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ORIGINAL ARTICLE

# Quality of life predicts overall survival in women with platinum-resistant ovarian cancer: an AURELIA substudy

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**Background:** Women with platinum-resistant ovarian cancer are a heterogeneous group whose median overall survival is 12 months. We hypothesized that their quality of life (QoL) scores would be prognostic.

**Patients and methods:** Data from AURELIA ($n = 326$), a randomized trial of chemotherapy with or without bevacizumab, were used to identify baseline QoL domains [EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30 and OV28] that were significantly associated with overall survival in multivariable Cox regression analyses. Patients were classified as having good, medium, or poor risk. Cutpoints were validated in an independent dataset, CARTAXHY ($n = 136$). Multivariable analyses of significant QoL domains on survival were adjusted for clinicopathological prognostic factors. The additional QoL information was assessed using *C* statistic.

**Results:** In AURELIA, all domains, except cognitive function, predicted overall survival in univariable analyses. Physical function ($P < 0.001$) and abdominal/gastrointestinal symptom ($P < 0.001$) scores remained significant in multivariable models. In high (score <67), medium (67–93), and low (>93) risk categories for physical function, median overall survival was 11.0, 14.7, and 19.3 months, respectively ($P < 0.001$). In CARTAXHY, median overall survival was 7.9, 16.2, and 23.9 months ($P < 0.001$), respectively. For high- (>44), medium- (13–44), and low- (<13) risk categories for abdominal/gastrointestinal symptoms, median overall survival was 11.9, 14.3, and 19.7 months in AURELIA ($P < 0.001$) and 10.5, 19.6, and 24.1 months in CARTAXHY ($P = 0.02$). Physical function ($P = 0.02$) and abdominal/gastrointestinal symptoms ($P = 0.03$) remained independent prognostic factors after adjustment for clinicopathological factors. The *C* statistic of the full model was 0.71. For QoL factors alone, patient factors alone and disease factors alone, the *C* statistics were 0.61, 0.61, and 0.67 respectively.

**Conclusions:** Physical function and abdominal/gastrointestinal symptom scores improved predictions of overall survival over clinicopathological factors alone in platinum-resistant ovarian cancer. This additional prognostic information could improve trial stratification, patient–doctor communication about prognosis, and clinical decision-making.

**Clinical trial registration:** NCT00976911.

**Key words:** patient-reported outcomes, prognosis, platinum-resistant ovarian cancer, quality of life

## Introduction

Most patients with ovarian cancer have advanced disease at diagnosis and are treated with surgery and platinum-based chemotherapy. Despite such treatment, most experience disease recurrence requiring further systemic therapy. Patients whose disease relapses within 6 months after platinum-containing

therapy are considered to have platinum-resistant ovarian cancer (PROC), as the likelihood of response to platinum re-exposure diminishes with decreasing interval since the last platinum chemotherapy [1, 2]. Patients with PROC have poor prognosis, with median survival 12–18 months [1, 3]. Little is known about the prognostic value of baseline patient-reported quality of life (QoL) in PROC. In patients with a new diagnosis of advanced ovarian cancer undergoing chemotherapy, poor global QoL is associated with poor progression-free and overall survival [4, 5]. In other advanced incurable cancers, systematic reviews report consistent association between QoL and survival even after clinicopathological factors are accounted for [6–8].

Accurate prediction of survival in PROC is vital for counselling patients. In patients with poor prognosis, accurate estimates of survival times could influence decisions to undergo chemotherapy. Clinicopathological factors such as performance status, CA125 level, ascites, platinum-free interval, and size of the tumour provide some information, but remain inadequate in accurately predicting survival in these patients.

We investigated whether baseline QoL, in addition to clinicopathological factors, could improve prognostic discrimination. As scores are frequently measured on continuous scales, we further developed and validated a categorization system to facilitate practical discrimination of patients in the clinical setting.

## Patients and methods

We used data from the AURELIA trial [9]. AURELIA is an open-label randomized phase III trial (NCT00976911) comparing bevacizumab plus chemotherapy versus chemotherapy alone in patients with PROC. Treatment was continued until progressive disease, unacceptable toxicity, or consent withdrawal. The primary endpoint was investigator-assessed progression-free survival.

### Analysis population

Patients with baseline QoL data formed the analysis population. Questionnaires were completed at baseline and during chemotherapy until disease progression. Health-related QoL was measured with the European Organisation for Research and Treatment of Cancer (EORTC) general health QoL questionnaire (EORTC QLQ-C30) [10] and the ovarian specific questionnaire (OV28) [11]. Both are validated, cancer-specific instruments designed for prospective clinical trials. The QLQ-C30 questionnaire evaluates the global health scale, five other domains (physical, role, cognitive, emotional, and social), and nine single-item symptoms. The QLQ-OV28 evaluates six domains (abdominal/gastrointestinal, peripheral neuropathy, hormonal, body image, attitude to disease/treatment, chemotherapy side-effects, and sexuality), and four single-item symptoms.

### Validation dataset

The validation population was from CARTAXHY [12], an open-label randomized phase II trial comparing weekly paclitaxel, weekly paclitaxel plus carboplatin, and weekly paclitaxel plus weekly topotecan. Patients with baseline QoL data were included in the validation data set.

### Statistical methods

In the AURELIA analysis population, we examined baseline QoL scores initially as continuous measures. All domains of the QLQ-C30 and the abdominal/gastrointestinal symptom subscale comprising items 31–36 of the QLQ-OV28 were examined [13]. We extended our prior work [13] to specifically examine abdominal/gastrointestinal symptoms because ascites/peritoneal disease results in significant symptoms that impair QoL and hence are considered to be of special interest in this patient population. We correlated each of the six domains of the QLQ-C30 and symptom scores from the OV28 with survival in univariable Cox proportional-hazard regression analysis. We used multivariable regression analysis to identify domains and/or symptom scores significantly correlated with overall survival. Box–whisker plots were produced to display the correlation between physical function and baseline characteristics (ECOG, ascites, CA125, measureable disease, progression-free interval, primary or secondary resistance) (supplementary Figure S2, available at *Annals of Oncology* online).

For practical clinical application, patients were categorized in four equal groups on the basis of their scores. For QLQ-C30 domains, the first quartile formed the poor group, the middle two were combined as the medium group, and the final quartile formed the good group. For the symptom score, interpreted in the opposite direction, the first quartile was classed as the good group and the last quartile the poor group. The cutpoints were based on the baseline distribution of QLQ-C30 domain or symptom score that significantly correlated with overall survival in the multivariable model for all the continuously measured QLQ-C30 and symptom scores. We validated the cutpoints in the CARTAXHY population. We explored the use of other cutpoints by performing an additional analysis and divided each functioning score into three groups based on the individual distribution of scores. The discriminatory value of the scores was graphically presented using the Kaplan–Meier approach.

We determined the independent prognostic value of baseline scores by adjusting for baseline clinicopathological factors in multivariable analysis. Previous work had identified these factors as having prognostic significance in PROC: performance status, ascites, CA125 level, platinum-free interval, primary platinum resistance, and size of measurable lesions [14]. Using the validated cutpoints, we used the *C* statistic to measure the performance of the statistical models in discriminating overall survival times in order to quantify the value of baseline QoL scores when examined with clinicopathological factors. The *C* statistic estimated the proportion of all pairwise combinations of patients whose survival times were ordered such that the patient with the higher predicted survival time was the one who actually survived longer (discrimination) [15]. The *C* statistic was a probability of concordance between predicted and observed survival, with 0.50 for random predictions and 1.00 for a perfectly discriminating model [16].

All statistical tests were two-sided. $P < 0.05$ was considered statistically significant, and there was no adjustment for multiplicity.

## Results

Of the 361 AURELIA participants, 90% completed baseline QoL assessments. Of the 165 CARTAXHY participants, 82% had baseline assessments (Table 1).

In univariable analysis in AURELIA, each unit increase in QLQ-C30 score (better functioning) in all domains, except cognitive function, was significantly associated with improvement in survival. Each unit increase in abdominal/gastrointestinal symptom score (more symptoms) was associated with worse survival. In multivariable analysis, the only significant predictors were QLQ-C30 physical function (HR 0.98; 95% CI 0.98–0.99; $P < 0.001$) and abdominal/gastrointestinal symptoms (HR 1.01; 95% CI 1.01–1.02; $P < 0.001$). See supplementary table 1 available at *Annals of Oncology* online.

The median physical function score was 80 [interquartile range (IQR) 67–93] (Table 2). On the basis of this distribution, the poor, medium, and good physical function groups comprised 76, 147, and 99 patients, with median overall survival 11.0, 14.7, and 19.3 months, respectively (log-rank $P < 0.001$, Figure 1). The median abdominal/gastrointestinal symptom score was 28 (IQR 11–44). The poor, medium, and good groups comprised 67, 159, and 76 patients with median survival 11.9, 14.3, and 19.7 months, respectively (log-rank $P < 0.001$).

With the same cutpoints, the poor, medium, and good physical function groups in the CARTAXHY dataset comprised 28, 56, and 52 patients with median survival 7.9, 16.2, and 23.9 months, respectively (log-rank $P < 0.001$, Figure 2). For abdominal/gastrointestinal symptoms, the groups comprised 38, 59, and 37 patients with median survival 24.1, 19.6, and 10.5 months, respectively (log-rank $P < 0.001$).

Consistent results were seen when utilizing other cutpoints by performing an additional analysis and dividing each subscale into three groups based on the individual distribution of scores (supplementary Figure S1, available at *Annals of Oncology* online).

In further multivariable analysis, after adjustment for clinicopathological factors, physical function ($P = 0.02$), and abdominal/gastrointestinal symptoms ($P = 0.03$) were significant independent predictors of survival (Table 2). As seen in supplementary Figure S2, available at *Annals of Oncology* online, although ECOG and PF are highly correlated, a number of patients who were rated as ECOG 2 had high PF and vice versa.

The *C* statistics of the multivariable statistical model (Table 2) with disease-related factors, patient-related factors, and QoL factors was 0.71. This multivariable model provided the best possible prediction of overall survival in the AURELIA trial population (Table 3). When QoL factors only were considered in a statistical model, the *C* statistic was 0.61, which was equivalent to 86% of the performance of the best multivariable model. When disease-related factors only were considered, the *C* statistic was 0.67, equivalent to 94% of the performance of the best multivariable model.

**Table 1. Characteristics of patients with quality of life scores available at baseline**

| | AURELIA (*n*=326) | | CARTAXHY (*n*=136) | | |
|---|---|---|---|---|---|
| **Characteristic** | ***n*** | **%** | ***n*** | **%** | ***P*** |
| ECOG score | | | | | |
| 0 | 190 | 58.3 | 59 | 43.4 | 0.01 |
| 1 | 114 | 35.0 | 66 | 48.5 | |
| 2 | 22 | 6.8 | 11 | 8.1 | |
| Serous histology | 241 | 73.9 | 103 | 75.7 | 0.68 |
| CA125 ≥100 IU/ml | 259 | 79.5 | 107 | 78.7 | 0.85 |
| Ascites | 101 | 31.0 | 56 | 41.2 | 0.04 |
| Measurable disease | | | | | |
| Non-measurable | 66 | 20.3 | 46 | 33.8 | <0.001 |
| Largest lesion measured <5 cm | 115 | 35.3 | 70 | 51.5 | |
| Largest lesion measured ≥5 cm | 145 | 44.5 | 20 | 14.7 | |
| Platinum-free interval | | | | | |
| <3 months | 89 | 27.3 | 73 | 53.7 | <0.001 |
| 3–6 months | 237 | 72.7 | 63 | 46.3 | |
| Primary platinum resistance | 238 | 73.0 | 102 | 75.0 | 0.66 |
| Treatment arm | | | | | |
| Chemotherapy and bevacizumab | 161 | 49.4 | 0 | 0 | <0.001 |
| Chemotherapy only | 165 | 50.6 | 136 | 100 | |

## Discussion

In PROC, good physical function and low abdominal/gastrointestinal symptom score are significantly associated with longer survival. Even after we accounted for clinicopathological factors, those who had the best physical function score (>92) had over 30% less chance of dying, with a median overall survival 19.3 months, compared with 13.0 months in those with poor physical function. Women with low abdominal/gastrointestinal symptom scores (<13) had almost 30% less chance of dying, with a median overall survival of 18.3 months, compared with 12.3 months for those with the most symptom burden.

Data on prognostic factors in women with PROC, including the prognostic role of patient-reported QoL, remain limited. Most studies on prognostic factors have been in platinum-sensitive trial settings. In this population, baseline global QLQ-C30 scores [4] and physical well-being in FACT-G [5] are associated with survival.

**Table 2. Prognostic value of physical function and abdominal/gastrointestinal symptoms for survival in the AURELIA dataset**

| | Univariable analysis | | | | | Multivariable analysis[a] | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Overall survival** | ***n*** | **Median overall survival (months)** | **HR** | **95% CI** | ***P*** | ***n*[b]** | **HR** | **95% CI** | ***P*** |
| Physical function score | 322 | | | | <0.001 | 300 | | | 0.02 |
| <67 | 76 | 11.0 | 1 | | | | 1 | | |
| 67–92 | 147 | 14.7 | 0.62 | (0.45–0.85) | | | 0.75 | (0.52–1.08) | |
| >92 | 99 | 19.3 | 0.44 | (0.31–0.63) | | | 0.56 | (0.37–0.85) | |
| Abdominal/gastrointestinal symptom score | 302 | | | | <0.001 | 300 | | | 0.03 |
| <13 | 76 | 19.7 | 1 | | | | 1 | | |
| 13–44 | 159 | 14.3 | 1.51 | (1.08–2.12) | | | 1.13 | (0.80–1.61) | |
| >44 | 67 | 11.9 | 2.56 | (1.74–3.76) | | | 1.67 | (1.10–2.54) | |

[a]Multivariable analysis adjusted for performance status, ascites, CA125 level, platinum-free interval, primary platinum resistance, and size of measurable lesions.
[b]*n* refers to patients with data available for both quality of life and clinicopathological factors.
HR, hazard ratio; CI, confidence interval.

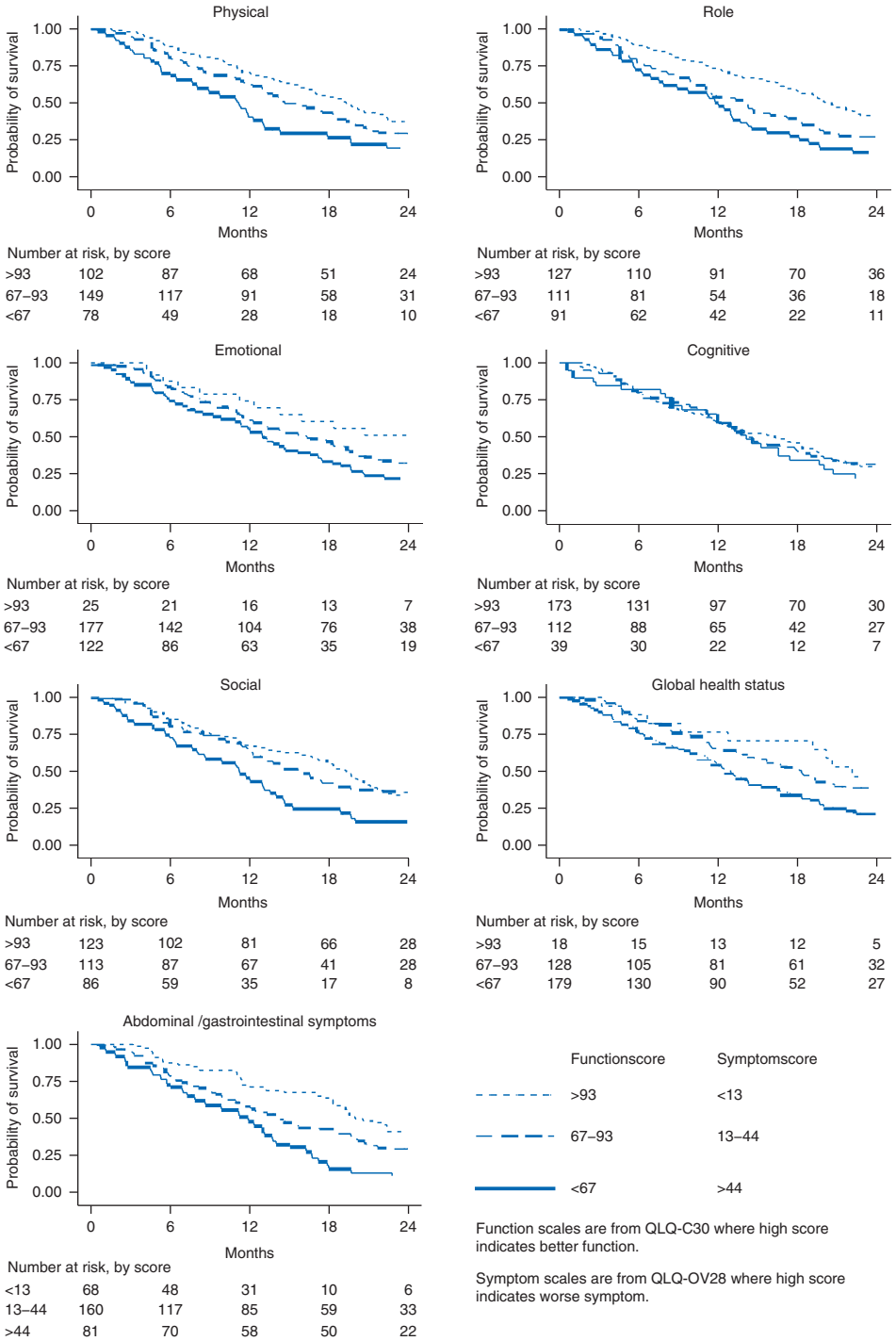


**Figure 1.** Kaplan–Meier estimates of the probability of overall survival according to different quality of life function and symptom scales in the AURELIA population.

In contrast, another study in ovarian cancer of all stages showed no statistically significant association between QoL index and survival [17]. Several recent studies have suggested that the prognostic domain may vary across cancer sites, and found that nausea/vomiting of QLQ C-30 correlated with survival in ovarian cancer [17–19]. The literature is conflicting, and studies on PROC are limited. Also no study has examined the association between abdominal/gastrointestinal symptoms and overall survival, although these symptoms are particularly relevant in PROC, because these patients have typically higher tumour burden, and therefore report more of these symptoms than those with early stage or newly diagnosed platinum-sensitive ovarian cancer. The result of this study is therefore highly relevant and contributes new data to this area of research.

Women with PROC are still a heterogeneous group with variable survival [1, 3, 20, 21]. Generally, oncologists tend to

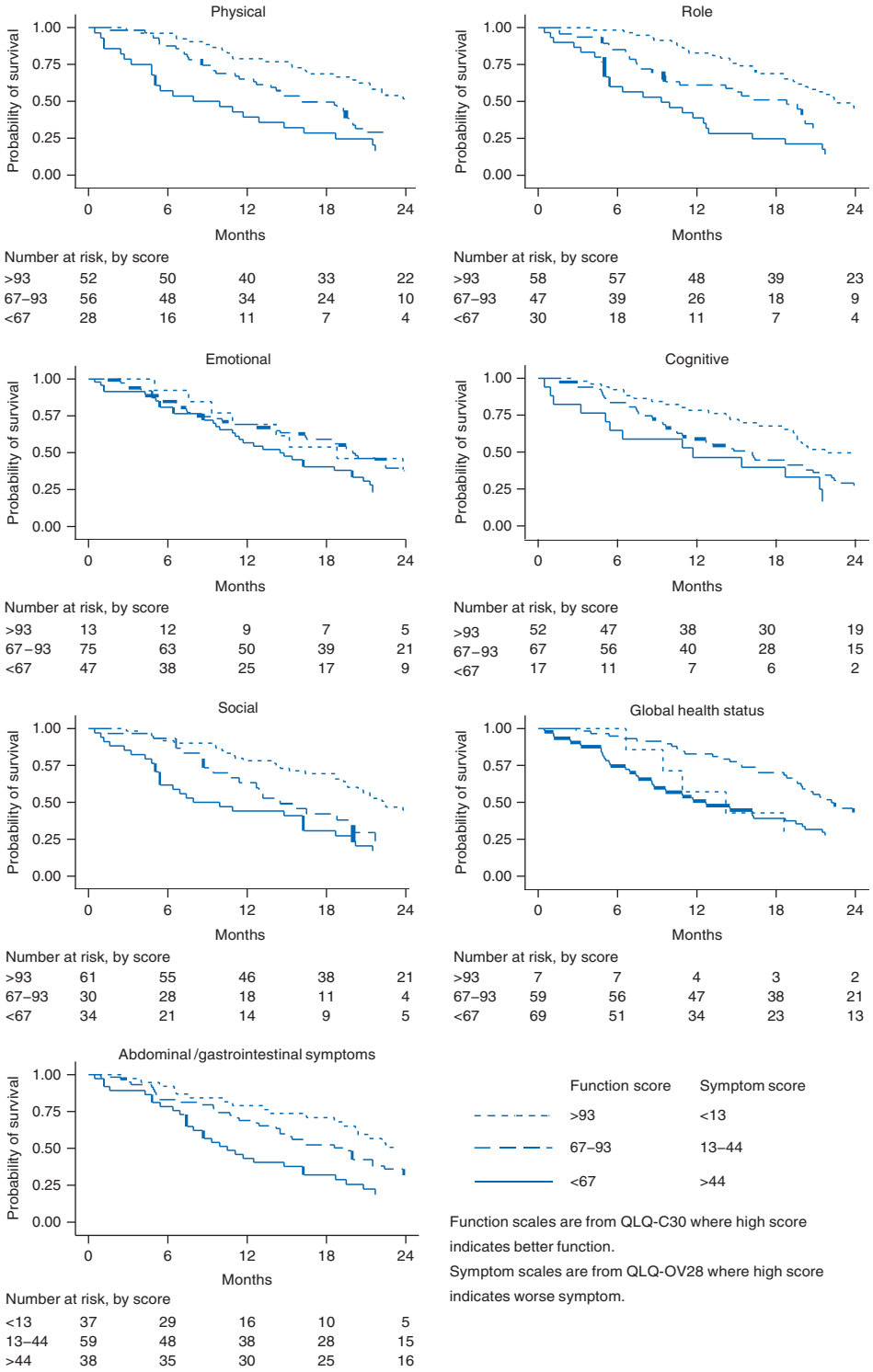


**Figure 2.** Kaplan–Meier estimates of the probability of overall survival according to different quality of life function and symptom scales in the CARTAXHY population.

overestimate survival times [22]. Our study demonstrates that incorporating QoL into a multivariable model of clinicopathological factors provides additional prognostic information and could improve prediction of survival times. Furthermore, our study demonstrates that statistical model with QoL alone carried out at 86% of the best multivariable model of clinicopathological and QoL factors. The statistical model with QoL alone was comparable to the model with patient factors (performance status) alone, as these two factors are highly correlated. Importantly, both QoL and performance status provided more prognostic information than either factor alone. QoL should be considered in the evaluation of prognosis in women with PROC.

**Table 3. Performance of statistical models with quality of life, patient and disease factors**

| Statistical model | *C* statistic | Performance of statistical model relative to the full model (%)[a] |
|---|---|---|
| Full[b] | 0.7131 | |
| Quality of life only[c] | 0.6099 | 85.5 |
| Disease only[d] | 0.6713 | 94.1 |
| Patient only[e] | 0.6101 | 85.6 |
| Quality of life and patient | 0.6557 | 92.0 |
| Quality of life and disease | 0.6968 | 97.7 |
| Patient and disease | 0.6950 | 97.5 |

[a]Performance is calculated as the *C* statistic relative to the full model *C* statistic.
[b]Full statistical model refers to the best statistical model with quality of life, disease, and patient factors for predicting overall survival.
[c]Quality of life only model refers to the statistical model with only physical functioning and abdominal/gastrointestinal scores for predicting overall survival.
[d]Disease-only model refers to the statistical model with only ascites, CA125 level, platinum-free interval, primary platinum resistance, and size of measurable lesions for predicting overall survival.
[e]Patient-only model refers to the statistical model with only performance status score for predicting overall survival.

Accurate prognostication influences patients' personal decisions and decisions for further lines of aggressive systemic therapy, assists patients and their families in planning remaining time together, and for clinicians, guides treatment decisions and helps them plan supportive care and allocate resources. It is also important for stratifying participants in future PROC clinical trials.

Our study has several other additional strengths. Patient-reported data and survival times were prospectively collected in a large well-conducted trial. Compliance was high (90%) for baseline patient-reported data. Unlike previous studies with heterogeneous populations of patients with platinum-sensitive ovarian cancer and PROC, all our patients had PROC and received contemporary systemic therapy. The instruments used, EORTC QLQ-C30 and QLQ-OV28, are validated, sensitive, and reliable. QLQ-C30 is the most widely used QoL instrument, which gives consistent results, as reported in two systematic reviews [7, 8]. As to limitations, although statistically significant in multivariable model, QoL provides relatively small additional information on prognosis over traditional measures of disease and patient characteristics. Despite this, QoL is easily measured at a minimal cost and reflects the direct impact of recurrent ovarian cancer on patients. Another possible limitation is that clinical trials participants generally have better performance status and may not be representative of patients not included in clinical trials We did not assess the reproducibility of patients' questionnaire responses. Certain domains are highly correlated with clinicopathological factors, such as performance status with physical and role function, raising the question of whether these factors should be examined together in multivariable analyses. However, our study has demonstrated that performance status and physical function are not collinear terms, and both exist as independent prognostic factors in multivariable analyses. When examined with other QLQ-C30 domains, to the best of our knowledge this study is the first to demonstrate the importance of abdominal/GI symptoms, together with physical functioning and other clinicopathological factors in prognostication in PROC. Although ECOG performance status and the physical functional domain are highly correlated, both variables remained significant in multivariable analyses suggesting that physical functional domain score contributed information in addition to performance status assessment as illustrated in supplementary Figure S2, available at *Annals of Oncology* online where a number of patients who were rated as performance status 2 had high physical functioning score. Conversely, some patients rated as ECOG 0 had low physical functioning score.

For information on QoL measures and other clinicopathological characteristics to be practically and effectively utilized in clinical settings, a prognostic index incorporating all these factors is needed to better predict survival times in PROC. A nomogram to address this clinical need is being developed.

In conclusion, physical function and abdominal/gastrointestinal symptoms predict overall survival in PROC even after clinicopathological factors are accounted for. Such patient-reported measures should be used, with clinicopathological factors, for patient stratification in clinical trials, patient–doctor communication about prognosis, and clinical decision-making.

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## Disclosure

The authors have declared no conflicts of interest.

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