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Correlation between progression-free survival and overall survival in patients with ovarian cancer after cytoreductive surgery: a systematic literature review

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ABSTRACT

Objectives This analysis aimed to better define the relationship between progression-free survival and overall survival in adult patients with ovarian cancer (including fallopian tube or primary peritoneal cancer) following primary cytoreductive surgery or interval cytoreductive surgery.

Methods A systematic literature review was carried out across the Medline, Embase, and Cochrane Central databases on 7 July 2020 (date limits 1 January 2011 to 7 July 2020) to identify studies with the following eligibility criteria: clinical trials/observational studies including >200 patients with ovarian cancer aged ≥18 years, evaluating overall survival/progression-free survival following cytoreductive surgery by residual disease status in the United States, Europe, Japan, or China. Weighted linear regression models were used to assess any correlation between median progression-free survival and overall survival, and between logHR for progression-free survival and logHR for overall survival. Risk of bias was assessed for all included studies.

Results Of the 50 studies reported, 43 were observational studies (41 retrospective and two prospective cohort studies), and seven were reporting for randomized clinical trials—of which four were retrospective data analyses. For analyses of the relationship between overall survival and progression-free survival, 21 studies were eligible. The weighted linear regression model showed a strong positive association between the two survival endpoints. Goodness-of-fit analysis measured the adjusted R^2 as 0.84 ($p<0.001$); a positive association was also observed between logHRs for overall survival and progression-free survival in the included studies.

Conclusions Median progression-free survival was predictive of median overall survival. This correlation between progression-free survival and overall survival after primary treatment for ovarian cancer highlights the validity of progression-free survival as a primary endpoint. Observational studies contributed most data, with limited information on disease stage and histology.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Overall survival is regarded as the gold standard endpoint in cancer clinical trials but often requires large, expensive, and time-consuming trials to demonstrate a benefit, compared with trials utilizing progression-free survival as a primary endpoint.

WHAT THIS STUDY ADDS

⇒ The results from this meta-analysis looking at standard first-line ovarian cancer treatment, including clinical trial and real-world data studies, supports an association between progression-free survival and overall survival status.

HOW THIS STUDY MIGHT AFFECT THIS RESEARCH, PRACTICE OR POLICY

⇒ This relationship supports the use of progression-free survival as a surrogate primary endpoint for overall survival in ovarian cancer trials, and may be useful in supporting the development of future clinical trials for ovarian cancer.

⇒ This analysis also expands on the growing body of evidence showing that ovarian cancer treatments, which are effective in delaying disease progression, are likely to demonstrate a benefit in overall survival.

INTRODUCTION

Ovarian cancer is one the most common gynecologic cancers, with an incidence rate of >300 000 women globally in 2020.[1] Unfortunately, ovarian cancer is often diagnosed in advanced stages, owing to its non-specific symptoms and a lack of effective screening.[2] Standard treatment for ovarian cancer includes cytoreductive surgery with adjuvant platinum-based chemotherapy.[3] Prognosis is based on clinical and biological variables, including tumor stage/grade at diagnosis, tumor size, and residual disease after cytoreductive surgery.[4]

Overall survival is regarded as the gold standard endpoint in cancer clinical trials, as it is an objective measure, can be measured precisely by documenting date of death, and has a low risk of bias in reporting.[5 6] However, obtaining statistically significant overall survival outcomes requires large clinical trials that are more expensive, time-consuming, and require longer follow-up compared with trials utilizing progression-free survival as a primary endpoint.[7] Progression-free survival is often evaluated as a

surrogate endpoint for overall survival in clinical trials, but it is difficult to assess the degree of correlation between progression-free survival and overall survival in certain cancer types, including ovarian cancer.[7]

The objective of this study was to evaluate the relationship between progression-free survival and overall survival in adult patients with ovarian cancer for whom residual disease was reported, including patients with fallopian cancer and primary peritoneal cancer following primary cytoreductive or interval cytoreductive surgery. We used a systematic literature review to identify observational studies and clinical trials that reported progression-free survival and overall survival outcomes, and extracted data to evaluate this potential relationship.

METHODS

Systematic Literature Review

Data Sources

The primary data sources were the Medline, Embase, and Cochrane Central databases. The database searches were performed on 7 July 2020 (date limits 1 January 2011 to 7 July 2020). To complement the database searches and identify relevant literature for the last 10 years (2011–2020), supplementary searches were conducted between 14 August and 20 August 2020, and comprised searches of gray literature (online keyword-based pragmatic searches in Google and Google Scholar), bibliographic sources, and conference proceedings (2019–2020) from the annual meetings of the American Society for Clinical Oncology, European Society for Medical Oncology, and Society of Gynecologic Oncology.

Eligibility Criteria

A comprehensive search strategy based on the population, intervention, comparator, outcome, and study type framework was used to evaluate search results (Table 1). Key eligibility criteria were publications that included studies of >200 adult patients (typically aged ≥18 years) with ovarian cancer (including fallopian tube cancer or primary peritoneal cancer) that evaluated overall survival and progression-free survival following cytoreductive surgery (primary cytoreductive surgery or interval cytoreductive surgery) as per residual disease status in the United States, Europe, China, Japan, or multinational studies including countries of interest. Online supplemental tables 1 and 2 list the search terms used. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were implemented during literature search and review.[8]

The identified studies were evaluated in two phases. First, the title and abstract of each record were evaluated according to the inclusion and exclusion criteria (Table 1). Next, full-text versions of the selected records were examined in detail to select the final list of studies to be included. For both steps, each record was assessed for inclusion or exclusion by two independent reviewers, and any discrepancies were resolved by a third reviewer. The selection process was documented at all stages.

Data Extraction and Quality Assessment

After full-text screening, data from the selected publications were extracted into Microsoft Excel by two independent reviewers, and conflict resolution and quality check were conducted by a third reviewer. Quality assessment of randomized controlled trials was carried out according to the National Institute for Health and Care

Table 1 Literature search and PICOS framework

Searches*	Details	
Structured searches	Medline, Embase, and Cochrane Central databases	
Supplementary searches	Gray literature, bibliographic searches, conference proceedings (ASCO, ESMO, SGO) 2019–2020	
Category		
Population	Adults aged ≥18 years with ovarian cancer (including fallopian tube cancer and primary peritoneal cancer)	
Intervention	Studies evaluating patient outcomes following cytoreductive surgery irrespective of the type of chemotherapy used as neoadjuvant and adjuvant treatment The following surgery types were considered: primary cytoreductive surgery and neoadjuvant chemotherapy followed by interval cytoreductive surgery	
Outcomes	Overall survival, progression-free survival as per residual disease status	
Study design	Inclusion criteria: ► Clinical trials ► Observational studies	Exclusion criteria: ► Case studies ► Case reports
Countries	United States, Europe, China, Japan	
Sample size	Studies with >200 patients	
Statistical criteria	Studies with results for multivariate analysis	

*Structured searches were conducted on 7 July 2020, with a timeframe of 1 January 2011 to 7 July 2020, and supplementary searches were conducted between 14 August and 20 August 2020 (for records from 2011–2020). Diagnosis of ovarian cancer included ovarian, fallopian tube cancer, and primary peritoneal cancer. Only English language studies were included.
ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; PICOS, population, intervention, comparator, outcome, and study type; SGO, Society of Gynecologic Oncology;

Excellence (NICE) checklist, and the Newcastle-Ottawa Scale[9] was used for assessing observational studies and retrospective analyses of randomized controlled trials.

Statistical Analysis

A weighted linear regression model was used to assess correlation between median progression-free survival and overall survival, with each datapoint's weight calculated as 1/(4 x n) for the overall survival median.[10] Residual disease status was entered as a factor in the linear regression. A weighted least squares linear regression model was conducted using the logHR for progression-free survival, to predict the correlation with logHR for overall survival. Each datapoint was weighted by its inverse variance, a measure of the precision of the effect estimate. Where studies reported outcomes by different subgroups rather than an overall population, these were treated as separate datapoints in the analysis.

In accordance with the journal's guidelines, we will provide our data for independent analysis by a team selected by the Editorial Team for the purposes of additional data analysis, or for the reproducibility of this study in other centers if such is requested.

RESULTS

Literature Search

Of 2848 total records identified through database searching, there were 52 publications that met inclusion criteria (online supplemental table 3). After linking multiple publications of the same study, 50 primary studies (all journal articles) were selected for final extraction and reporting (Figure 1).

Overview of Included Studies

Of the 50 included studies, 43 were observational studies (41 retrospective cohort[11–50] and two prospective cohort studies),[51 52] three were randomized controlled trials,[53–55] and four were retrospective analyses of randomized controlled trial.[56–59] The overall study sample sizes for each publication ranged from 203 to 8652. The majority (n=26) of studies consisted of 100–500 patients with ovarian cancer; nine, four, six, and five studies had 501–1000, 1001–1500, 1501–3000, and >3000 patients with ovarian cancer, respectively.

Across all 50 studies, 18 assessed combinations of surgery types, of which 16 assessed interval cytoreductive surgery and primary cytoreductive surgery,[15 18 20–23 25 26 31 33 35 36 43 46–48 51 52] and two assessed interval cytoreductive surgery and cytoreductive surgery/primary cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.[22 36] Primary cytoreductive surgery was assessed in 15 studies,[11–14 16 24 27 29 30 32 37 42 45 54 59] 13 reported cytoreductive surgery without specifying surgery type,[17 18 28 34 39–41 50 53 55–58] and four assessed interval cytoreductive surgery.[19 38 44 49]

Seven studies were conducted in multiple countries,[18 21 52 54 55 57 59] and 43 were conducted in single countries (Europe n=23;[11–13 20 22 23 25 28 31 33 36–38 41–46 48 49 52 57] North America n=14;[15 16 18 19 21 29 30 32 34 50 51 53 56 58] Asia n=7[17 21 24 26 39 40 60]). Among studies conducted in a single country, most were conducted in the

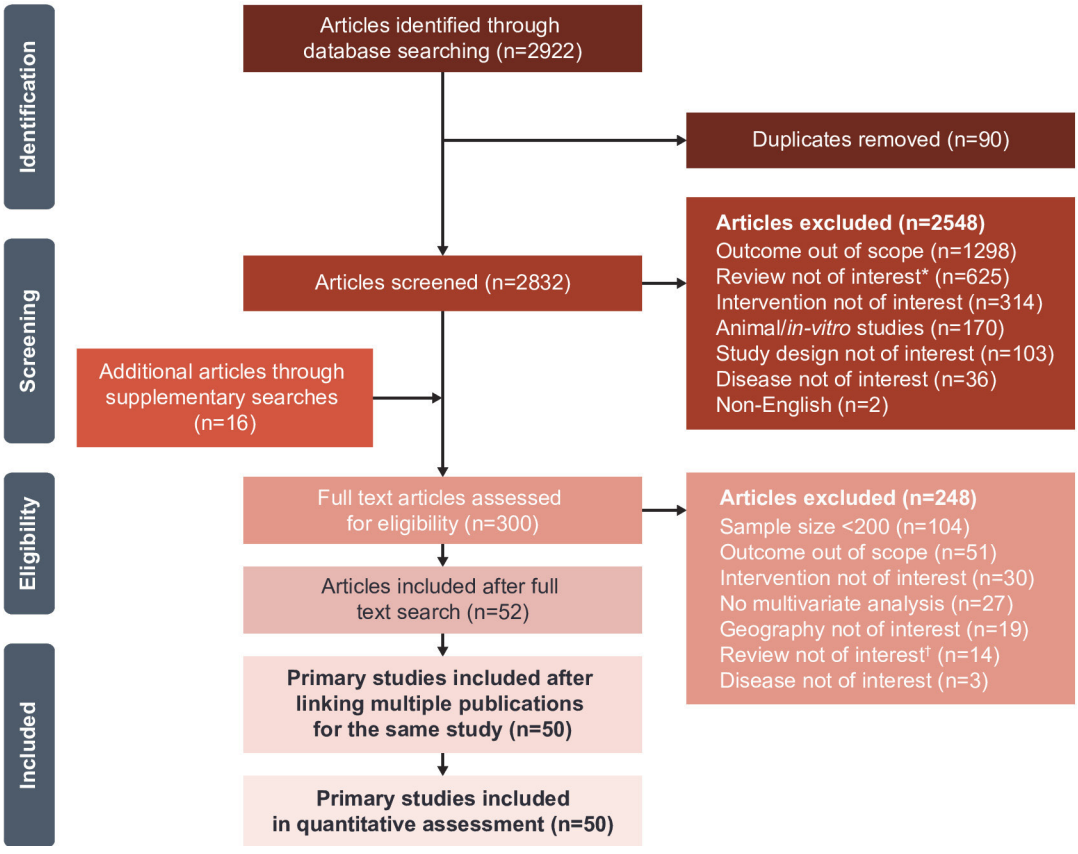


Figure 1 PRISMA flow chart of included studies. *Includes narrative reviews, editorials, commentaries, and letters containing no relevant data†Articles that do not provide any additional data for inclusion in the analyses.PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

United States (n=14),[15 16 18 19 21 29 30 32 34 50 51 53 56 58] followed by China (n=5).[17 24 26 39 40] Twenty-one studies were published from 2011 to 2015,[11 14–17 23 27 28 30 31 33 35 40 43 47 48 52 53 56–58] and 29 were published from 2016 to 2020.[12 13 18–22 24–26 29 32 34 36–39 41 42 44–46 49–51 54 55 59 60]

There was heterogeneity between the studies in terms of patient baseline characteristics, including which variables were reported (online supplemental tables 4–6). Median age ranged from 46–75 years. Ethnicity data were available in 13 studies.[18 19 21 29 32 34 50 51 53 55 56 58 59] Performance status was assessed using Eastern Cooperative Oncology Group in 22 studies,[11–13 17 21 22 24 25 35 40 41 43 45 47 48 51–53 55–57 59 60] of which one study used the WHO performance scale,[47] one study used the Gynecologic Oncology Group performance scale,[56] and one study used the Karnofsky performance scale;[48] performance status was not assessed in the other 24 studies. The majority of studies (n=34) enrolled patients with either stage III, stage IV disease, or both;[12 13 15 16 19 20 22 23 25–27 29–38 40 41 43–45 47 49 50 53 55 56 58 59] 16 studies included patients with mixed ovarian stage disease (stage I–IV).[11 14 17 18 21 24 28 39 42 46 48 51 52 54 57] Most studies (n=47) included patients with mixed histology subtypes, with only three including patients with a single histology subtype. CA-125 status was available in 21 studies[14–16 20–22 24 26–28 31 32 35 39 40 43 49 51 53 55 60] and *BRCA* mutation status was available in two studies.[49 51]

Study Quality Assessment

Risk of bias was assessed for all 50 studies. The three clinical trials were rated as having low to unclear risk of bias using NICE assessment.[61] Of the 43 observational studies and four retrospective analyses of randomized controlled trials, 30 were rated as good quality, and 17 were rated to be of fair quality, as assessed using the Newcastle-Ottawa Scale.[62]

Study Outcomes: Overall Survival and Progression-Free Survival

Overall survival data were available from 41 observational studies, three clinical trials, and four retrospective analyses of randomized controlled trials (Table 2). In these studies, overall survival was defined as either the time from surgery (time from initial treatment) to the date of death or last follow-up, whichever occurred first (n=25 studies); the time from ovarian cancer diagnosis to death from any cause or last follow-up (n=9); or the time from study entry to death or last follow-up (n=4). In the remaining 10 studies, overall survival was not defined.

Progression-free survival data were available from 15 observational studies, two clinical trials, and four retrospective analyses of randomized controlled trials (Table 2). This endpoint was defined as either the time from treatment (surgery or chemotherapy) to disease progression or disease recurrence (n=11); the time from initial diagnosis to the time of first recurrence (n=5); or the time from diagnosis to the date that recurrence was confirmed on tissue biopsy or imaging (n=1). Progression-free survival was not defined in four studies.

Relationship Between Median Overall Survival and Median Progression-Free Survival

For the analysis of the relationship between overall survival and progression-free survival, only 21 studies reported overall survival/logHR overall survival and progression-free survival/logHR progression-free survival, and were therefore eligible for both analyses. In the weighted linear regression model, there was a strong positive association between overall survival and progression-free survival. The relationship between median overall survival and progression-free survival of all studies reporting both overall survival and progression-free survival is shown in Figure 2A. The intercept co-efficient was 4.49 (standard error 3.26), and the median progression-free survival co-efficient was 2.27 (standard error 0.17); thus, median overall survival= 4.49 + (2.27 x median progression-free survival).

Goodness-of-fit analysis measured the adjusted R^2 as 0.84 ($p<0.001$), indicating a good fit for the data.

LogHR Overall Survival and LogHR Progression-Free Survival Analysis

There was a positive association between logHRs for overall survival and progression-free survival in all studies (Figure 2B). The intercept co-efficient was 0.03 (standard error 0.06) and the median progression-free survival co-efficient was 1.01 (standard error 0.10); thus, logHR overall survival= 0.03 + (1.01 x logHR progression-free survival).

The adjusted R^2 was 0.86 ($p<0.001$), further supporting a good fit for the data.

DISCUSSION

Summary of Main Results

Across a combined total of 19 077 patients with ovarian cancer from the 21 studies which reported both overall survival and progression-free survival by residual disease status, there was a direct and positive correlation between overall survival and progression-free survival among those who had received first-line treatment (primary cytoreductive surgery or interval cytoreductive surgery) and chemotherapy. Median progression-free survival was highly predictive of median overall survival. There was also a positive association between logHRs for overall survival and progression-free survival in all studies.

Results in the Context of Published Literature

Although extending overall survival is typically a key objective of treatment in patients with ovarian cancer, demonstrating a statistically significant improvement in overall survival using a therapeutic intervention is particularly challenging within a research setting.[63] Assessing overall survival is complicated by the need for a large number of patients and longer duration of follow-up, as well as modest treatment efficacies, leading to most patients receiving multiple post-progression treatments (including chemotherapy, biological-targeted therapies, and surgery), which can confound and dilute the effects of investigational therapies on overall survival.[7] In addition, with such protracted follow-up periods, the analysis of overall survival for a particular intervention can be confounded by treatment effects from subsequent therapies that are used following disease progression, and by the inclusion of non-cancer-related deaths.[5 64 65] Indeed, part of the improvement in overall survival within ovarian cancer that has occurred previously may be influenced by the additive effects of multiple therapies, each of which improve progression-free survival.[65–70] Demonstration of a progression-free survival benefit has been more common in

Table 2 Key characteristics of outcomes reported in studies included in the systemic literature review

Study name	Type of surgery	Overall survival (time to event)	Progression-free survival (time to event)	HR for overall survival	HR for progression-free survival	Predictors for survival
Ataseven 2014[11]	Primary cytoreductive surgery	Yes	No	Yes	No	No
Ataseven 2016[12]	Primary cytoreductive surgery	Yes	No	Yes	No	No
Ataseven 2018[13]	Primary cytoreductive surgery	Yes	No	Yes	No	No
Braicu 2011[14]	Primary cytoreductive surgery	No	No	Yes	No	No
Bristow 2011[15]	Both (interval cytoreductive surgery, cytoreductive surgery)	No	No	Yes	No	No
Chang 2012[16]	Primary cytoreductive surgery	Yes	Yes	Yes	Yes	No
Chen 2014[17]	Cytoreductive surgery	Yes	Yes	Yes	Yes	No
Cheng 2020a[18]	Cytoreductive surgery	No	No	Yes	No	No
Cheng 2020b[60]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	No	No	Yes*	Yes*	No
Davidson 2019[19]	Interval cytoreductive surgery	Yes	No	Yes	No	Yes
Delga 2020[20]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	Yes	Yes	Yes	No	Yes
Deng 2017[21]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	No	No	Yes*	Yes*	No
Di Giorgio 2017[22]	Both (interval cytoreductive surgery, primary cytoreductive surgery) and hyperthermic intraperitoneal chemotherapy	No	No	Yes*	No	No
Fader 2013 (GOG protocol 182)[53]	Cytoreductive surgery	Yes	Yes	Yes	Yes	Yes
Fagö-Olsen 2014[23]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	Yes	No	Yes	No	No
Feng 2016[24]	Primary cytoreductive surgery	No	No	Yes	Yes	No
Fleming 2018[51]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	No	Yes	No	Yes	No
Gadducci 2017[25]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	No	No	Yes	Yes	No
Gao 2019[26]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	Yes	Yes	Yes*	Yes*	No
González Martín 2019 (ICON7 Trial)[54]	Primary cytoreductive surgery	Yes	Yes	No	No	Yes
Hosono 2011[27]	Primary cytoreductive surgery	No	No	Yes	No	Yes
Kalapotharakos 2012[28]	Cytoreductive surgery	No	No	Yes†	No	No
Kumar 2016[29]	Primary cytoreductive surgery	No	No	Yes	No	No
Landrum 2013[56]	Cytoreductive surgery	Yes	Yes	Yes	Yes	No
Langstraat 2011[30]	Primary cytoreductive surgery	Yes	No	Yes	No	No
Luyckx 2012[31]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	Yes	No	Yes	No	No
Mahner 2013[57]	Cytoreductive surgery	No	No	Yes	Yes	No
Manning-Geist 2018[32]	Primary cytoreductive surgery	Yes	Yes	Yes	Yes	No

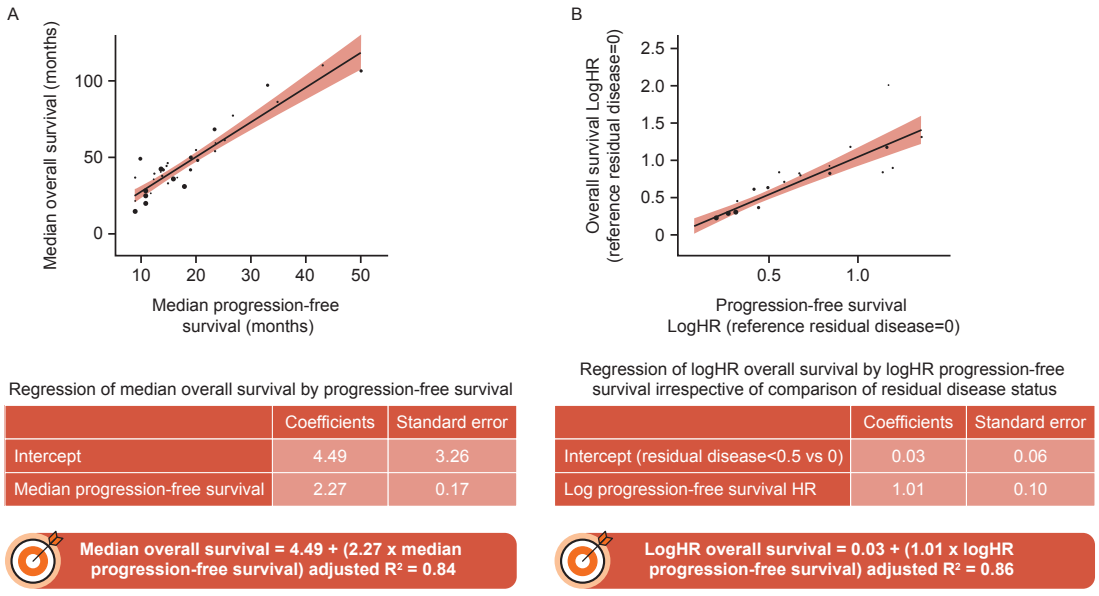
Continued

Table 2 Continued

Study name	Type of surgery	Overall survival (time to event)	Progression-free survival (time to event)	HR for overall survival	HR for progression-free survival	Predictors for survival
Markauskas 2014[33]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	Yes	Yes	Yes	No	No
Melamed 2017[34]	Cytoreductive surgery	No	No	Yes	No	No
Mizuno 2015[35]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	Yes	No	Yes	No	No
Munoz-Casares 2016[36]	Both (interval cytoreductive surgery, cytoreductive surgery) and hyperthermic intraperitoneal chemotherapy	Yes	No	Yes*	No	No
Phelps 2017[37]	Primary cytoreductive surgery	Yes	No	Yes	Yes	No
Phillips 2018[38]	Interval cytoreductive surgery	Yes	No	Yes	No	No
Ren 2015[40]	Cytoreductive surgery	Yes	Yes	Yes	Yes	No
Ren 2017[39]	Cytoreductive surgery	Yes	No	Yes	No	No
Rodriguez 2013 (GOG 182)[58]	Cytoreductive surgery	Yes	Yes	No	No	Yes
Rosendahl 2018[41]	Cytoreductive surgery	Yes	No	Yes	No	No
Rungruang 2017[59]	Primary cytoreductive surgery	No	No	Yes	Yes	No
Rutten 2015[43]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	Yes	Yes	Yes	No	No
Rutten 2017[42]	Primary cytoreductive surgery	No	No	Yes	No	No
Searle 2020[44]	Interval cytoreductive surgery	No	No	Yes	Yes	No
Sorensen 2019[45]	Primary cytoreductive surgery	Yes	No	Yes	No	No
Tewari 2016 (GOG protocol 0218)[55]	Cytoreductive surgery	No	No	Yes	No	No
Timmermans 2018[46]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	No	No	No	No	Yes
Trillsch 2013[52]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	Yes	Yes	Yes	Yes	No
Trope 2012[47]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	Yes	No	Yes	No	No
Van Altena 2013[48]	Both (interval cytoreductive surgery, primary cytoreductive surgery)	No	No	Yes	No	No
Vincent 2020[49]	Interval cytoreductive surgery	Yes	No	Yes	No	No
Zhou 2018[50]	Cytoreductive surgery	No	No	Yes	No	No

*All studies reported HR, except five studies, where OR was reported (Cheng 2020b, Deng 2017, Di Giorgio 2017, Gao 2019, and Munoz-Casares 2016).
†Univariate analysis result was available as per residual disease status only.
GOG, Gynecologic Oncology Group; HR, hazard ratio; ICON7, International Collaboration on Ovarian Neoplasms 7; OR, odds ratio.

interventional clinical studies, and has been accepted as a primary endpoint for clinical trials, despite a lack of consensus that it is an appropriate surrogate for overall survival.[5 65] Progression-free survival, as an objective primary endpoint, can be vulnerable to observational bias (ie, different clinical interpretations with different readers);[71] however, the Gynecological Cancer InterGroup (GCIG) consider progression-free survival to be an acceptable primary endpoint in front-line ovarian cancer, because it is a more proximal readout than overall survival.[72] Progression-free survival can be assessed earlier using smaller sample sizes than overall survival, is not confounded by treatment effects of subsequent therapies, and also factors in achievement of stable disease.[5] Shorter and less costly trials aimed at demonstrating progression-free survival rather than overall survival benefits conserve both patient and



Regression of median overall survival by progression-free survival

	Coefficients	Standard error
Intercept	4.49	3.26
Median progression-free survival	2.27	0.17

Median overall survival = 4.49 + (2.27 x median progression-free survival) adjusted R^2 = 0.84

Regression of logHR overall survival by logHR progression-free survival irrespective of comparison of residual disease status

	Coefficients	Standard error
Intercept (residual disease<0.5 vs 0)	0.03	0.06
Log progression-free survival HR	1.01	0.10

LogHR overall survival = 0.03 + (1.01 x logHR progression-free survival) adjusted R^2 = 0.86

Figure 2 A) Relationship between median overall survival and median progression-free survival overall B) Relationship between logHR overall survival and logHR progression-free survival. Each datapoint represents experimental arms within the studies included in the analysis (13/21 for median overall survival and progression-free survival [A] and 11/21 for logHR overall survival and progression-free survival [B]). The size of each datapoint corresponds to the inverse variance of each experimental arm.

HR, hazard ratio.

monetary resources, and might also support earlier access for patients to novel treatments.[72]

The results from this analysis support a stronger relationship between progression-free survival and overall survival than has been reported in previous studies,[7 73 74] including a meta-analysis that considered only randomized control trials examining first-line platinum-based therapies in ovarian cancer.[7] Unlike our study, Sjoquist et al reported a moderate correlation between progression-free survival and overall survival, which may be due to differences in study methodologies and patient populations. As Sjoquist et al limited their analysis to randomized controlled trials, there is likely to be greater homogeneity in the analysis population compared with our analysis, which included both observational studies and randomized controlled trials. In addition, Sjoquist et al did not require surgical treatment for inclusion in their analysis, although it is likely that most studies included patients who received some sort of cytoreductive surgery. Additionally, they required platinum-based chemotherapy, whereas our analysis did not specify chemotherapy type. In another meta-analysis, which also consisted of randomized controlled trials only, Paoletti et al reported a high correlation between progression-free survival and overall survival at the individual level, but a low correlation at the trial level, and suggested that progression-free survival could not be validated as a strict surrogate endpoint in randomized controlled trials of first-line advanced ovarian cancer.[74] They found that despite large sample sizes, some trials with a similar treatment effect on progression-free survival had a different effect on overall survival, which generated uncertainty in the predictive ability of progression-free survival in relation to overall survival. Since this analysis was performed, two notable studies have published long-term (5–7 years) survival outcomes in advanced ovarian cancer, namely the SOLO-1 and PAOLA-1 trials.[75 76] In both studies, the long-term overall survival findings supported the positive progression-free survival findings reported initially,[75 76] potentially reflecting the association between progression-free survival and overall survival observed in our analysis.

Strengths and Weaknesses

Study limitations for our analysis include the fact that most data were from observational studies rather than clinical trials. While observational studies may be more prone to bias because confounding factors and reported outcomes are reliant on complete and correct data entries, these studies still provide a valuable contribution to the growing body of evidence pointing to an association between progression-free survival and overall survival in ovarian cancer.[77 78] In addition, overall study quality assessments were carried out for all studies, including observational and randomized controlled trials studies using NICE[61] and Newcastle-Ottawa Scale[9] assessments, which showed that most studies were of fair to good quality, providing further strength to the findings of this analysis. This analysis was, however, limited to studies which reported progression-free survival and overall survival by residual disease status only. This formed part of a separate analysis to determine the impact of residual disease status on progression-free survival and overall survival, described in another publication.[79] Another limitation is that data availability per disease stage and histology was limited, and these factors have previously been shown to be associated with overall survival outcomes.[80] Comparison across treatments was not feasible owing to the wide range of interventions used in the adjuvant and neoadjuvant settings.

Implications for Practice and Future Research

Finally, we used a linear fit to quantify the association between progression-free survival and overall survival; a more complex

polynomial or spline function could be considered to evaluate the relationship between progression-free survival and overall survival, while accounting for additional patient-related variables.

Despite the difficulty in obtaining statistically significant overall survival improvements in clinical studies, these data derived from studies reporting overall survival and progression-free survival by residual disease status demonstrate a direct, positive relationship between progression-free survival and overall survival after primary treatment for ovarian cancer. This positive relationship highlights the validity of progression-free survival as a surrogate primary endpoint for overall survival in ovarian cancer trials, and may be useful in supporting the development of future treatments for ovarian cancer. This analysis expands on the growing body of evidence showing that ovarian cancer treatments that are effective in delaying disease progression are likely to meaningfully extend overall survival.

CONCLUSIONS

Across the 21 studies included in this analysis, a direct and positive correlation between overall survival and progression-free survival was demonstrated from a combined total of 19 077 patients with ovarian cancer who had received first-line treatment and chemotherapy, supporting progression-free survival as a valid primary endpoint in ovarian cancer trials.

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Contributors DC: Conceptualization; Roles/Writing - original draft; Writing - review and editing; AM: Data curation, Formal analysis; Validation; Roles/Writing - original draft; Writing - review and editing; DAS: Data curation, Formal analysis; Validation; Data Curation; Roles/Writing - original draft; Writing - review and editing; NH: Data curation, Formal analysis; Validation; Roles/Writing - original draft; Writing - review and editing; LK: Conceptualization; Data curation; Formal analysis; Validation; Data Curation; Roles/Writing - original draft; Writing - review and editing. LK is guarantor of this manuscript.

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Competing interests DC reports speakers' bureau fees and/or advisory roles from GSK, AstraZeneca, Seagen, Eisai, Takeda, Clovis, Roche, and Merck. AM, DAS, and NH have no conflict of interest to disclose. LK is an employee of GSK.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. GSK makes available anonymized individual participant data and associated documents from interventional clinical studies that evaluate medicines, upon approval of proposals submitted to https://www.gsk-studyregister.com/en/.

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