

Treatment and outcome of elderly patients with advanced stage ovarian cancer

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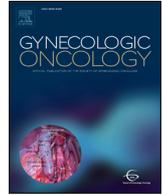
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Treatment and outcome of elderly patients with advanced stage ovarian cancer: A nationwide analysis



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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.

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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 comorbidity 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/combo) 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 comprised 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

Table 1
General characteristics of women diagnosed with advanced stage EOC in the Netherlands according to age group (2002–2013).

	Age group			P-value
	<70 years	70–79 years	≥80 years	
	N (%)	N (%)	N (%)	
Number of patients	6131 (58.7)	2738 (26.2)	1571 (15.1)	
Histological subtype				<0.001
Serous	3710 (60.5)	1485 (54.2)	557 (35.5)	
Endometrioid	461 (7.5)	121 (4.4)	57 (3.6)	
Clear cell	245 (4.0)	47 (1.7)	18 (1.2)	
Mucinous	262 (4.3)	109 (4.0)	48 (3.1)	
Adenocarcinoma, NOS ^a	1117 (18.2)	833 (30.4)	778 (49.5)	
Unspecified/other	336 (5.5)	143 (5.2)	113 (7.2)	
FIGO				<0.001
IIB/IIC	620 (10.1)	219 (8.0)	107 (6.8)	
III	3902 (63.6)	1727 (63.1)	954 (60.7)	
IV	1609 (26.2)	792 (28.9)	510 (32.5)	
Tumor grade				<0.001
Well differentiated	296 (4.8)	94 (3.4)	33 (2.1)	
Moderately differentiated	844 (13.8)	298 (10.9)	115 (7.3)	
Poorly differentiated	2672 (43.6)	1022 (37.3)	387 (24.6)	
Unknown	2319 (37.8)	1324 (48.4)	1036 (66.0)	
SES^b				0.005
High	1.921 (31.3)	785 (28.7)	429 (27.3)	
Medium	2434 (39.7)	1104 (40.3)	636 (40.5)	
Low	1776 (29.0)	849 (31.0)	506 (32.2)	
Period of diagnosis				<0.001
2002–2004	1499 (62.7)	590 (24.7)	302 (12.6)	
2005–2007	1428 (60.6)	577 (24.5)	350 (14.9)	
2008–2010	1536 (57.3)	720 (26.8)	427 (15.9)	
2011–2013	1668 (55.4)	851 (28.3)	492 (16.3)	

^a NOS: not otherwise specified.

^b SES; socioeconomic status.

patients aged ≥90 years. Five-year RS were 33% and 7%, respectively. No marked changes in the gap in relative survival rates between young and elderly patients have been observed over time (Fig. 3).

Subgroup analyses revealed an increase in relative survival rates in elderly surgically treated patients over time. One year survival increased from 73% in 2002–2004 to 84% in 2011–2013 and five year from 25% in 2002–2004 to 31% in 2008–2010. Survival rates did not increase in elderly patients who did not undergo surgery (data not shown).

4. Discussion

Standard treatment modalities are less often applied to elderly ovarian cancer patients compared to younger patients. We observed a clear gradual decline in proportion of patients receiving (standard)

treatment by advancing age. The results of our study are in line with several other studies indicating that elderly patients are treated less aggressively compared to younger patients [3,5–7]. Decreased physical functioning and the presence of comorbidity, which can result in lower tolerance towards (radical) surgery and chemotherapy, are regularly mentioned as explanations for differences in treatment patterns between young and elderly patients. However, several studies showed that age is also an independent factor of administration of chemotherapy or surgery [3,7]. Maas et al. [3], showed a decreased likelihood of receiving standard combination therapy by age, independent of co-morbidity.

An independent effect of age on (non-) administration of standard therapy may reflect, among others, the influence of and physicians' attitude towards treatment of the elderly patients and patients' wishes.

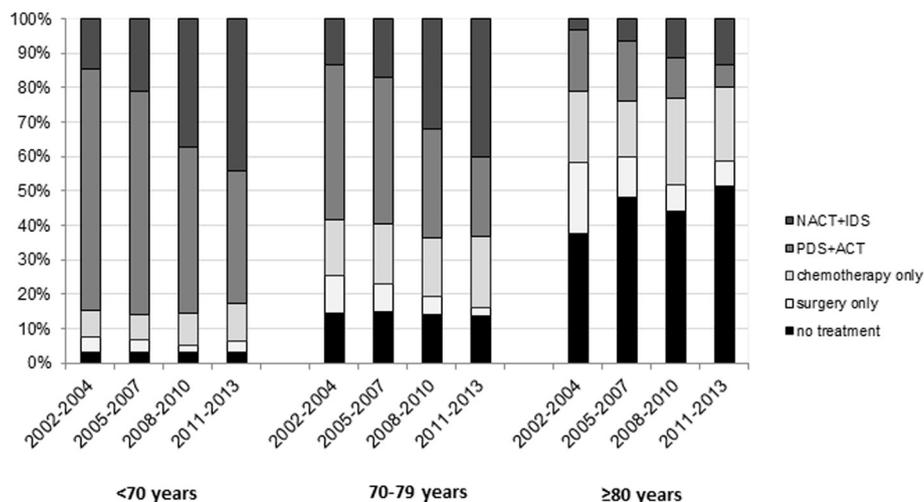


Fig. 1. Treatment patterns of advanced stage EOC patients by age category and period of diagnosis.

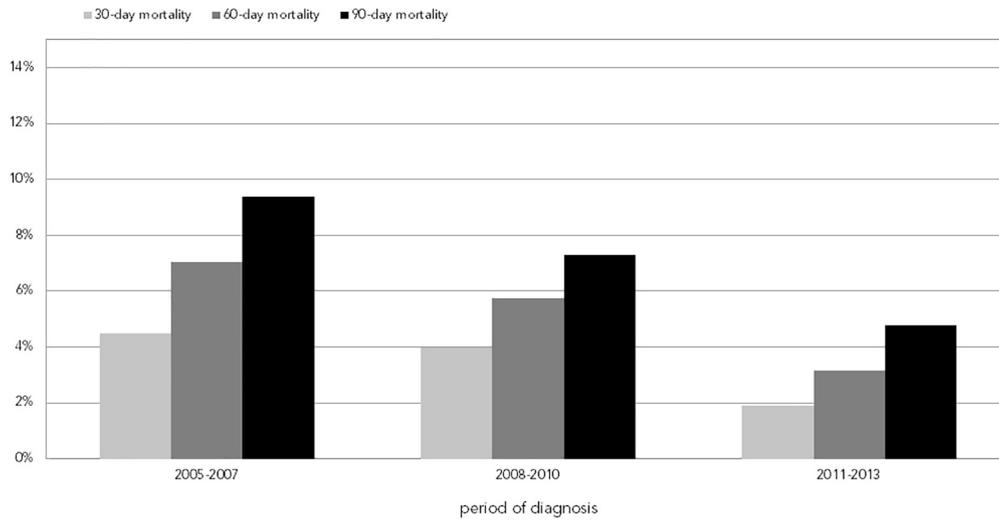


Fig. 2. Postoperative mortality rates in elderly (aged ≥ 70 years) patients with advanced stage EOC according to period of diagnosis.

Unfortunately, we were not able to adjust for physical functioning and comorbidity since nationwide data were not available.

While most studies on treatment of elderly patients with EOC described differences between younger and elderly patients, only few described changes over time [3,6,8].

As expected, we observed a shift in treatment sequence from PDS + ACT towards NACT+IDS in all age categories over time. NACT + IDS is associated with lower postoperative morbidity and mortality compared to PDS + ACT [9]. While PDS + ACT is still recommended as standard therapy, NACT+IDS is increasingly considered in patients with bulky irresectable tumors and/or in patients with a poor performance status. Various other studies also observed an increase in application of NACT + IDS over time [10–12].

Considering the effect on treatment patterns of the elderly patients, previous studies showed inconsistent results. More patients aged ≥ 75 years with advanced stage EOC received combination therapy (surgery and chemotherapy) between 1989 and 2009 in the Netherlands [6], while in the US a decrease was seen during 1995–2008 [8].

Our study showed that the effect of the implementation of NACT + IDS slightly differed between the age categories. In the young patients we predominantly observed a shift from PDS + ACT towards NACT+IDS while the proportion who received treatment and combination therapy remained stable.

In elderly patients aged 70–79 years, the implementation of NACT+IDS seemed to have resulted in a higher proportion of patients treated with combination therapy. Besides, more patients were treated with chemotherapy only. When chemotherapy fails due to either toxicity or progressive disease, surgical therapy cannot result in curation and may therefore be omitted. This can explain this small increase in chemotherapy only.

In the very elderly (≥ 80 years) a more conservative attitude towards treatment over time was seen. Less of them received treatment. While the shift from PDS + ACT towards NACT + IDS did not affect the proportion of patients treated with combination therapy, considerably less patients underwent only surgery over time. When PDS + ACT is the intention of treatment, complicated postoperative recovery may subvert

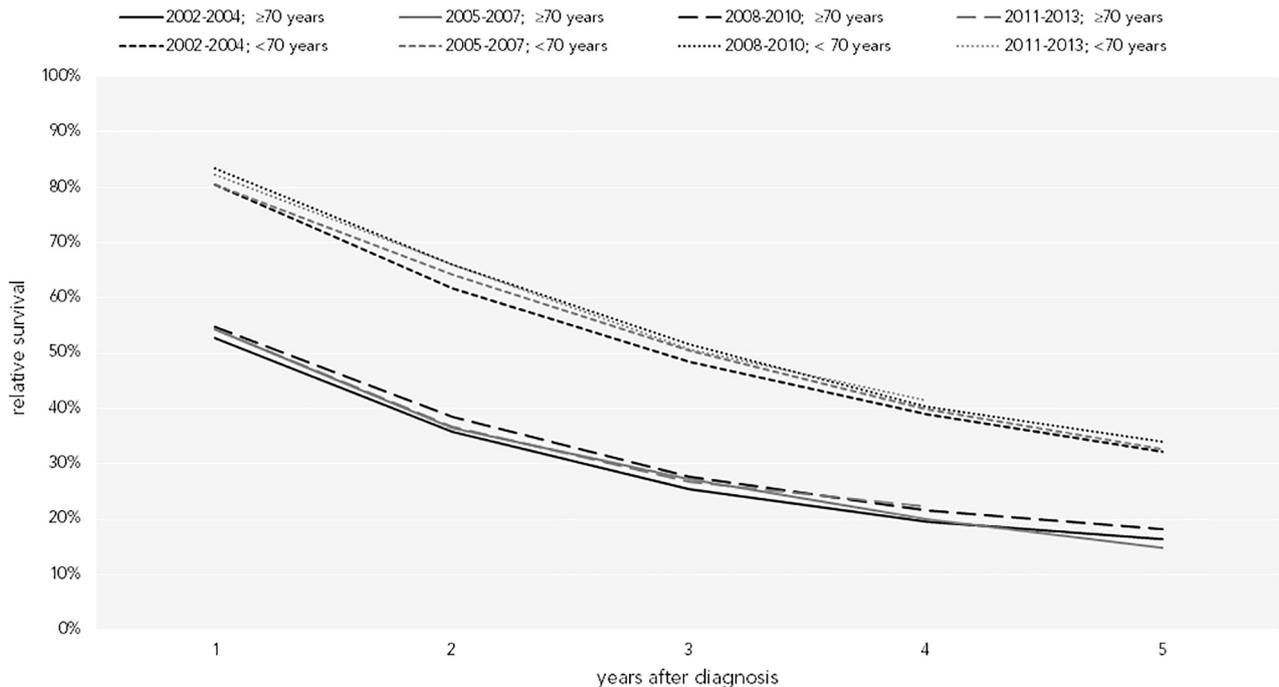


Fig. 3. Relative survival of women diagnosed with advanced stage EOC in 2002–2013, according to age and period of diagnosis.

adjuvant chemotherapy. Our results suggest that this group, who started treatment but not completed standard treatment regimes, declined.

While in patients ≥ 90 years we also observed a decrease in treatment over time, the number of patients was too small to describe their treatment patterns by period of diagnosis separately.

Postoperative mortality in elderly EOC patients decreased over time. It may be that the selection of patients eligible for curative surgery improved. This is supported by the lower proportion of surgically treated elderly patients and the stable proportion of elderly patients receiving standard therapy. Among others, neoadjuvant chemotherapy might have served to better select patients for potentially curative surgery.

In elderly patients, the percentage of complete debulking surgery is lower compared to younger patients [13]. Since the completeness of the surgical procedures is one of the major prognostic factors [14] it would be of interest to test whether incomplete surgeries decreased simultaneously with the decrease in number of surgeries in elderly patients. Nonetheless, these data were not available. Alternatively, subgroup survival analyses were performed which revealed a large increase in 1 to 5 years survival rates for surgically treated patients and stable rates for non-surgically treated elderly patients. This might indicate that mainly the patients with a poor prognostic outcome (in which complete surgery or optimal treatment could not be accomplished) were left untreated in the more recent time periods.

Considering the higher proportion of patients with stage IV and the differences in treatment, not surprisingly, elderly patients showed poorer survival. Also comorbidities and poorer health status of the elderly will have contributed to the observed differences. The gap in relative survival rates between patients aged < 70 years and ≥ 70 years remained constant over the years, survival rates of elderly patients remains low.

The lower survival rates in elderly EOC patients are in line with results of prior studies [15–18]. It has been shown that when elderly patients receive the optimal treatment the effect of age on survival disappears [7,19]. Receiving standard therapy seemed to be the most important prognostic factor [3,20]. Therefore, it is important to be able to select the patients eligible for standard therapy and prevent over-treatment in those who would not benefit from it. Geriatric assessments may be of value in predicting the tolerability of treatment and mortality in elderly cancer patients but its role in treatment-decision making in ovarian cancer patients needs to be established. Furthermore, more emphasis should be placed on optimizing knowledge on effective treatments in frail elderly patients to be able to effectively tailor treatment.

Strengths our study are its nationwide character and the large number of elderly patients with EOC included. Major limitation is its observational design and the unavailability of several characteristics (e.g. comorbidity, performance status, chemotherapy schemes, completeness of treatment) for the entire cohort.

Summarized, treatment patterns of elderly EOC patients largely differ from younger patients. The selection of elderly patients eligible for curative surgical therapy may have improved as a larger proportion of the patients was treated with combination therapy, less patients underwent surgical treatment and surgical mortality decreased over time. However, the large number of elderly patients without treatment, the poor survival rates and the gap in survival between young and

elderly patients, suggests opportunities for further improvements in the care for elderly EOC patients.

Conflict of interests

None declared.

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