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Original Articles

# Impact of hospital type and treatment on long-term survival among patients with FIGO Stage IIIC epithelial ovarian cancer: follow-up through two recurrences and three treatment lines in search for predictors for survival

**W. Szczesny[1,2], I. Vistad[3], J. Kærn[4], J. Nakling[1], C. Tropé[4,5], T. Paulsen[2,4]**

*[1] Department of Gynecology, Sykehuset Innlandet Hospital Trust, Brumunddal*
*[2] Cancer Registry of Norway, Oslo*
*[3] Department of Gynecology, Sørlandet Hospital Hospital Trust, Kristiansand*
*[4] Oslo University Hospital Radiumhospitalet, Department of Gynecological Oncology, Oslo*
*[5] Faculty of Medicine, Department Group of Clinical Medicine, University of Oslo, Oslo (Norway)*

**Summary**

The purpose of this study was to investigate the impact of hospital type determined at primary treatment and find possible predictors of survival in a cohort of patients with advanced epithelial ovarian cancer (EOC) who recurred twice and received three lines of treatment during eight-year follow-up. Using the Norwegian Cancer Registry, the authors identified 174 women with FIGO Stage IIIC EOC diagnosed in 2002. First-line treatment consisted of up-front debulking surgery and chemotherapy, received in either a teaching hospital (TH, n=84) or a non-teaching hospital (NTH, n=90). After recurrence all patients in Norway are equally consulted at TH. Survival determined for three time intervals (TI): TI-1, from end date of first-line treatment to first recurrence or death, TI-2, from beginning of second-line treatment until second recurrence or death, and TI-3, from beginning of third-line treatment to death or end of follow-up. Extensive surgery carried out in TH followed by at least six cycles of platinol-taxan chemotherapy resulted in longer survival in the TH group during TI-1. Altogether, the majority of those who receive treatment for recurrences were primary better debulked with following platinol-taxane chemotherapy. Survival in TI-2 was influenced by platinol-sensitivity. During TI-3 the majority (96%) had good performance status and their mean age at primary diagnosis at either hospital type was 57 years. Extensive primary surgery at TH, platinol sensitivity, age, and performance status were predictors of survival in this cohort.

*Key words:* Recurrent ovarian neoplasm; Follow-up; Second recurrence; Third treatment line; Predictors of survival.

## Introduction

Worldwide, it has been shown that when treatment of epithelial ovarian cancer (EOC) is centralized to large hospitals where primary surgery is performed by specialized gynecological oncologists, it has a positive impact on survival [1-5]. Several studies have demonstrated that patients who undergo surgery performed by a gynecological oncologist have an improved median survival, from seven to 48 months [3-5]. EOC patients treated in hospitals with a high volume of EOC cases also have improved survival [6]. The impact of hospital level and centralization on survival from EOC investigated regionally in Norway [7, 8], and nationally in Denmark [9], showed superior effect of treatment at tertiary referral gynecological-oncological centers versus regional hospitals. A population-based Norwegian cohort study by Paulsen *et al.* showed that when it comes to short-term survival, patients with FIGO Stage IIIC EOC benefit from having primary surgical treatment at teaching hospitals (TH) compared to non-teaching hospitals (NTH), due to better debulking (such as to zero, < one cm or ≤ two cm residual disease) carried out at TH [10]. These results led to the decision in 2005 to centralize the surgical treatment of EOC in Norway. Before 2005, primary surgical treatment was performed either at a TH located in one of the four national health regions (one TH in each region) by a gynecological oncologist, or at one of the 34 NTH by either a general gynecologist or sometimes a general surgeon. However, when primary surgical treatment was carried out in an NTH, chemotherapy was usually initiated only after consultation with a TH. The decision to initiate second- and third-line treatment was based on confirmation of first and second recurrence, respectively, usually after consultation with a TH.

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An updated publication by Paulsen *et al.* [11] covered eight years of follow-up in the same patients, and again showed improved overall survival for those receiving first-line debulking at TH (35.6 months *vs.* 23.4 months at NTH, $p < 0.05$; hazard ratio (HR) 1.38 (95% CI 1.00–1.89). This was attributed to the fact that more patients underwent better debulking to either zero, less than one, or at least two cm residual disease followed by at least six cycles platinol/taxane chemotherapy as a first-line treatment in the TH group versus the NTH group [11]. However, during eight years of follow-up, some of these patients were prone to recurrence and received second-line and third-line treatments. Indeed, it is common for EOC patients to face the challenge of platinol-resistant tumors [12-14], which affects the efficiency of second- and third-line chemotherapy regimens [15, 16]. The impact of hospital type on survival until first recurrence or death, or after subsequent lines of treatment in Norwegian population-based cohort, has not been previously described.

Therefore, the present study aimed to investigate the impact of hospital type, treatment, and patient characteristics at first-line treatment on recurrence and eight-year survival in the cohort of EOC patients described by Paulsen *et al.* [10, 11], in order to identify possible predictors for survival.

## Materials and Methods

The study sample has been described previously [10, 11]. Briefly, data on all patients with a primary diagnosis of FIGO Stage IIIC EOC in Norway between January 1st, 2002 and December 31st, 2002 (n=198) were obtained from the Cancer Registry of Norway, which includes detailed data on cancer incidence, treatment, clinical follow-up, and mortality. Registration of all solid tumors in the Cancer Registry of Norway has been mandatory since 1954, and completeness is close to 100% [17-19]. Data on migration, death, and cause of death are regularly updated in the registry, which effectively eliminates the problem of loss to follow-up.

To be included, patients had to have undergone surgery followed by chemotherapy as a first-line treatment. Therefore, 24 patients were excluded as they received neoadjuvant chemotherapy [12], leaving 174 patients in the present analysis. Data was collected on hospital type where first-line treatment took place (TH or NTH); performance status according to the classification of the World Health Organization (good 0-1, poor 2-4); serious comorbidity (Charlson Comorbidity Index 1-5) [20]; residual disease after first-line surgical debulking at three different cut-off levels (no residual disease, residuals < one cm, residuals ≤ two cm); histology (serous, mucinous, endometroid, clear cell, other epithelial), and type of first-line chemotherapy treatment (platinol/taxane, platinol alone, other, no chemotherapy) with number of cycles (≥ 6 or < 6).

Follow-up data, collected from the Cancer Registry of Norway, included detailed information on up to two subsequent recurrences and second- and third-line treatments. Confirmation criteria for first and second recurrence were biopsy or a combination of biopsy and radiological imaging, which provided an exact date for recurrence. In Norway, if an EOC patient shows no recurrence after first-line treatment, they are followed every three months for the first two years, then every six months for years three to five, and yearly thereafter. Patients with recurrence within six months of finishing platinol chemotherapy were considered to have platinol-resistant tumors, and those with recurrences after six months were considered to have platinol-sensitive tumors.

Follow-up time was divided into three time intervals (TI), counting survival in months as follows:

- TI-1 was defined from the end date of first-line treatment (last chemotherapy cycle) to the date of first recurrence or death.
- TI-2 was defined from the beginning of second-line treatment until the second recurrence or death.
- TI-3 was defined from the beginning of third-line treatment to death whichever occurred first.

*Statistical analysis*

Analyses were performed with SPSS version 18.0. The Pearson chi–square test was used to compare the frequencies of the prognostic factors, residual disease, and chemotherapy according to hospital type. Kaplan–Meier plots were used to compare survival between patient groups, with November 1st, 2010 being the end of follow-up (end of observation time). The log rank test or Breslow's unproportional hazard model were used when appropriate to compare survival between patient groups. The Cox proportional hazards model was used to identify prognostic factors for survival. A two-sided significance level of 5% was used.

## Results

*TI-1*

Of the 174 included patients, 84 underwent first-line treatment at TH and 90 at NTH (Figure 1, Table 1). The authors found improved median survival during TI-1 in the TH versus the NTH group (10.3 *vs.* 7.2 months, $p = 0.02$) (Figure 2), due to significantly better debulking at either of three studied cut-off levels carried out at TH followed by at least six cycles of platinol-based chemotherapy in the TH *vs.* NTH group. There were significantly more patients with lower performance status in the NTH group (Table 1). After adjustment for performance status, there was still a significant difference in survival between the two groups, with the TH group having better survival (hazard ratio, HR=1.3, 95% confidence interval, CI 0.51-0.98, $p = 0.04$).

Sixteen patients had complete remission (CR) of EOC from first-line treatment until the end of follow-up (14 were alive: ten in TH group versus four in NTH group; one died from pulmonary cancer and one died from heart failure, one in each group). Forty-nine died of progression of EOC before recurrence. Nine patients received consolidation tamoxifen- therapy at the end of first-line treatment (TH: n=4; NTH: n=5).

*TI-2*

No difference in survival was found between the TH and NTH groups. Ninety-nine of 109 patients with first recurrence received second-line treatment (TH: n=54; NTH: n=45, Figure 1). Treatment was either contraindicated for ten patients or the patients denied treatment themselves. In the present study these patients were classified as ineligible for treatment.

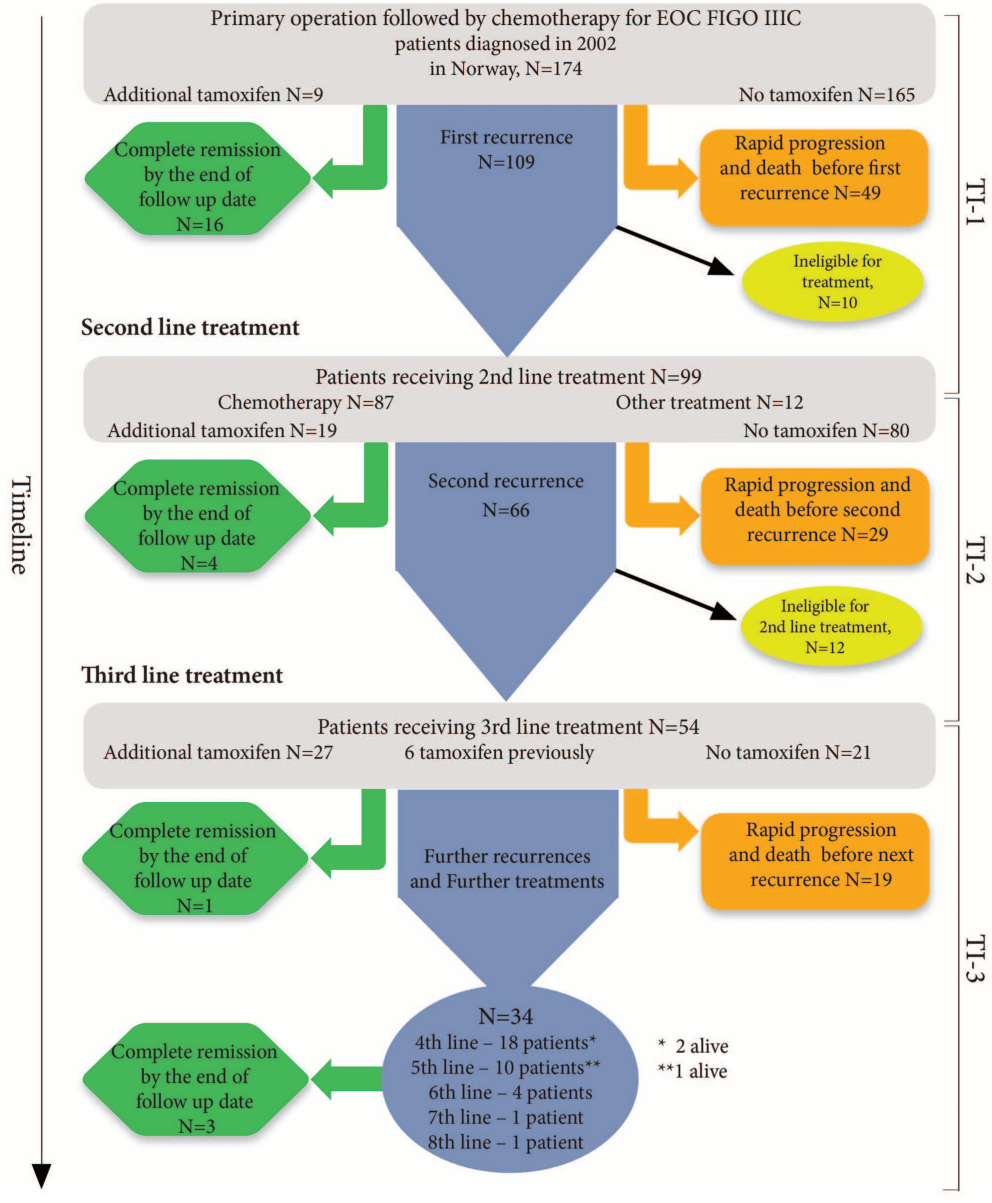


Figure 1. — Flow chart. The course of epithelial ovarian cancer (EOC) FIGO III C diagnosed in 2002 in Norway. Follow-up, decision-making, and treatment in a cohort of 174 patients treated with primary surgery followed by chemotherapy. Two recurrences. Second- and third-line of treatment in three following time intervals (TI-1, TI-2, TI-3). After third line of treatment, no further recurrences specified for 34 patients.
*Two patients alive, complete remission (CR) after 4th line.
**One patient alive, CR after 5th line.

The patients who received second-line treatment had good performance in 96% cases and, over 84% of them received at least six cycles platinol-based chemotherapy in their first treatment line at either TH or NTH (Table 1). Primary debulking at cut-off levels zero and < one cm did not differ between TH- and NTH groups in TI-2. Nevertheless, the distribution of patients with residuals ≤ two cm *vs.* > two cm left after primary debulking differed significantly between TH and NTH in TI-2 (Table 1). Increase in residuals after primary debulking (≤ two cm vs. > two cm) was significantly associated with increase in odds for platinol-resistance (OR=3.5 95% CI 1.3- 9.1), (Table 2). The patients debulked to ≤ two cm had significantly better survival in TI-2 than those of residuals > two cm (data not shown). Seventy-one patients had platinol-sensitive tumors, while 28 had platinol-resistant tumors; there was no significant difference in mean age between these two groups 63 ±10.5 *vs.* 61 ±12.1 years, $p = 0.4$, respectively. Patients with platinol-sensitive tumors had better survival during TI-2 than those with platinol-resistant tumors (10.9 *vs.* 4.3 months, 95% CI 8.3-10.8, $p < 0.01$) (Figure 3). After adjustment for residuals ≤ two cm *vs.* > two cm in Cox regression only platinol-sensitivity *vs.* resistance remained significantly associated with survival (HR=2.0, 95% CI 1.2- 3.2, $p = 0.01$).

In the NTH group, 43 (96%) patients received chemotherapy alone as second-line treatment *vs.* 44 (82%) in TH group ($p = 0.03$, data not shown). In the TH group, second line treatment was more varied than in NTH; only two patients

Table 1. — *Distribution of patient characteristics assessed at primary treatment and hospital type where first-line treatment took place (TH= teaching hospital, NTH= non-teaching hospital) each time the patients approach a new line of treatment. Age shows the age at primary diagnosis, and how old the patients were at primary diagnosis when second- and third-line of treatment began, respectively.*

| Characteristics | Primary characteristics on approach to primary treatment (n=174) by hospital level | | | Distribution of primary characteristics (age at primary diagnosis time) and type of hospital from primary treatment on approach to second line treatment (n=99) | | | Distribution of primary characteristics (age at primary diagnosis time) and type of hospital from primary treatment on approach to third line treatment (n=54) | | |
|---|---|---|---|---|---|---|---|---|---|
| | TH (%) n = 84 | NTH (%) n = 90 | *p* value $\chi^2$ | TH (%) n = 54 | NTH (%) n = 45 | *p* value $\chi^2$ | TH (%) n = 28 | NTH (%) n = 26 | *p* value $\chi^2$ |
| Age mean ± SD [range] | 64±11.5 [34-85] | 66±13.3 [31-92] | 0.5 | 61.4±10.7 [34-81] | 59.9±10.7 [42-85] | 0.8 | 57.4±9.5 [34-74] | 57.3±8.5 [43-74] | 0.6 |
| Performance status WHO | | | <0.01 | | | 0.5 | | | 1 |
| Good (0-1) | 73 (92) | 65 (74) | | 49 (96) | 42 (93) | | 25 (96) | 25 (96) | |
| Poor (2-4) | 7 (8) | 23 (26) | | 2 (4) | 3 (7) | | 1 (4) | 1 (4) | |
| Missing | 4 | 2 | | 3 | | | 2 | 0 | |
| Serious comorbidity (Charlson [20], score 1-5) | | | 0.5 | | | 0.3 | | | 0.7 |
| Score 0 | 38 (44) | 31 (34) | | 25 (47) | 16 (36) | | 13 (46) | 9 (35) | |
| Score 1 | 35 (43) | 44 (49) | | 24 (44) | 24 (53) | | 13 (46) | 14 (54) | |
| Score 2 | 8 (9) | 11 (12) | | 5 (9) | 3 (7) | | 2 (7) | 2 (8) | |
| Score 3 | 3 (4) | 4 (4) | | 0 | 2 (4) | | 0 | 1 (4) | |
| Score 4-5 | 0 | 0 | | 0 | 0 | | 0 | 0 | |
| Residual disease | | | 0.01 | | | 0.3 | | | 0.4 |
| 0 (no visible residuals) | 27 (32) | 15 (17) | | 17 (32) | 10 (22) | | 10 (36) | 6 (23) | |
| > 0 | 57 (68) | 75 (83) | | 37 (68) | 35 (78) | | 18 (64) | 20 (77) | |
| Residual disease by 1 cm | | | < 0.01 | | | 0.06 | | | 0.06 |
| < 1cm | 45 (42) | 28 (31) | | 32 (59) | 18 (40) | | 19 (68) | 11 (42) | |
| ≥ 1cm | 39 (58) | 62 (69) | | 22 (41) | 27 (60) | | 9 (32) | 15 (58) | |
| Residual disease by 2 cm | | | <0.01 | | | 0.03 | | | 0.01 |
| ≤ 2 cm | 67 (80) | 49 (54) | | 44 (82) | 28 (62) | | 26 (93) | 17 (65) | |
| > 2 cm | 17 (20) | 41 (46) | | 10 (18) | 17 (38) | | 2 (7) | 9 (35) | |
| Histology | | | 0.3 | | | 0.6 | | | 0.5 |
| Serous | 65 (77) | 68 (76) | | 46 (85) | 35 (78) | | 23 (82) | 20 (77) | |
| Mucinous | 5 (6) | 3 (3) | | 1 (2) | 1 (2) | | 1 (4) | 0 | |
| Endometroid | 7 (8) | 5 (6) | | 4 (7) | 3 (7) | | 3 (10) | 3 (11) | |
| Clear cell | 4 (5) | 4 (4) | | 2 (4) | 2 (4) | | 1 (4) | 1 (4) | |
| Other epithelial | 3 (4) | 10 (11) | | 1 (2) | 4 (9) | | 0 | 2 (8) | |
| Type of primary chemotherapy | | | <0.01 | | | 0.5 | | | 0.5 |
| Platinol/taxan | 68 (81) | 51 (57) | | 48 (89) | 39 (87) | | 26 (93) | 23 (89) | |
| Platinol single | 12 (14) | 13 (14) | | 5 (9) | 5 (11) | | 1 (4) | 2 (8) | |
| Other | 1 (1) | 1 (1) | | 1 (2) | 0 | | 1 (4) | 0 | |
| No chemotherapy | 3 (3) | 25 (28) | | 0 | 1 (2) | | 0 | 1 (4) | |
| Number of cycles | | | <0.01 | | | 0.3 | | | 0.7 |
| cycles ≥ 6 | 69 (82) | 51 (57) | | 49 (91) | 38 (84) | | 25(89) | 22 (85) | |
| cycles < 6 | 15 (18) | 39 (43) | | 5 (9) | 7 (16) | | 3 (11) | 4 (15) | |

from the NTH group received other treatment (one secondary cytoreductive surgery (SCS) followed by chemotherapy, one radiotherapy) *vs.* ten form the TH group (three SCS, one radiotherapy, and six thermotherapy [21, 22]. Survival differences could not be statistically explored given the small size of these groups. Among the 87 patients treated with chemotherapy alone, platinol-based chemotherapy was given to 56 and 31 patients received non-platinol-based chemotherapy.

Consolidation tamoxifen-therapy was received by 19 patients at the end of second-line treatment (TH, n=10; NTH, n= 9). After second-line treatment, four patients had CR by the end of follow-up time: one patient after radiotherapy, two after SCS from TH, and one patient after SCS from NTH.

*TI-3*

No difference in survival was found between the TH and NTH groups in TI-3. Sixty-six patients had second recur-

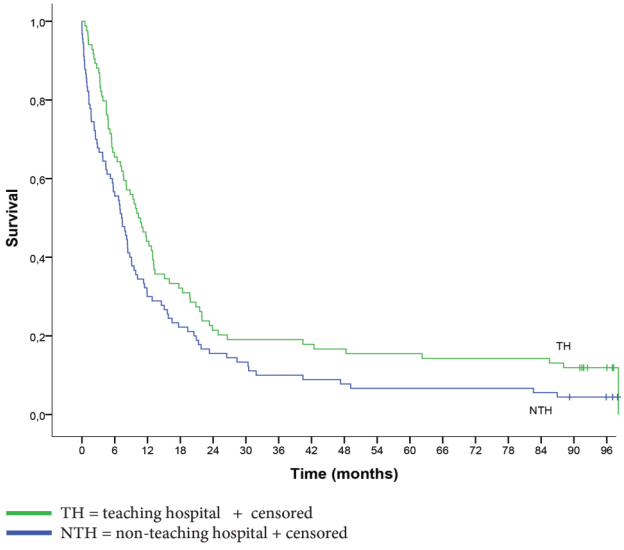


Figure 2. — Survival to first recurrence or death during time interval 1 (TI-1) in relation to hospital type where primary surgery was performed, n= 174. TH = teaching hospital. NTH = non-teaching hospital. Median survival TH: 10.3 months, NTH: 7.2 months, $p = 0.02$.

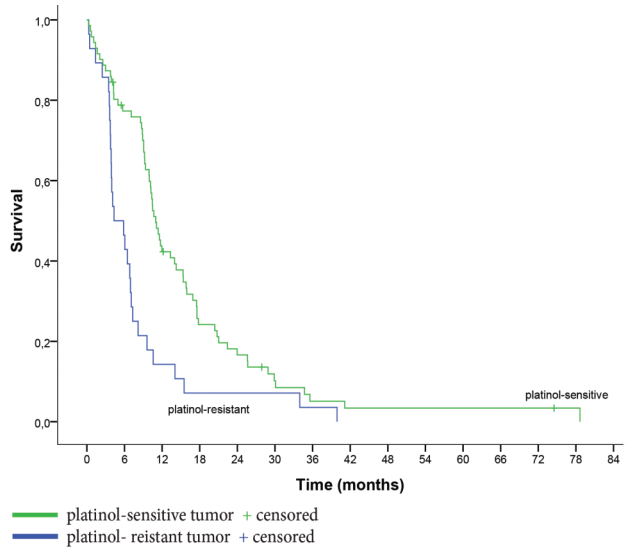


Figure 3. — Survival to second recurrence or death during TI-2 in relation to platinol sensitivity/resistance, n= 99. Median survival for platinol sensitive patients: 10.97 months, platinol resistant: 4.33 months, $p < 0.01$.

Table 2. — *Association between residual disease after primary debulking and platinol-resistance at second line treatment, after first recurrence, n = 99. OR 95%, 95%CI.*

| Primary residuals | Platinol resistant YES (%) | Platinol resistant NO (%) | *p* value $\chi^2$ | OR [95% CI] |
|---|---|---|---|---|
| 0 cm (no macroscopic residuals) | 5 (18) | 22 (82) | | |
| > 0 cm | 23 (32) | 49 (68) | 0.2 | 2.1 [0.6; 6.1] |
| < 1 cm | 9 (18) | 41 (82) | | |
| ≥ 1 cm | 19 (39) | 30 (61) | 0.02 | 2.9 [1.1; 7.3] |
| ≤ 2 cm | 15 (21) | 57 (79) | | |
| > 2 cm | 13 (48) | 14 (52) | < 0.01 | 3.5 [1.3; 9.1] |

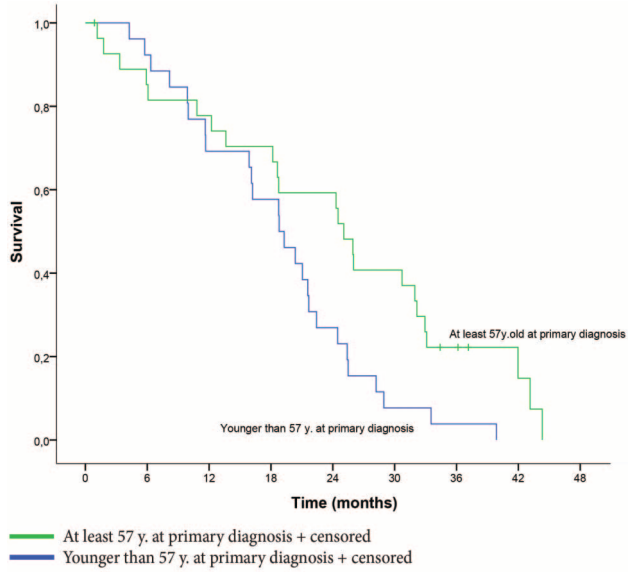


Figure 4. — Survival in months after second recurrence in time interval 3 (TI-3), third line of treatment, n = 54. Better survival for 28 patients who were at least 57 years old at primary diagnosis compared to 26 patients younger than 57 years at primary diagnosis. Median survival 25.4 *vs.* 19.0 months, $p = 0.02$.

rence, 12 of whom were ineligible for third-line treatment. Of the 54 who were eligible (TH, n=28 *vs.* NTH, n=26), the majority had good performance status after first-line treatment (96% in each group, Table 1). The mean age at the third-line treatment was 60 years, similar in the TH and NTH groups. These patients had also a similar mean age of 57 years at primary diagnosis (Table 1), and in most of them surgery was followed by at least six cycles of platinol/taxane chemotherapy as a first-line treatment at either TH or NTH. The number of patients with ≤ two cm *vs.* > two cm residual disease was significantly higher in the TH group compared to the NTH group, but in TI-3 this was not associated with survival.

Median survival among patients over 60 years of age (28 patients) at second recurrence *vs.* those younger than 60 years (26 patients) differed (25.4 *vs.* 19.0 months, $p = 0.01$, data not shown). Eight of 28 patients over 60 years of age received platinol-based chemotherapy, as they had platinol-sensitive tumors, *vs.* two of those younger than 60 years. At the end of third-line treatment, 27 patients received con-

solidation tamoxifen-therapy (TH: 13 *vs.* NTH: 14). Tamoxifen treatment was not age-related. Patients who received tamoxifen had longer median survival compared to those who did not (24.4 *vs.* 13.7 months, $p = 0.047$) (data not shown). After third-line treatment, four patients had CR by the end of follow-up time (Figure 1). At the end of eight years of follow-up, 24 patients (13.8%) had CR and 22 were alive.

## Discussion

The finding of superior effect on survival of first-line treatment performed at TH compared with NTH in this cohort confirm the importance of more complex treatment approaches and better debulking at primary surgery performed in larger hospitals, which had already been described by others [6, 15, 23, 24]. However, the study of the first recurrence in this cohort reveals the fact that patients, with the most favorable primary characteristics (good performance status, low residual disease and ≥ six cycles of platinol/taxane chemotherapy) from either TH or NTH, survive TI-1 and TI-2.

It is probable that the small number of patients with no residual disease, or < one cm residual disease in this cohort make the statistical analysis non-significant, and was the reason that only a cut-off of ≤ two cm residuals gave a larger proportion, making the difference between TH and NTH groups significant through all three studied TIs (Table 1). Nevertheless, residual disease after primary debulking was considered a confounder for survival in TI-2 in this cohort, because in the Cox regression model only platinol-sensitivity was identified as a predictor for survival in TI-2 regardless of residual disease.

All patients with platinol-sensitive tumors had improved survival in TI-2 compared to those with platinol-resistant tumors. The present results confirm previous findings of the superiority of platinol-based treatment compared to other chemotherapy regimens as a second-line treatment for platinol-sensitive tumors [13, 14, 25]. The association between low residual disease after first-line surgical treatment and platinol-sensitivity after recurrence was beyond the scope of this study. The TH group had significantly more varied treatment in TI-2 than the NTH group, probably because some treatment options were not available at NTH.

The present authors cannot explain the better survival observed in TI-3 for patients older than 60 years of age versus those below 60 years of age. Indeed, this finding is not in accordance with the findings of Markman *et al.* [26], who reported better survival for younger patients compared with older ones. However, age 50-59 was previously reported as prognostic factor in EOC patients operated with SCS in Norwegian patients [27]. The investigation of aging in this cohort was beyond the scope of the preset study.

The effect of prolonged survival after tamoxifen treatment in TI-3 may be biased by a response to chemotherapy, or enrollment in a phase III study not registered in the Cancer Registry of Norway. There is no evidence of any therapeutic effect of tamoxifen on EOC survival in the Cochrane review [28]. However, some authors have pointed toward the beneficial role of this medicine in recurrent, advanced EOC given as consolidation after chemotherapy [29].

The present study is based on the principle of population-adjusted clinical epidemiology (PACE), where follow-up data is systematically gathered and evaluated, without loss to follow-up, or exclusions due to age or poor health [30]. Some authors reported the exclusion of a rather large number of patients from their studies because of missing or unreliable data concerning therapy or progression [15]. The quality of PACE [30] is considered to be as high as that of randomized clinical trials in case where randomized trial is difficult to perform. The Cancer Registry of Norway provides a prospective, clinical registry comprising all EOC patients in the Norwegian population. Nevertheless, the cohort presented here is small, and few patients were alive after second recurrence. Hence, the study does not have the necessary power to evaluate the efficacy of SCS or other regimens than chemotherapy alone after recurrence.

The completeness of data in the Cancer Registry of Norway was satisfactory until the end of third-line treatment. However, data is reported less precisely beyond second recurrence, which meant that the present authors were unable to analyze survival to third recurrence or death. Hanker *et al.* stated that application of three lines of treatment seems to be the maximum acceptable therapy [15], which is in accordance with the present findings.

## Conclusion

Extensive primary surgery performed at TH, platinol sensitivity, age, and performance status were predictors of survival in this cohort.

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Address reprint requests to:
W. SZCZESNY, M.D.
PO Box 5213 Majorstuen, NO–0304
Oslo (Norway)
e-mail: witold.szczesny@kreftregisteret.no