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# Intracrine Regulation of Estrogen and Other Sex Steroid Levels in Endometrium and Non-gynecological Tissues; Pathology, Physiology, and Drug Discovery

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Original Research

# No improvement in long-term survival for epithelial ovarian cancer patients: A population-based study between 1989 and 2014 in the Netherlands

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**KEYWORDS**
Epithelial ovarian cancer;
Surgery;
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Overall survival

**Abstract** ***Aim:*** This study investigates changes in therapy and long-term survival for patients with epithelial ovarian cancer (EOC) in the Netherlands.
***Methods:*** All patients with EOC, including peritoneal and fallopian tube carcinoma, diagnosed in the Netherlands between 1989 and 2014 were selected from the Netherlands Cancer Registry. Changes in therapy were studied and related to overall survival (OS) using multivariable Cox regression models.
***Results:*** A total of 32,540 patients were diagnosed with EOC of whom 22,047 (68%) had advanced stage disease. In early stage, lymph node dissection as part of surgical staging procedures increased over time from 4% in 1989–1993 to 62% in 2009–2014 ($P < 0.001$). In advanced stage, the number of patients receiving optimal treatment with surgery and chemotherapy increased from 55% in 1989–1993 to 67% in 2009–2014 ($P < 0.001$). Five-year survival rates improved in both early stage (74% versus 79%) and advanced stage (16% versus 24%) as well as in all patients combined (31% versus 34%). Ten-year survival rates, however, slightly improved in early stage (62% versus 67%) and advanced stage (10% versus 13%) but remained essentially unchanged at 24% for all patients combined.
***Conclusion:*** Despite intensified treatment and staging procedures, long-term survival for women with EOC has not improved in the last 25 years. The observed improvements in 5-year

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OS reflect a more prolonged disease control rather than better chances for cure. Furthermore, the apparent better long-term outcome, when early and advanced stage patients are analysed separately, is largely due to improved staging procedures and the ensuing stage migration. These effects disappear in a combined analysis of all patients.
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## 1. Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynaecologic cancer worldwide [1]. The 5-year overall survival (OS) rates range between 30% and 46% [2,3]. Due to a lack of specific symptoms, patients are often diagnosed with advanced stage disease, which is associated with poor prognosis and 5-year OS rates of 14–29% [2,4].

Patients who are diagnosed with early stage disease are recommended to undergo a complete staging procedure, consisting of inspection of the abdominal cavity, omentectomy, adequate lymph node sampling and several prescribed biopsies. If patients cannot be staged properly adjuvant chemotherapy is recommended [5,6].

Current management for advanced EOC patients consists of debulking surgery in combination with platinum- and taxane-based chemotherapy. Complete resection of all macroscopic tumour is an independent factor for prolonged survival and is therefore an important goal during debulking surgery [7,8]. The timing of surgery is an ongoing topic of debate; patients were traditionally treated with primary debulking surgery (PDS), but neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) could be an alternative for advanced stage patients [9,10].

Improvements in therapy and diagnostic work-up should ultimately lead to better disease-free survival and OS for EOC patients. Multiple international studies were conducted, which analysed trends in survival. Outcomes varied, but most studies reported improved 5-year survival rates [11–28] (S7). In combination with a decline in incidence for ovarian cancer, among others due to the introduction of the oral contraceptive pill, these studies often result in decreasing ovarian cancer mortality rates [28–31].

The population-based study of van Altena *et al.* [19] analysed trends in relative survival for both early and advanced stage EOC until 2009 in the Netherlands. Since this publication, the role of adequate staging surgery for early stage patients and the introduction of NACT for advanced stage patients have been put forward as important factors for prolonged OS [5,32]. Therefore, we analysed whether long-term survival has indeed improved for both early and advanced stage patients with respect to these changes in treatment.

## 2. Methods

Patients were selected from the Netherlands Cancer Registry (NCR), which is a population-based registry with coverage of all newly diagnosed malignancies in the Netherlands since 1989. Dedicated registration clerks routinely extract patient information from medical records within the hospitals. Information on vital status and date of death were obtained from the municipal demography registries [33].

### 2.1. Study population

All consecutive patients diagnosed with EOC, including peritoneal and fallopian tube carcinoma (International Classification of Diseases for Oncology (ICD-O) codes C48.1, C48.2, C56.9 and C57.0), in the Netherlands between 1989 and 2014 were selected from the NCR [34]. Trends in therapy and survival were studied separately for early (International Federation of Gynaecologists and Obstetricians (FIGO) IA–IIA) and advanced stage patients (FIGO IIB–IV). FIGO stage 2009 was derived from the tumour-nodal-metastasis (TNM) staging system and based on postoperative findings [35]. If patients did not receive surgery or when patients underwent NACT-IDS, clinical tumour stage was used to avoid downstaging. Debulking surgery is registered nationwide from 2004, and outcome of surgery was defined as optimal if macroscopic residual lesions were smaller than one centimetre in maximal diameter. In 2010, complete debulking surgery was implemented in the NCR defined as no macroscopic residual disease.

### 2.2. Statistical analysis

Patients were distributed among period groups according to their date of diagnosis to analyse differences over time for the following time periods; 1989–1993, 1994–1998, 1999–2003, 2004–2008 and 2009–2014. Trends in therapy were analysed using the Cochrane–Armitage test for trends, and patients were divided in two age groups (<65 years at diagnosis and ≥65 years). OS was defined as the date of diagnosis until death or last follow-up date for patients who were still alive (1 February 2017) and was analysed by Kaplan–Meier survival curves and multivariable Cox regression models. A separate analysis was performed on the Eindhoven Cancer Registry data to

adjust our models for comorbidity, which is solely collected in this region of the Netherlands [36]. Besides OS, relative survival analysis was conducted using the Pohar-Perme estimator. Since age influences the cancer-specific hazard, this method accounts for this heterogeneity by age-standardisation [37]. Furthermore, multivariable relative survival analysis was calculated using Poisson regression modelling. A $P$-value $< 0.05$ was considered statistically significant. Statistical analyses were performed using STATA/SE, version 14.1 (StataCorp, College Station, Texas, USA).

## 3. Results

Between 1989 and 2014, 32,540 patients were diagnosed with EOC in the Netherlands. The mean age at diagnosis increased from 63 in 1989–1993 to 66 years in 2009–2014 ($P < 0.001$). The number of advanced stage patients increased over time from 4049 (67%) in 1989–1993 to 5945 (76%) in 2009–2014, most strikingly due to an increase of FIGO stage IIIC (19% in 1989–1993 to 42% in 2009–2014, $P < 0.001$). The number of adenocarcinoma not otherwise specified (NOS) decreased over time, whereas the number of patients diagnosed with serous EOC increased. Since 1999, serous EOC was the most common histologic subtype (Table 1).

### 3.1. Trends in therapy

In early stage patients an increase in second-look surgeries was observed (1% in 1989–1993 and 17% in 2009–2014, $P < 0.001$). Staging procedures more often consisted of lymph node dissections (4% in 1989–1993 and 62% in 2009–2014, $P < 0.001$). Furthermore, the use of adjuvant chemotherapy increased from 31% in 1989–1993 to 46% in 1999–2003; hereafter, it decreased to 35% in 2009–2014 (S1). Specific subgroups of high-risk patients more often received adjuvant chemotherapy, including clear-cell histology (odds ratio [OR] 2.5, 95% confidence interval [CI] 2.1–3.1) and grade III tumours (OR 5.5 [4.6–6.6]).

The percentage of advanced stage patients receiving optimal treatment with surgery and chemotherapy increased from 55% in 1989–1993 to 70% in 2004–2008. Since 2008, this percentage declined to 67% ($P = 0.001$), but this decline was absent in patients aged $\geq 65$ years. Simultaneously, a decrease in the use of chemotherapy only was seen for all patients, from 23% in 1989–1993 to 12% in 2004–2008 with an increase in 2009–2014 to 15%. The number of patients who received no therapy remained essentially stable over time, and the use of radiotherapy in this population was negligible (0.5%, S2).

PDS followed by adjuvant chemotherapy was preferred as first-line treatment for the majority of patients with advanced stage EOC, but in the most recent period (2009–2014), NACT-IDS was more frequently used compared with PDS (S2). Furthermore, an increase in complete/optimal surgery was observed in the last period (75% 2004–2008 and 82% 2009–2014, $P < 0.001$), where patients undergoing NACT-IDS had

Table 1
Characteristics of all epithelial ovarian cancer patients diagnosed in the Netherlands between 1989 and 2014, by period of diagnosis (N = 32,540).

| | 1989–1993 n (%) | 1994–1998 n (%) | 1999–2003 n (%) | 2004–2008 n (%) | 2009–2014 n (%) | $P$-value |
|---|---|---|---|---|---|---|
| **Age** | | | | | | <0.001[a] |
| <65 | 3067 (50.5) | 3041 (47.7) | 2987 (49.4) | 3068 (49.3) | 3314 (42.4) | |
| ≥65 | 3009 (49.5) | 3332 (52.3) | 3053 (50.6) | 3159 (50.7) | 4510 (57.6) | |
| Mean (SD) | 62.7 (13.9) | 64.0 (13.7) | 64.0 (13.4) | 64.5 (13.2) | 66.3 (12.9) | <0.001[b] |
| **FIGO stage** | | | | | | <0.001[a] |
| IA–IIA | 1551 (25.5) | 1577 (24.8) | 1402 (23.2) | 1282 (20.6) | 1436 (18.4) | |
| IIB–IIIB | 1889 (31.1) | 1308 (20.5) | 1004 (16.6) | 736 (11.8) | 918 (11.7) | |
| IIIC | 1163 (19.2) | 1834 (28.8) | 2026 (33.6) | 2226 (35.7) | 3249 (41.5) | |
| IV | 997 (16.4) | 900 (14.1) | 894 (14.8) | 1125 (18.1) | 1778 (22.7) | |
| Unknown | 476 (7.8) | 754 (11.8) | 714 (11.8) | 858 (13.8) | 442 (5.7) | |
| **Histologic type** | | | | | | <0.001[a] |
| Serous | 1616 (26.6) | 2000 (31.4) | 2332 (38.6) | 2918 (46.9) | 4030 (51.5) | |
| Mucinous | 864 (14.2) | 819 (12.8) | 613 (10.2) | 485 (7.8) | 551 (7.0) | |
| Endometrioid | 560 (9.2) | 612 (9.6) | 588 (9.7) | 617 (9.9) | 661 (8.4) | |
| Clear-cell | 238 (3.9) | 260 (4.1) | 279 (4.6) | 310 (5.0) | 365 (4.7) | |
| Adenocarcinoma NOS | 2510 (41.3) | 2234 (35.1) | 1759 (29.1) | 1435 (23.0) | 1571 (20.1) | |
| Other | 288 (4.8) | 448 (7.0) | 469 (7.8) | 462 (7.4) | 646 (8.3) | |
| **Grade** | | | | | | <0.001[a] |
| I | 708 (11.6) | 704 (11.0) | 548 (9.1) | 564 (9.1) | 622 (7.9) | |
| II | 1301 (21.4) | 1293 (20.3) | 1165 (19.3) | 1013 (16.3) | 740 (9.5) | |
| III | 2081 (34.3) | 2238 (35.1) | 2299 (38.0) | 2245 (36.0) | 2619 (33.5) | |
| Unknown | 1986 (32.7) | 2138 (33.6) | 2028 (33.6) | 2405 (38.6) | 3843 (49.1) | |
| Total | 6076 (18.7) | 6373 (19.6) | 6040 (18.6) | 6227 (19.1) | 7824 (24.0) | |

SD, standard deviation; NOS, not otherwise specified.
[a] Chi-square test.
[b] ANOVA test.

a higher probability of complete/optimal debulking (OR 1.7 [1.4–1.9]).

### 3.2. Survival analysis

In early stage patients, 5-year OS increased from 74% in 1989–1993 to 79% in 2009–2014. Long-term survival, at 10 years, increased from 62% in 1989–1993 to 67% in 2004–2008 (Table 2). Relative survival analysis was also conducted but trends did not differ from OS analysis (S5–S6). When corrected for age, tumour stage, histologic type and differentiation grade this increase was statistically significant (hazard ratio [HR] 0.8 [0.7–0.9]). Moreover, patients who underwent a lymph node dissection as a part of their surgical staging procedure experience improved survival (HR 0.70 [0.63–0.78]). Also the administration of adjuvant chemotherapy in patients without lymph node dissection contributes to improved survival (HR 0.8 [0.7–0.9]).

In advanced stage patients, 5-year OS increased from 16% in 1989–1993 to 24% in 2009–2014. Ten-year survival increased from 10% in 1989–1993 to 13% in 2004–2008. This effect persisted after adjustment for patient and tumour characteristics (HR 0.6 [0.6–0.7]). Median OS improved from 15 months in 1989–1993 to 25 months in 2009–2014. The effects for OS were attenuated when correcting for treatment combination but remained statistically significant (HR 0.7 [0.7–0.8], S3). Patients treated with surgery and chemotherapy experienced comparable trends in survival over time (HR 0.6 [0.5–0.6]), but their survival was higher than the entire cohort (5-year survival rates in 2009–2014 34% and 24% respectively). In contrast, survival rates remained similar over time for patients who did not receive this treatment combination (HR 1.0 [0.9–1.0]). The trends in survival in the Eindhoven region were consistent with those in the complete data set, and adjustment for comorbidity did not alter the results (data not shown).

In all patients combined, short-term OS improved until 1999–2003 (5-year survival rates being 31% in 1989–1993 and 35% in 1999–2003). After this period, the 5-year OS remained stable (35% in 2004–2008 and 34% in 2009–2014). OS at 10 years did not improve, and the cure rate for EOC patients was still not more than 24% (24% in 1989–1993 and 23% in 2004–2008, S4). A sensitivity analysis including only patients who survived the first 5 years did not show any improvement in long-term survival over time for all patients combined (HR 1.0 [0.9–1.2]).

## 4. Discussion

Despite all efforts in intensifying treatment, this study showed that overall long-term survival for patients diagnosed with EOC has not improved in the last 25 years. Patients were more often diagnosed with advanced stage disease, suggesting improved surgical staging, and more frequently received optimal treatment according to contemporary standards. This resulted in prolonged disease control, as shown by the improved short-term survival, but not in better cure rates.

Between 1989 and 2014, an increasing number of early stage patients underwent lymph node dissection as part of their surgical staging procedure, whereas adjuvant chemotherapy was largely restricted to specific high-risk groups. Advanced stage EOC patients were increasingly treated with the combination of (debulking) surgery and chemotherapy. Furthermore, an increase in the use of chemotherapy only is seen in the last period, which could imply that these patients were up for NACT-IDS but were considered ineligible for debulking surgery. Still, 13% of patients did not receive any therapy, and this percentage is consistent over the decades.

In the last two periods, NACT-IDS became an alternative for advanced stage patients and is currently used for the majority of these patients in the Netherlands [32]. Some have criticised this trend and stated that the non-inferiority character of NACT-IDS is caused by poor surgical results of PDS with rather low percentages of patients with no macroscopic residual tumour after surgery [38,39]. In our study we showed that the rate of complete/optimal surgery did increase over time in both the patients treated with PDS and NACT-IDS. This might be explained by a more accurate selection for patients who could be optimally

Table 2
Crude observed 5- and 10-year overall survival (OS) and adjusted hazard ratios (HRs) for all EOC patients by period of diagnosis and stage at diagnosis (N = 32,540).

| Time period | FIGO IA–IIA | | | FIGO IIB–IV | | | All patients combined | | |
|---|---|---|---|---|---|---|---|---|---|
| | 5-year OS | 10-year OS | HR (CI)[a] | 5-year OS | 10-year OS | HR (CI)[a] | 5-year OS | 10-year OS | HR (CI)[a] |
| 1989–1993 | 74.4 | 62.4 | Reference | 16.0 | 9.8 | Reference | 31.1 | 23.5 | Reference |
| 1994–1998 | 75.1 | 62.7 | 1.00 (0.90–1.13) | 18.1 | 9.9 | **0.91 (0.87–0.95)** | 31.7 | 22.7 | **0.95 (0.91–0.99)** |
| 1999–2003 | 75.5 | 63.2 | 0.90 (0.80–1.02) | 24.7 | 13.3 | **0.73 (0.70–0.77)** | 35.1 | 24.2 | **0.80 (0.77–0.84)** |
| 2004–2008 | 78.9 | 67.2 | **0.81 (0.71–0.92)** | 24.7 | 12.6 | **0.69 (0.66–0.73)** | 34.6 | 23.0 | **0.74 (0.71–0.77)** |
| 2009–2014 | 79.1 | N.A.[1] | **0.75 (0.65–0.87)** | 24.1 | N.A.[1] | **0.62 (0.59–0.65)** | 33.7 | N.A.[1] | **0.65 (0.62–0.68)** |

A $P$-value $< 0.05$ was considered statistically significant.
N.A.[1], not applicable (10 year follow-up not yet available); HR, hazard ratio; CI, confidence interval.
[a] Adjusted for age, stage at diagnosis, histologic type and differentiation grade.

debulked in the primary setting [40,41]. In addition, EOC care is increasingly centralised in the Netherlands, resulting in a higher percentage of surgeries performed by registered gynaecologic oncologists [32,42,43].

Short- and long-term survival seem to improve over time when early and advanced stage patients are analysed separately. However, long-term survival at 10 years does not improve in a combined analysis of all patients. In addition, 5-year survival rates also remain stable at 35% after 1998 in all patients combined. The discrepancy between a combined analysis and an analysis stratified by stage can be explained by stage migration. Patients were more often diagnosed in advanced stage disease. Probably due to improved routine preoperative imaging, the introduction of diagnostic laparoscopy and improved staging procedures. Therefore initially low-stage patients, with, for example, undetected lymph node metastases, are now diagnosed as advanced stage patients. This improves outcome rates for both groups but not for all patients together. It is not possible to correct for stage migration in statistical analyses. So survival trends in selected patient groups, for example, only advanced stage patients, should be interpreted with caution [44].

Survival rates in single- or multi-centre studies tend to be higher than those in population-based studies. In the latter, information about therapy or stage is often lacking, but by the near completeness and high quality of the registered data in the NCR, we can provide high-quality population-based research [33]. In this study, we showed that 5-year survival rates for advanced stage patients in the entire cohort versus those who were treated with surgery and chemotherapy differed by almost 10%. And because we have shown by stratified analysis that improvements in short-term OS were mainly, although not entirely, caused by treatment-associated factors, comparison between different types of studies is complicated.

The majority of published population-based studies report improved 5-year (relative) survival rates [11–28] (S7). In combination with a decline in incidence, this often results in optimistic conclusions about mortality from ovarian cancer [28–31]. Other population-based studies, however, indicate levelling in 5-year survival in the early 21st century as we found [4,45,46]. Moreover, with the extended follow-up available in our study, we were able to show that 10-year survival rates did not improve between 1989 and 2014 (S4). Thus, although changes in diagnosis and therapy have extended the duration of disease control, the cure rate of patients remains unchanged. Two other studies with extended follow-up until 10-year confirm our findings [16,19].

Survival rates in our study are lower than most of the other population-based studies in high-income countries and even lower than previous Dutch studies. This may be the result of different inclusion criteria. In contrast to other studies, our study is the only population-based study that included primary peritoneal ovarian cancer patients as well (S7). This diagnosis is associated with worse prognosis because, by definition, it cannot be limited to the ovaries. Contemporary clinical trials in ovarian cancer typically include primary peritoneal cancers because they are considered as one entity, justifying our decision to include these patients in our analyses [35,47].

The limitations of this study are mainly related to the lack of detailed information about chemotherapy agents and schedules. Information about surgical procedures and the result of debulking surgery was also lacking for earlier years. Furthermore, performance status and comorbidity were available for a limited number of patients only, but multivariable analyses in this subgroup did not indicate any effect of these variables on our main outcome measures. In addition, we objectified a 'shift' in histological subtype (i.e. from adenocarcinoma NOS to serous), which is probably explained by the improved classification and increase in surgical procedures.

To truly analyse the changes in long-term OS with respect to changed treatment protocols in the most recent years, most importantly the introduction of NACT-IDS, the follow-up of this last period must be extended. However, we do not expect that these changes increase OS drastically because the use of NACT-IDS is based on non-inferiority in randomised controlled studies [9,10]. In addition, period analysis was not performed on this cohort because 5- and 10-year survival rates are quite stable for the past 15 years.

The population-based character and therefore inclusion of all EOC patients, including primary peritoneal and fallopian tube cancers, in our analyses provide information on the varied presentation of this patient group. The combined and stratified analysis by stage shows that optimistic trends in survival should be interpreted with caution. The lack of improvements in long-term OS urges us to put major efforts into improving cure rates for women with EOC.

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## Conflict of interest statement

None declared.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2017.10.030.

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