Original Research

Characteristics of long-term survival in advanced stage ovarian cancer: a nationwide cohort in the Netherlands

Lilian van Wagensveld1,2,*, Gabe Steven Sonke3, Koen Kris Van de Vijver4,5, Hugo Mark Horlings6, Rutgerus Franciscus Petrus Maria Kruijswagen2,7, Maaike Anne van der Aa1

1Department of Research and Development, Netherlands Comprehensive Cancer Organization (IKNL), 3511 DT Utrecht, the Netherlands
2GROW, School for Oncology and Developmental Biology, Maastricht university, 6229 ER Maastricht, the Netherlands
3Department of Medical Oncology, The Netherlands Cancer Institute, 1066 CX Amsterdam, the Netherlands
4Department of Pathology, Ghent University Hospital, Cancer Research Institute Ghent (CRIG), 9000 Gent, Belgium
5Department of Pathology, Antwerp University Hospital, 2000 Antwerpen, Belgium
6Division of Molecular Pathology, The Netherlands Cancer Institute, 1066 CX Amsterdam, the Netherlands
7Department of Obstetrics and Gynecology, Maastricht University Medical Centre, 6229 HX Maastricht, the Netherlands

*Correspondence: l.vanwagensveld@iknl.nl (Lilian van Wagensveld)

Academic Editor: Enrique Hernandez
Submitted: 3 November 2021 Revised: 14 December 2021 Accepted: 15 December 2021 Published: 15 February 2022

Abstract

Objective: Despite optimal treatment with debulking surgery and chemotherapy, the majority of patients with advanced stage epithelial ovarian cancer (EOC) die within five years. Survival beyond eight years is rare and the mechanisms that lead to such favorable outcomes are incompletely understood. We aimed to identify characteristics associated with long-term survival (LTS) in a population-based cohort of patients with advanced stage EOC. Methods: Patients with advanced stage (FIGO IIB-IV) EOC diagnosed between 2008 and 2012 were identified from the Netherlands Cancer Registry. LTS was defined as survival for more than eight years after diagnosis, based on 20% survival within this cohort. Patient, tumor, and treatment characteristics were analyzed using multivariable logistic regression to find predictors for LTS. Results: We identified 2744 eligible patients of whom 571 were long-term survivors (survival longer than eight years). Younger age, lower tumor stage, low-grade histology, FIGO IV based on extra-abdominal lymph node compared to pleural metastasis, primary debulking surgery vs neo-adjuvant chemotherapy followed by interval debulking surgery, residual disease less than one cm or no macroscopic disease, and ascites less than 100 mL were associated with LTS. Furthermore, less than six chemotherapy cycles compared to six, and carboplatin plus paclitaxel combined with other chemotherapy agents compared to carboplatin plus paclitaxel, were associated with a lower odds of LTS. Conclusion: Characteristics of the tumor, patient and treatment play a substantial role in respect to the prognosis of advanced stage EOC, and can assist in the prediction of LTS.

Keywords: Long-term survivor; Epithelial ovarian cancer; Prognostic factors; Cancer survivors

1. Introduction

Epithelial ovarian cancer (EOC) is the most common type of ovarian cancer and accounts for approximately three percent of all cancer types in women in the Netherlands. Among all gynecological cancers, EOC is the leading cause of cancer related death in Western countries [1,2]. Most women present with advanced stage disease and have a high risk of disease recurrence and death [3]. Despite the knowledge gained about prognostic factors and treatment enhancements, patients continue to show poor survival [4,5]. Nevertheless, 15% of women with advanced stage EOC survive for more than 10 years [6–8]. Several studies have attempted to evaluate these so-called ‘long-term survivors’, yet the underlying mechanism responsible for this extraordinary survival remains poorly understood [6–12].

Comparisons of treatment with primary debulking surgery (PDS) versus neo-adjuvant chemotherapy followed by interval debulking surgery (NACT-IDS), the extent of residual disease after surgery and tumour characteristics such as stage and differentiation grade have often been studied in association with long-term survival (LTS) [6–12]. However, chemotherapy characteristics, including drug class and number of cycles, but also tumour characteristics such as number and localization of metastasis, have been studied to a lesser extent. A better understanding of patient and treatment characteristics associated with LTS could help predict patient prognosis and stratify patient populations in future trials. Therefore, this study aimed to evaluate the association between LTS and tumor, patient and treatment characteristics in a population-based cohort from the Netherlands.
2. Materials and methods

2.1 Study population

Patient data were extracted from the Netherlands Cancer Registry (NCR); a nationwide registry comprising of data from all malignancies in the Netherlands since 1989. Clinical data (e.g., tumor-, treatment- and patient-characteristics) are retrieved from hospital files by dedicated clerks. Data on vital status and date of death are obtained from the municipal population registration. Patients diagnosed with advanced stage (FIGO IIB-IV) EOC between January 01, 2008 and February 01, 2012, and undergoing NACT-IDS or PDS were selected (Supplementary Fig. 1).

2.2 Definitions

Tumors were staged based on FIGO staging (2014) [13]. Tumor histotypes were classified as serous (high or low-grade), mucinous, endometrioid, clear cell, or other. Histotypes were based on the International Classification of Diseases for Oncology 3rd edition (ICD-O-3) (Supplementary Table 1) [14]. Chemotherapy regimens were classified as: carboplatin and paclitaxel (standard regimen), carboplatin and paclitaxel combined with one or more other chemotherapy agents (excluding biological agents, such as bevacizumab), carboplatin regimens without paclitaxel, and platinum-free regimens. Outcome of debulking surgery was defined as complete when no macroscopic lesions were present, optimal if the residual tumor was less than one cm, and suboptimal if the residual tumor was one cm or more. Distant metastases, related to the tumor was one cm or more. Distant metastases, related to the tumor was less than one cm, and suboptimal if the residual tumor was one cm or more. Distant metastases, related to the tumor was one day, and maximum was 12 years and 30 days.

2.3 Outcomes

LTS was defined as the time between diagnosis and death at more than eight years, based on 20% survival. Vital status, dead or alive, was extracted from the municipal population register and last checked on February 1, 2020. To investigate the influence of several characteristics on overall survival, subanalyses were performed. Overall survival (OS) was calculated as the interval between the date of diagnosis and death. If the patients were alive, the date of the last check at the municipal population register was used, and patients were right-censored thereafter.

2.4 Statistical analysis

Baseline distributions were reviewed and summarized using descriptive statistics. Clinical characteristics of long-term survivors and patients who died within eight years after diagnosis were compared using Fisher’s exact and Chi square tests for categorical variables, and t-test and Wilcoxon rank sum tests for continuous variables. Univariable and multivariable logistic regression analyses were performed to assess characteristics associated with LTS. Multiple imputation was used to adjust for missing log CA-125, omental cake, differentiation grade, and ascites. Twenty multiple imputed datasets were created; incomplete variables were imputed under a fully conditional specification. The parameters of substantive interest were separately estimated for each imputed dataset and combined using Rubin’s rules. In subanalysis, the influence of histology on OS was depicted using Kaplan-Meier curves and assessed using multivariable Cox regression. The influence on survival within the first year after diagnosis and after five years was assessed by right censoring and left truncation, respectively. \( p < 0.05 \) were considered statistically significant. All statistical analyses were performed using STATA software, version 14.1 (STATA, College Station, TX; Computing Resource Center, Santa Monica, CA, USA).

3. Results

3.1 Baseline

A total of 2744 patients were enrolled (Supplementary Fig. 1), of which 571 (20.8%) survived for more than eight years, and 1616 (79.2%) died within eight years (Table 1). Minimum follow-up time was one day, and maximum was 12 years and 30 days. Long-term survivors were younger, had less comorbidities, presented with favorable tumor characteristics (non-serous histology and a lower tumor stage, grading, and number of distant metastases), and had fewer surgical complications than patients who died in eight years. Long-term survivors less frequently presented with more than 100 mL ascites or omental cake, and had lower levels of pretreatment CA-125 levels.

Descriptive analysis of treatment (Table 2) showed that long-term survivors more frequently received PDS (71.1% vs 45.4%), a complete debulking (56.9% vs 37.9%), regular carboplatin-paclitaxel combination chemotherapy (91.6% vs 85.0%), six chemotherapy cycles (83.7% vs 67.4%), optimal dose intensity (74.3% vs 66.2%) and less frequently than six cycles (5.3% vs 13.2%) or more than six cycles (8.6% vs 17.3%) than patients who died within eight years.

Univariable analysis (Table 3) demonstrated a significant association between LTS and treatment type, residual disease, histotype, age, FIGO stage, number of distant metastases, differentiation grade, CCI, the presence of omental cake, more than 100 mL ascites, and CA-125. Furthermore, univariable analyses of therapy characteristics (Table 4) exhibited a significant relationship between LTS and chemotherapy regimen, number of cycles, and dose reduction.
Table 1. Baseline characteristics.

| Characteristics                      | Dead ≤8 years (n = 2173) | Alive >8 years (n = 571) | p     |
|---------------------------------------|--------------------------|--------------------------|-------|
| Age, mean (SD)                        | 64.5 (11.1)              | 60.3 (11.2)              | <0.001|
| Stage                                 |                          |                          |       |
| FIGO II*                              | 124 (5.7)                | 157 (27.5)               | <0.001|
| FIGO III                              | 1504 (69.2)              | 348 (60.9)               |       |
| FIGO IV                               | 545 (25.1)               | 66 (11.6)                |       |
| Omental cake                          |                          |                          | <0.001|
| yes                                   | 1009 (46.4)              | 128 (22.4)               |       |
| Unknown                               | 227 (10.4)               | 89 (15.6)                |       |
| Number of metastases**                |                          |                          | <0.001|
| 0                                     | 1628 (74.9)              | 505 (88.4)               |       |
| 1                                     | 426 (19.6)               | 57 (10.0)                |       |
| 2                                     | 99 (4.6)                 | 8 (1.4)                  |       |
| 3                                     | 17 (0.8)                 | 0 (0.0)                  |       |
| 4                                     | 3 (0.1)                  | 1 (0.2)                  |       |
| Localization of metastases           |                          |                          |       |
| Malignant pleural effusion            | 231 (42.4)               | 18 (27.3)                | 0.005 |
| Lymphnodes                            | 68 (12.5)                | 18 (27.3)                |       |
| Visceral                              | 169 (31.0)               | 22 (33.3)                |       |
| Other                                 | 77 (14.1)                | 8 (12.1)                 |       |
| Morphology                            |                          |                          | <0.001|
| High-grade serous                     | 1693 (77.9)              | 363 (63.6)               |       |
| Low-grade serous                      | 84 (3.9)                 | 43 (7.5)                 |       |
| Mucinous                              | 61 (2.8)                 | 24 (4.2)                 |       |
| Endometrioid                          | 115 (5.3)                | 77 (13.5)                |       |
| Clear cell                            | 84 (3.9)                 | 30 (5.3)                 |       |
| Others                                | 136 (6.3)                | 34 (6.0)                 |       |
| Differentiation grade                 |                          |                          | <0.001|
| Grade I                               | 102 (4.7)                | 67 (11.7)                |       |
| Grade II                              | 353 (16.2)               | 89 (15.6)                |       |
| Grade III                             | 1193 (54.9)              | 299 (52.4)               |       |
| Unknown                               | 525 (24.2)               | 116 (20.3)               |       |
| Ascites                               |                          |                          | <0.001|
| <100 mL                               | 897 (41.3)               | 265 (46.4)               |       |
| ≥100 mL                               | 794 (36.5)               | 127 (22.2)               |       |
| Unknown                               | 482 (22.2)               | 179 (31.3)               |       |
| log CA-125, median(IQR)               | 6.45 (5.46–7.43)         | 5.81 (4.85–7.14)         | <0.001|
| CA-125                                |                          |                          | <0.001|
| 0–35                                  | 52 (2.4)                 | 38 (6.7)                 |       |
| >35                                   | 1685 (77.5)              | 391 (68.5)               |       |
| Unknown                               | 436 (20.1)               | 142 (24.9)               |       |
| Charlson comorbidity index            |                          |                          | 0.004 |
| Charlson 0                            | 1504 (69.2)              | 431 (75.5)               |       |
| Charlson 1–2                          | 549 (25.3)               | 111 (19.4)               |       |
| Charlson ≥3                           | 47 (2.2)                 | 7 (1.2)                  |       |
| Unknown                               | 73 (3.4)                 | 22 (3.9)                 |       |
| Surgical complication                 |                          |                          | 0.040 |
| yes                                   | 635 (29.2)               | 142 (24.9)               |       |

*Consisting of FIGO III and IIC.

**Number of localizations of distant (FIGO IV) metastases.
Table 2. Therapy characteristics.

| Characteristics                                      | Dead ≤8 years | %     | Alive >8 years | %     | p     |
|-----------------------------------------------------|---------------|-------|----------------|-------|-------|
|                                                     | (n = 2173)    |       | (n = 571)      |       |       |
| Therapy                                             |               |       |                |       |       |
| PDS                                                 | 986           | 45.4  | 406            | 71.1  | <0.001|
| NACT                                                | 1187          | 54.6  | 165            | 28.9  |       |
| Residual tumor status                                |               |       |                |       | <0.001|
| Suboptimal                                          | 383           | 17.6  | 18             | 3.1   |       |
| Optimal                                             | 841           | 38.7  | 149            | 26.1  |       |
| Complete                                            | 823           | 37.9  | 325            | 56.9  |       |
| Unknown                                             | 126           | 5.8   | 79             | 13.8  |       |
| Chemotherapy regimen                                 |               |       |                |       |       |
| Carboplatin and paclitaxel                          | 1846          | 85.0  | 523            | 91.6  | 0.021 |
| Carboplatin and paclitaxel combined with ≥1 other chemotherapy agents | 94    | 4.3   | 11             | 1.9   |       |
| Carboplatin based                                    | 104           | 4.8   | 21             | 3.7   |       |
| Platinum free                                       | 27            | 1.2   | 8              | 1.4   |       |
| Unknown                                             | 102           | 4.7   | 8              | 1.4   |       |
| Number of cycles                                     |               |       |                |       |       |
| <6 cycles                                            | 286           | 13.2  | 30             | 5.3   | <0.001|
| 6 cycles                                             | 1465          | 67.4  | 478            | 83.7  |       |
| >6 cycles                                            | 376           | 17.3  | 49             | 8.6   |       |
| Unknown                                             | 46            | 2.1   | 14             | 2.5   |       |
| Reduction in chemotherapy dose                       |               |       |                |       | <0.001|
| Yes                                                  | 696           | 32.0  | 133            | 23.3  |       |
| Unknown                                             | 38            | 1.7   | 14             | 2.5   |       |
| Chemotherapy interrupted                             |               |       |                | 0.48  |       |
| Interrupted/postponed                                | 291           | 13.4  | 70             | 12.3  |       |
| Chemotherapy medium stopped                          |               |       |                |       |       |
| One medium stopped                                   | 149           | 6.9   | 30             | 5.3   | 0.17  |

Abbreviations: PDS, Primary debulking surgery; NACT, neoadjuvant chemotherapy.

3.2 Multivariable analyses, influence of patient and tumor characteristics

Multivariable analyses (Table 3) demonstrated that, after correction for confounders, higher age, NACT-IDS, FIGO stages III and IV, a higher differentiation grade, and more than 100 mL ascites remained associated with lower odds of LTS. Complete and optimal debulking were associated with a higher odds of LTS compared with suboptimal debulking. The same accounted for complete debulking vs optimal debulking (odds ratio [OR], 1.91; 95% confidence interval [CI], 1.52–2.42; p < 0.001) (data not shown). FIGO stage IV, based on extra-abdominal lymph node metastases, showed higher odds of LTS than malignant pleural effusion (OR, 3.21; 95% CI, 1.49–6.93; p = 0.003) (Table 5).

Subanalysis showed a time-dependent survival pattern in histotype (Supplementary Fig. 2). In multivariable Cox regression, an inferior survival for non-serous histotypes was observed in the first year compared to high-grade serous (mucinous: hazard ratio [HR], 4.77; 95% CI, 3.19–7.14; p < 0.001; endometrioid: HR, 1.67; 95% CI, 1.05–2.64; p = 0.030; and clear cell: HR, 2.09; 95% CI, 1.27–3.45; p = 0.004) (Supplementary Table 2). However, after five years, a superior survival was observed for low-grade serous and clear cell cases compared to high-grade serous (clear cell: HR, 0.51; 95% CI, 0.26–0.99; p = 0.049) (low-grade serous: HR, 0.56; 95% CI, 0.32–0.96; p = 0.035).

3.3 Multivariable analyses, influence of therapy characteristics

Multivariable analyses of therapy characteristics (Table 4) showed that after correction for confounders and number of chemotherapy cycles, administration of carboplatin and paclitaxel combined with other chemotherapy agents remained associated with lower odds of LTS than the standard regimen. Patients receiving less than six cycles had significantly lower odds of LTS than patients receiving six. Reduction in chemotherapy dose had a non-significant influence on LTS than standard chemotherapy after correction for confounders (data not shown).

As stated in the statistical methodology, multiple imputation was performed for missing log CA-125, presence of omental cake, differentiation grade, and more than 100 mL of ascites. The percentage of missing values across the imputed variables varied between 12% (omental cake) and 24% (ascites). For comparison, all multivariable analyses performed on the complete cases showed no significant difference in OR or HR.
Table 3. Logistic regression analysis exploring factors associated with long-term survival.

| Characteristics              | Univariable analysis | Multivariable analysis* |
|------------------------------|----------------------|-------------------------|
|                              | Odds Ratio (95% CI)  | p                       | Odds Ratio (95% CI)  | p                       |
| Age, continuous              | 0.97 (0.96–0.98)     | <0.001                  | 0.97 (0.96–0.98)     | <0.001                  |
| Treatment                    |                      |                         |                        |                         |
| PDS                          | Ref                  |                          | Ref                   |                          |
| NACT                         | 0.34 (0.28–0.41)     | <0.001                  | 0.45 (0.35–0.57)      | <0.001                  |
| Residual disease             |                      |                         |                        |                         |
| Suboptimal                   | Ref                  |                          | Ref                   |                          |
| Optimal                      | 3.77 (2.28–6.24)     | <0.001                  | 3.16 (1.89–5.30)      | <0.001                  |
| Complete                     | 8.40 (5.15–13.71)    | <0.001                  | 6.05 (3.64–10.06)     | <0.001                  |
| FIGO stage                   |                      |                         |                        |                         |
| Stage II**                   | Ref                  |                          | Ref                   |                          |
| Stage III                    | 0.18 (0.14–0.24)     | <0.001                  | 0.32 (0.23–0.45)      | <0.001                  |
| Stage IV                     | 0.10 (0.07–0.14)     | <0.001                  | 0.21 (0.14–0.32)      | <0.001                  |
| Omental cake, present*       | 0.35 (0.27–0.45)     | <0.001                  |                        |                         |
| Number of metastases         | 0.47 (0.38–0.59)     | <0.001                  |                        |                         |
| Morphology                   |                      |                         |                        |                         |
| High-grade serous            | Ref                  |                          |                        |                         |
| Low-grade serous             | 2.38 (1.63–3.51)     | <0.001                  |                        |                         |
| Mucinous                     | 1.83 (1.13–2.98)     | 0.014                   |                        |                         |
| Endometrioid                 | 3.12 (2.29–4.25)     | <0.001                  |                        |                         |
| Clear cell                   | 1.67 (1.08–2.57)     | 0.021                   |                        |                         |
| Other                        | 1.17 (0.79–1.73)     | 0.443                   |                        |                         |
| Differentiation grade*       |                      |                         |                        |                         |
| Grade I                      | Ref                  |                          |                        |                         |
| Grade II                     | 0.38 (0.26–0.56)     | <0.001                  | 0.50 (0.32–0.80)      | 0.003                   |
| Grade III                    | 0.38 (0.27–0.53)     | <0.001                  | 0.60 (0.40–0.89)      | 0.011                   |
| Ascites, ≥100 mL*            | 0.54 (0.4–0.68)      | <0.001                  | 0.62 (0.48–0.81)      | 0.023                   |
| Log CA-125*                  | 0.80 (0.75–0.86)     | <0.001                  |                        |                         |
| CA-125, categorized          |                      |                         |                        |                         |
| <35                          | Ref                  |                          |                        |                         |
| >35                          | 0.32 (0.21–0.49)     | <0.001                  |                        |                         |
| Charlson index               |                      |                         |                        |                         |
| Charlson <1                  | Ref                  |                          |                        |                         |
| Charlson 1–2                 | 0.71 (0.56–0.89)     | 0.003                   |                        |                         |
| Charlson ≥3                  | 0.52 (0.23–1.16)     | 0.109                   |                        |                         |
| Surgical complications, yes  | 0.80 (0.65–0.99)     | 0.040                   |                        |                         |

All covariates added in the multivariable model are depicted; age, treatment type, residual disease, FIGO and differentiation grade and ascites.
Abbreviations: Ref, reference; PDS, Primary debulking surgery; NACT, neoadjuvant chemotherapy.
*Multiple imputation.
** Consisting of stage IIb and IIc.

4. Discussion

In this study, the association between extensive patient, tumor and treatment characteristics, and LTS was studied in a large population-based cohort of 2744 patients with advanced stage EOC. The analyses suggested that 20% of the women survived for more than eight years and that there were significant associations between LTS and younger age, favorable tumor characteristics (lower tumor stage and differentiation grade, and extra-abdominal lymph node vs pleural metastases), treatment characteristics (positive influence of PDS and less residual disease), less than 100 mL ascites, and chemotherapy characteristics (negative influence of less than six cycles and a positive influence of standard chemotherapy regimen).
Multiple studies have highlighted tumor and clinical characteristics associated with LTS, but have shown inconsistencies [6–12]. Most studies included patients treated before 2007 and were restricted to a demographic region [6–10,12]. Frequently studied were patients’ age, and tumor stage, histology and grade, yet many therapy characteristics remained neglected. For instance, most studies only included patients who underwent PDS [8,10,12], while others provided little information regarding therapy type and residual disease [6,7]. Chemotherapy regimen and cycle numbers remain scarcely reported [8,12]. The NCR enabled us to collect complete LTS data, generating a nationwide cohort that is larger and more complete than most other studies.

Consistent with many other studies, we showed that younger age is associated with LTS [7,8,11]. As hypothesized, old age leads to higher overall and postoperative mortality in general and EOC-related complications in particular [16]. Also well described in other studies, our study confirmed that a higher FIGO stage and higher differentiation grade is associated with lower odds of LTS [7,8,17,18]. Also shown in this study is that extra-abdominal lymph node metastases were associated with higher odds of LTS than malignant pleural effusion, similar to other studies [19,20], suggesting that EOC with isolated distant extra-abdominal lymph node metastases may exhibit less aggressive behavior.

The influence of histological subtypes on the other hand is often debated. Non-serous histotypes are predominantly associated with LTS [7,17]. Consistent with other studies, we showed that high-grade serous tumors, when compared with low-grade and non-serous tumors, had lower odds of LTS in univariable, but not in multivariable analyses (with exception of ‘others’) [8,21]. However, sub-analysis showed a time-dependent survival pattern of histotype, concordant with a previous study [22]. In the first year after diagnosis, an inferior OS was observed in non-serous histotypes compared with high-grade serous. But, after five years a superior OS was observed in low-grade serous and clear cell histotypes compared with high-grade

| Characteristics                      | Univariable analysis | Multivariable analysis* |
|--------------------------------------|----------------------|-------------------------|
|                                      | Odds Ratio (95% CI)  | p                       | Odds Ratio (95% CI)  | p                       |
| Chemotherapy subgroups               |                      |                         |                        |                         |
| Carboplatin and paclitaxel           | Ref                  | Ref                     |                          |                          |
| Carboplatin and paclitaxel combined with ≥1 other chemotherapy agents | 0.41 (0.22–0.78) 0.006 | 0.46 (0.22–0.99)** 0.047 |                          |                          |
| Carboplatin based                     | 0.71 (0.44–1.15) 0.166 | 0.63 (0.34–1.17)** 0.146 |                          |                          |
| Platinum free                         | 1.05 (0.47–2.32) 0.912 | 1.25 (0.44–3.56)** 0.675 |                          |                          |
| Number of cycles                      |                      |                         |                        |                         |
| 6 cycles                              | Ref                  | Ref                     |                          |                          |
| <6 cycles                             | 0.32 (0.22–0.47) <0.001 | 0.47 (0.27–0.82)** 0.008 |                          |                          |
| >6 cycles                             | 0.40 (0.29–0.55) <0.001 | 0.82 (0.58–1.16)** 0.266 |                          |                          |
| Reduction in chemotherapy             |                      |                         |                        |                         |
| No                                   | Ref                  | -                       |                          |                          |
| Yes                                  | 0.65 (0.52–0.80) <0.001 | -                       |                          |                          |

Abbreviations: Ref, reference.
*Multiple imputation.
**Adjusted for morphology, FIGO, age, residual disease and amount chemo cycles.
***Adjusted for morphology, FIGO, age, residual disease and chemotherapy regime.

Table 5. Logistic regression analysis exploring localization of distant (FIGO IV related) metastases associated with long-term survival.

| Characteristics                  | Univariable analysis (n = 611) | Multivariable analysis* (n = 611) |
|----------------------------------|--------------------------------|----------------------------------|
| Metastases localization          | Odds Ratio (95% CI) p          | Odds Ratio (95% CI) p            |
| Pleural malignant effusion       | Ref                            | Ref                              |
| Lymph nodes**                    | 3.40 (1.68–6.89) 0.001         | 3.21 (1.49–6.93) 0.003           |
| Parenchymal                      | 1.67 (0.87–3.21) 0.124         | 1.73 (0.85–3.52) 0.127           |
| Other                            | 1.33 (0.56–3.19) 0.518         | 1.47 (0.57–3.78) 0.424           |

* Adjusted for age, differentiation grade, therapy and residual disease.
** Extra-abdominal lymph node.

Abbreviations: Ref, reference.
serous, and a non-inferior OS in the remaining histotypes. This could be explained by differences in treatment effectiveness. For instance, mucinous and clear cell histotypes initially respond poorly to platinum-based chemotherapy, while high-grade serous histotype initially responds well but develops a higher resistance in later years [23–25].

Studies have found significant associations between pretreatment or preoperative CA-125 levels and LTS [10, 26], while others have failed to find any such associations [21]. The present study showed that pretreatment CA-125 levels >35 U/mL were associated with lower odds of LTS in univariable analysis, but not in multivariable analysis. The correlation between CA-125 and stage, differentiation, ascites, and histology was observed in this study and recent reports; therefore, correcting for these factors could explain the change in odds [26]. Another frequently reported marker is ascites. This study indicates that more than 100 mL of ascites is significantly associated with lower odds of LTS, consistent with other studies [10–12]. Ascites is postulated to be a result of malignant cells spreading to serosal surfaces causing peritoneal effusion [27], which leads to abdominal distension, nausea, asphyxia, electrolyte disturbances, and negatively influences overall condition and prognosis [28].

The choice between PDS vs NACT-IDS is often debated. The importance of aiming for total macroscopic debulking surgery is widely accepted [29,30]. Consistent with this and other reports, the present study showed significantly higher odds of LTS in case of less residual disease [8–11,29]. Currently, the American Society of Clinical Oncology (ASCO) and the Society of Gynecologic Oncology (SGO) guidelines recommend PDS as the treatment of choice and advise considering NACT-IDS for patients with a high perioperative risk or a low likelihood of achieving complete or optimal debulking [31]. In concordance, our data showed that PDS resulted in a significantly higher odds of LTS. However, PDS is associated with a higher risk of postoperative complications compared to NACT-IDS [32]. Therefore, NACT-IDS could be a preferable strategy in women who already have a higher perioperative risk, consistent with current guidelines [31].

The recommended chemotherapy regimen for treatment of advanced stage EOC is carboplatin and paclitaxel administered over six cycles [31,33]. This study showed that often neither the recommended regimen nor the advised number of cycles were administered. Consistent with the ASCO and SGO guidelines and other reports, the present study showed no significant benefit of administering more than six chemotherapy cycles [34,35]. Similarly, a lower odds of LTS was observed in patients who received less than six cycles than in those who received six. The present study also demonstrated a significantly lower odds of LTS when a third chemotherapy agent was included along with carboplatin and paclitaxel. Both the negative influence of less cycles and administration of additional agents can partially be explained by the observation that patients who do not respond well, and presumably have a worse survival, are more likely to discontinue therapy or receive additional chemotherapy agents.

The present study is limited by the restrictions of a population-based cohort and its historical nature. The use of a population-based cohort, with many heterogeneities arising from different histotypes, stages, or treatment, provides benefits and challenges. Benefits are the extrapolating ability to real-life settings, and the diversity and completeness of the studied characteristics. A challenge is the high number of possible confounding factors. Treatment selection was based on the guidelines at the time of treatment and shared decision-making between doctors and patients. Furthermore, selection of treatment regimen and cycles were likely influenced by patient performance status, which might have induced confounding by indication. The outcomes of this study were from patients treated before the broad use of poly ADP ribose polymerase inhibitors (PARPi); therefore, the influence of PARPi on LTS has not been studied and further investigation is warranted. Survival was not associated with the year of diagnosis in our data, but changes in practice over time influencing survival must be considered. Moreover, LTS and OS characteristics were used rather than cancer-specific survival, possibly inducing a bias of death due to causes other than the disease itself. Due to the high mortality of EOC and the adjustment for patient characteristics, we hypothesize that this influence is minimal. Pretreatment serum CA-125 levels were measured at different times, and can therefore potentially affect the results, though only levels determined within eight weeks before starting treatment were included. Furthermore, it cannot be ignored that some confounders were not addressed. Finally, this study was restricted by the lack of a central pathological review.

5. Conclusions

This study supports previous studies hypothesizing that in advanced stage EOC, younger age, lower FIGO stage, lower differentiation grade, treatment type, less residual tumor and less ascites are associated with LTS. Furthermore, we showed that extra-abdominal lymph node metastases as the only distant metastatic site, chemotherapy regimen, and number of cycles are also associated with LTS. Characteristics of the tumor, patient, and treatment play a substantial role in prognosis; yet these characteristics, whether individual or combined, cannot accurately predict LTS in EOC. Therefore, more prospective research on molecular characteristics of EOC to accurately predict long-term survival is warranted.

Author contributions

LW conceived and designed the study, contributed to materials, analyzed the data and wrote the manuscript; KKV contributed to the analysis and revised
the manuscript; MA contributed to the materials, interpreted the data and revised the manuscript; HMH, GSS, and RFPMK interpreted and revised the manuscript. All authors have read and approved the manuscript.

**Ethics approval and consent to participate**

All research activities were approved by the institutional review board of the NCR (K19.074). The requested dataset was considered anonymous and the use is therefore exempt from ethics review board approval according to Dutch legislation.

**Acknowledgment**

The authors thank the Netherlands Comprehensive Cancer Organization (IKNL) for the collection of data for the Netherlands Cancer Registry.

**Funding**

This research was supported by the Dutch Cancer Society [grant number IKNL2014-6838]. The funder of the study had a role in data collection.

**Conflict of interest**

The authors declare no conflict of interest.

**Supplementary material**

Supplementary material associated with this article can be found in the online version, at https://www.impress.com/journal/EJGO/43/1/10.31083/j.ejgo4301007.

**References**

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: A Cancer Journal for Clinicians. 2018; 68: 7–30.

[2] IKNL. Cijfersoverkanker. Available at: https://cijfersoverkanker.nl (Accessed: 19 April 2020).

[3] Hennessy BT, Coleman RL, Markman M. Ovarian cancer. The Lancet. 2009; 374: 1371–1382.

[4] Timmermans M, Sonke GS, Van de Vijver KK, van der Aa MA, Kruitwagen RFPM. No improvement in long-term survival for epithelial ovarian cancer patients: a population-based study between 1989 and 2014 in the Netherlands. European Journal of Cancer. 2018; 88: 31–37.

[5] Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JWW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancers since the 1990s. European Journal of Cancer. 2008; 44: 1345–1389.

[6] Baldwin LA, Huang B, Miller RW, Tucker T, Goodrich ST, Podzielinski I, et al. Ten-year relative survival for epithelial ovarian cancer. Obstetrics and Gynecology. 2012; 120: 612–618.

[7] Cress RD, Chen YS, Morris CR, Petersen M, Leiserson GS. Characteristics of Long-Term Survivors of Epithelial Ovarian Cancer. Obstetrics and Gynecology. 2015; 126: 491–497.

[8] Äkeson M, Jakobsen A, Zetterqvist B, Holmberg E, Brännström M, Horvath G. A Population-Based 5-Year Cohort Study Including all Cases of Epithelial Ovarian Cancer in Western Sweden: 10-Year Survival and Prognostic Factors. International Journal of Gynecologic Cancer. 2009; 19: 116–123.

[9] Dao F, Schlapp BA, Tseng J, Lester J, Nick AM, Lutgendorf SK, et al. Characteristics of 10-year survivors of high-grade serous ovarian carcinoma. Gynecologic Oncology. 2017; 141: 260–263.

[10] Hamilton CA, Miller A, Casablanca Y, Horowitz NS, Runguang B, Krivak TC, et al. Clinicopathologic characteristics associated with long-term survival in advanced epithelial ovarian cancer: an NRG Oncology/Gynecologic Oncology Group ancillary data study. Gynecologic Oncology. 2018; 148: 275–280.

[11] Hoppenot C, Eckert MA, Tienda SM, Lengyel E. Who are the long-term survivors of high grade serous ovarian cancer? Gynecologic Oncology. 2018; 148: 204–212.

[12] Kaern J, Aghmesheh M, Nesland JM, Danielsen HE, Sandstad B, Friedlander M, et al. Prognostic factors in ovarian carcinoma stage III patients. can biomarkers improve the prediction of short- and long-term survivors? International Journal of Gynecological Cancer. 2005; 15: 1014–1022.

[13] Prat J, FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. International Journal of Gynecology and Obstetrics. 2014; 124: 1–5.

[14] Fritz A, Percy C, Jack A, Shannugaratnam K, Sobin LH, Parkin DM, et al. International classification of diseases for oncology. 3rd edn. World Health Organization: Geneva. 2000.

[15] Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. Journal of Clinical Epidemiology. 1994; 47: 1245–1251.

[16] Thrall MM, Goff BA, Symons RG, Flum DR, Gray HJ. Thirty-day mortality after primary cytoreductive surgery for advanced ovarian cancer in the elderly. Obstetrics and Gynecology. 2011; 118: 537–547.

[17] Heintz APM, Odicino F, Maisonneuve P, Quinn MA, Benedet JL, Creasman WT, et al. Carcinoma of the ovary. FIGO 26th Annual Report on the Results of Treatment in Gynaecological Cancer. International Journal of Gynecology and Obstetrics. 2006; 95: S161–S192.

[18] Chi DS, Liao JB, Leon LF, Venkatraman ES, Hensley ML, Bhaskaran D, et al. Identification of prognostic factors in advanced epithelial ovarian carcinoma. Gynecologic Oncology. 2001; 82: 532–537.

[19] Deng K, Yang C, Tan Q, Song W, Lu M, Zhao W, et al. Sites of distant metastases and overall survival in ovarian cancer: a study of 1481 patients. Gynecologic Oncology. 2018; 150: 460–465.

[20] Timmermans M, Sonke GS, Van de Vijver KK, Ottevanger PB, Nijman HW, van der Aa MA, et al. Localization of distant metastases defines prognosis and treatment efficacy in patients with FIGO stage IV ovarian cancer. International Journal of Gynecological Cancer. 2019; 29: 392–397.

[21] Tinguistad S, Skjeldested FE, Halvorsen TB, Hagen B. Survival and prognostic factors in patients with ovarian cancer. Obstetrics and Gynecology. 2003; 101: 885–891.

[22] Peres LC, Cushing-Haagen KL, Köbel M, Harris HR, Berchuck A, Rossing MA, et al. Invasive Epithelial Ovarian Cancer Survival by Histotype and Disease Stage. Journal of the National Cancer Institute. 2011; 111: 60–68.

[23] Hess V, A’Hern R, Nasiri N, King DM, Blake PR, Barton DPJ, et al. Mucinous Epithelial Ovarian Cancer: a Separate Entity Requiring Specific Treatment. Journal of Clinical Oncology. 2004; 22: 1040–1044.

[24] Pectasides D, Fountzilas G, Aravantinos G, Kalofonos C, Efstratiou H, Farmakis D, et al. Advanced stage clear-cell epithelial ovarian cancer: the Hellenic Cooperative Oncology Group experience. Gynecologic Oncology. 2006; 102: 285–291.

[25] Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. CA: A Cancer Journal for Clinicians. 2011; 61: 183–203.
Cooper BC, Sood AK, Davis CS, Ritchie JM, Sorosky JI, Anderson B, et al. Preoperative CA 125 levels: an independent prognostic factor for epithelial ovarian cancer. Obstetrics and Gynecology. 2002; 100: 59–64.

Bonnefoi H, A’Hern RP, Fisher C, Macfarlane V, Barton D, Blake P, et al. Natural history of stage IV epithelial ovarian cancer. Journal of Clinical Oncology. 1999; 17: 767–775.

don Gruenigen VE, Frasure HE, Reidy AM, Gil KM. Clinical disease course during the last year in ovarian cancer. Gynecologic Oncology. 2003; 90: 619–624.

Winter WE, Maxwell GL, Tian C, Sundborg MJ, Rose GS, Rose PG, et al. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. Journal of Clinical Oncology. 2008; 26: 83–89.

Timmermans M, van der Hel O, Sonke GS, Van de Vijver KK, van der Aa MA, Kruitwagen RF. The prognostic value of residual disease after neoadjuvant chemotherapy in advanced ovarian cancer: a systematic review. Gynecologic Oncology. 2019; 153: 445–451.

Wright AA, Bohlke K, Armstrong DK, Bookman MA, Cliby WA, Coleman RL, et al. Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology. 2016; 34: 3460–3473.

Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet. 2015; 386: 249–257.

Morgan RJ, Armstrong DK, Alvarez RD, Bakkum-Gamez JN, Behbakht K, Chen L, et al. Ovarian Cancer, Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network. 2016; 14: 1134–1163.

Dizon DS, Weitzen S, Rojan A, Schwartz J, Miller J, Disilvestro P, et al. Two for good measure: six versus eight cycles of carboplatin and paclitaxel as adjuvant treatment for epithelial ovarian cancer. Gynecologic Oncology. 2006; 100: 417–421.

Kim HS, Park NH, Chung HH, Kim JW, Song YS, Kang SB. Are three additional cycles of chemotherapy useful in patients with advanced-stage epithelial ovarian cancer after a complete response to six cycles of intravenous adjuvant paclitaxel and carboplatin? Japanese Journal of Clinical Oncology. 2008; 38: 445–450.