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Original Articles

Correlation of progression-free and post-progression survival with overall survival in phase III trials of first-line chemotherapy for advanced epithelial ovarian cancer

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Summary

Purpose of Investigation: The authors examined the relation between post-progression survival (PPS) and overall survival (OS) in phase III trials of first-line chemotherapy for advanced epithelial ovarian cancer. *Materials and Methods*: The authors partitioned OS into progression-free survival (PFS) and PPS and evaluated the relation between OS and either PFS or PPS. They also examined whether any association might be affected by the year of completion of trial enrollment. *Results*: The average PPS was longer in recent trials than in older trials (26.9 *vs.* 20.2 months, $p = 0.0002$). For all trials, PPS was strongly associated with OS ($r = 0.94$), whereas PFS was more moderately but still strongly correlated with OS ($r = 0.83$). The average proportion of median OS accounted for by median PPS significantly increased from 54.1% in older trials to 60.3% in recent trials ($p = 0.0001$). *Conclusion*: The present findings indicate that, especially for recent trials, PPS is more highly associated than PFS with OS in first-line chemotherapy for advanced epithelial ovarian cancer.

Key words: Chemotherapy; Ovarian cancer; Overall survival; Progression-free survival; Phase III trial.

Introduction

Ovarian cancer is one of the most pernicious female cancers. Each year, approximately 255,000 females will be diagnosed with cancer of the ovaries and roughly 140,000 will die from the disease worldwide. The most common type of ovarian cancer is epithelial, which accounts for about 90% of all ovarian cancers. Epithelial ovarian cancers are frequently diagnosed at an advanced stage of the disease with a consequent poor prognosis. The response rate to chemotherapy is, however, highest among gynecologic cancers with many patients who undergo a combination of surgery and chemotherapy achieving complete remission.

Overall survival (OS) is the most objective parameter in selecting the best treatment regimen for cancer patients because it most accurately reflects a clear benefit to humanbeings. In recent clinical trials, however, substantial improvements in progression-free survival (PFS) do not necessarily imply a prolonged OS. This is because there are various effective therapies that can be administered after failure of first-line treatment, or after trial completion or withdrawal from a trial according to protocol, all of which make it difficult to demonstrate that gain in OS results from first line treatment alone rather than as a result of the sequential administration of later effective therapies.

The effect of therapies instituted after disease progression on survival in clinical trials is thus of interest. Since it has been shown that post-progression therapies influence OS, post-progression survival (PPS) has recently become of interest as a determinant of OS. However, little is known about PPS.

For this study, we divided OS of phase III randomized controlled trials for treatment-naïve patients with advanced epithelial ovarian cancer into PFS and PPS and assessed the association of each with OS.

Materials and Methods

Literature search strategy and results of trials included

The search strategy and selection of phase III randomized control clinical trials are summarized in Figure 1.

A search for PubMed (US National Library of Medicine) was conducted between January 1st, 2000 and December 31st, 2012. Key words included in the search were 'ovarian', 'carcinoma or cancer', 'clinical trial', and 'chemotherapy'. The search was limited to randomized, controlled trials and articles published in English. Each publication was reviewed with those selected being phase III randomized controlled trials that compared two or more first-line systemic chemotherapies including treatment with molecularly targeted agents for advanced epithelial ovarian cancer. To find any additional controlled trials, the reference lists of in-

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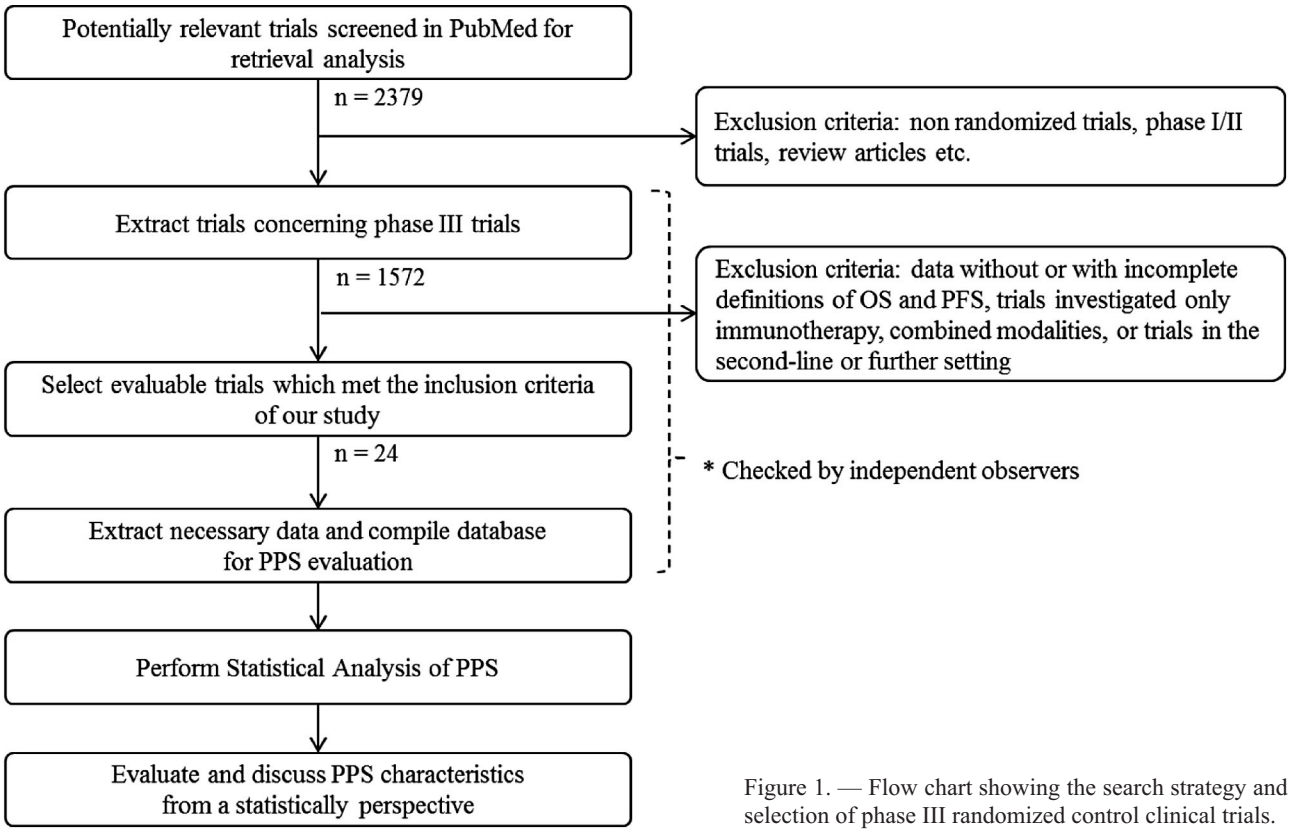


Figure 1. — Flow chart showing the search strategy and selection of phase III randomized control clinical trials.

cluded trials and of large systematic reviews were searched. Trials that provided data for both OS and either PFS or time to progression (TTP) were included, whether or not these parameters were explicitly defined. Trials were excluded if they investigated only immunotherapy regimens or hormonal therapies.

Data abstraction and clinical endpoint

Primary endpoints were analyzed in detail, following the definitions used by the authors of each trial. When not specifically stated by the authors, the primary endpoint was taken to be that used for calculation of sample size. Two endpoints (PFS and TTP) based on tumor assessment were collectively referred to as PFS in this study, in line with the approach adopted in recent reports [1, 2]. Median OS and median PFS were extracted from all trials that provided data for each treatment group. Median PPS was defined as median OS minus median PFS for each trial. The following information was obtained from each report: year of trial publication, line of treatment, number of patients in each treatment arm, number of treatment arms in each trial/ type of agents, age of the patients, number of patients with serous cystadenofibroma, and number of patients with clear cell adenocarcinoma.

The aims of this analysis were: (i) to evaluate (quantify) the correlation of PFS and PPS with OS in phase III randomized controlled trials in advanced epithelial ovarian cancer, (ii) to evaluate if these correlations changed according to the period within which the trial was published (before or after December 1999)

Data analysis

The survival data (median OS, median PFS, median PPS, median PFS, and median OS) was summarized as the mean for all trial arms. The percentage of OS accounted for by PPS for each trial arm was calculated as: 100 – (100×median PFS/median OS). To assess the relation between median OS and either median PFS or median PPS, Spearman's rank correlation coefficient was used. To account for differences in sample size and patient's characteristics among trial arms, analyses were weighted by the number of patients in each arm.

In addition, all trials were divided into two groups on the basis of the year in which trial enrollment was completed. Given that the median year for completion of enrollment for the 24 analyzed trials [3–27] was December 1999, a division was made at year 1999 (older trials being June 1993 to December 1999 inclusive recent trials being January 2000 to August 2006 inclusive) in order to evaluate a possible change in PPS, and to assess whether the evaluated relations might be dependent on the year of completion of trial enrollment. Differences in the survival data between older and recent trials were determined by Students's *t*-test the average survival data using Students's *t*-test. All reported *p*-values correspond to two-sided tests, and those with p-values < 0.05 were considered statistically significant. Analyses were carried out with SAS for Windows release 9.3.

Results

Characteristics of the trials

A total of 2,379 potentially relevant publications were identified from the search. Of these, 2,335 studies were excluded for at least one of the following reasons: they examined other malignancies or combined modality treatments, they investigated only immunotherapy regimens or hormonal therapies; they examined other malignancies or combined modality treatments (e.g. radiotherapy); they were not randomized;

Table 1. — *Characteristics of the 24 phase III trials for advanced epithelial ovarian cancer included in the present analysis*

Trial characteristics	
Median no. of patients per trial	456.5 (42.0 - 4312.0)
Average of median age (years)[a]	59.0
Median of serous[b]	150.0 (9.0 - 650.0)
Median of clear cell[c]	3.0 (0.0 - 40.0)
Primary endpoint (no. of trials)	
OS	10
PFS or TTP	11
Other	3

[a] Five trials were excluded (data are not shown).
[b] Four trials were excluded (data are not shown).
[c] Eight trials were excluded (data are not shown).

they were phase I or II trials; they were review articles, letters or commentaries; they represented subgroup analyses of other trials or they were the duplicates of similar retrieved studies; they contained no information about the year of completion of trial enrollment; they were phase III randomized controlled trials investigating second and sequential chemotherapies.

Review of the remaining publications yielded 24 trials that were considered to be highly relevant for the present study. The main characteristics of the 24 phase III trials included in the analysis are listed in Table 1. A total of 6,386 patients with advanced epithelial ovarian cancer were enrolled, with a median number of patients per study of 456.5 (range 42–4,312). The average median age of the patients was 59.0 years. Eleven trials used an endpoint based on tumor assessment (PFS or TTP) as the primary endpoint, whereas OS was assessed as the primary endpoint in ten trials. In the other three trials the primary endpoint was not specified.

Median OS, PFS, and PPS of all trials and subgroups based on year of completion of trial enrollment (older trials, up to December 1999; recent trials, January 2000 and later)

The survival data (all trials and trial arms according to the year in which trial enrollment was completed) are shown in Table 2. The median OS was 41.2 months, while the median PFS and PPS were 17.2 and 24.1 months, respectively, for all arms (n = 52). The median OS, PFS and PPS in older trials were 36.8, 16.6, and 20.2 months, respectively. The median OS, PFS, and PPS in recent trials were 44.5, 17.6 and 26.9 months, respectively. Although the average median PFS in older trials was the same as that in recent trials, the average median PPS was longer in the recent trials than in the older trials (26.9 and 20.2 months, respectively, $p = 0.0002$). The average proportion of median OS accounted for by median PPS significantly increased from 54.1% in older trials to 60.3% in recent trials ($p = 0.0001$).

Relation between OS and either PFS or PPS

The relation between median OS and either median PFS or median PPS for all trials (52 arms, PPS/OS ratio: 57.7%) is shown in Figures 2 and 3, respectively. It was found that median PPS was strongly associated with median OS ($r = 0.94$, $p < 0.0001$) on the basis of Spearman's correlation coefficient, whereas median PFS was more moderately but still strongly correlated with median OS ($r = 0.83$, $p < 0.0001$).

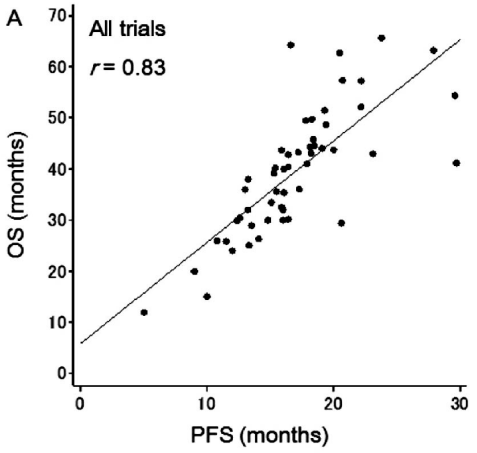
The correlation between median OS and median PFS in recent trials ($r = 0.79$, $p < 0.0001$) was similar to that in older trials ($r = 0.84$, $p < 0.0001$). In addition, the slope of the two regression lines were found to be roughly parallel ($p = 0.6187$). The association between median OS and median PPS in recent trials ($r = 0.86$, $p < 0.0001$) was similar to that in older trials ($r = 0.85$, $p < 0.0001$) with no difference in the slope of the regression lines ($p = 0.8652$).

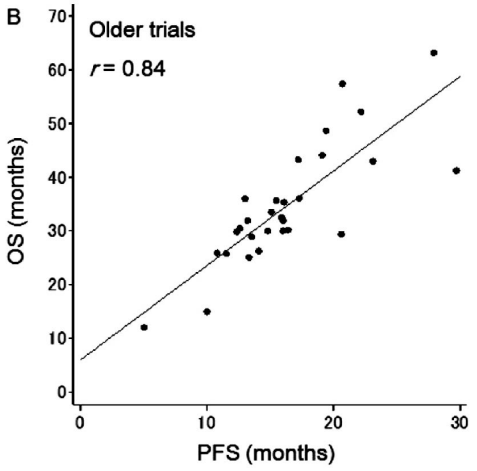
Discussion

In the present study, median PPS was defined as median OS minus median PFS for each treatment arm of phase III randomized controlled trials for chemotherapy-naïve patients with advanced epithelial ovarian cancer, as previously described [1, 28]. The relation between median OS and either median PPS or median PFS by correlation analysis was also investigated revealing that median OS was more strongly associated with median PPS than with median PFS. Moreover, the average proportion of median OS accounted for by median PPS was found to be significantly increased in recent trials than in older trials. According to recent studies, chemotherapy sensitivity affects the overall survival greatly [29, 30]. Therefore the choice of drugs should be decided by whether the patient is chemotherapy-sensitive or not. Specifically, monotherapy has been selected for women who relapsed more than six months after completing initial chemotherapy [31, 32], whereas combination therapy with platinum-based therapy was selected for women who experienced relapse ≥ six months after therapy [33–35]. The recent prolongation of PPS is likely the result of the increasing number of active compounds, being adminis-

Table 2. — *The survival data (all trials and trial arms according to the year in which trial enrollment was completed).*

Trial type	n	PFS (months)		PPS (months)		OS (months)		PPS/OS (%)	
		mean	*p*-value	mean	*p*-value	mean	*p*-value	mean	*p*-value
Overall	52	17.2		24.1		41.2		57.7	
1st-line (up to December 1999)	29	16.6	0.3058	20.2	0.0002	36.8	0.0018	54.1	0.0001
1st-line (December 1999 and later)	23	17.6		26.9		44.5		60.3	





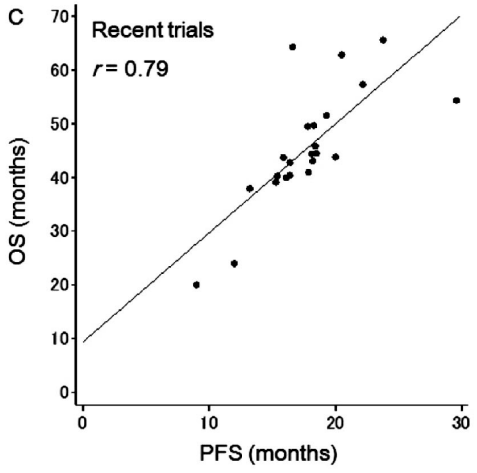
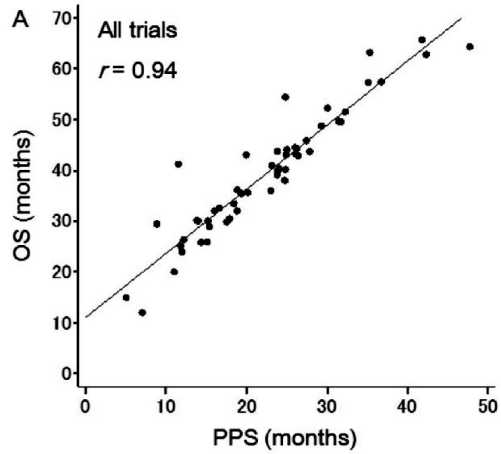
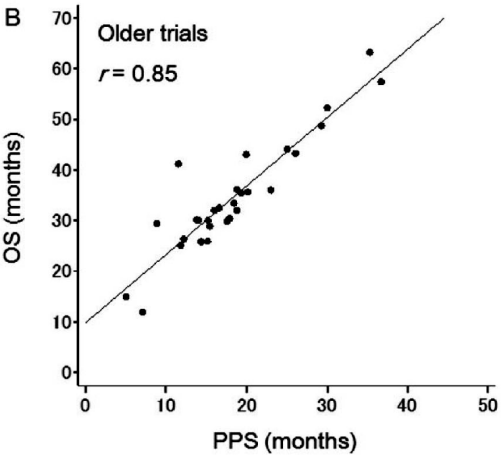


Figure 2. — Relation between median OS and median PFS for 52 arms of 24 phase III trials for advanced epithelial ovarian cancer. (A) All trials. (B) Older trials (trial enrollment finished between June 1993 and December 1999). (C) Recent trials (trial enrollment finished between January 2000 and August 2006). The area of each dot is proportional to the number of patients in each trial arm. The *r* values represent Spearman's rank correlation coefficient.





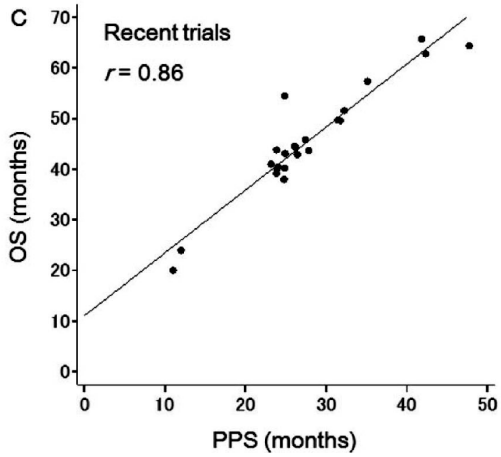


Figure 3. — Relation between median OS and median PPS for 52 arms of 24 phase III trials for advanced epithelial ovarian cancer. (A) All trials. (B) Older trials (trial enrollment finished between June 1993 and December 1999). (C) Recent trials (trial enrollment finished between January 2000 and August 2006). The area of each dot is proportional to the number of patients in each trial arm. The *r* values represent Spearman's rank correlation coefficient.

tered appropriately. Many factors other than more effective cures could be contributing to prolonged survival in trials of advanced epithelial ovarian cancer patients: inclusion criteria in modern trials are more stringent and treatment of ovarian cancer increasingly effective. Broglio and Berry [28] recently focused on PPS, which they termed survival post-progression (SPP) and defined as OS minus PFS, in a hypothetical clinical trial setting under the assumption that there was a treatment difference in PFS but not in PPS. As the median PPS increased, the probability of detecting a statistically significant difference in OS decreased substantially. For a trial with an observed p value for improvement in PFS of 0.001, there was > 90% probability for statistical significance of the difference in OS if the median PPS was two months, whereas this probability decreased to only 50% if the median PPS was six months. In the present study, for recent trials for advanced epithelial ovarian cancer, it was found that median PPS constituted more than half of median OS and that median PPS was > 27 months. Similar results were found by Hayashi *et al.* [2] in non-small-cell lung cancer (NSCLC) for which an increasing number of effective drugs are available. Hayashi *et al.* evaluated the relation between PPS and OS, and found that median PPS constituted more than half of median OS and that median PPS was > six months for NSCLC, which was a similar trend as the present study.

Evaluation of PFS as a surrogate endpoint for OS has often been conducted by quantifying the strength of the association between these endpoints at the individual level (referred to as individual-level surrogacy) and of that between the effects of treatment on these endpoints (trial-level surrogacy) [36–39]. The present examination of the correlation between PFS and OS was not an exercise in surrogate validation because of the lack of investigation into the correlation between the effects of chemotherapy on these endpoints. However, the present study has yielded the key finding that PPS, not PFS, is highly associated with OS.

The present study has several limitations. First, the analysis was based on abstracted data rather than on individual patient data. The use of individual patient data might have allowed a better characterization of the relation between OS and other endpoints based on tumor assessment, including PFS and TTP. However, if such an approach had been used, it would have restricted the analysis to a small number of trials and would have hindered its replication by independent researchers. Second, the results of this study potentially have several confounders because many heterogeneous trials have been included into the analysis. The results would be generally uninterpretable without appropriate adjustment for patient characteristics dependent on differences in predefined eligibility criteria for enrollment in the clinical trials. Third, the assessment of disease progression could be subject to measurement error and bias in individual patients, and the quality of measurement for endpoints based on tumor assessment can vary between centers and trials. Finally, following the example of a previous report for ovarian cancer, the two endpoints (PFS and TTP) based on tumor assessment are considered as the same parameter. PFS is defined as the time from patient random selection to tumor progression or death, whereas TTP is defined similarly but considers death as the time point when censoring occurs. TTP is the same as PFS if death does not occur during treatment. Given that death rarely occurs before disease progression in ovarian cancer, PFS could reasonably be considered the same as TTP for the analysis. Indeed, separate analysis of clinical trials that use PFS (46 arms) or TTP (six arms) revealed a consistent association between OS and PPS (data not shown). These data thus support this approach in which these two endpoints (PFS and TTP) are collectively referred to as PFS in the present analysis.

To the best of the present authors' knowledge, this study is the first to analyze PPS in advanced epithelial ovarian cancer. The findings indicate that, especially for recent trials, PPS is strongly associated with OS for first-line chemotherapy in patients with advanced epithelial ovarian cancer. Therefore, OS remains an appropriate endpoint of clinical trials for chemotherapy-naïve patients with advanced epithelial ovarian cancer. Given the great effect of PPS on OS, appropriate assessment of clinical course after disease progression (second-line and later) in each clinical trial will be required.

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