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Early initiation of chemotherapy following complete resection of advanced ovarian cancer associated with improved survival: NRG Oncology/Gynecologic Oncology Group study†

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Background: To determine whether time from surgery to initiation of chemotherapy impacts survival in advanced ovarian carcinoma.

Patients and methods: This is a post-trial *ad hoc* analysis of Gynecologic Oncology Group protocol 218, a phase III randomized, double-blind, placebo-controlled trial designed to study the antiangiogenesis agent, bevacizumab, in primary and maintenance therapy for patients with newly diagnosed advanced ovarian carcinoma. Maximum attempt at debulking was an eligibility criterion. Stage III patients, not stage IV, were required to have gross macroscopic or palpable residual disease following surgery. The survival impact of time from surgery to initiation of chemotherapy was studied using Cox regression models and stratified by treatment arm, residual disease and other clinical and pathologic factors.

Results: One thousand seven hundred eighteen assessable patients were randomized (stage III ($n = 1237$); stage IV ($n = 477$), including those with complete resection (stage IV only, $n = 81$), low-volume residual (≤1 cm, $n = 701$), and suboptimal (>1 cm, $n = 932$). On multivariate analysis, time to chemotherapy initiation was predictive of overall survival ($P < 0.001$), with the complete resection group (i.e. stage IV) encountering an increased risk of death when time to initiation of chemotherapy exceeded 25 days (95% confidence interval 16.6–49.9 days).

Conclusion: Survival for women with advanced ovarian cancer may be adversely affected when initiation of chemotherapy occurs >25 days following surgery. Our analysis applies to stage IV only as women with stage III who underwent complete resection were not eligible for this trial. These results, however, are consistent with Gompertzian first-order kinetics where patients with microscopic residual are most vulnerable.

Clinical Trials Identifier: NCT00262847.

Key words: ovarian cancer, chemotherapy initiation, complete resection, NRG Oncology/GOG

introduction

Epithelial ovarian cancer is the most lethal gynecologic malignancy, with nearly 42 000 cases diagnosed annually in Europe resulting in 29 000 deaths [1]. During 2015 in the United States, the American Cancer Society has estimated that there will be 21 290 new cases of ovarian cancer and 14 180 deaths [2]. Important clinicopathologic prognostic factors include International Federation of Gynecology and Obstetrics (FIGO) stage, tumor grade, cell type, age, performance status, and volume of residual disease following maximal cytoreductive surgery. Critical factors related to primary chemotherapy include platinum sensitivity, inherent and acquired drug resistance, and possibly, timing of initiation of chemotherapy following surgical debulking.

A recent meta-analysis by Mahner et al. pooled time from surgery to initiation of chemotherapy and outcome data for 3326 patients from three phase III randomized studies of primary therapy for ovarian cancer conducted in Europe by the AGO-OVAR and GINECO [3]. Delayed chemotherapy was associated with earlier disease recurrence and significantly decreased OS in patients with complete resection following initial surgery.

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To study this question further, we carried out an exploratory analysis on data collected on a phase III randomized trial in newly diagnosed ovarian carcinoma [4].

methods

background on GOG protocol 218

Gynecologic Oncology Group (GOG) protocol 0218 was a phase III, randomized, double-blind, placebo-controlled trial designed to determine whether the incorporation of bevacizumab with chemotherapy, and in the maintenance setting, improves progression-free survival (PFS) in women with newly diagnosed International Federation of Gynecology and Obstetrics stage III and IV ovarian, peritoneal, or fallopian tube carcinoma [4]. Patients with stage III disease and residual lesions ≤1 cm in maximal diameter were initially excluded but, after a protocol modification, they were permitted as long as gross macroscopic or palpable residual disease following surgery was present. Stage IV patients were eligible even if they had undergone complete resection in the abdomen. Patients were required to enroll between 1 and 12 weeks following surgery and begin cycle 1 within 14 days of randomization.

Between October 2005 and June 2009, 1873 patients were randomly assigned to one of three arms. At the time of primary analysis, a significant improvement in PFS was observed for the bevacizumab-throughout arm (i.e. carboplatin–paclitaxel–bevacizumab plus maintenance bevacizuamb) when compared with carboplatin–paclitaxel, with a hazard ratio (HR) of progression of 0.717 [05% confidence interval (CI) 0.625–0.824; $P < 0.001$] [4]. No significant differences in overall survival (OS) were observed. GOG 218 was the first of (thus far) eight phase III randomized trials involving five different antiangiogenesis drugs in primary or recurrent ovarian carcinoma to meet its primary end point, and led directly to European Medicines Agency approval of bevacizumab in newly diagnosed ovarian cancer [4, 5].

ancillary data statistical analysis

Clinical and pathologic data were collected and underwent univariate and multivariate analyses. Categorical variables were compared between subgroups by the Pearson's χ^2 test and continuous variables by the Wilcoxon–Mann–Whitney test or the Kruskal–Wallis test [6–8]. Survival was estimated using the Kaplan–Meier method [9]. The Cox proportional hazards model was used to evaluate independent prognostic factors and to estimate their covariate-adjusted effects on survival [10].

Adjusted survival curves were derived from the Cox OS model. Survival probabilities were calculated at every failure time of the whole population, using representative covariate values for adjustment [11]. Continuous variables (e.g. time to initiation of chemotherapy) exhibiting skewed distribution were included in the survival model after log transformation, and the nonlinearity of the effect was assessed using restricted cubic splines, which in turn were validated by Molinari's threshold selection method [12, 13]. All statistical tests were two-tailed with the significance level set at $\alpha = 0.05$. Statistical analyses were carried out using the R programming language and environment [14].

results

Of 1837 patients enrolled, 1718 were evaluable in this analysis. Clinical and pathologic characteristics of patients were reported in the original publication and are contained in supplementary Table S1, available at *Annals of Oncology* online. The median time from surgery to initiation of chemotherapy in each arm was 31 days (interquartile range, 23–41 days).

For 467 patients (27%), time from surgery to initiation of chemotherapy was >40 days (5.5 weeks). Initiation of therapy under 25 days was not associated with an increased risk of death due to wide CIs, but after 25.0 days (95% CI 16.6–49.9 days), the risk appears to increase sharply (Figure 1A). The time interval from surgery to initiation of chemotherapy was not associated with further treatment delays beyond cycle 1, grade 3–4 toxicity, dose reductions, or PFS (adjusted hazard of progression 1.06; 95% CI 0.94–1.18; $P = 0.347$).

In the study population, 54.2% had large-volume residual disease (i.e. residual disease >1 cm), 40.8% had low-volume residual disease (≤1 cm), and 4.9% underwent complete resection

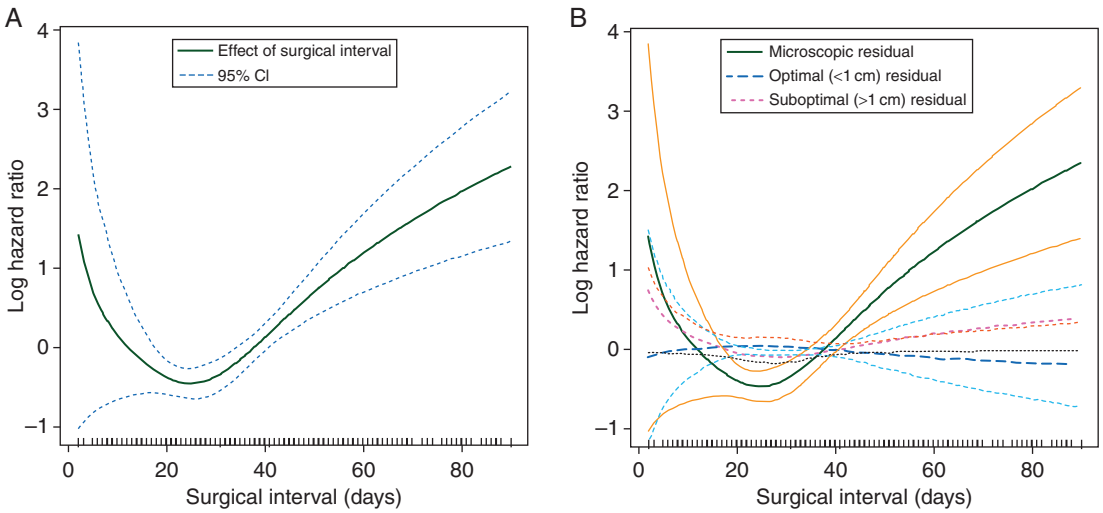

Figure 1. Association of time from surgery to initiation of chemotherapy with overall survival (OS). (A) This restricted cubic spline shows the impact of the interval from surgery to initiation of chemotherapy on the log hazard of death in the OS model. Note that the risk of death increases after 25 days. (B) Relationship between the interval between surgery and initiation of chemotherapy and log hazard ratio for each disease residual group. The lighter lines around each partial effects curve represent point-wise 95% confidence intervals. The figure suggests that the complete resection group is most affected by a longer interval from surgery to chemotherapy, whereas the other groups are affected very little. Importantly, this observation applies only to stage IV patients (81 of 477 had undergone complete resection); patients with stage III disease were required to have macroscopic visible/palpable residual disease following surgery. Note that the associated risk of time from surgery to initiation of chemotherapy is flat (15 days) or increasing (40 days, specifically for microscopic patients).

Table 1. Patient demographics and clinical characteristics by residual disease

	Microscopic $N = 85$[b]	Optimal (≤1 cm) $N = 701$	Suboptimal (>1 cm) $N = 932$	Test statistic, P
Age (years)	51.5 58.5 64.2	52.5 60.1 66.9	52.3 60.2 67.6	0.227*
BSA (m^2)	1.57 1.70 1.85	1.60 1.72 1.87	1.60 1.73 1.87	0.642*
Race/ethnicity				0.405**
White	87.1% (74)	83.2% (583)	83.7% (780)	
Asian	4.7% (4)	6.4% (45)	6.5% (61)	
Black	4.7% (4)	3.6% (25)	4.8% (45)	
Hispanic	2.4% (2)	5.1% (36)	2.9% (27)	
Other	1.2% (1)	1.7% (12)	2.0% (19)	
Performance status				0.008**
Normal, asymptomatic	42.4% (36)	52.4% (367)	47.7% (445)	
Symptomatic, ambulatory	48.2% (41)	42.9% (301)	43.2% (403)	
Symptomatic, in bed <50%	9.4% (8)	4.7% (33)	9.0% (84)	
Top-level FIGO stage				<0.001**
III	4.7% (4)	80.7% (566)	72.0% (671)	
IV	95.3% (81)	19.3% (135)	28.0% (261)	
Tumor grade (differentiation)[a]				0.121**
Good	3.8% (3)	6.5% (44)	3.6% (32)	
Moderate	17.5% (14)	16.9% (114)	18.0% (159)	
Poor	78.8% (63)	76.6% (518)	78.4% (694)	
Histology				0.949**
Serous	85.9% (73)	86.3% (605)	85.7% (799)	
Mixed epithelial	3.5% (3)	5.0% (35)	4.1% (38)	
Endometrioid	3.5% (3)	3.1% (22)	3.3% (31)	
Clear-cell/mucinous	4.7% (4)	2.9% (20)	3.9% (36)	
Other	2.4% (2)	2.7% (19)	3.0% (28)	
Ascites				<0.001**
No	25.9% (22)	24.8% (174)	16.1% (150)	
Yes	74.1% (63)	75.2% (527)	83.9% (782)	
Baseline CA 125 (IU/ml)	106.0 318.0 868.0	97.8 232.0 706.0	165.8 407.5 1313.8	<0.001*
Best response to therapy				<0.001**
Stable/increased disease	17.6% (15)	11.0% (77)	17.8% (166)	
Partial response	17.6% (15)	22.4% (157)	42.0% (391)	
Complete response	10.6% (9)	9.1% (64)	16.6% (155)	
Nonmeas./not evaluated	54.1% (46)	57.5% (403)	23.6% (220)	
Recurrence				<0.001**
No	22.4% (19)	23.4% (164)	15.7% (146)	
Yes	77.6% (66)	76.6% (537)	84.3% (786)	
Progression-free survival status				<0.001**
Censored	17.6% (15)	20.8% (146)	11.5% (107)	
Progression or death	82.4% (70)	79.2% (555)	88.5% (825)	
Overall survival status				<0.001**
Censored	45.9% (39)	59.8% (419)	41.0% (382)	
Death	54.1% (46)	40.2% (282)	59.0% (550)	
TSIC (days)	28 35 44	25 33 42	22 29 39	<0.001*
Treatment arm				0.475**
I (standard chemo.)	25.9% (22)	35.1% (246)	33.5% (312)	
II (concurrent bev.)	40.0% (34)	32.0% (224)	33.5% (312)	
III (extended bev.)	34.1% (29)	33.0% (231)	33.0% (308)	

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables.
N is the number of nonmissing values.
Numbers after percent are frequencies.
[a]$n = 1641$;
[b]Includes four patients with stage III (protocol violations).
Tests used:
*Kruskal–Wallis test;
**Pearson test.
TSIC, time from surgery to initiation of chemotherapy.

Table 2. Multivariate overall survival analysis

Covariate	AHR	95% CI	*P**
Age (years)[a]	1.02	1.01–1.02	<0.001
Race/ethnicity[b]			0.006
White	1.00	referent	
TSIC = 15 days			
Asian	0.38	0.18–0.80	
Black	2.25	1.02–4.96	
Hispanic	1.08	0.57–2.07	
Other	0.54	0.17–1.72	
Performance status			<0.001
0	1.00	referent	
1	1.34	1.16–1.56	
2	2.37	1.86–3.02	
Grade			0.153
1	1.00	referent	
2	1.30	0.87–1.95	
3	1.10	0.75–1.61	
Stage			0.046
III	1.00	referent	
IV	1.18	1.00–1.38	
Histology			<0.001
Serous	1.00	referent	
Mixed epithelial	1.33	0.97–1.84	
Endometrioid	0.70	0.44–1.11	
Clear-cell/mucinous	4.97	2.46–10.05	
Other	1.14	0.73–1.78	
Ascites			0.001
No	1.00	referent	
Yes	1.39	1.14–1.71	
CA 125 (μg/ml)[c]	1.01	1.00–1.01	0.001
Tumor residual (cm)[b]			<0.001
Microscopic	1.00	referent	
TSIC = 15 days			
≤1 cm	1.41	0.77–2.58	
>1 cm	1.87	1.05–3.31	
TSIC (days)[d,b]			<0.001
Residual = micro.			
15 days, any race/eth.		covers 1	
40 days, race/eth. = White	1.27	1.15–1.40	
40 days, race/eth. = Asian	1.51	1.27–1.80	
40 days, race/eth. = Black	1.18	1.00–1.40	
40 days, race/eth. = Hispanic	1.18	0.97–1.43	
40 days, race/eth. = other	1.41	1.15–1.74	
Residual ≤1 cm			
15 days, any race/eth.		covers 1	
40 days, race/eth. = non-Asian		covers 1	
40 days, race/eth. = Asian	1.17	1.01–1.35	
Residual >1 cm			
15 days, any race/eth.		covers 1	
40 days, race/eth. = non-Asian		covers 1	
40 days, race/eth. = Asian	1.24	1.07–1.44	
TSIC (days) × race/ethnicity			0.019
TSIC (days) × tumor residual			<0.001

Note: Continuous variables exhibiting skewed distribution (e.g. baseline CA 125, time from surgery to initiation of chemotherapy) were included in the model after log transformation.

[a]The AHR denotes the change in risk of death associated with an increase of 1 year in age.

[b]The AHR for a covariate involved in an interaction is given for representative values of the other covariates in the interaction.

[c]The AHR denotes the change in risk of death associated with a 10% increase in CA 125 (μg/ml).

[d]The AHR denotes the change in risk of death associated with a 10% increase in TSIC (days) at representative values.

*The *P* values are from the overall test of significance of each covariate in the model.

TSIC, time from surgery to initiation of chemotherapy.

and were rendered R_0 (i.e. microscopic residual) (Table 1). The OS model (Table 2) and effects plot (Figure 1B) suggests that the microscopic residual group is most affected by a long interval $P < 0.001$), whereas the other groups are affected very little. For White patients with complete resection, for example, the risk of death increases by 27% in the increasing part of their respective curve, i.e. after ~25 days, for every 10% lengthening of time from surgery to initiation of chemotherapy (TSIC). Note that, at 15 days, time to initiation of chemotherapy does not increase the risk of death for any patients, whereas at 40 days most patients have an increased risk of death. This represents a change-point in increasing time at which some patients start to become affected negatively. The OS model given in Table 2 also included a moderate time from surgery to initiation of chemotherapy × race/ethnicity interaction ($P = 0.019$). The HRs show that Asian patients were susceptible to risk from longer time from surgery to initiation of chemotherapy regardless of residual status.

Figure 2 shows a set of adjusted survival curves for a 'typical' patient in GOG 218 with large-volume tumor residual (>1 cm, 1A), optimally debulked (≤1 cm, 2B), and no gross residual (2C), with various lengths of time from surgery to initiation of chemotherapy in days. The three curves in Figure 2Aand B represent the survival of three typical patients whose covariate values were exactly the same (including large-volume residual disease or optimally debulked) except for time from surgery to initiation of chemotherapy, which is fixed at 20, 40, and 60 days for each curve. Note that the curves keep fairly close together over time. In Figure 2C, however, the situation is different. For three typical patients with complete resection and otherwise identical covariate values, varying time from surgery to initiation of chemotherapy spreads the curves farther apart so that the survival probability drops off more quickly with increasing time from surgery to initiation of chemotherapy.

discussion

For the 81 patients with stage IV disease who underwent complete resection, this exploratory analysis indicates that the risk of death increased when the time from surgery to initiation of chemotherapy exceeded 25 days. Patients were permitted to enroll up to 12 weeks from surgery and therefore initiation of chemotherapy after 25 days was not considered a 'delay in therapy' as long as it was started before 84 days had elapsed (i.e. 12 weeks). Reasons for initiating chemotherapy after 25 days were therefore not collected but may have been related to the time required to obtain insurance authorizations for referral to oncology, lack of health care insurance, or increased recovery time required by patients in the complete resection group who underwent extensive cytoreductive procedures and possibly experienced more postoperative complications. The more medically infirm and/or those who were increasingly symptomatic due to a large tumor burden may have been too sick to initiate chemotherapy immediately. Given that our findings concerning microscopic residual disease pertain only to those with stage IV disease (since stage III rendered R_0 were not eligible), it is possible that, without expeditious initiation of chemotherapy, recurrent pleural effusions/upper abdominal tumor regrowth may have had a significant detrimental impact on outcome. The correlation between time to chemotherapy and residual disease is unlikely to be a false positive because the model is fairly small with only the time to initiation of chemotherapy and nine covariates known to be prognostic for survival in this disease and the interaction is quite strong ($P < 0001$).

One year after Magrath's 1974 report on improved survival in patients with abdominal Burkitt's lymphoma who underwent cytoreduction of the intra-abdominal tumor burden, Griffiths demonstrated an inverse relationship between residual tumor diameter following abdominal surgery and survival among 100 consecutive patients with ovarian cancer [15, 16]. In the 2002 meta-analysis by Bristow et al. involving 6886 patients with stage III and IV ovarian carcinoma treated with platinum-based chemotherapy, maximal cytoreduction was found to be the most important determinant of survival [17]. Complete resection leaving only microscopic residual disease (i.e. no gross residual designated R_0) sets the stage for platinum- and taxane-based chemotherapy [18]. However, as stated earlier, perioperative complications associated with extended cytoreductive surgery may lead to a protracted

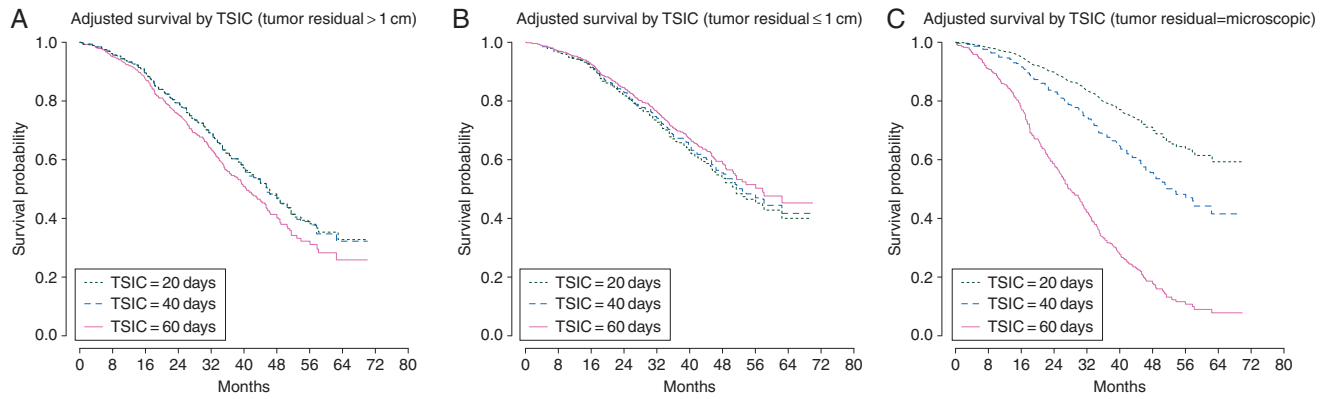

Figure 2. Adjusted overall survival (OS) curves modeled for surgical outcome. (A) Adjusted survival curves for OS model for patients with large-volume residual disease (>1 cm) by various surgical intervals. Note that, although survival decreases with lengthening surgical interval, the differences are not profound. (B) Adjusted survival curves for OS model of patients with optimal cytoreduction (≤1 cm) for various surgical intervals. (C) Adjusted survival curves for OS model of patients with complete resection by various surgical intervals. Note that survival significantly decreases with lengthening surgical interval. Importantly, this observation applies only to stage IV patients (81 of 477 had undergone complete resection); patients with stage III disease were required to have macroscopic visible/palpable residual disease following surgery.

postoperative convalescence, ultimately resulting in a delay in initiation of chemotherapy [19]. The impact of time from surgery to initiation of chemotherapy on outcome in patients with solid tumors has been previously investigated (Table 3) [3, 19–29]. The most extensive research includes four Medicare-linked Surveillance Epidemiology and End Results (SEER) database studies in ovarian, breast, colon, and rectal cancer, and a meta-analysis of three phase III trials in ovarian cancer [19–22].

The interval between resection and chemotherapy may provide opportunity for micrometastases to proliferate as the curable fraction with microscopic residual may be most sensitive to this effect. The biological mechanism to account for this vulnerability is suggested by multiple experimental observations. In animal models developed to assess classical and hyperexponential Gompertzian growth kinetics, surgical resection leads to accelerated metastatic tumor growth due to shuttling of noncycling cells in G_0 phase into the cell cycle [30, 31]. Using a murine mammary adenocarcinoma, Fisher et al. detected that the shorter the interval between operation and cyclophosphamide administration, the more complete the abrogation of the kinetic changes in distant tumor foci, the more effective suppression of residual tumor, and the more prolonged the survival [32]. Residual disease following cytoreductive surgery may have a high growth fraction making it more susceptible to cell cycle-specific drugs (e.g. taxanes). These principles following complete resection may also apply to stage I–III. In this study, a lack of impact of initiation of chemotherapy on PFS may have resulted from the relative indeterminacy of PFS when compared with death as an end point and also because both RECIST and increasing CA 125 were permitted in GOG 218 to document progression.

Cytoreduction results in increased proliferation of microscopic residual disease and depletion of endogenous antiangiogenesis factors [33]. Early initiation of chemotherapy plus exogenous antiangiogenesis therapy may not be as critical to those with gross residual disease for whom these subtle biological phenomena may not be relevant. Given the hierarchy of angiogenesis pathways and the genomic instability which governs ovarian carcinoma, the potential to favorably exploit time from surgery to initiation of chemotherapy through manipulation of the microenvironment with angiogenesis inhibitors is implicit (supplementary Figure S1, available at *Annals of Oncology* online). Finally, the vulnerability to Asian patients with lengthening interval from surgery to initiation of chemotherapy found in this study may be related to ethnic differences in the expression of allelic variants that produce altered pharmacokinetics of anticancer drugs, including paclitaxel in Asians, or to certain genetic polymorphisms recognized for their role in intrinsic and/or acquired drug resistance [34, 35].

The time interval within which postoperative chemotherapy for ovarian cancer should be initiated is unknown. Neither National Comprehensive Cancer Network guidelines nor those published by the American Society of Clinical Oncology specify explicitly a time interval within which chemotherapy for ovarian cancer should be initiated. Patients managed at tertiary centers may be treated earlier following surgery and these patients may have access to more treatment options for management of recurrent disease, making the time interval from surgery to the initiation of first-line chemotherapy a confounding factor for survival. A further limitation previously noted was that because enrollment was permitted up to 12 weeks following surgery, the reasons for initiating treatment after certain intervals (e.g. 25 days) were not collected.

Forthcoming trials should be designed to examine the relationship between time to initiation of chemotherapy and survival end points as a protocol-specified exploratory objective and track reasons that may contribute to treatment initiation 'delays'. Prospective evaluation of identifiable clinical factors that lengthen the time from surgery to initiation of chemotherapy (e.g. perioperative complications, patient behavioral factors, health care system logistic factors) could be formally assessed. This will allow for better delineation of disease-specific mortality as a function of treatment delay and/or perioperative events and medical co-morbidities. Some oncologists have advocated for centralization of ovarian cancer cytoreduction to high-volume cancer centers with access to clinical trials, similar to what has

Table 3. Selected studies: impact of time from surgery to initiation of chemotherapy (TSIC) on survival (literature review)

Author	Study	Site	*N*	TSIC	Findings
Hershman et al. [20]	SEER-Medicare	Breast	5003	≥ 3 months	HR 1.69; 95% CI 1.21–1.75
Hershman et al. [21]	SEER-Medicare	Colon	4382	≥ 3 months	HR 1.48; 95% CI 1.15–1.92
Cheung et al. [22]	SEER-Medicare	Rectum	6059	>3 months	OS worse 54 versus 76 months; $P < 0.01$
Wright et al. [19]	SEER-Medicare	Ovary	3991	>12 weeks	HR 1.32; 95% CI 1.07–1.64
Mahner et al. [3]	Meta-Analysis	Ovary	3326	>19 days	Microscopic residual: HR 1.087; 95% CI 1.005–1.176; $P = 0.038$
Omura et al. [23]	Phase III RCT	Ovary	349	Up to 6 weeks	Increasing TSIC significant predictor of OS
Hofstetter et al. [24]	OVCAD	Ovary	191	>28 days	Gross residual: HR 2.24; 95% CI 1.08–4.66; $P = 0.031$
Gaducci et al. [25]	Retrospective	Ovary	313	<11 to >31 days	No significant impact on OS
Flynn et al. [26]	Retrospective	Ovary	472	Median 22 days	No significant impact on PFS
Paulsen et al. [27]	Norwegian CR	Ovary	349	≥ 6 weeks	No significant impact on OS
Rosa et al. [28]	Retrospective	Ovary	394	>4 to 12 weeks	No significant impact on OS
Aletti et al. [29]	Retrospective	Ovary	298	Median 25 days	No significant impact on OS
Tewari et al.[a]	Phase III RCT	Ovary	1718	>25 days	Microscopic residual: HR 3.44; 95% CI 1.68–7.03

TSIC, time from surgery to initiation of chemotherapy; SEER, Surveillance Epidemiology End Results; CR, cancer registry; OVCAD, Ovarian CAncer Diagnosis multicenter study; RCT, randomized clinical trial; HR, hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression-free survival.
[a]This study.

been done for esophageal cancer surgery in parts of Europe [36]. Centralization may also carry with it the added benefit of increasing patient access to the 25-day window which may be important as suggested by these data.

funding

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disclosure

KT reports that his institute, University of California, Irvine, participated on GOG-218 clinical trial as a member of the NCI's Gynecologic Oncology Group. His institution also received points from the N.C.Z. for patients accrued on to GOG-218 study. BM discloses that his institution has received grants/contracts from Genentech. BM has received honorarium from speaker's bureaus from Roche/Genentech and has been a consultant for Roche/Genentech. All remaining authors have declared no conflicts of interest.

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appendix 1

The following institutions participated in this study: Roswell Park Cancer Institute, University of Alabama at Birmingham, Duke University Medical Center, Abington Memorial Hospital,

Walter Reed Army Medical Center, Wayne State University, University of Minnesota Medical School, Mount Sinai School of Medicine, Northwestern Memorial Hospital, University of Mississippi Medical Center, Colorado Gynecologic Oncology Group P.C., University of California at Los Angeles, University of Washington, University of Pennsylvania Cancer Center, Milton S. Hershey Medical Center, University of Cincinnati, University of North Carolina School of Medicine, University of Iowa Hospitals and Clinics, University of Texas Southwestern Medical Center at Dallas, Indiana University School of Medicine, Wake Forest University School of Medicine, University of California Medical Center at Irvine, Rush-Presbyterian-St Luke's Medical Center, Magee Women's Hospital, SUNY Downstate Medical Center, University of Kentucky, University of New Mexico, The Cleveland Clinic Foundation, State University of New York at Stony Brook, Washington University School of Medicine, Memorial Sloan-Kettering Cancer Center, Cooper Hospital/University Medical Center, Columbus Cancer Council, MD Anderson Cancer Center, University of Massachusetts Medical School, Fox Chase Cancer Center, Women's Cancer Center, University of Oklahoma, University of Virginia Health Sciences Center, University of Chicago, Mayo Clinic, Case Western Reserve University, Tampa Bay Cancer Consortium, Yale University, GOG Japan-Saitama Medical University International Medical Center, University of Wisconsin Hospital, Cancer Trials Support Unit, University of Texas - Galveston, Women and Infants Hospital, Korean Gynecologic Oncology Group, The Hospital of Central Connecticut, Georgia Core, GYN Oncology of West Michigan, PLLC, Aurora Women's Pavilion of West Allis Memorial Hospital, and Community Clinical Oncology Program.

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Randomized phase III trial in elderly patients comparing LV5FU2 with or without irinotecan for first-line treatment of metastatic colorectal cancer (FFCD 2001–02)†

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Background: Metastatic colorectal cancer (mCRC) frequently occurs in elderly patients. However, data from a geriatric tailored randomized trial about tolerance to and the efficacy of doublet chemotherapy (CT) with irinotecan in the elderly are lacking. The benefit of first-line CT intensification remains an issue in elderly patients.

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