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Journal

Gynecologic Oncology, 143(3)

ISSN

0090-8258

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Publication Date

2016-12-01

DOI

10.1016/j.ygyno.2016.09.015

Peer reviewed

HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2017 December 13.

Published in final edited form as:

Gynecol Oncol. 2016 December ; 143(3): 490–495. doi:10.1016/j.ygyno.2016.09.015.

The association between timing of initiation of adjuvant therapy and the survival of early stage ovarian cancer patients – An analysis of NRG Oncology/Gynecologic Oncology Group trials

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Abstract

Objectives—To determine the association between timing of adjuvant therapy initiation and survival of early stage ovarian cancer patients.

Methods—Data were obtained from women who underwent primary surgical staging followed by adjuvant therapy from two Gynecologic Oncology Group trials (protocols # 95 and 157). Kaplan-Meier estimates and Cox proportional hazards model adjusted for covariates were used for analyses.

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Conflict of interest statement

JK Chan: Consultant: Acerta, Clovis, Mateon, Roche/Genentech; Honoraria speaker: AstraZeneca, Roche/Genentech, T. Herzog: Consultant: AstraZeneca, Johnson & Johnson, Pfizer, Roche/Genentech. R. Young: Stock/options: AVEO Pharmaceuticals Inc., J. Java, K. Fuh, B.J. Monk, D.S. Kapp, J. Bell: these authors declare no conflicts of interest.

Results—Of 497 stage I–II epithelial ovarian cancer patients, the median time between surgery and initiation of adjuvant therapy was 23 days (25th–75th%: 12–33 days). The time interval from surgery to initiation of adjuvant therapy was categorized into three groups: <2 weeks, 2–4 weeks, and >4 weeks. The corresponding 5-year recurrence-free survival rates were 72.8%, 73.9%, and 79.5% ($p = 0.62$). The 5-year overall survival rates were 79.4%, 81.9%, and 82.8%, respectively ($p = 0.51$; $p = 0.33$ - global test). As compared to <2 weeks, the hazard ratio for recurrence-free survival was 0.90 (95%CI = 0.59–1.37) for 2–4 weeks and 0.72 (95%CI = 0.46–1.13) for >4 weeks. Age, stage, grade, and cytology were important prognostic factors.

Conclusions—Timing of adjuvant therapy initiation was not associated with survival in early stage epithelial ovarian cancer patients.

Keywords

Early stage ovarian cancer; Prognosis; Survival

1. Introduction

Ovarian cancer is the most lethal gynecologic malignancy in the United States [1]. Important clinico-pathologic factors associated with response to adjuvant therapy and survival include optimal cytoreductive surgery and more favorable histologic cell types [2–6]. However, the benefit of early initiation of adjuvant therapy after surgery is unclear.

In preclinical models, the resection of the primary tumor has been shown to accelerate the growth phase of micrometastases [7–12]. Other studies have revealed that early administration of chemotherapy prevented this accelerated growth after surgical cytoreduction [13,14]. Moreover, early initiation of adjuvant therapy or biologic treatment inhibited tumor growth by attenuating early angiogenesis associated with tumor resection [15]. In contrast, a delay in the initiation of systemic therapy has been shown to increase the emergence of drug-resistant micrometastases [16].

Clinical studies have reported on the prognostic significance of timing of adjuvant therapy after surgery in epithelial ovarian cancers with inconsistent results [17–24]. In a Gynecologic Oncology Group (GOG) study on stage III ovarian cancer with minimal residual disease, Omura et al. showed that time from surgery to initiation of adjuvant therapy was an independent predictor of overall survival on multivariate analysis [17]. Others have also found that the most optimal treatment interval may be 4–6 weeks after surgery [25]. In a recent study, investigators showed that outcome may be adversely affected when initiation of adjuvant therapy occurs beyond 25 days following surgery [26]. However, others were unable to show a survival benefit associated with early treatment initiation after controlling for other prognostic factors such as residual disease and presence of ascites [18,19,21]. The National Comprehensive Cancer Network guidelines and American Society of Clinical Oncology guidelines have not addressed the issue of optimal timing of adjuvant treatment.

In these advanced ovarian cancer patients, the rationale for early initiation of adjuvant therapy may be due to progressive disease in the peri-operative period or rather for convenience in those with good performance status. Thus, it is difficult to study the effect of

timing of adjuvant therapy in a heterogeneous cohort of advanced stage cancers. As such, we used ancillary data from two prospective GOG clinical trials on early stage ovarian cancer patients to examine the association between timing of adjuvant therapy initiation and outcome of early stage ovarian cancer patients.

2. Methods

Of 506 patients enrolled in two prospective randomized clinical trials conducted by the GOG, protocol 95 and protocol 157, 497 patients with complete follow up information were included in the analysis [27,28]. In both trials, all patients were diagnosed with stage IA or IB (grade 3), stage IC or II (any grade), stage I or II clear cell cancers and were enrolled within six weeks of surgery. In GOG 95 arm 1 ($n = 98$), women were treated with IV cyclophosphamide 1 g/m^2 and cisplatin 100 mg/m^2 every 21 days for three cycles while arm 2 patients ($n = 107$) underwent single dose 15 mC intraperitoneal ^{32}P (phosphate). In GOG 157 arm 1 ($n = 155$), women received IV paclitaxel 175 mg/m^2 and carboplatin (AUC = 7) every 21 days for 3 cycles while arm 2 patients ($n = 146$) had IV paclitaxel 175 mg/m^2 and carboplatin (AUC = 7) every 21 days for 6 cycles. GOG 95 reported no significant difference in survival between the two treatment arms. GOG 157 found no significant differences in recurrence rate or overall death rates in patients randomized to 3 versus 6 cycles of chemotherapy. Those without documented information on the surgical or adjuvant therapy start date were excluded. Patients provided written informed consent consistent with all federal, state, and local requirements prior to receiving protocol therapy. Baseline performance status prior to initiating adjuvant therapy was defined according to GOG criteria as: 0 = normal activity, 1 = symptomatic, fully ambulatory; 2 = symptomatic, in bed <50% of the time. Patients with a GOG performance status of 1 or 2 were combined due to a relative small number of patients with performance status of 2. Stage was classified into stage IA/IB, stage IC, and stage II prior to evaluation of clinical outcomes. All clear cell carcinomas were assigned as grade 3 disease. For illustrative purposes, the time interval from surgery to initiation of adjuvant therapy was categorized into three groups: <2 weeks, 2–4 weeks, and >4 weeks. However, time was entered as a continuous variable in the multivariate analyses. The patient characteristics by three groups were compared using Pearson's Chi-square test [29] and the median age was compared by Kruskal-Wallis test [30]. The primary endpoints were disease recurrence-free survival (RFS) and overall survival (OS). RFS was calculated from the date of initial adjuvant therapy to the date of disease recurrence (confirmed on physical, serological or radiological exam), or most recent follow-up visit. Overall survival was calculated from the date of adjuvant therapy to the date of death or last contact.

The five-year survival was estimated by Kaplan-Meier method [31]. Cox proportional hazards model was used to assess the association between the time interval and survival controlled for age, performance status, stage of disease, tumor grade, and type of adjuvant treatment. [32] All statistical tests were two-tailed with a significance level set at 5%. Analyses were performed using Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC).

3. Results

Four hundred ninety-seven patients enrolled in GOG protocols 95 and 157 were included for the study. Table 1 compares the demographics and clinical characteristics of patients based on time interval between surgery and initiation of adjuvant therapy. The median time between surgery and adjuvant therapy was 23 days (25th–75th%: 12–33 days). The median times for GOG 95 and GOG 157 were 20 and 25 days, respectively. The demographic and clinico-pathologic factors such as age, race, stage, histology, tumor grade, presence of ascites, cytologic status and tumor rupture were comparable across the three groups. However, performance status of zero was more frequently observed among patients with longer interval between surgery and adjuvant therapy.

The 5-year recurrence-free survivals (RFS) were 72.8%, 73.9%, and 79.5% in those who received adjuvant therapy <2 weeks, 2–4 weeks, >4 weeks after surgery, respectively (p = 0.62) (Fig. 1). The corresponding 5-year overall survival (OS) was 79.4%, 81.9%, and 82.8%. (p = 0.51) (Fig. 2). On multivariate analysis, time interval between surgery and initiation of adjuvant therapy was not associated with survival after adjusting for age, performance status, stage of disease, tumor grade, cytology, and type of treatment (p = 0.33 for global test). The adjusted hazard ratio for disease recurrence was 0.90 (95% CI: 0.59–1.37, p = 0.62) for 2–4 weeks and 0.72 (95% CI: 0.46–1.13, p = 0.15) for >4 weeks as compared to <2 weeks. The adjusted hazard ratio for death was 0.87 for 2–4 weeks and 0.78 for >4 weeks relative to <2weeks (Table 2). As previously reported, age, stage, grade, and cytology were important prognostic factors for survival [33].

4. Discussion

The majority of women with advanced epithelial ovarian cancer will ultimately recur from their disease. Even in early stage cancers, nearly 30%with high-risk disease recur [33]. Current practice guidelines for adjuvant chemotherapy for high-risk, early stage patients (Stage IA, IB, grade 3; all Stage I clear cell cancers; and all stage IC patients) recommend intravenous taxanes and carboplatin for 3–6 cycles. In addition to advancing the therapeutic efficacy of novel drugs, it is also important to identify better methods of administering treatment to improve outcome. Early studies have reported on the importance of the timing of initiation of adjuvant therapy after surgery [17,21–23]. Moreover, many studies were reported from single institutions with incomplete documentation on the extent of residual disease, lack of uniformity in adjuvant therapy, and scant information on other clinico-pathologic prognosticators. All of these factors may influence their reported findings. To our knowledge, there are no studies that have evaluated the timing of initiation in a homogenous group of early stage cancer patients using data from prospective randomized trials.

Prior investigations using animal models have revealed that cytoreductive surgery may accelerate tumor growth [7–12], induce cellular division [12], and increase angiogenesis [15,34,35]. Given these changes following surgery, the early administration of adjuvant therapy can theoretically prevent these events associated with accelerated tumor growth [13,14]. Alternatively, a delay in the initiation of systemic therapy may result in the emergence of drug-resistant micrometastatic disease [16]. Furthermore, the removal of

primary tumor leads to an increase in angiogenesis in the vascular bed surrounding the resected disease [15]. Thus, early initiation of treatment can potentially impede tumor growth, prevent the development of drug resistant clones, and inhibit early angiogenesis after cytoreduction [34,35].

In the clinical setting, studies on breast cancer showed that initiation of adjuvant therapy within 28 to 35 days of surgery improves disease-free survival [36,37]. In a review of the International Breast Cancer Study Group trials, investigators found a significant improvement in disease-free survival in patients who started chemotherapy within 21 days of surgery [38]. However, another early breast cancer study did not show a benefit from early initiation of chemotherapy [39].

In ovarian cancer, the benefit of earlier treatment initiation is also unclear. While several investigators have demonstrated a benefit for earlier treatment initiation [17],[19],[25],[40] others were unable to show this effect [21],[22],[23] and few even observed adverse effects of early initiation [18],[20],[24]. Many studies found an initial association based on univariate analysis but lost significance in the multivariate model after adjusting for other prognostic factors [18],[19],[20],[24]. In addition, many of the studies used in the literature review pertain to advanced disease or had a higher proportion of stage III–IV patients.

One of the first reports of advanced ovarian cancer from the GOG showed that time from surgery to initiation of chemotherapy was an independent predictor of overall survival. Of 349 patients with stage III ovarian cancer, Omura et al. found that for each additional week of delay in chemotherapy initiation, 2, 3, 4, 5, and 6 weeks, the hazard rate increased from 1.2, 1.4, 1.5, 1.7, to 1.8, respectively [17]. In another population-based study of older (>65 years) patients, Wright et al. showed that the most optimal treatment interval might be 4–6 weeks after surgery [25]. In a recent analysis of prospective randomized phase III trials, Mahner et al. showed that early initiation (<19 days) of chemotherapy was associated with an improved survival in patients who had complete cytoreduction whereas those with residual disease did not benefit from earlier initiation of therapy [40]. In contrast, other studies have shown that timing interval is not an independent prognostic factor after adjusting for other important variables on multivariate analysis. For example, Gadducci et al. studied 313 women with advanced ovarian cancer who received taxane with platinum-based chemotherapy and was unable to demonstrate a significant difference in complete response and survival based on timing of therapy after adjusting for residual disease and ascites [21]. Other studies have also failed to show a survival advantage in early initiation of chemotherapy after adjusting for various prognostic factors.[18],[19],[20,22,23],[41] Although these prior reports did not clearly demonstrate an associated survival advantage from early initiation of chemotherapy, there may be a detrimental effect of delaying the start of chemotherapy. In a recent study by Tewari et al., these investigators showed that outcome may be adversely affected when initiation of adjuvant therapy occurs beyond 25 days following surgery [26]. In their exploratory analysis of 81 patients with stage IV disease, these authors found an increased risk of death associated when the time from surgery to initiation of chemotherapy exceeded 25 days. The results of studies are summarized in Table 3.

The discrepancies in the published literature may be attributed to the inclusion of a heterogeneous populations of both early and advanced-stage disease, reporting from single institutions, inclusion of unstaged patients, incomplete documentation on the extent of residual disease, limited information on performance status, lack of uniformity in adjuvant therapy, and limited data on other clinico-pathologic and biologic variables related to clinical outcome. Several of these reports showed that patients were more likely to start chemotherapy early if they had more advanced cancers or residual disease after surgery [18], [24]. Thus, it is difficult to determine the rationale for early initiation of adjuvant therapy based on retrospective or population data. Some clinicians may choose to administer chemotherapy early for patients who had large volume residual disease and ascites to provide symptomatic relief in the peri-operative setting [40]. In contrast, others may elect to start treatment earlier for younger patients with good performance status after a rapid and uncomplicated surgical recovery. Moreover, patients who had an extensive surgical resection or stage IV disease may require longer recovery and delayed start of treatment.

Since the investigation of treatment interval is challenging due to the heterogeneity of patients with advanced disease, we elected to limit our study to a more homogenous group of patients with early stage cancer. In addition, all patients underwent surgery by gynecologic oncologists with complete surgical staging and adjuvant therapy under the GOG protocol. We also characterized our subgroups based on treatment interval to demonstrate that they were comparable with respect to their demographic and clinic-pathologic prognostic factors. Of these 497 patients, we did not find any survival difference in those who received adjuvant therapy <2 weeks, 2–4 weeks, and >4 weeks after surgery.

There are several limitations of our study that may encumber the interpretation of our results. Since early stage ovarian cancer patients have an overall favorable prognosis, our study may lack the statistical power to show a survival benefit. As the potential benefit of early initiation of adjuvant therapy is projected to be small, it may require significantly larger numbers of patients to demonstrate this difference. However, it is unlikely that larger studies with prospective data will be available particularly in this homogenous population. Furthermore, one of the trials in our study, GOG 95, included cyclophosphamide and intraperitoneal ^{32}P, neither of which is commonly used for early stage ovarian cancer today. [27] However, the goal of the study was to determine if early initiation of adjuvant therapy not simply standard chemotherapy improved the survival of patients. In addition, since this study did not find a significant survival advantage of one regimen over another, we elected to include all patients in the study to increase the sample size. In addition, we performed an additional analysis only including data from GOG 157 and showed that the effect of the early initiation of treatment variable on risk of recurrence ($p = 0.11$) and risk of death ($p = 0.15$) were not significant in the Cox models.

Furthermore, these trials enrolled only women who volunteered or were able to be randomized within a certain time after surgery. Since early initiation of adjuvant treatment was not a quality metric, there may exist unknown selection biases for early initiation of treatment that are not documented in the demographic and clinico-pathologic factors of our study. Although we did not identify a benefit associated with earlier initiation of adjuvant therapy, it remains unclear if a significant delay in starting adjuvant therapy may worsen

outcome. Since the median time from surgery to initiation of adjuvant therapy was only 23 days in our study group, we did not have sufficient numbers to study the effect of long treatment delays. Nevertheless, Rosa et al. studied a group of patients who started chemotherapy from 8 to 12 weeks after surgery but did not find a detrimental effect in this time interval; suggesting that it may be safe to allow patients to fully recover from their operation without compromising their overall prognosis. We also lack information on whether patients were treated by a medical oncologist or gynecologic oncologist. The strengths of our study include the fact that the data were extracted from randomized controlled clinical trials with surgery by gynecologic oncologists, central pathology review, standardized adjuvant therapy, and long term follow-up. Most patients underwent comprehensive staging procedures followed by taxane and platinum combination treatment. The timing of initiation of treatment was incorporated into the Cox model as a continuous variable, though the time intervals in the tables were selected for illustrative purposes. We also performed an analysis using the median (<21d vs. ≥21d) and did not demonstrate a recurrence or survival difference. To our knowledge, this is the largest study that evaluates the timing of adjuvant therapy after surgery in early stage ovarian cancers.

In this current report of early stage ovarian cancer patients from two prospective randomized trials, we did not find a survival benefit associated with earlier initiation of adjuvant therapy. Age at diagnosis, FIGO stage, grade, and cytology status were independently predictive of both disease recurrence and overall survival. A controlled prospective randomized trial would be necessary to definitively assess the potential impact of timing of adjuvant therapy in ovarian cancer.

Acknowledgments

Supported by the GOG Young Investigator's Award to JKC.

Acknowledgement Denis Cobb Hale Chair for administrative support.

This study was supported by National Cancer Institute grants to the Gynecologic Oncology Group Administrative Office (CA 27469), the Gynecologic Oncology Group Statistical and Data Center (CA 37517), and the NRG Oncology 1 U10CA180822. The following Gynecologic Oncology institutions participated in this study: University of Alabama at Birmingham, Oregon Health Sciences University, Duke University Medical Center, Abington Memorial Hospital, University of Rochester Medical Center, Walter Reed Army Medical Center, Wayne State University, University of Minnesota Medical School, University of Southern California at Los Angeles, University of Mississippi Medical Center, Colorado Gynecologic Oncology Group PC, University of California at Los Angeles, University of Pennsylvania Cancer Center, University of Miami School of Medicine, Milton S. Hershey Medical Center, Georgetown University Hospital, 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, Albany Medical College, University of California Medical Center at Irvine, Tufts-New England Medical Center, Rush-Presbyterian-St. Luke's Medical Center, SUNY Downstate Medical Center, University of Kentucky, Eastern Virginia Medical School, The Cleveland Clinic Foundation, Johns Hopkins Oncology Center, State University of New York at Stony Brook, Eastern Pennsylvania GYN/ONC Center, P.C., Southwestern Oncology Group, Washington University School of Medicine, Cooper Hospital/ University Medical Center, Columbus Cancer Council, North Central Cancer Treatment Group, University of Massachusetts Medical School, Fox Chase Cancer Center, Medical University of South Carolina, Women's Cancer Center, University of Oklahoma, University of Chicago, Tacoma General Hospital, University of Washington, Thomas Jefferson University Hospital, Mayo Clinic, Case Western Reserve University, Tampa Bay Cancer Consortium, North Shore University Hospital and Gynecologic Oncology Network.

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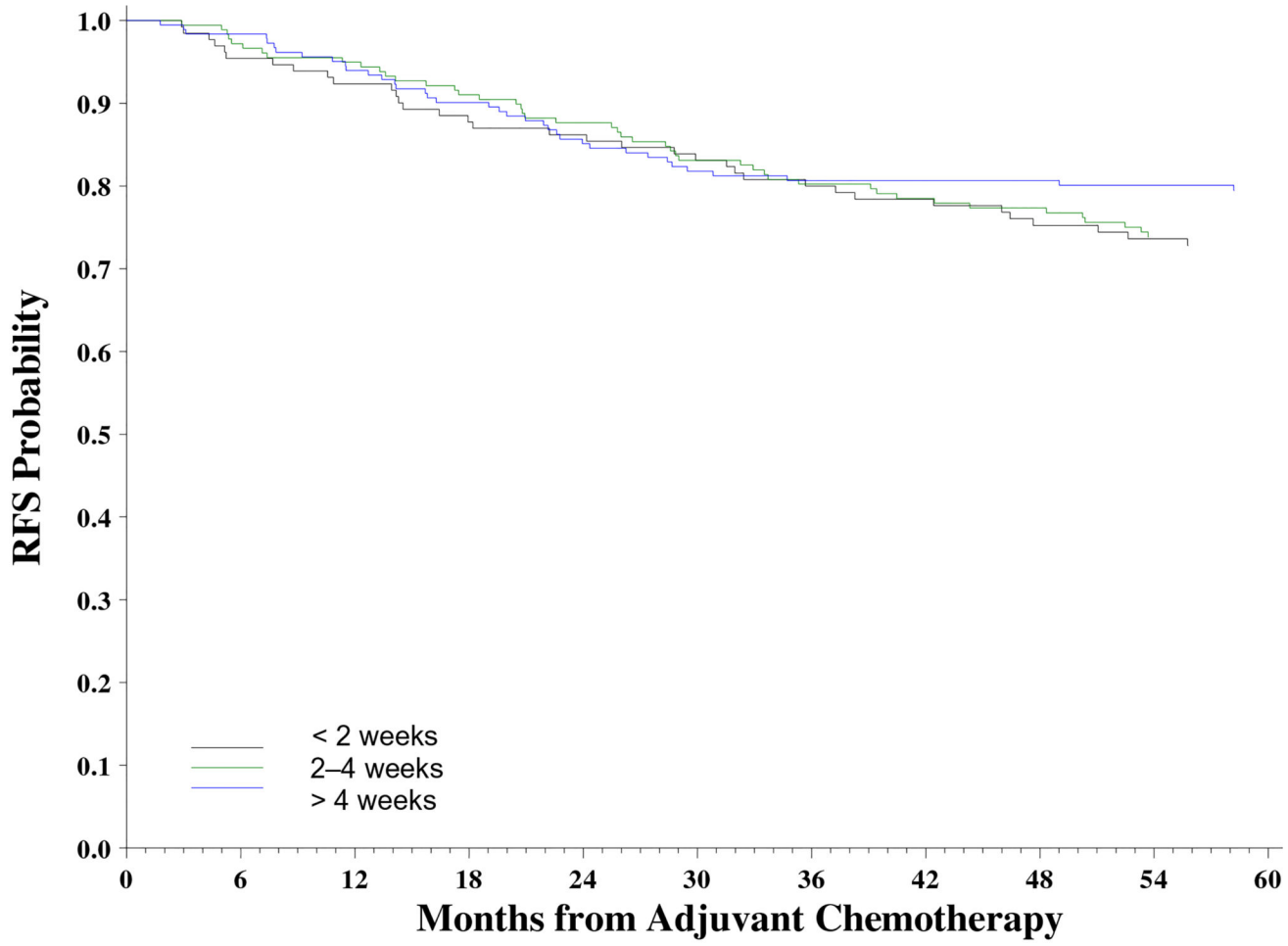
HIGHLIGHTS

- Early initiation of chemotherapy was not associated with improve survival.
- Age, stage, cytology were prognostic factors in early stage ovarian cancer



RFS = recurrence-free survival

Fig. 1.

Kaplan-Meier estimate of recurrence-free survival by interval from surgery to initiation of adjuvant therapy ($p = 0.62$).

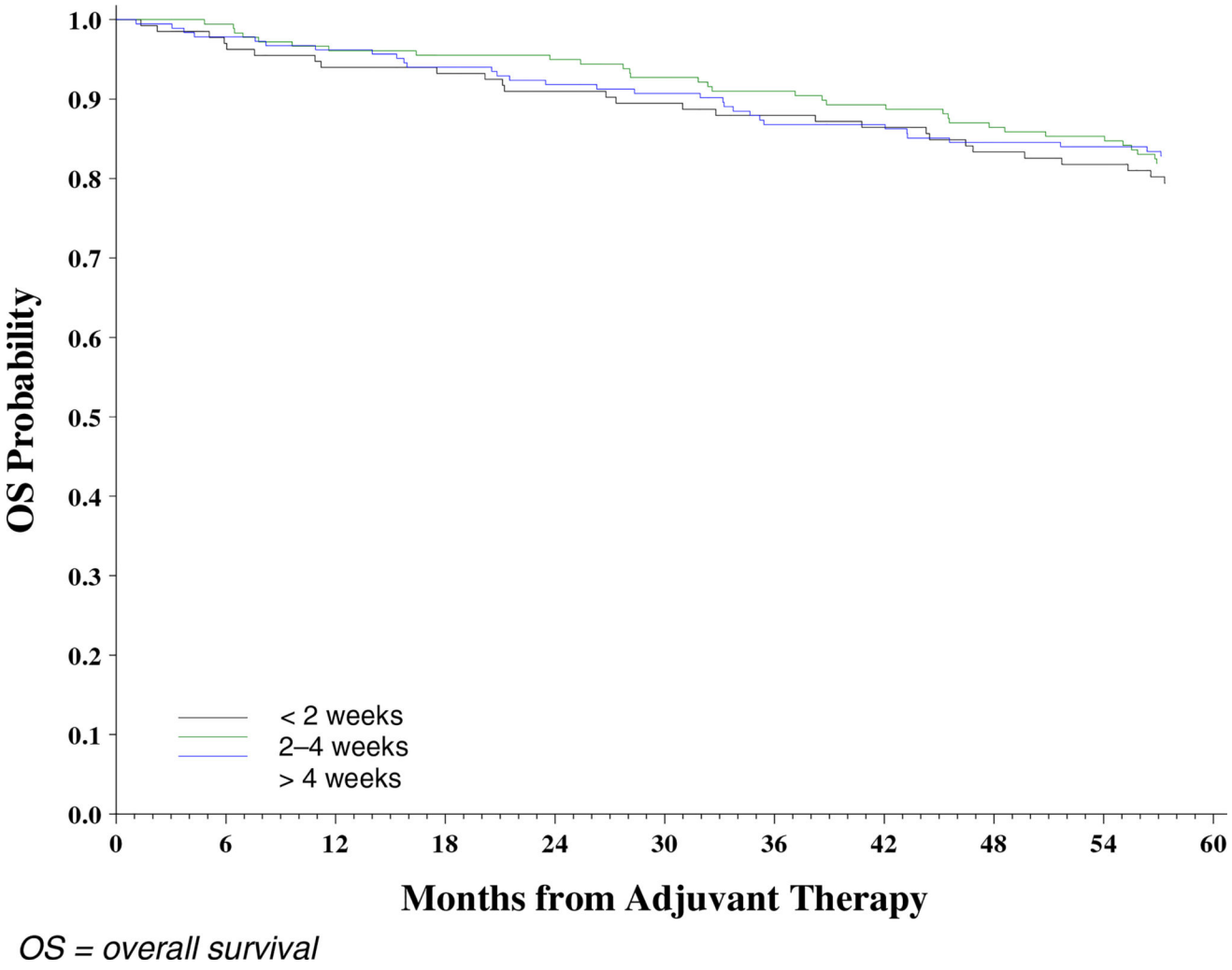


Fig. 2.

Kaplan-Meier estimate of overall survival by interval from surgery to initiation of adjuvant therapy ($p = 0.51$).

Table 1

Patient characteristics by interval from surgery to initiation of adjuvant therapy.

	Interval from surgery to initiation of adjuvant therapy			
	<2 weeks (*n* = 134)	**2–4 weeks (*n* = 179)**	**≥4 weeks (*n* = 184)**	***p* value**
Age (median years)	58.4	56.7	55.5	0.16
Race (%)				0.06
White	89.6	92.2	86.4	
Black	6.7	2.2	3.8	
Other	3.7	5.6	9.8	
Performance status (%)				0.001
0	46.3	52.0	55.4	
1	44.0	44.7	44.0	
2	9.7	3.4	0.5	
Stage (%)				0.83
IA/IB	17.2	14.0	16.3	
IC	48.5	54.8	52.7	
II	34.3	31.3	31.0	
Histology (%)				0.96
Serous	23.1	22.9	18.5	
Endometrioid	25.4	25.7	28.8	
Clear cell	27.6	26.3	28.3	
Mucinous	9.7	8.9	13.6	
Other	14.2	16.2	10.8	
Tumor grade (%)				0.27
1	21.6	16.2	18.5	
2	18.7	27.9	28.3	
3	59.7	55.9	53.3	
Ascites (%)				0.65
Presence	33.6	30.2	28.8	
Absence	66.4	69.8	71.2	
Cytology (%)				0.95
Positive	29.9	29.1	28.3	
Negative	70.2	71.0	71.7	
Rupture (%)				0.64
Yes	41.0	45.8	41.9	
No	59.0	54.2	58.2	
Treatment				<0.001
^{32}P	23.9	16.8	17.9	
CP	36.6	15.1	16.9	
PC 3 cycles	18.7	38.0	32.1	
PC 6 cycles	20.9	30.2	33.2	

^{32}P = intraperitoneal phosphate, CP = Cyclophosphamide + Cisplatin, PC = Paclitaxel + Carboplatin.

Table 2

Survival outcomes by interval from surgery to initiation of adjuvant therapy.

	Interval from surgery to initiation of adjuvant therapy		
	<2 weeks (*n* = 134)	**2–4 weeks (*n* = 179)**	**≥4 weeks (*n* = 184)**
RFS			
5-year	72.8%	73.9%	79.5%
Adjusted HR (95%CI)	1.0	0.90 (0.59–1.37)	0.72 (0.46–1.13)
p for HR		0.62	0.15
OS			
5-year	79.4%	81.9%	82.8%
Adjusted HR (95%CI)	1.0	0.87 (0.58–1.31)	0.78 (0.51–1.19)
p for HR		0.51	0.25

RFS = recurrence-free survival, OS = overall survival.

Table 3

Ovarian cancer studies on the effect of interval from surgery to initiation of adjuvant therapy.

Author (year of publication)	Type of data	Number of patients	Stage	Early initiation adjuvant therapy (TI)		Other significant prognostic factors
				(Univariate analysis)	(Multivariate analysis)	
Omura et al. (1989) [17]	Ancillary data - randomized trials	415	III	No data	Shorter TI (per week) = better survival	Age, residual disease, cell type
Warwick (1995) [19]	Ancillary data - randomized trials	333	II–IV	Shorter TI ≤ 21 days = better survival	No association	Performance status, residual disease, albumin level
Flynn et al. (2002) [18]	Ancillary data - randomized trials	472	I–IV	Shorter TI < 22 days = worse survival	No association	Stage, residual disease, performance status
Sorbe et al. (2004) [20]	Population data	1220	I–IV	Shorter TI < 25 days = worse survival	No association	Histology, grade, residual disease
Gadducci et al. (2005) [21]	Retrospective data - multi-institution	313	IIC–IV	No association	No association	Stage, residual disease
Rosa et al. (2006) [24]	Retrospective data - single institution	394	III	Shorter TI < 16 days = worse outcome	No association	Type of surgery, performance status, postoperative CA-125, residual disease
Aletti et al. (2006) [22]	Retrospective data - single institution	218	IIIC–IV	No association	No association	Residual disease
Paulsen et al. (2006) [23]	Cancer registry	371	IIC–IV	No association	No association	Age, histology, stage, ascites, residual disease
Wright et al. (2008) [25]	Population data (women > 65 years)	2558	III–IV	No data	Shorter TI < 42 days = better outcome	Age, stage, histology, medical comorbidities
Mahner et al. (2013) [40]	Ancillary data - randomized trials	3388	IIB–IV	No data	Shorter TI < 19 days = better survival in patients with no residual disease No association in patients with residual disease	Age, performance status, stage, ascites, residual disease
Tewari et al. (2015) [26]	Ancillary data - 1 randomized trial	1718	IV only	Shorter TI < 25 days = better survival	Shorter TI < 40 days = better survival	Age, performance status, race, stage, histology, ascites, residual disease, CA-125
Chan et al. (2016)	Ancillary data - randomized trials	497	I–II high risk	No association	No association	Age, stage, grade, and cytology

TI = Timing of initiation adjuvant therapy.