# Treatment and outcome of elderly patients with advanced stage ovarian cancer: A nationwide analysis

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## HIGHLIGHTS

- With advancing age less patients receive (standard) treatment
- Over time, less elderly patients received treatment
- Neoadjuvant chemotherapy mainly influenced treatment of patients aged 70–79 years.
- The selection of elderly patients eligible for curative surgery seemed improved.
- 5-year survival of patients aged ≥70 years is nearly half of the younger patients.

## ARTICLE INFO

## ABSTRACT

*Objective.* To provide an overview of treatment strategies for elderly patients with advanced stage epithelial ovarian cancer (EOC) in daily practice, evaluate changes over time and relate this to surgical mortality and survival.

*Methods.* All women diagnosed with advanced stage (FIGO IIB and higher) EOC between 2002 and 2013 were selected from the Netherlands Cancer Registry ($n = 10,440$) and stratified by age, stage and period of diagnosis. Elderly patients were defined as aged ≥70 years. Time trends in treatment patterns and postoperative mortality were described by age category and tested using multivariable logistic regression. Relative survival was calculated.

*Results.* With advancing age, less patients received ((neo-)adjuvant) treatment. Over time, elderly patients were less often treated (OR 2002–2004 versus 2011–2013: 0.73; 95%CI:0.58–0.92). But if treated, more often standard treatment was provided and 30-day postoperative mortality decreased from 4.5% to 1.9% between 2005 and 2007 and 2011–2013. In all age categories treatment shifted from primary surgery towards primary chemotherapy, in patients aged 70–79 years combination therapy increased (+5%) between 2002 and 2004 and 2011–2013. Five-year relative survival for patients diagnosed in 2008–2010 aged <70 years was 34% compared to 18% for elderly patients.

*Conclusion.* Large treatment differences exist between younger and elderly patients. Over time, selection of elderly patients eligible for curative surgical treatment may have improved. More elderly patients were treated with neoadjuvant chemotherapy while less patients underwent surgery and simultaneously postoperative mortality decreased. However, the large and increasing number of elderly patients without treatment and the large survival gap suggests opportunities for further improvements in the care for elderly EOC patients.

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## 1. Introduction

Approximately 1300 women are diagnosed with ovarian cancer in the Netherlands each year. More than one third of these patients are aged 70 years or older at diagnosis [1]. Due to the ageing population and increased life expectancy the number and proportion of elderly patients is expected to rise.

Elderly patients are often excluded from participation in randomized clinical trials even if the disease of interest mainly occurs in elderly [2]. Elderly patients more often have a low performance score and more co-morbidity which poses challenges to study design and recruitment. Consequently, evidence-based guidelines are often largely based on outcomes in younger patients, while evidence for the optimal treatment in (frail) elderly patients is scarce.

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The majority of ovarian cancer patients are diagnosed in an advanced stage of disease for which standard treatment entails cytoreductive surgery combined with chemotherapy. In early stage ovarian cancer standard treatment is less aggressive; often surgery alone is sufficient as curative treatment. An earlier regional population-based study in the Netherlands using data up to 2001 demonstrated that in FIGO stage II and III ovarian cancer patients age and comorbidities were independent predictors of receiving standard treatment. Elderly patients were treated less aggressively than their younger counterparts even in the absence of co-morbidities [3].

In this nationwide study, we will provide an overview of treatment strategies for elderly patients with advanced stage EOC in daily practice, evaluate changes over time and relate this to surgical mortality and survival.

## 2. Materials and methods

### 2.1. Data source

The nationwide Netherlands Cancer Registry (NCR) records data on all newly diagnosed malignancies. The primary source of notification is the automated pathology anatomy archive (PALGA), supplemented by other sources as the National Registry of Hospital Discharge Diagnoses and radiotherapy institutes.

Since 1989 the NCR has a nationwide coverage. Specially trained registry clerks extract data on patient, tumor and treatment characteristics from medical records in all Dutch hospitals. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O). Tumor stage was based on tumor node, metastasis classification system (TNM) that was applicable and converted to the FIGO (2009) classification system. Information on vital status is obtained by annual linkage to the Municipal Personal Records Database and was available up to 1 January 2015.

### 2.2. Patient and data selection

Data on all women diagnosed with advanced stage (FIGO IIB and higher) epithelial ovarian cancer (EOC), including peritoneal and fallopian tube carcinoma, or diagnosed with ovarian cancer with an unspecified morphology during 2002–2013 were selected from the NCR ($n =$ 10,493) and included in this study. Patients who were diagnosed or (partially) treated outside the Netherlands ($n = 42$) or had incomplete data on treatment ($n = 11$) were excluded. Patients were divided into different age-categories (<70 years, 70–79 years and ≥80 years). Elderly patients were defined as aged ≥70 years. Tumor stage was based on pathological stage information, supplemented by clinical stage information if pathological stage was unavailable or unknown. In case of neoadjuvant chemotherapy, tumor stage was based on clinical stage information only. Advanced stage tumors were defined as FIGO IIB or higher. Socioeconomic status (SES) was based on reference data from The Netherlands Institute for Social Research. Scores on social deprivation were derived from income, education and occupation per four-digit postal code. Scores were assigned to three SES categories: low (1st–3rd decile), intermediate (4th–7th decile) and high (8th–10th decile).

Receiving chemotherapy (yes versus no) was defined as the administration of any kind of chemotherapy and surgery (yes versus no) as any attempt to perform cytoreductive surgery which actually resulted in tumor removal. Treatment (yes versus no) was defined as undergoing surgery and/or chemotherapy.

### 2.3. Statistical analyses

Chi square tests were used to compare tumor characteristics by age category. Multivariable logistic regression was performed to evaluate the effect of period of diagnosis on receiving (adjuvant/combination) treatment and 30-day postoperative mortality in advanced stage EOC patients aged<70 years and ≥70 years separately. Relative survival rates were calculated as an estimation of cause-specific survival according to the Ederer II method [4]. One to five-year relative survival analyses were calculated by age category and tumor stage.

Survival was defined as the time from date of diagnosis to date of death or until the last date of follow-up. All analyses were performed using STATA/SE 13.0 (StataCorp, College Station, TX). A two-sided $p$-value of <0.05 was considered statistically significant.

## 3. Results

Of the 10,440 women diagnosed with advanced stage EOC between 2002 and 2013, 4309 (41%) were aged 70 years or older. The proportion of elderly patients increased over time (Table 1).

With advancing age the proportion of patients with adenocarcinoma Not Otherwise Specified (NOS), stage IV disease and unknown tumor grade increased (Table 1).

Treatment patterns of advanced stage patients according to age and period of diagnosis are shown by Fig. 1. Nearly all patients below 70 years (97%) received primary treatment versus 54% of the patients aged ≥80 years. Also the proportion of patients who underwent either only surgery or only chemotherapy increased markedly with advancing age, 85% of the patients aged <70 years received combination therapy (debulking surgery and chemotherapy) versus 61% and 22% for patients aged 70–79 years and ≥80 years respectively.

Over time, treatment shifted from primary debulking surgery followed by adjuvant chemotherapy (PDS + ACT) towards neoadjuvant chemotherapy followed by interval debulking surgery (NACT + IDS) in all age categories. In the age category <70 years the decrease in PDS + ACT was accompanied with a proportionally equal increase in NACT + IDS and a small (3.5%) increase in patients treated with only chemotherapy (2002–2004 versus 2011–2013).

In patients aged 70–79, we observed an increase in combination treatment over time. PDS + ACT decreased with 22% while NACT + IDS increased by 27%. Also 5% more patients received chemotherapy only, while the proportion who only underwent surgery decreased from 11% to 3%.

In the very elderly (aged ≥80 years) patients, the proportion who received treatment decreased considerably from 62% in 2002–2004 to 49% in 2011–2013. There was no large variation in patients receiving combination therapy over time, PDS + ACT decreased from 18% to 7%, while NACT+IDS increased from 3% to 13%. However, a large decrease was seen in patients treated with surgery only (21% in 2002–2004 versus 7% in 2011–2013). If we only considered the treated patients, combination therapy increased from 34% in 2002–2004 to 40% in 2011–2013.

Patients aged ≥90 years or older compromised 1% of the total study population in all time periods. The vast majority (84%) did not receive treatment, varying from 62% ($n = 13$) in 2002–2004 to 100% ($n =$ 34) in 2011–2013.

Multivariable regression analyses (adjusted for age at diagnosis, histological subtype, FIGO stage and SES) confirmed that diagnosis during the most recent time period was associated with a decreased chance of receiving treatment in elderly patients (≥70 years) (OR 2002–2004 versus 2011–2013: 0.73; 95%CI:0.58–0.92). Furthermore, it confirmed that, if treated, elderly patients diagnosed in latter time periods had an increased chance of receiving combination therapy (OR 2002–2004 versus 2008–2010: 1.31; 95%CI:1.03–1.66).

Similar to younger patients, postoperative mortality in elderly patients (≥70 years) decreased over time (Fig. 2). Thirty-day mortality was 4.5% during 2005–2007 and 1.9% in 2011–2013, this was 2.3% and 0.4% for younger patients, respectively. The decrease observed in elderly patients was confirmed by multivariable analysis adjusted for age at diagnosis, histological subtype, FIGO stage, tumor grade and SES (OR 30 day mortality: 0.46; 95%CI: 0.23–0.94 in 2011–2013 compared to 2005–2007).

Relative survival rates (RS) of advanced stage EOC patients differed by age. One-year RS for patients below 70 years was 82% and 15% for