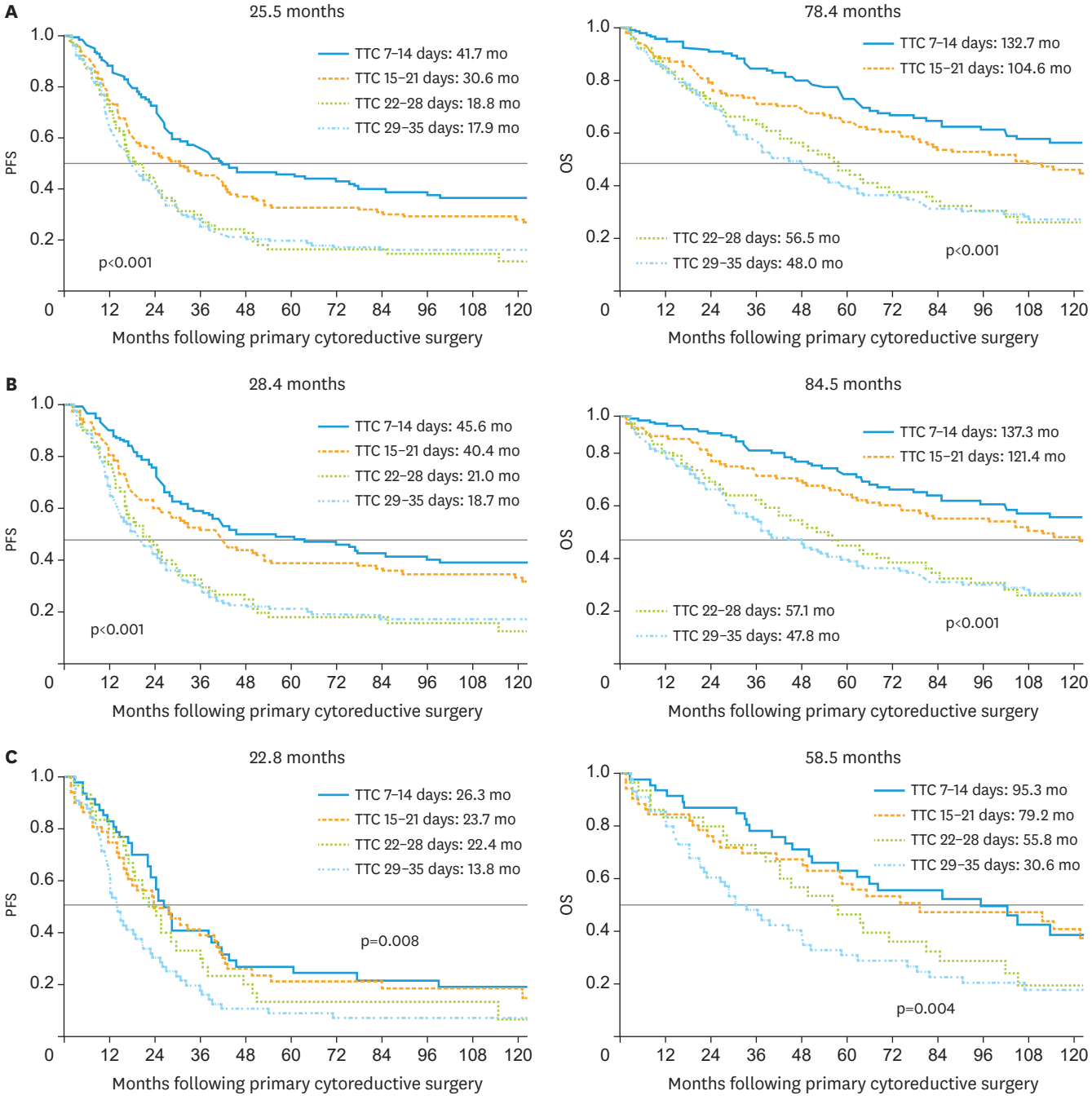

Fig. 1. Kaplan-Meier survival curves with log-rank to estimate PFS and OS stratified by the TTC for the: (A) study cohort, (B) R0 subgroup (absence of macroscopic residual disease), and (C) R0 subgroup with extensive upper abdominal disease.
OS, overall survival; PFS, progression-free survival; TTC, time to chemotherapy.

OS, without case selection, restrictive eligibility, or an increased risk of post-chemotherapy complications (**Tables 1-4**). Predictors of survival in prior TTC and cytoreductive studies were combined with prognostic factors limited to cytoreductive settings to reinforce the investigation. The age, ECOG, histology, grade, stage, ascitic volume, residual disease size, and route of chemotherapy administration were predictors of PFS and OS in cytoreductive settings and TTC studies [[3-9,14-24,29-31]. Associations of the ACCI, the extent of UAD,

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Table 2. Cox proportional regression univariate analysis and model for factors associated with PFS

Categorical variable	Univariate HR (95% CI)	p-value*	Multivariate HR (95% CI)	p-value†
Median age (62.42 yr)				
Below median age	1.00		-	NS
Above median age	1.37 (1.16–1.69)	**0.003**		
Age-ACCI				
0–1	1.00	**<0.001**	1.00	0.058
2–3	1.36 (1.08–1.70)	**0.008**	1.21 (0.96–1.54)	0.110
≥4	1.95 (1.39–2.73)	**<0.001**	1.54 (1.06–2.23)	**0.022**
ECOG				
0–1	1.00	**<0.001**	1.00	**0.014**
2	1.63 (1.30–2.04)	**<0.001**	1.13 (0.88–1.46)	0.331
3	2.74 (1.92 –3.90)	**<0.001**	1.84 (1.24–2.74)	**0.003**
Histology				
Serous	1.00	**<0.001**	1.00	**<0.001**
Endometroid, mixed, other	0.44 (0.30–0.65)	**<0.001**	0.72 (0.48–1.10)	0.126
Mucinous	1.97 (1.17–3.32)	**0.009**	2.54 (1.48–4.35)	**<0.001**
Clear cell	0.73 (0.34–1.55)	0.697	2.00 (0.97–4.17)	0.063
Anaplastic	1.51 (1.08–2.12)	**0.009**	1.51 (1.07–2.14)	**0.019**
Grade				
1–2	1.00		-	NS
3	1.60 (1.18–2.15)	**0.002**		
Stage-FIGO 2014				
IIIB, IIIC	1.00		-	NS
IVA, IVB	1.38 (1.07–1.77)	**0.014**		
Volume of ascites (mL)				
<500	1.00		-	NS
≥500	1.82 (1.43–2.30)	**<0.001**		
Extent of upper abdominal disease				
Absent	1.00	**<0.001**	1.00	**0.002**
Minimal	2.15 (1.56–2.97)	**<0.001**	1.68 (1.17–2.40)	**0.005**
Extensive	3.11 (2.33–4.16)	**<0.001**	1.86 (1.29–2.67)	**<0.001**
Surgical complexity score				
Low (<3)	1.00	**<0.001**	1.00	0.600
Intermediate (4–7)	1.13 (0.81–1.56)	0.520	1.12 (0.80–1.59)	0.490
High (>8)	1.88 (1.35–2.60)	**<0.001**	1.44 (1.01–2.06)	**0.044**
Residual disease				
R0 (none)	1.00	**<0.001**	1.00	**<0.001**
≤5 mm residual disease	2.16 (1.50–3.03)	**<0.001**	1.81 (1.26–2.61)	**0.001**
>5 mm residual disease	3.91 (2.18–7.00)	**<0.001**	4.13 (2.21–7.69)	**<0.001**
TTC interval (days)				
7–14	1.00	**<0.001**	1.00	**<0.001**
15–21	1.38 (1.03–1.84)	**0.032**	1.26 (0.93–1.71)	0.131
22–28	2.15 (1.56–2.96)	**<0.001**	1.65 (1.18–2.30)	**0.003**
>28	2.10 (1.59–2.78)	**<0.001**	1.20 (1.50–2.67)	**<0.001**
Maintenance therapy‡				
Used	1.00		1.00	
None	2.08 (1.50–2.88)	**<0.001**	1.58 (1.13–2.22)	**0.008**

ACCI, adjusted Charlson Comorbidity Index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NS, not significant; PFS, progression-free survival; TTC, time to chemotherapy.
*p-value for univariate Cox regression; †p-value for multivariate Cox regression; p≤0.05 in bold. ‡The maintenance included bevacizumab, olaparib, niraparib, or a combination ± somatic or genetic BRCA mutation.

surgical complexity, and usage of maintenance therapy with survival were previously limited to cytoreductive settings [4,5,7-9,30,31]. The ECOG performance status influenced PFS and OS by quantifying a reduction of functional capability secondary to metastatic disease and age-related frailty (**Tables 2-4**) [28]. The ACCI was a predictor of the OS with a baseline prognosis for life expectancy owing to advancing age with adjustments for comorbidity

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Table 3. Cox regression univariate analysis and Cox model for factors associated with OS

Categorical variable	Univariate HR (95% CI)	p-value*	Multivariate HR (95% CI)	p-value†
Median age (62.42 yr)				
Below median age	1.00		-	NS
Above median age	1.58 (1.25–2.00)	**<0.001**		
Age-AACI				
0–1	1.00	**<0.001**	1.00	**0.001**
2–3	1.56 (1.20–2.03)	**<0.100**	1.44 (1.10–1.88)	**0.009**
≥4	2.71 (1.87–3.93)	**<0.001**	2.00 (1.35–2.96)	**<0.001**
ECOG				
0–1	1.00	**<0.001**	1.00	**0.005**
2	2.01 (1.54–2.62)	**<0.001**	1.57 (1.16–2.11)	**0.003**
3	2.87 (1.91–4.30)	**<0.001**	1.18 (1.16–2.80)	**0.012**
Histology				
Serous	1.00	**<0.001**	1.00	**<0.001**
Endometroid, mixed, other	0.52 (0.34–0.81)	**0.003**	0.97 (0.61–1.53)	0.889
Mucinous	2.88 (1.68–4.96)	**<0.001**	3.79 (2.16–6.60)	**<0.001**
Clear cell	0.75 (0.31–1.82)	0.533	1.59 (0.65–3.92)	0.313
Adenocarcinoma	1.95 (1.34–2.82)	**<0.001**	2.05 (1.39–3.02)	**<0.001**
Grade				
1–2	1.00		-	NS
3	1.45 (1.05–2.02)	**0.026**		
Stage-FIGO 2014				
IIIB, IIIC	1.00		-	NS
IVA, IVB	1.25 (1.03–2.07)	**0.039**		
Volume of ascites (mL)				
≤500	1.00		-	NS
>500	2.04 (1.55–2.69)	**<0.001**		
Extent of upper abdominal disease				
None	1.00	**<0.001**	1.00	**0.004**
Minimal	2.05 (1.42–2.97)	**<0.001**	1.59 (1.05–2.32)	**0.029**
Extensive	3.00 (2.15–4.18)	**<0.001**	1.90 (1.28–2.80)	**0.001**
Surgical complexity score				
Low (<3)	1.00	**0.001**	-	NS
Intermediate (4–7)	1.06 (0.73–1.55)	0.751		
High (≥8)	1.67 (1.16–2.42)	**0.006**		
Residual disease (macroscopic)				
R0 (none)	1.00	**<0.001**	1.00	**<0.001**
≤5 mm	2.10 (1.45–3.05)	**<0.001**	1.91 (1.26–2.89)	**0.002**
>5 mm	2.98 (1.40–6.38)	**0.005**	3.60 (1.65–7.83)	**0.001**
TTC interval (days)				
7–14	1.00	**<0.001**	1.00	**<0.001**
15–21	1.38 (0.97–1.95)	0.075	1.41 (0.99–2.01)	0.061
22–28	2.44 (1.68–3.53)	**≤0.001**	1.94 (1.33–2.83)	**<0.001**
≥28	2.48 (1.80–3.43)	**≤0.001**	2.43 (1.75–3.38)	**<0.001**
Route of chemotherapy				
Intravenous	1.00		1.00	
Intraperitoneal	0.40 (0.18–0.89)	**0.027**	0.39 (0.17–0.89)	**0.025**

ACCI, adjusted Charlson Comorbidity Index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NS, not significant; TTC, time to chemotherapy.
*p-value for univariate Cox regression; †p-value for multivariate Cox regression; p≤0.05 in bold.

(**Table 3**) [25,26]. Extensive UAD can occur due to both delayed diagnosis and poor prognostic tumor biology, resulting in rapid growth and an increased risk of baseline and acquired chemoresistance. The use of maintenance therapy was limited to 79 (15.5%) patients selectively, with multiple peritoneal implants rendered R0 or with ≤5 mm residual disease following clinically disease-free serological monitoring and imaging studies. The frequency of maintenance therapy inversely paralleled TTC due primarily to a higher probability of a complete response to chemotherapy (**Table 1**). The use of bevacizumab, a poly adenosine

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Table 4. Cox proportional regression model for factors associated with: PFS vs. OS

Categorical variable	Multivariate HR (95% CI)	p-value*	Multivariate HR (95% CI)	p-value†
Median age (62.42 yr)				
Below median age	-	NS	-	NS
Above median age				
Age-ACCI				
0–1	-	NS	1.00	**0.003**
2–3			1.39 (1.06–1.82)	**0.017**
≥4			1.94 (1.31–2.87)	**0.001**
ECOG				
0–1	1.00	**0.019**	1.00	**0.010**
2	1.10 (0.86–1.42)	0.443	1.51 (1.13–2.03)	**0.017**
3	1.78 (1.20–2.63)	**0.004**	1.75 (1.12–2.72)	**0.014**
Histology				
Serous	1.00		1.00	**<0.001**
Endometroid, mixed, other	0.08 (0.47–1.07)	0.103	0.95 (0.60–1.50)	0.815
Mucinous	2.49 (1.46–4.27)	**<0.001**	3.78 (2.16–6.61)	**<0.001**
Clear cell	1.89 (0.91–3.91)	0.087	1.44 (0.58–3.53)	0.430
Anaplastic	1.41 (1.06–2.10)	**0.022**	2.02 (1.38–2.45)	**<0.001**
Grade				
1–2	-	NS	-	NS
3				
Stage-FIGO 2014				
IIIB, IIIC	-	NS	-	NS
IVA, IVB				
Volume of ascites (mL)				
<500	-	NS	-	NS
≥500				
Extent of upper abdominal disease				
Absent	1.00	**0.001**	1.00	**0.002**
Minimal	1.70 (1.19–2.42)	**0.003**	1.60 (1.08–2.37)	**0.020**
Extensive	1.91 (1.34–2.76)	**<0.001**	1.97 (1.34–2.89)	**<0.001**
Surgical Complexity score				
Low (<3)	1.00	0.056	-	NS
Intermediate (4–7)	1.14 (0.81–1.61)	0.440		
High (>8)	1.46 (1.02–2.08)	**0.037**		
Residual disease; R0	1.00	**<0.001**	1.00	**<0.001**
≤5 mm residual disease	1.81 (1.26–2.60)	**0.001**	1.90 (1.23–2.86)	**0.002**
>5 mm residual disease	4.32 (2.33–7.97)	**<0.001**	3.76 (1.73–8.18)	**<0.001**
TTC (continuous)	1.02 (1.02–1.04)	**<0.001**	1.28 (1.02–1.04)	**<0.001**
Route of Chemotherapy				
Intravenous	NA		1.00	**0.023**
Intraperitoneal			0.39 (0.17–0.88)	
Maintenance therapy				
None	1.00	**0.008**	NA	
Yes	1.58 (1.13–2.10)			

ACCI, adjusted Charlson Comorbidity Index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NA, not applicable due to being not significant on univariate analysis; NS, not significant; TTC, time to chemotherapy.
*p-value for multivariate Cox regression for progression-free survival; †p-value for multivariate Cox regression for overall survival; p<0.05 in bold.

diphosphate-ribose polymerase inhibitor, or a combination for the current study cohort depended on the year of patient care, germline and somatic BRCA mutations, insurance coverage, and the physician administrating chemotherapy. Although maintenance therapy was demonstrated to improve PFS, the limited number of patients and variations used precluded stratification of maintenance therapy by the agents used and BRCA (**Tables 2** and **4**).

Although R0 for advanced EOC is consistently reported to optimize PFS and OS, the percentages of R0 reported in TTC and cytoreductive settings vary considerably due to

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case selection, restrictive eligibility, operative strategy, and possibly surgeon-dependency [3-11,14-24,30-32]. Achievement of R0 for 86.8% of the current study cohort without case selection other than a medical contraindication to surgery or metastatic disease noted with preoperative imaging that precluded R0 was equivalent to prior reports of a maximal surgical effort [8]. Accomplishment of R0 for 86.8% of patients in the current study cohort resulted in an equal distribution of R0 patients in the TTC subgroups and inclusion in the extensive UAD cohort (**Table 1**). Prior reports of the disease distribution to be prognostic, offset surgical complexity as a predictor of survival, and reduce but not neutralize the efficacy of achieving R0 were paralleled in this study (**Tables 2** and **3**) [4,5]. The extent of UAD offset the surgical complexity as a predictor of the TTC and survival by reflecting both the complexity of specific procedures and tumor biology. For example, a procedure was classified as a diaphragmatic peritonectomy if completed for numerous 1-3 mm implants on 60% of the diaphragmatic peritoneum (minimal UAD) or replacement of the diaphragmatic peritoneum with confluent metastatic disease that extended through the coronary ligament to the bare area of the liver (extensive UAD). Of note, the contribution of postoperative chemotherapy administration as early as possible towards the efficacy of R0 was reduced but not precluded by extensive UAD (**Tables 2-4**, **Fig. 1C**).

The prognostic significance of chemosensitivity augmentation for EOC is theoretically possible through a surgically induced increased cancer cell kinetic growth rate linked to tumor biology, the size of the disease, and the duration of the increased kinetic growth rate [12,13]. Accordingly, the independent association of TTC with survival may be influenced by the category of TTC applied as a variable and cohort characteristics that reflect baseline platinum sensitivity and the probability of an increased kinetic growth rate to augment chemosensitivity. Application of TTC as binary variables, in categorical distributions, and as a continuous variable to analyze an association between TTC and survival has produced inconsistent results [14-24]. An association between the TTC and survival has been demonstrated by stratifying the TTC to binary variables, weekly intervals, and as a continuous variable [14,15]. The TTC in the current study was stratified to weekly intervals with a 7–14 days reference while also used as a continuous variable to assist in resolving contrasting results of prior studies that focused on determining the prognostic impact of a TTC without delay [14-17].

The TTC for EOC was originally stratified to weekly intervals in a 1989 GOG study that demonstrated equivalent survival in two platinum based arms for 349 patients with stage III EOC; 98 (28%) were R0 [14]. An inverse relationship (p=0.02) between TTC and OS was reported using a categorical range of 1–6 weeks. An analysis of 3,226 patients with stage IIB–IV EOC from three collective platinum-taxane phase III trials by Mahner et al. demonstrated a continuous weekly TTC delay to be associated with a declining OS (p=0.038) for 1,106 (34.3%) (873 [26.3%] with stage IIB–IIIB) R0 patients [15]. A more significant association between an early TTC and survival for the current R0 subgroup suggests a potential greater efficacy of TTC without delay for poor prognostic stage IIIB-IV EOC (**Fig. 1B**). Inclusion of 509 continuous patients with stage IIIB–IV EOC in the current study cohort with 86.8% rendered R0 assured patients with poor prognostic tumor biology to be in all TTC subgroups (**Table 1**). The PFS/OS for the R0 subgroup decreased most significantly with a 15–21 day TTC (40.4/121.4 months) delay to 22–28 days (21.0/57.1 months) (p<0.001) and corresponding PFS/OS's for R0 patients with extensive UAD diminished from 23.7/79.2 months to 22.4/55.8 months (PFS: p=0.008, OS: p=0.004) (**Tables 2** and **3**, **Fig. 1B and C**). A trend was noted for a 7–14 days TTC to extend OS relative to a 15–21 days TTC for the study cohort (p=0.061) (**Table 3**). Additionally, regression with cubic models for PFS and OS displayed a slightly

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steeper decline by extending a 7–14 days TTC to 15–21 days (**Fig. S1**). Hence, survival of the advanced-stage R0 cohort and subset of R0 patients with poor prognostic tumor biology were potentially increased by enhancing chemosensitivity of tumor, that was mainly but not confirmed to be uniformly discontinued between 22 and 28 days postoperatively. A post-trial study of 1,781 GOG-218 patients with stage III EOC and residual disease plus 81(4.4%) with R0 and stage IV disease was completed by Tewari et al. [16]. An OS benefit of a ≤25-day TTC (p=0.001) was exclusive to patients with R0. For 625 stage I–IV Asian patients, 209 (33.4%) that were R0 with a median TTC of 15 days, Feng et al. [17] reported the TTC not to be prognostic when adjusting for age, stage, and residual disease; but advised a TTC as early as possible, based on current evidence. Different criteria to define an optimal TTC may be required for Asian patients resulting from genetic variants of pharmacokinetics for cytotoxic agents [33]. Race was not prognostic in the current study, possibly due to the limited number of Asian patients (n=24, 4.07%), administration of adjunctive chemotherapy as early as possible (median, 17 days), and the therapeutic strategy for a recurrence (**Fig. S1**).

A limitation of this study was an analysis of operator-dependent cytoreductive outcomes by one investigator retrospectively. However, a single investigator provided operative and observational uniformity. Additionally, although small fractions of patients with ≤5 and >5 mm residual disease limited the scope of the investigation, the achievement of R0 for 86.8% of the study cohort ensured the inclusion of R0 patients in the subgroups of all categorical variables and confirmed the efficacy of R0 to be independent of the extent of UAD and TTC. Details of operative strategy and techniques to determine an independent association of factors with TTC utilized were not presented due to the study's focus on examining an association between TTC and survival. Analysis of the association between IV/IP chemotherapy and survival was limited due to selective usage for 23 (4.5%) patients who had R0 or ≤5 mm residual disease after extensive ablation and aspiration of peritoneal implants (**Table 3**).

In summary, a ≤21-day TTC was observed to optimize PFS and OS, and a 7–14 days TTC trended towards a further OS improvement. Extensive UAD did not completely offset the efficacy of an early TTC or R0, and the efficacy of achieving R0 was not entirely offset by TTC or the extent of UAD (**Tables 2**-**4**). Accordingly, the findings of the current study did not justify abbreviating the operative goal of R0 to facilitate the initiation of an early TTC. A future investigation is necessary to confirm the efficacy of an early TTC, its acceptable morbidity, applicability in settlings with a decreased fraction of R0, and determine homologous genetic recombinations that correlate with benefits from TTC ranges [34].

SUPPLEMENTARY MATERIALS

Table S1

The surgical complexity index and surgical procedures utilized procedures per the surgical complexity index to remove visible disease.

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Fig. S1

Plot of cubic and linear regression for hazard for PFS and OS.

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Fig. S2

OS Kaplan-Meier estimated survival curve with log-rank stratified by (A) the race (Asian vs. other races) and (B) the occurrence (occurrence vs. no occurrence of a postoperative infectious complication).

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