

# Treatment patterns in elderly women with ovarian cancer: single center experience in the Netherlands

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## Summary

**Introduction:** Standard treatment of advanced ovarian cancer consists of cytoreductive surgery (CRS) and combination chemotherapy (CT). As elderly patients with ovarian cancer are underrepresented in trials defining standard treatment, it remains unclear which patient can endure this burdensome standard therapy and for whom therapy should be adapted. **Materials and Methods:** A retrospective cohort study was performed in all patients aged 70 years and older diagnosed with primary ovarian cancer between 2013 and 2014 at the Dutch Cancer Institute in Amsterdam. Patient characteristics, tumor characteristics, and treatment modalities were analyzed. **Results:** Eighty-two patients aged 70 years and older (median 76 years, range 70-86) were included. Patients were stratified by age into three groups: 70-74 years (G1, n=30), 75-79 years (G2, n=34), and 80+ years (G3, n=18). Patients with FIGO III-IV disease (n=72) were treated with CRS + CT (75%), CT only (15%), CRS only (4%) or no treatment (6%). The percentage of patients who started and completed standard treatment was significantly lower in the very elderly: 97% and 86% (G1), 62% and 67% (G2), and 33% and 50% (G3), respectively ( $p < 0.05$ ). Median survival was not reached in group 1 and 21 months (95% CI 15-27 months) and 11 months (95% CI 7-15 months) in groups 2 and 3, respectively ( $p = 0.006$ ). **Conclusion:** Even in this highly selected cohort of patients with advanced ovarian cancer, about one-third of patients aged 75-80 years and two-thirds of patients aged 80+ years did not start with standard treatment. The difficulty in predicting whether a patient is fit enough for the strenuous standard treatment emphasizes the need for a more objective screening tool to prevent both under- and overtreatment.

**Key words:** Ovarian cancer; Elderly; Treatment patterns.

## Introduction

Ovarian cancer is the leading cause of death from gynecological cancer in Europe and the Western world [1]. In the Netherlands, approximately 1,400 women are diagnosed with ovarian cancer every year, of whom 40% is aged 70 years and older. Due to a lack of specific symptoms, 80% of patients is diagnosed with advanced disease with FIGO Stage III or IV [2]. It is expected that ageing of the population in the Western world will lead to an increase of the incidence of ovarian cancer.

The standard treatment of ovarian cancer currently consists of surgery for early-stage disease and six cycles of combination chemotherapy (carboplatin and paclitaxel) in combination with cytoreductive surgery for advanced disease. This multimodality treatment of extensive surgery and chemotherapy is burdensome for all patients and not always feasible especially in the elderly and/or frail patients.

A French observational study between 1997 and 2011 by Fourcadier *et al.* reported that elderly women aged 70 years or older with ovarian cancer were less often treated with surgery and/or chemotherapy [3]. Furthermore, a study by Janssen-Heijnen *et al.* showed the five-year cancer-specific survival in the Netherlands between 1995 and 2002 was

lower in elderly patients aged 70+ (25%, 95% confidence interval (CI) 20-31%) compared to younger patients (45%, 95% CI 40-50%) [4]. However, it remains unclear if elderly patients are currently undertreated or if this reflects an appropriate adjustment to a state of increased vulnerability. To improve outcome, in the Netherlands, surgical treatment of ovarian cancer has been concentrated in oncological centers such as the Dutch Cancer Institute in Amsterdam. This institute serves as a tertiary oncology center in the Netherlands and is part of the Center of Gynecology Oncology in Amsterdam (CGOA). The aim of this study is therefore to evaluate current treatment patterns in the elderly patients with ovarian cancer in this hospital.

## Materials and Methods

This retrospective cohort study included all women aged 70 years and older who were newly diagnosed with ovarian cancer and who were referred to the Dutch Cancer Institute in Amsterdam between 2013-2014. All patients were discussed in a multidisciplinary tumor board.

For this study, the authors collected information on the following variables: patient characteristics (age, American Society of Anaesthesiologists' (ASA) classification of Physical Health comorbidity (range I-VI), breast cancer (BRCA) gene mutation, the

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Table 1. — Patient characteristics per age group.

	All patients (n=82)	70-74 years (n=30)	75-79 years (n=34)	80+ years (n=18)	p-value
Stage of disease					
• FIGO I-II	10 (12%)	6 (20%)	4 (12%)	-	0.330
• FIGO III-IV	72 (88%)	24 (80%)	30 (88%)	18 (100%)	
Tumor morphology					
• Serous	73 (89%)	28 (93%)	30 (88%)	15 (83%)	0.594
• Other	9 (11%)	2 (7%)	4 (12%)	3 (17%)	
ASA score					
• 1	17 (21%)	7 (23%)	4 (11%)	6 (33%)	0.301
• 2	49 (60%)	20 (67%)	21 (62%)	8 (44%)	
• 3	13 (16%)	2 (7%)	8 (24%)	3 (17%)	
• 4-6	0	0	0	0	
• Missing	3 (4%)	1 (3%)	1 (3%)	1 (6%)	
CCI score					
• 0	18 (22%)	5 (17%)	6 (18%)	7 (39%)	0.748
• 2-4	59 (73%)	25 (83%)	24 (71%)	10 (56%)	
• 4-6	5 (6%)	-	4 (12%)	1 (6%)	
ECOG-score					
• 0-1	72 (88%)	28 (94%)	28 (83%)	16 (88%)	0.456
• 2-3	8 (10%)	1 (3%)	5 (14%)	2 (12%)	
• Missing	2 (2%)	1 (3%)	1 (3%)	-	

ASA-score = American Society of Anaesthesiologists, CCI-score = Charlson Comorbidity Index, ECOG = Eastern Cooperative Oncology Group, FIGO = The International Federation of Gynecology and Obstetrics classification.

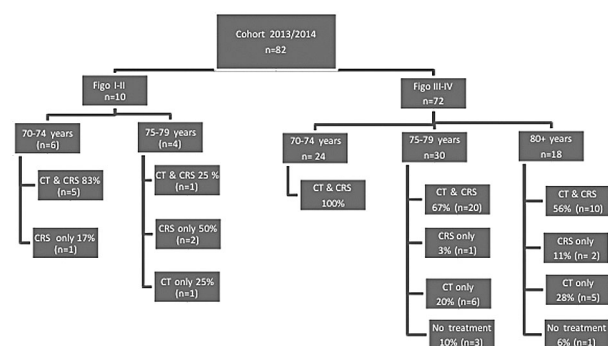


Figure 1. — Initiated treatment per tumor stage and age group  
CT = chemotherapy, CRS = cytoreductive surgery. CT and CRS defined as at least one cycle of chemotherapy (including monotherapy) in combination with cytoreductive surgery.

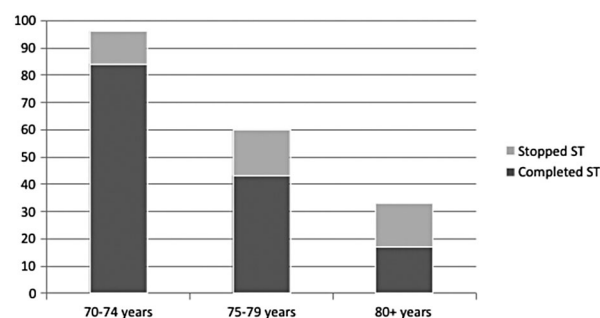


Figure 2. — FIGO III-IV: Starting and completing treatment according to age.  
ST = standard treatment.

Eastern Cooperative Oncology Group (ECOG) performance status (PS), cancer characteristics (date of diagnosis, the International Federation of Gynecology and Obstetrics (FIGO) classification [2], histology, grade), treatment modality (type and number of chemotherapy cycles, type of surgery), and survival. Cause of death could not be retrieved in this retrospective analysis. Data was collected by using information from patient charts, surgical records, and pathology reports. If the available data were not sufficient, other treating hospitals and general practitioners were contacted. Patients in this cohort did not undergo a geriatric assessment. Information about comorbidity was collected through patients' charts and correspondence with other treating physicians and was evaluated according to the Charlson's Comorbidity Index (CCI) [5]. For

all patients the rate of starting and completing treatment was compared to guideline recommended treatment. Standard treatment for FIGO Stages IA, IB, and IIA consists of surgery. For FIGO Stages IC-IIB-IIC-III and IV, it is defined as the combination of cytoreductive surgery with at least six cycles of combination chemotherapy (carboplatin and paclitaxel). According to Dutch guidelines, METC approval was not necessary.

For the statistical analysis SPSS Statistics version 23 was used. A chi-square or likelihood ratio test was used for between-group comparisons. Overall survival was estimated using the Kaplan-Meier method with a log-rank analysis. All tests were two-sided and a  $p$ -value  $< 0.05$  was considered statistically significant.

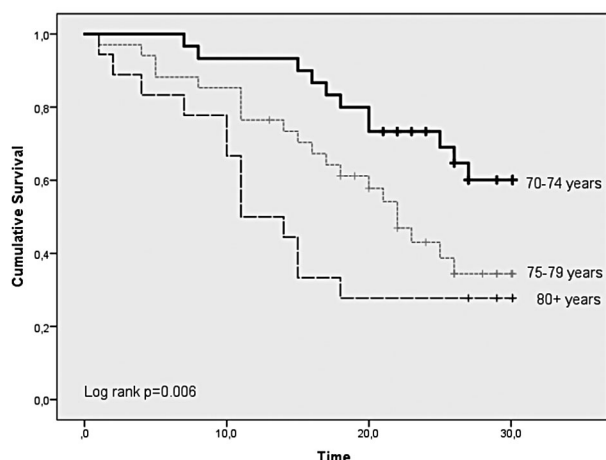


Figure 3. — Kaplan-Meier plot of overall survival cohort 2013-2014 in patients with ovarian cancer (n=82). Time in months after diagnosis.

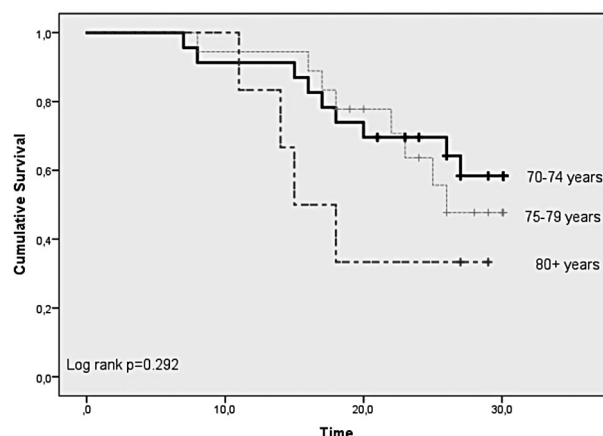


Figure 4. — Kaplan-Meier plot of overall survival in patients with FIGO Stages III-IV ovarian cancer (n=47). Time in months after diagnosis.

## Results

A cohort of 383 patients was diagnosed with a malignant ovarian tumor in 2013 and 2014 at the Dutch Cancer Institute in Amsterdam. Of these, 110 patients were aged 70 years and older (29%). Twenty-eight patients were excluded from this analysis due to insufficient available data (n=8), recurrent disease (n=14) or another primary tumor (n=6). Therefore, a total of 82 patients aged 70 years and older was included in this study. Follow up in this analysis was 30 months. The median age was 76 years (range 70-89). Patients were stratified according to age into three groups: group 1 aged 70-74 years (n=30), group 2 aged 75-79 years (n=34), and group 3 aged 80+ years (n=18).

Baseline characteristics are shown in Table 1. In this cohort, ten patients (12%) were diagnosed with FIGO Stage I-II and 88% (n=72) were diagnosed with FIGO Stage III-IV. Tumor morphology was serous carcinoma (n=73, 89%), endometrioid carcinoma (n=2, 3%), clear cell carcinoma (n=1, 1%) or unknown (n=6, 7%). Most patients (n=49, 60%) were classified as ASA 2 (defined as a patient with mild systemic disease). When comparing patient and tumor characteristics between different age groups, no statistically significant differences were found ( $p > 0.05$ ).

Figure 1 shows initiated treatment per FIGO stage and per age group. Six out of ten patients diagnosed with FIGO Stages I-II were treated with both chemotherapy (at least one cycle of monocarboplatin or carboplatin/paclitaxel) and cytoreductive surgery. Three patients underwent only surgery and one patient received only chemotherapy.

Forty-seven out of 72 patients (65%) diagnosed with FIGO Stages III-IV started standard treatment of whom 36 (77%) completed the full six cycles of combination

chemotherapy and cytoreductive surgery (Figure 1). Of the 11 patients stopping standard treatment (23%), seven switched to carboplatin monotherapy, and four patients did not receive any further treatment. Reasons for stopping chemotherapy or switching to carboplatin monotherapy were neuropathy (n=2), pancytopenia (n=2), loss of hearing and mobility (n=1), and reasons unknown (n=6).

When analyzing treatment plan and completion according to age group (Figure 2), results showed the decision to start standard treatment decreased significantly with age: 96% (n=23) in group 1, 60% (n=18) in group 2, and 33% (n=6) in group 3 ( $p = 0.000103$ ). Likewise, for those who started treatment the completion of standard treatment was significantly lower with increasing age: 87% (n=20) in group 1, 72% (n=13) in group 2, and 50% (n=3) in group 3 ( $p = 0.000068$ ). In patients not receiving standard treatment, three (4%) received surgery only and 11 (15%) received only chemotherapy (Figure 1). Four patients (6%) received no treatment at all. Figure 3 shows overall survival of this cohort.

In patients diagnosed with FIGO Stages I-II, median overall survival was not reached. After 30 months, 83% of patients in group 1 (70-74 years) and 75% in group 2 (75-79 years) were still alive.

In patients with FIGO Stages III-IV, median survival was 21 months (95% CI 14-28 months). Median survival was not reached in group 1. In groups 2 and 3, median survival was 21 months (95% CI 15-27 months) and 11 months (95% CI 7-15 months), respectively. Survival after 30 months according to age was as follows: 58% in group 1, 37% in group 2, and 28% in group 3 ( $p = 0.026$ ) (Figure 4).

After a follow up of 30 months, 55% of patients starting standard treatment was still alive compared to 16% of pa-

tients not starting standard treatment ( $p < 0.001$ ). When comparing different age groups of patients starting standard treatment, no significant differences were found.

In age group 1, 61% was still alive after 30 months compared to 55% in age group 2, and 33% in age group 3 ( $p = 0.2929$ ). Median overall survival in patients starting standard treatment was not reached in groups 1 and 2. In group 3 median survival was 15 months (95% CI 10-20 months).

In the group of patients not starting standard treatment median overall survival was not reached in group 1. Median overall survival in groups 2 and 3 were 11 months (95% CI 4-18 months) and ten months (95% CI 7-14 months), respectively ( $p = 0.763$ ).

## Discussion

The present authors evaluated treatment patterns in a cohort of 82 patients aged 70 years and older diagnosed with ovarian cancer between 2013-2014. Almost two-thirds of patients diagnosed with ovarian cancer FIGO Stages III-IV (65%) started standard treatment consisting of surgery and combination chemotherapy, while 77% of them managed to complete the treatment. This study showed that the decision to start standard treatment is made less with increasing age: 96% in patients aged 70-74 years compared to 60% in patients aged 75-79 years, and 33% in patients aged 80+ years, respectively. The percentage of patients actually completing standard treatment also declined with age, from 87% in patients aged 70-74 years to 50% in patients aged 80+ years. The high percentage of patients starting but not completing therapy clearly demonstrates difficulties in predicting whether an elderly woman with ovarian cancer is fit enough to tolerate treatment at all.

Several other studies have evaluated treatment patterns of ovarian cancer in elderly women. A study performed by Maas *et al.* demonstrated that patients aged 70 years and older are seven times less likely to receive standard treatment compared to younger patients, even after adjustment for comorbidities (OR 0.14, 95% CI 0.07 to 0.21,  $p < 0.001$ ) [6]. A study of Hershman *et al.* reported that only half of women aged 65 years and older received platinum-based treatment, while survival improved by 38% in treated women [7]. Also, a recent French study demonstrated that the probability of elderly patients receiving guideline recommended treatment is two times lower compared to younger patients. Fourcadier *et al.* and Maas *et al.* suggest that age of 65-70 years or older is an independent factor for withholding standard treatment [3, 6]. In general, standard treatment is likely to improve survival. The present study showed a significant difference in overall survival between patients starting standard treatment and those who do not (30-month survival of 55% vs. 16%). This might emphasize the importance of giving standard treatment to patients who are fit enough. However, the same treatment could be detrimental when given to a vulnerable patient with insuf-

ficient reserves. Therefore a screening tool should be developed to help decide if a patient is fit enough to undergo this treatment, especially in patients above 75 years of age. A geriatric assessment (GA) is a valuable screening tool and has been shown useful in identifying strengths and weaknesses of elderly patients [8]. However, a complete GA can be time consuming. Therefore, it would be useful to have a screening tool for selecting patients who are fit for standard treatment and those requiring a CGA. In the latter group, patients can be analysed in more detail and based on these findings, receive treatment that is tailored to their overall health status. Multiple screening tools exist, but none have been validated specifically for gynaecological patients [9]. In 2013 the prospective Elderly Women with Ovarian Cancer (EWOC)-1 study from the French GINECO group has begun. In this study, three different randomized chemotherapy regimens are compared in elderly patients with a Geriatric Vulnerability Score  $\geq 3$ , which consists of an ADL score, IADL score, albuminaemia  $< 35$  g/l, lymphopaenia 1 g/l and hospital anxiety depression subscale (HADS)  $> 14$ . [10] The cut-off is based on the GINECO study published in 2013, which showed that a geriatric vulnerability score of  $\geq 3$  predicts toxicity and survival in the elderly patient. Patients are randomized to either paclitaxel 175 mg/m<sup>2</sup>/3 hours, I.V. and carboplatin AUC 5, I.V. every three weeks or carboplatin monotherapy AUC 5 or 6 every three weeks or paclitaxel 60 mg/m<sup>2</sup>/1 hour and weekly carboplatin AUC 2 (d1, d8, d15 every four weeks). This study will address, among other things, overall survival, safety and tolerability, quality of life, and progression-free survival of the three different types of treatment [10]. The present study has some limitations. Because of the retrospective study design, not all desired data was available for analysis. A geriatric assessment was not performed, which results in insufficient information about frailty and quality of life. Another limitation is the fact that the Dutch Cancer Institute is a tertiary referral center; patients referred to this hospital are likely to be those considered fit enough to undergo treatment. Despite these limitations, the present study demonstrated the complexity of decision-making for the elderly and highlights opportunities for improving cancer care in this growing patient population.

In conclusion, even in this highly selected cohort of elderly patients with ovarian cancer, one-third of patients did not start with standard therapy at all. The decision to start and complete standard therapy declines with the increase of age, especially in those aged  $\geq 75$  years. The difficulty in predicting whether a patient is fit enough for the aggressive standard treatment, emphasizes the need for a more objective screening tool to prevent both under- and overtreatment.

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