The effect of adjuvant chemotherapy on survival in patients with FIGO stage I high-grade serous ovarian cancer

JOAM van Baal[1], KK Van de Vijver[2, 3], M Algera[1], MA van der A[4], GS Sonke[5], WJ van Driel[1], GG Kenter[1], FC Amant[1,6], CAR Lok[1]

1 Department of Gynecology, Center for Gynecologic Oncology Amsterdam (CGOA), location The Netherlands Cancer Institute, P.O. Box 90203, 1006 BE, Amsterdam, the Netherlands

2 Department of Pathology, Netherlands Cancer Institute, Amsterdam, the Netherlands

3 Department of Pathology, Ghent University Hospital, Cancer Research Institute Ghent (CRIG), Ghent, Belgium

4 Department of Research, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, the Netherlands

5 Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands

6 Department of Oncology, KU Leuven, Belgium

Corresponding author: J.O.A.M. van Baal

Address: Plesmanlaan 121, P.O. Box 90203, 1006 BE, Amsterdam, the Netherlands

Telephone: +3120512975, Fax: +31205126105, Electronic address: j.v.baal@nki.nl

Keywords:

Adjuvant chemotherapy, early stage ovarian cancer, high-grade serous ovarian cancer, staging

ABSTRACT

Objective. The benefit of adjuvant chemotherapy for FIGO stage I, high-grade serous ovarian cancer (HGSOC) after optimal staging is a matter of debate. We investigated the effect of adjuvant chemotherapy on recurrence-free survival (RFS) and overall survival (OS) in a population-based cohort study.

Methods. All patients diagnosed in the Netherlands between 2002-2014 with FIGO stage I HGSOC who underwent surgical staging were included. Data on clinical characteristics, histopathology, completeness of staging and survival were collected from the Netherlands Cancer Registry and Dutch Pathology Registry. Recurrence data was collected from hospital files. We used Kaplan-Meier methods to estimate RFS and OS and Cox-proportional hazard analyses to control for differences in baseline characteristics between patients who did or did not receive chemotherapy.

Results. We identified 223 patients who underwent optimal staging procedures including lymph node sampling. Events of disease recurrence occurred in 21 of the 101 patients (21%) who received adjuvant chemotherapy and in 46 of the 122 patients (38%) who did not (multivariable hazard ratio (HR), 0.37; 95%CI 0.22-0.64; p<0.01). Five-year RFS was 81% after staging plus chemotherapy and 59% after staging only. At a median follow-up of 105 months, 21 patients (21%) in the chemotherapy group and 38 patients (31%) in the no-chemotherapy group had died (multivariable HR 0.50; 95%CI 0.28-0.89; p=0.02). Ten-year OS was 78% with chemotherapy and 62% without chemotherapy.

Conclusions. Adjuvant chemotherapy improves long-term RFS and OS in patients with FIGO stage I HGSOC after optimal staging.

INTRODUCTION

Epithelial ovarian cancer (EOC) occurs yearly in approximately 205,000 women worldwide, causing 125,000 deaths. Only 30% of patients with EOC presents with localized or early stage disease (FIGO stage I-IIa). Although prognosis is relatively good for patients with early stage disease, approximately 10-30% of patients develops recurrent disease [1-3]. The development of recurrent disease in patients with early stage EOC, is caused by the unnoticed presence of (micro)metastasis. Therefore, for all patients without apparent metastasized disease, a surgical staging procedure is recommended. The Gynecologic Oncology Group (GOG) and European Organisation for Research and Treatment of Cancer (EORTC) formulated clear guidelines for early stage EOC [4, 5]. Optimal staging procedures include bilateral oophorectomy, hysterectomy and omentectomy, and sampling of peritoneal fluid, peritoneal surfaces, pelvic and para-aortic lymph nodes.

After staging surgery, adjuvant platinum-containing chemotherapy can be considered for patients with early stage high-grade EOC. In the combined analyses of two large randomized controlled trials on early stage EOC (ACTION and ICON1), a significant survival benefit and prolonged time-to-recurrence after adjuvant chemotherapy was demonstrated [3, 6]. This analysis included patients with tumors of all histological subtypes, and the majority of staging procedures was not optimal. High-grade histology was shown to be an independent prognostic factor. In addition, patients with high-risk EOC, which was defined as either high-grade or grade 2-3 histology with stage Ib-c, were demonstrated to benefit most from adjuvant chemotherapy [3, 7]. In predefined subgroup analyses of patients who had optimal staging procedures, no survival benefit was found with adjuvant chemotherapy, whereas a significant gain in overall survival (OS) and recurrence-free survival (RFS) was observed after adjuvant chemotherapy in patients who had non-optimal staging procedures [3]. However, tests to determine differences in survival between staging subgroups and treatment effects, were not statistically different. Thus, patient with high-grade tumors are considered to benefit from adjuvant chemotherapy, although the value of adjuvant chemotherapy after optimal staging in these patients remains unclear. This leads to differences between national and international guidelines with regard to the decision to administer adjuvant chemotherapy in this specific group of patients.

In the present cohort study, we investigated the effect of adjuvant chemotherapy in patients with FIGO stage I high-grade serous ovarian cancer (HGSOC) after optimal staging on RFS and OS.

METHODS

Patient Selection

This observational study was performed with clinical data from the Netherlands Cancer Registry (NCR) and hospital records, and histopathological data from the Dutch Pathology Registry (PALGA). All data on patients with primary malignancies, diagnosed in the Netherlands since 1989, are documented within the NCR, which is managed by the Netherlands Comprehensive Cancer Organization (IKNL). Quality of NCR data is maintained by regular consistency checks and accuracy is considered at least 95% [8]. PALGA comprises a nationwide network in the Netherlands and registers all records of histopathology and cytopathology with a full coverage since 1991 [9].

After approval from the privacy committee of both the NCR and PALGA, a database was set up by the IKNL, comprising all patients with HGSOC FIGO stage I, diagnosed in the Netherlands between January 2002 and December 2014. Dates of death were retrieved from the municipal population register on 31st of January 2018. The minimal follow-up duration was three years. Exclusion criteria were tumor of low malignant potential, non-serous histology, low-grade carcinoma, ovarian metastasis of different primary origin, neo-adjuvant chemotherapy and patients <17 years. Clinical data on age at diagnosis, date of surgery and adjuvant chemotherapy were collected from the NCR. Histological subtype, tumor grade, surgical FIGO stage and accuracy of staging procedures were thoroughly examined based on pathology reports. Data on recurrences and data on death were collected from different sources. Information on recurrent disease was retrieved from the hospital files. All cases were matched with histopathological data from PALGA. All pathological reports were reviewed by one investigator of the research team. In case of unspecified tumor grade or doubts regarding histological subtype or origin of recurrence, reports were discussed with a gynecologic oncology-oriented pathologist. If pathological data were inconsistent or inconclusive with regard to histological type, tumor grade or FIGO stage, patients were excluded from the study.

Accuracy of staging procedures was analyzed and performance of the following procedures was documented: hysterectomy, bilateral oophorectomy, infracolic omentectomy, peritoneal washing, biopsies of peritoneal surfaces including pouch of Douglas, bladder, left and right pelvis, paracolic

gutters and right diaphragm, and sampling of pelvic and para-aortic lymph nodes. Number of regions that were sampled for lymph node assessment was documented as well as total number of resected lymph nodes during sampling. Procedures were considered as optimal staging procedures if hysterectomy, oophorectomy, omentectomy, ≥1 peritoneal biopsies, and sampling of ≥1 lymph nodes was performed. Based on the surgical staging, FIGO stage was determined for all cases.

IKNL itemizes all patients with a unique NCR-code. PALGA excerpts are anonymized and linkage of histopathological data with the NCR is performed by a trusted third party. Anonymized data on recurrences was collected retrospectively from the hospitals via an intermediate procedure of PALGA and via IKNL. Researchers had no access to information that could possibly lead to patient identification. Therefore, no patient informed consent and no additional approval of the Institutional Review Board was required in the present study.

Statistical analysis

Data analysis was performed with IBM SPSS (Statistical Package for the Social Sciences) version 22.0 (SPSS Inc., Chicago, Illinois). Recurrence-free survival (RFS) was interpreted as the time elapsed between date of surgical staging and recurrent disease or last follow-up. Recurrent disease was defined as evidence of metastasis based on physical, biochemical, radiological, cytological or histological examination. Overall survival (OS) was calculated as the time interval between primary diagnosis and date of death or last follow-up. Different sources were used to retrieve data on recurrence and data on death, which caused a difference in median follow-up time until recurrence and median follow-up time until death. Disease-specific death was defined as death after recurrence. Disease-specific survival (DSS) was calculated as the time between primary diagnosis and disease-specific death. Median RFS, median OS and median DSS were not reached. Therefore, in our paper we reported five-year RFS rates, and both five-year and ten-year OS and DSS rates. Kaplan-Meier survival curves and log-rank tests were performed to assess the effects of adjuvant chemotherapy on survival in patients with FIGO stage I disease. Patients who were lost to follow-up but without evidence of recurrent disease, were right censored in the survival curves. Univariate logistic regression analyses were performed to identify individual predictors of outcome in patients with FIGO stage I HGSOC. In multivariable logistic

regression analyses, significant predictors age at diagnosis, FIGO stage at diagnosis and adjuvant chemotherapy were included.

Subgroups analyses were performed to investigate the effect of chemotherapy in different subgroups. Subgroups were created based on age, FIGO stage and number of resected lymph nodes during staging surgery. In the first subgroup analysis, patients were categorized in either younger than 60 years or older than 59 years. Next, we analyzed patients with different FIGO stages in which we dichotomized patients in either FIGO stage Ia or FIGO Ib-Ic. For early stage EOC, the Dutch national guidelines recommend optimal staging including sampling of at least ten lymph nodes [10]. Therefore, we analyzed the impact of adjuvant chemotherapy in patients who had optimal staging with either <10 resected lymph nodes or ≥10 resected lymph nodes. Cox proportional hazard analyses were performed for all subgroups, adjusted for age and FIGO stage. P-values <0.05 were considered significant.

RESULTS

From January 2002 to December 2014, 393 patients with HGSOC stage I disease underwent a staging procedure. Of the 393 patients with FIGO stage I HGSOC, 170 patients did not fulfill our criteria of optimal staging. In 145 patients lymph node sampling was not performed, in 14 patients omentectomy was omitted and in 66 patients no peritoneal biopsies were taken. In total 223 (57%) patients met the criteria of optimal staging.

101 of 223 (45%) patients received adjuvant chemotherapy following optimal staging surgery. Figure 1 demonstrates the number of patients who underwent optimal staging and their adjuvant treatment per year. Baseline characteristics of patients who underwent optimal staging, stratified by chemotherapy treatment, can be found in Table 1. Age at diagnosis was similar in these groups. Chemotherapy was more frequently administered in patients who had tumor positive ascites, capsule rupture or tumor located on the ovarian surface (i.e. FIGO stage Ic). Percentage of patients who received adjuvant chemotherapy for FIGO stage I HGSOC varied between topographic regions in the Netherlands from 8-67%. This reflects the different regional guidelines that are used in the Netherlands regarding the decision to administer adjuvant chemotherapy for this specific patient group.

Recurrence-free survival

Total median follow-up (time-to-censoring) for RFS was 61 months (IQR 36-93) and was similar between patients who had optimal staging followed by adjuvant chemotherapy and patients who had optimal staging alone (Table 1). Recurrent disease occurred in 21 (21%) patients after optimal staging and adjuvant chemotherapy with a median time-to-recurrence of 32 months (IQR 22-68), and in 46 (38%) patients after 27 months (IQR 14-47) in those who had optimal staging alone (p<0.01). Patients who received adjuvant chemotherapy showed a more favorable five-year RFS of 81%, compared with 59% in patients who did not receive chemotherapy (Figure 2). After adjustment for FIGO stage, multivariable analyses showed a significant RFS benefit of adjuvant chemotherapy (HR 0.37; 95%CI 0.22-0.64; p<0.01; Table 2).

Overall survival

By January 31st 2018, after a median follow-up (time-to-censoring) of 105 months (IQR 71-142), 59 patients had died. 21 (36%) patients had received adjuvant chemotherapy and 38 (64%) were treated with optimal staging alone. For patients who had received adjuvant chemotherapy five-year and ten-year OS were 84% and 78% respectively, whereas a five-year and ten-year OS of 83% and 62% were observed in patients who did not receive adjuvant chemotherapy after optimal staging (Figure 2). Similarly, five-year DSS was 88% in patients who had staging followed by adjuvant chemotherapy and 88% after staging alone, whereas a ten-year DSS of 85% was observed in the chemotherapy group and 70% in the no-chemotherapy group (Figure 2). To investigate whether year of diagnosis was correlated with OS, univariate analyses were performed (Table 2). Diagnosis between 2011 and 2014 was not associated with improved survival compared with diagnosis between 2002 and 2006 (HR 1.05; 95% CI 0.50-2.24; p=0.89). After adjustment for age and FIGO stage, multivariable analyses showed a significant OS benefit from adjuvant chemotherapy in patients who had optimal staging surgery (HR 0.50; 95% CI 0.28-0.89; p=0.02) (Table 2).

Subgroup analyses

We analyzed the impact of adjuvant chemotherapy in different subgroups based on age, FIGO stage and total number of resected lymph nodes during optimal staging surgery. Figure 3 demonstrates the results of Cox-proportional hazard analyses of all subgroups in a forest plot. In summary, our subgroup analyses showed that the survival benefit of adjuvant chemotherapy in FIGO stage I HGSOC, found in the main cohort, are consistent among different categories of patients.

DISCUSSION

After optimal staging surgery including lymph node sampling for early stage HGSOC, adjuvant chemotherapy should be considered to minimize risk of recurrent disease and to increase OS. Until now, no consensus has been reached on the benefit of adjuvant chemotherapy resulting in different policies among different regions in the Netherlands. The present study shows that adjuvant chemotherapy after optimal staging, significantly improves five-year RFS from 59% to 81% and ten-year OS from 62% to 78%.

Various studies investigated the effect of adjuvant chemotherapy on survival for early stage EOC [3, 6, 11-13]. Although chemotherapy is considered most beneficial for patients with high-risk tumors, including high-grade tumors and FIGO stage Ic-IIa, the effect of chemotherapy after optimal staging surgery in this specific group of patients has not been investigated thoroughly. In most studies, extent of surgery has not been documented and different histological subtypes are included. The ACTION trial is the largest randomized controlled trial reporting accuracy of staging procedures and the impact of adjuvant chemotherapy on survival in early stage EOC [3]. In this study, the adjuvant chemotherapy arm showed an 8% increase of five-year RFS, and 7% increase of five-year OS. However, predefined subgroup analyses showed that the effect of chemotherapy was more pronounced in non-optimally staged patients than in optimally staged patients. These differences were not observed in those who underwent optimal staging. Ten-year follow-up data of the ACTION trial confirmed the overall results, but tests to analyze subgroup differences did not reach statistically significance (Chi-square test 3.32, p=0.07) [14]. A Cochrane meta-analysis, based on three studies, addressing the adequacy of surgical staging and the impact of adjuvant chemotherapy on survival concluded that there is no survival benefit of chemotherapy after optimal staging (five-year OS HR 1.22; 95%CI 0.63-2.37) [15]. However, patient numbers in the included studies were small, with only a limited number of events. The ACTION trial included a total of 151 optimally staged patients and reported only 17 deaths after a follow-up of 10 years. Therefore, reviewers emphasized that quality of evidence of these subgroup analyses is of very low quality [15].

Our study showed a significant RFS and OS benefit of adjuvant chemotherapy after optimal staging. In our study, a higher incidence of events occurred compared with the ACTION trial. This can be explained

by the inclusion of low-grade carcinomas and other histologies such as mucinous and endometrioid carcinomas in the ACTION trial, which are known to exhibit a more indolent behavior than HGSOC [16-18]. Possibly, this explains the contradicting results of our study and the ACTION trial. In our study, patients who received chemotherapy had FIGO stage Ic disease more frequently. Patients in the non-chemotherapy group more often had FIGO stage Ia. Based on the FIGO stages, the chemotherapy group had a higher chance of recurrent disease, compared to the non-chemotherapy group [1, 19, 20]. Still, patients who had chemotherapy showed a significant better recurrence rate and survival than those who had no chemotherapy.

In optimally staged patients, five-year OS was similar between patients who had staging plus chemotherapy and staging alone. In contrast, ten-year OS increased from 62% to 78% with the addition of chemotherapy. Although a significant better five-year RFS was observed, no five-year OS survival difference was seen. Similarly, these differences were observed when DSS was analyzed, demonstrating that differences in OS were caused by EOC-relating deaths. Hypothetically, chemotherapy-naive recurrences respond more efficiently to chemotherapeutic agents than recurrences that occur after adjuvant chemotherapy. In various *in vivo* studies, differences between primary chemo-naive EOC cells and cells of post-chemotherapy recurrent disease were analyzed [21-23]. In isolated tumor cells which survived chemotherapy, changes in the proteome were demonstrated which enable the tumor cells to resist cytotoxic effects of chemotherapeutic agents [21-23]. Presumably, early post-chemotherapy recurrences, although less frequently occurring than early chemo-naive recurrences, are more aggressive and less chemotherapy responsive, resulting in a similar overall prognosis within five years.

Lymph node sampling is considered an important element of optimal staging. Nevertheless, lymph node sampling is frequently omitted during staging procedures. In our study, we excluded 37% of patients, because lymph node sampling was omitted during staging surgery. Previously, it has been concluded that lack of intention to treat with chemotherapy irrespective of lymph node status is an important reason to omit this procedure [24]. With respect to the extent of lymph node sampling, resection of at least ten lymph nodes retrieved from pelvic and para-aortic regions, is recommended [10]. However, studies demonstrating clear prognostic differences for this cut-off of ten lymph nodes are lacking. Kleppe et al. investigated the impact of lymph node dissection for clinical early stage EOC [24]. In this retrospective cohort study, an improved survival was found with resection of a minimum of 20 lymph nodes [24]. In

subgroup analyses of the present study we analyzed whether survival differences were consistent within subgroups, including patients who had resection of at least ten lymph nodes during staging. Although patient cohorts were small, hazard ratios were similar among all subgroups and in favor for patients who had received adjuvant chemotherapy.

A randomized clinical trial including only patients with HGSOC after optimal staging surgery, including resection of at least 20 lymph nodes would answer all questions with a high level of evidence. However, in the two large international multicenter randomized controlled trials in which these questions were investigated, all histological subtypes were included and majority of staging surgeries were performed incompletely, despite strong study recommendations regarding staging requirements. These two trials had a long inclusion period of 8 [3] and 9 years [6], respectively. Thus, a new randomized trial evaluating patients with HGSOC who had optimal staging surgery with adequate lymph node sampling, is virtually unfeasible. Therefore, this large nationwide cohort study investigating the impact on OS and RFS of adjuvant chemotherapy after optimal staging will add to the existing knowledge and will help to counsel patients.

In the Netherlands, standard protocols regarding adjuvant chemotherapy for HGSOC differ between clinics and according to the national guidelines adjuvant chemotherapy is optional for this group of patients. Indeed, number of patients who were treated with adjuvant chemotherapy, differed between regions in the Netherlands. This finding emphasizes that patients in our study were treated based on regional protocols rather than on prognostic characteristics.

Limitations of our study are related to the retrospective design. Performance status, *BRCA* status, type of chemotherapy, number of chemotherapy cycles and reasons to refrain from adjuvant chemotherapy were unknown. In our study we adjusted outcomes for age and FIGO stage. However, due to the observational design of the study, results may not have been sufficiently corrected for residual confounding factors including performance status and co-morbidity.

Central pathology review of all tumors was not performed. However, all pathological reports were scrutinized and, together with a dedicated gynecologic oncologic pathologist, histology and histological tumor grade were confirmed. Besides, since 2010 the care for patients with EOC is centralized in hospitals performing at least 20 cytoreductive surgeries for EOC annually, where expert review of the pathology is part of the standard pre-operative work up.

Type of chemotherapy, the number of cycles, and possible dose reductions were unknown in the present study. EOC is generally treated with carboplatin and paclitaxel combination chemotherapy. Currently, single-agent carboplatin is increasingly administered to patients with early stage EOC as the advantage of combination therapy over single-agent carboplatin is considered low [7, 25], and negative side-effects of paclitaxel are high [26, 27]. Paclitaxel and, to a lesser extent carboplatin, can cause peripheral neuropathy leading to poorer health related quality of life [26, 27]. Furthermore, paclitaxel causes hair loss, which is associated with increased distress and psychological impact [28]. To minimize toxicity associated with paclitaxel, single-agent carboplatin, fewer courses, and the use of coldcap can be considered. The Gynecologic Oncology Group (GOG 157) compared the recurrence rate of high-risk FIGO stage I-II EOC after either three or six cycles of carboplatin and paclitaxel, and evaluated which patient would benefit most from more cycles of chemotherapy based on clinical and histological characteristics [29-32]. For patients with high-risk serous FIGO stage I-II, a significant improved RFS was demonstrated with six cycles of combination chemotherapy, compared with three cycles. However, six cycles of adjuvant chemotherapy was associated with increased toxicity. In our cohort, less toxic schedules may have been administered to patients, for example to patient older (or fragile) patients or patients with extensive comorbidity. The standard chemotherapy regimens during our study period, based on the national guideline, consisted of a combination of carboplatin and paclitaxel. Thus the majority of our study population who had adjuvant chemotherapy will have received combination therapy.

In conclusion, our study shows that adjuvant chemotherapy improves long-term RFS and OS in patients who received optimal staging for early stage HGSOC. The present study is the first study demonstrating clear survival benefit of adjuvant chemotherapy following optimal staging in HGSOC. These results should be discussed with patients to optimize the shared decision process.

ACKNOWLEDGEMENT

The authors thank the registration team of the Netherlands Comprehensive Cancer Organization (IKNL) for the collection of data for the Netherlands Cancer Registry as well as IKNL staff for scientific advice. The authors also thank the Dutch Pathology Registry PALGA for providing the histopathological data, and hospital's physicians for providing additional clinical data.

CONFLICT OF INTEREST

FA is senior investigator for the Research Fund Flanders (F.W.O.). GSS declares institutional research funding from AstraZeneca, Merck, Novartis, and Roche outside the scope of this study. The other authors have no conflict of interest to declare.

AUTHOR CONTRIBUTION

All authors contributed equally to this study. JOAMB was the principal author, performed analyses and interpretation of data. KKV aided with the analysis and interpretation of data, and performed revision of the manuscript. MA aided with collection of data. MAA aided with data collection and contributed intellectually to research goals and study design, and performed revision of the manuscript. GSS contributed to the interpretation of results and revision of manuscript. WJD, GGK and FCA provided intellectual contribution to research goals, and performed revision of the manuscript. CARL was project leader, designed the study, supervised the project and contributed to interpretation of results and revision of the manuscript.

REFERENCES

1. Vergote, I., J. De Brabanter, A. Fyles, K. Bertelsen, et al., *Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma.* Lancet, 2001. **357**(9251): p. 176-82.
2. Chan, J.K., C. Tian, B.J. Monk, T. Herzog, et al., *Prognostic factors for high-risk early-stage epithelial ovarian cancer: a Gynecologic Oncology Group study.* Cancer, 2008. **112**(10): p. 2202-10.
3. Trimbos, J.B., I. Vergote, G. Bolis, J.B. Vermorken, et al., *Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and*

Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm trial. J Natl Cancer Inst, 2003. **95**(2): p. 113-25.

4. Trimbos, J.B. and G. Bolis, *Guidelines for surgical staging of ovarian cancer.* Obstet Gynecol Surv, 1994. **49**(12): p. 814-6.

5. Hoskins, W.J., *Epithelial ovarian carcinoma: principles of primary surgery.* Gynecol Oncol, 1994. **55**(3 Pt 2): p. S91-6.

6. Colombo, N., D. Guthrie, S. Chiari, M. Parmar, et al., *International Collaborative Ovarian Neoplasm trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer.* J Natl Cancer Inst, 2003. **95**(2): p. 125-32.

7. Collinson, F., W. Qian, R. Fossati, A. Lissoni, et al., *Optimal treatment of early-stage ovarian cancer.* Ann Oncol, 2014. **25**(6): p. 1165-71.

8. van der Sanden, G.A., J.W. Coebergh, L.J. Schouten, O. Visser, et al., *Cancer incidence in The Netherlands in 1989 and 1990: first results of the nationwide Netherlands cancer registry. Coordinating Committee for Regional Cancer Registries.* Eur J Cancer, 1995. **31A**(11): p. 1822-9.

9. Casparie, M., A.T. Tiebosch, G. Burger, H. Blauwgeers, et al., *Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive.* Cell Oncol, 2007. **29**(1): p. 19-24.

10. IKNL, *Integraal Kankercentrum Nederland. Landelijke richtlijn Epitheliaal Ovariumcarcinoom; Versie 2.0.* Verantwoording: CRGO; www.oncoline.nl/ovariumcarcinoom, 05-12-2012.

11. Bolis, G., N. Colombo, S. Pecorelli, V. Torri, et al., *Adjuvant treatment for early epithelial ovarian cancer: results of two randomised clinical trials comparing cisplatin to no further treatment or chromic phosphate (32P). G.I.C.O.G.: Gruppo Interregionale Collaborativo in Ginecologia Oncologica.* Ann Oncol, 1995. **6**(9): p. 887-93.

12. Young, R.C., L.A. Walton, S.S. Ellenberg, H.D. Homesley, et al., *Adjuvant therapy in stage I and stage II epithelial ovarian cancer. Results of two prospective randomized trials.* N Engl J Med, 1990. **322**(15): p. 1021-7.

13. Trope, C., J. Kaern, T. Hogberg, V. Abeler, et al., *Randomized study on adjuvant chemotherapy in stage I high-risk ovarian cancer with evaluation of DNA-ploidy as prognostic instrument.* Ann Oncol, 2000. **11**(3): p. 281-8.

14. Trimbos, B., P. Timmers, S. Pecorelli, C. Coens, et al., *Surgical staging and treatment of early ovarian cancer: long-term analysis from a randomized trial.* J Natl Cancer Inst, 2010. **102**(13): p. 982-7.
15. Lawrie, T.A., B.A. Winter-Roach, P. Heus, and H.C. Kitchener, *Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer.* Cochrane Database Syst Rev, 2015(12): p. Cd004706.
16. Baal van, e.a., *Incidence of lymph node metastases during staging procedures in mucinous ovarian carcinoma.* In preparation, 2015.
17. Chen, M., Y. Jin, Y. Bi, J. Yin, et al., *A survival analysis comparing women with ovarian low-grade serous carcinoma to those with high-grade histology.* Onco Targets Ther, 2014. **7**: p. 1891-9.
18. Groen, R.S., D.M. Gershenson, and A.N. Fader, *Updates and emerging therapies for rare epithelial ovarian cancers: One size no longer fits all.* Gynecol Oncol, 2014.
19. Lenhard, S.M., A. Bufe, C. Kumper, P. Stieber, et al., *Relapse and survival in early-stage ovarian cancer.* Arch Gynecol Obstet, 2009. **280**(1): p. 71-7.
20. Kolomainen, D.F., R. A'Hern, F.Y. Coxon, C. Fisher, et al., *Can patients with relapsed, previously untreated, stage I epithelial ovarian cancer be successfully treated with salvage therapy?* J Clin Oncol, 2003. **21**(16): p. 3113-8.
21. Latifi, A., R.B. Luwor, M. Bilandzic, S. Nazaretian, et al., *Isolation and characterization of tumor cells from the ascites of ovarian cancer patients: molecular phenotype of chemoresistant ovarian tumors.* PLoS One, 2012. **7**(10): p. e46858.
22. Bellone, S., E.R. Siegel, E. Cocco, M. Cargnelutti, et al., *Overexpression of epithelial cell adhesion molecule in primary, metastatic, and recurrent/chemotherapy-resistant epithelial ovarian cancer: implications for epithelial cell adhesion molecule-specific immunotherapy.* Int J Gynecol Cancer, 2009. **19**(5): p. 860-6.
23. Ahmed, N., D. Greening, C. Samardzija, R.M. Escalona, et al., *Unique proteome signature of post-chemotherapy ovarian cancer ascites-derived tumor cells.* Sci Rep, 2016. **6**: p. 30061.
24. Kleppe, M., M.A. van der Aa, T. Van Gorp, B.F. Slangen, et al., *The impact of lymph node dissection and adjuvant chemotherapy on survival: A nationwide cohort study of patients with clinical early-stage ovarian cancer.* Eur J Cancer, 2016. **66**: p. 83-90.

25. *ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. ICON Collaborators. International Collaborative Ovarian Neoplasm Study.* Lancet, 1998. **352**(9140): p. 1571-6.
26. Ezendam, N.P., B. Pijlman, C. Bhugwandass, J.F. Pruijt, et al., *Chemotherapy-induced peripheral neuropathy and its impact on health-related quality of life among ovarian cancer survivors: results from the population-based PROFILES registry.* Gynecol Oncol, 2014. **135**(3): p. 510-7.
27. Gutierrez-Gutierrez, G., M. Sereno, A. Miralles, E. Casado-Saenz, et al., *Chemotherapy-induced peripheral neuropathy: clinical features, diagnosis, prevention and treatment strategies.* Clin Transl Oncol, 2010. **12**(2): p. 81-91.
28. Choi, E.K., I.R. Kim, O. Chang, D. Kang, et al., *Impact of chemotherapy-induced alopecia distress on body image, psychosocial well-being, and depression in breast cancer patients.* Psychooncology, 2014. **23**(10): p. 1103-10.
29. Bell, J., M.F. Brady, R.C. Young, J. Lage, et al., *Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynecologic Oncology Group study.* Gynecol Oncol, 2006. **102**(3): p. 432-9.
30. Chan, J.K., C. Tian, G.F. Fleming, B.J. Monk, et al., *The potential benefit of 6 vs. 3 cycles of chemotherapy in subsets of women with early-stage high-risk epithelial ovarian cancer: an exploratory analysis of a Gynecologic Oncology Group study.* Gynecol Oncol, 2010. **116**(3): p. 301-6.
31. Chan, J.K., J.J. Java, K. Fuh, B.J. Monk, et al., *The association between timing of initiation of adjuvant therapy and the survival of early stage ovarian cancer patients - An analysis of NRG Oncology/Gynecologic Oncology Group trials.* Gynecol Oncol, 2016. **143**(3): p. 490-495.
32. Chan, J.K., C. Tian, D. Teoh, B.J. Monk, et al., *Survival after recurrence in early-stage high-risk epithelial ovarian cancer: a Gynecologic Oncology Group study.* Gynecol Oncol, 2010. **116**(3): p. 307-11.

Table/Figure legends

Figure 1. Number of staging procedures per year

Number of patients receiving optimal staging procedures and number of patients who had adjuvant chemotherapy per year in the Netherlands. Number of patients who had chemotherapy did not change from 2002 to 2014.

Figure 2. Survival functions of patients with FIGO stage I HGSOC after optimal staging

Kaplan-Meier curves depicting RFS, OS and DDS in months of all FIGO stage I patients with HGSOC per treatment strategy. RFS improved significantly after adjuvant chemotherapy (Log Rank 9.24; p = 0.002). Five-year RFS was 81% after chemotherapy and 59% after staging only. Five-year OS was 84% after chemotherapy and 82% after staging only. Ten-year OS increased for 62% to 78% after adjuvant chemotherapy (Log Rank 3.27; p = 0.07). DSS for chemotherapy group and no-chemotherapy group were similar after five years (88%), but ten-year DSS was 85% after adjuvant chemotherapy, whereas DSS was 70% after staging alone (Log Rank 2.94; p= 0.09).

Figure 3. Forest plot of subgroups

Forest plot of all subgroups, which demonstrates the effect of chemotherapy on OS per subgroup. Hazard ratios are indicated by squares. The bars indicate corresponding 95% confidence intervals.

Table 1. Characteristics of patients who had optimal staging surgery for FIGO stage I HGSOC (n=223)

Table 2. Univariate and multivariate Cox model for recurrence-free and overall survival in patients who had optimal staging surgery (n=223)