

Treatment patterns and associated factors in patients with advanced epithelial ovarian cancer: a population-based study

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HIGHLIGHTS

- Some 14% of women with advanced epithelial ovarian cancer do not receive cancer-directed treatment.
- The percentage of women with advanced epithelial ovarian cancer not receiving cancer-directed treatment has increased in the last decade in the Netherlands.
- The main reasons for no cancer-directed treatment were patient's choice and poor condition of the patient.

ABSTRACT

Objectives A significant proportion of women with advanced-stage ovarian cancer receive no cancer-directed treatment and limited research has been devoted to this group. This population-based study aimed to gain insight into treatment patterns and trends in patients with advanced epithelial ovarian cancer in the Netherlands and the main reasons for deciding for no cancer-directed treatment.

Methods All patients diagnosed with advanced epithelial ovarian cancer, International Federation of Gynecology and Obstetrics (FIGO) classification IIB–IV, between 2008 and 2016 were identified from the Netherlands Cancer Registry. Trends in the number of patients receiving cancer-directed treatment were analyzed. Multivariable logistic regression analysis was used to identify factors associated with no cancer-directed treatment. The main reasons for no cancer-directed treatment were analyzed.

Results A total of 9303 patients were included, of whom 14% (n=1270) received no cancer-directed treatment while 67% (n=6218) received a combination of cytoreductive surgery and chemotherapy. Some 15% (n=1399) received chemotherapy only, and 4.5% (n=416) surgical resection or hormonal therapy only. The proportion of patients receiving no cancer-directed treatment was higher in 2014–2016 (16%, n=496/3175) compared with 2008–2010 (11%, n=349/3057, p<0.001). Associated factors with no cancer-directed treatment were higher age, FIGO stage IV, lower socioeconomic status, co-morbidity, and more recent years of diagnosis (p<0.001). Main reasons for no cancer-directed treatment were patient's choice (40%) and poor condition of the patient (29%).

Conclusions The proportion of patients with advanced epithelial ovarian cancer not receiving cancer-directed treatment has increased in the last decade in the Netherlands. Patient's choice was the main reason for the decision to undergo no cancer-directed treatment, which indicates patient involvement in the decision-making process. The second most common reason for no cancer-directed treatment was poor condition of the patient, which might indicate careful selection of patients for treatment. Decision-making regarding treatment is well-considered,

but more insight is needed, especially from the patient's perspective.

INTRODUCTION

Ovarian cancer is the fifth most common cancer in women and the leading cause of death from gynecologic malignancies in developed countries.¹ The majority of patients with epithelial ovarian cancer are diagnosed at an advanced stage (60%–76%) and therefore have a poor prognosis, reflected in a 5-year survival rate of 24%.^{2,3} Most studies reported an improvement in 5-year survival for patients with epithelial ovarian cancer during the last decades, with an overall increase of 5%–10%.^{3–5} This increased survival has been attributed to improved diagnostic staging procedures and improvements in treatment, such as increased use of recommended chemotherapy and centralization of surgery.^{6,7} For advanced epithelial ovarian cancer, current standard treatment consists of cytoreductive surgery combined with platinum-based chemotherapy.^{8,9} While the sequence of surgery and chemotherapy as standard treatment is an ongoing topic of debate and varies in different guidelines, more patients received standard treatment during the last decades.^{2,4,10}

Increases in guideline compliance do not seem to apply to all patients. Particularly among elderly patients with advanced epithelial ovarian cancer, less frequent use of standard or even any cancer-directed treatment and poorer survival is observed, compared with younger patients.^{11–13} Plausible explanations for this difference between young and old patients are age-related factors, such as higher burden of co-morbid conditions, advanced stage at diagnosis, lower performance status, and increased frailty among elderly patients.^{14–16} In addition, patient preferences may influence decision-making regarding treatment and adherence to guidelines, when

weighing treatment burden, quality of life, and expected survival benefit.¹⁷

In recent years, several studies reported on treatment patterns in (advanced) epithelial ovarian cancer. A significant proportion of patients with advanced epithelial ovarian cancer receive no cancer-directed treatment, ranging from 9%–11%.^{4,18} So far, limited research has been devoted to the characterization of patients with advanced epithelial ovarian cancer not receiving cancer-directed treatment and the underlying reasons for this decision. A recent Dutch, small, single-center, retrospective analysis demonstrated physical condition, patient preference, and age as the main reasons for withholding guideline-recommended care in ovarian cancer patients.¹⁹

This study aimed to gain insight into the trends in treatment patterns in patients with advanced epithelial ovarian cancer in the Netherlands, the characteristics of patients not receiving cancer-directed treatment, and the reasons for this decision on a population-based level.

METHODS

Patients were selected from the Netherlands Cancer Registry. This nationwide registry collects data on all patients newly diagnosed with cancer in the Netherlands, covering nearly 17 million inhabitants. Primary source of notification is the automated nationwide pathologic archive, supplemented by additional sources, such as the national registry of hospital discharge diagnoses. After notification, trained registration administrators routinely extract information on diagnosis, initial treatment, and patient and tumor characteristics in all Dutch hospitals.

Data on all adult women diagnosed with advanced epithelial ovarian cancer, defined as International Federation of Gynecology and Obstetrics (FIGO) classification IIB–IV, including peritoneal and fallopian tube carcinoma, or diagnosed with ovarian cancer with an unspecified morphology during 2008–2016, were selected (n=9314). Patients diagnosed on autopsy were excluded (n=11). Clinical registry data included tumor stage, histologic subtype, date of diagnosis, vital status, and initial treatment received. Also, the Charlson Comorbidity Index²⁰ was assessed, but only data for the years 2015–2016 were available for analysis because of incompleteness of data in other years. Tumor stage was defined according to the FIGO staging system 2009, derived from the tumour-nodal-metastasis staging system.²¹ When patients received primary cytoreductive surgery, stage was based on post-operative findings. If patients did not receive surgery or underwent neoadjuvant chemotherapy, clinical tumor stage was used to avoid downstaging. Sociodemographic registry data of patients included age at diagnosis and socioeconomic status. Socioeconomic status was based on four-digit postal code of the residence area of the patient, combining aggregated individual fiscal data on the economic value of the home and household incomes, and was categorized into low, medium, or high.²²

Reported initial treatment was classified as standard treatment (combined cytoreductive surgery and chemotherapy, no specific order), chemotherapy only, surgical resection only, or no cancer-directed treatment. In order to assess trends over time, we compared treatments during three consecutive timeframes (2008–2010,

2011–2013, 2014–2016). The main reason for deciding for no cancer-directed treatment in epithelial ovarian cancer patients has been recorded in the Netherlands Cancer Registry since 2015; hence, in this study, this parameter was evaluated in patients diagnosed in the years 2015–2016. The main reason was extracted from medical records by the trained administrators and categorized into one of eight predefined options: co-morbidity, functional status, social context, old age, short life expectancy, patient's choice, extensive disease, and other.

To compare clinical and sociodemographic characteristics between patients who did or did not receive cancer-directed treatment univariately, a t-test was used for continuous variables normally distributed, a Mann–Whitney U-test for continuous variables not normally distributed, and a Chi-square test for categorical variables. Multivariable logistic regression was performed to compare characteristics between treatment groups (cancer-directed treatment, yes vs no) regarding age, stage, socioeconomic status, co-morbidity, and timeframe. Trends in whether or not receiving cancer-directed treatment were analyzed using the Cochran–Armitage trend test. Two-sided p values <0.05 were considered statistically significant. Descriptive analysis was used to describe the main reasons for no cancer-directed treatment. Statistical analyses were performed using STATA (release 14.1, StataCorp, College Station, Texas, USA).

RESULTS

Patient Characteristics

Between 2008 and 2016, a total 9303 women were diagnosed with advanced epithelial ovarian cancer or ovarian carcinoma with unspecified morphology in the Netherlands. Median age at diagnosis was 68 (range 18–101) years. The proportion of patients aged ≥80 years increased slightly (15% in 2008–2010 vs 18% in 2014–2016, p=0.028) and the percentage of stage IV disease increased to some extent (29% in 2008–2010 vs 34% in 2014–2016, p<0.001). Of all patients, 14% (n=1270) received no cancer-directed treatment (Table 1). The other 86% (n=8033) of patients received cancer-directed treatment: 67% (n=6218) received combined cytoreductive surgery and chemotherapy, 15% (n=1399) chemotherapy only, and 3.8% (n=350) surgical resection only. The remaining patients received hormonal therapy only (n=66).

Patients not receiving cancer-directed treatment had a higher age (median age 81 vs 66 years when cancer-directed treated; OR 1.14 per adjusted year, 95% CI 1.13 to 1.15), more often FIGO stage IV (43% vs 28% when cancer-directed treated; OR 3.71, 95% CI 2.63 to 5.24), more often a low socioeconomic status (36% vs 29% when cancer-directed treated; OR 1.54, 95% CI 1.29 to 1.84), more prevalent co-morbidity (Charlson Comorbidity Index ≥1 51% vs 34% when cancer-directed treated; OR 1.49, 95% CI 1.13 to 1.96), and were more frequently diagnosed in the most recent timeframe 2014–2016 (39% vs 33% when cancer-directed treated; OR 1.29, 95% CI 1.09 to 1.54, all p<0.05).

Treatment Trends

Over time, the proportion of women with advanced epithelial ovarian cancer not receiving cancer-directed treatment increased from 11% in 2008 to 16% in 2016 (p<0.001; Figure 1). An increase from 39% to 50% in no cancer-directed treatment was observed in

Table 1 Distribution of characteristics of patients with advanced epithelial ovarian cancer in the Netherlands across treatment groups (n=9303)

Characteristic	CDT (n=8033)	No CDT (n=1270)	P value
Age (years) (median (range))	66 (18–95)	81 (26–101)	<0.001
Age group (years) (n (%))			<0.001
<70	4924 (61)	203 (16)	
70–79	2283 (28)	363 (29)	
≥80	826 (10)	704 (55)	
Histologic subtype (n (%))			<0.001
Serous	5559 (69)	338 (27)	
Mucinous	219 (2.7)	42 (3.3)	
Endometrioid	374 (4.7)	11 (0.9)	
Clear cell	279 (3.5)	8 (0.6)	
Adenocarcinoma NOS	1211 (15)	673 (53)	
Other	391 (4.9)	198 (16)	
FIGO stage (n (%))			<0.001
2B–2C	705 (8.8)	44 (3.5)	
3A–3B	586 (7.3)	75 (5.9)	
3C	4249 (53)	557 (44)	
4	2227 (28)	552 (43)	
Unknown	266 (3.3)	42 (3.3)	
Socioeconomic status (n (%))			<0.001
Low	2360 (29)	463 (36)	
Medium	3184 (40)	504 (40)	
High	2489 (31)	303 (24)	
Period of diagnosis (n (%))			<0.001
2008–2010	2708 (34)	349 (27)	
2011–2013	2646 (33)	425 (33)	
2014–2016	2679 (33)	496 (39)	
Charlson Comorbidity Index (not age-adjusted)*			<0.001
0	1126 (62)	134 (40)	
1–2	532 (29)	125 (37)	
≥3	79 (4.4)	45 (13)	
Unknown	78 (4.3)	31 (9.3)	

Italicised type indicates statistical significant p value (<0.05)

*Assessed in a subsample, only during 2015 and 2016.

CDT, cancer-directed treatment; FIGO, International Federation of Gynecology and Obstetrics; NOS, not otherwise specified.

the age group of ≥80 years between 2008–2010 and 2014–2016 ($p=0.001$). The percentage of patients receiving cytoreductive surgery combined with chemotherapy differed between 2008–2010 and 2014–2016 ($p<0.001$), with percentages of 70% vs 63%, respectively. Simultaneously, chemotherapy only increased slightly

from 14% to 16% ($p=0.015$). The use of other treatment modalities remained similar over time.

Reasons for Deciding on No Cancer-directed Treatment

In 96% of patients not receiving cancer-directed treatment in the years 2015–2016 ($n=320$), the reason for this decision was recorded. The main reasons for no cancer-directed treatment were patient's choice (40%) and poor condition of the patient (29%) (Table 2). "Social context" was never reported as a reason. In 43% of elderly patients (≥70 years) not receiving cancer-directed treatment, patient's choice was indicated as the main reason for this decision, compared with 23% in younger patients (<70 years). In 12% of patients, "other than the predefined reasons" was indicated: more than one reason applicable, or early or premature death, which made it impossible for the patient to have started initial treatment at all.

DISCUSSION

This population-based study showed that the proportion of patients with advanced epithelial ovarian cancer not receiving cancer-directed treatment has increased in the last decade in the Netherlands. Patient's choice was the most prevalent reason for deciding for no cancer-directed treatment, followed by poor condition of the patient. In our study, during the period 2008–2016, 14% of patients received no cancer-directed treatment and the proportion of women with advanced epithelial ovarian cancer not receiving cancer-directed treatment increased over time, especially in patients aged ≥80 years. This treatment trend among very elderly patients in the Netherlands is in line with the results of Schuurman *et al* in the time period 2002–2013.¹² International data regarding the proportion of patients with advanced epithelial ovarian cancer not receiving cancer-directed treatment are scarce. A study based on the United States National Cancer database (2003–2011) reported 9% of patients with FIGO III–IV epithelial ovarian cancer not receiving treatment.¹⁸ The authors of the article do however suggest that the number of patients not receiving treatment may be underestimated since the National Cancer Database describes a population most likely to receive care consistent with best clinical practices.

In line with previous studies, factors associated with not receiving cancer-directed treatment were higher age and FIGO stage IV at initial diagnosis.^{11 13 23} During the studied time period, the proportion of patients of ≥80 years increased slightly, but this small increase did not seem to be sufficient explanation for the total increase in no cancer-directed treatment as the trend in increase in no cancer-directed treatment is visible in all the separate age groups. Also, the percentage of stage IV disease increased to some extent, possibly as a result of better staging. According to international guidelines, stage IV epithelial ovarian cancer as such should not be a reason for not receiving cancer-directed treatment; nevertheless, a higher tumor stage might affect performance status by having more extensive tumor localization and, as a result, patients may be judged unfit for treatment. Furthermore, having stage IV epithelial ovarian cancer involves a worse prognosis compared with lower stages, which may influence treatment considerations in the decision-making process. Also, non-clinical aspects may play a role in medical decision-making, as our data suggest that socioeconomic status might be a factor in this process. This result is consistent

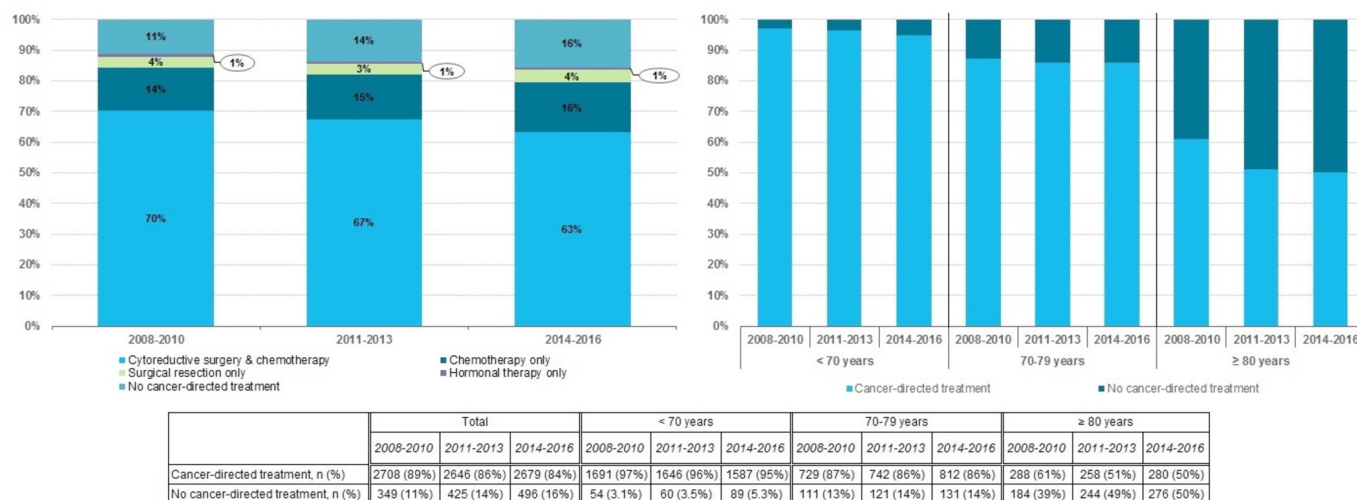


Figure 1 Treatment trends in patients with advanced epithelial ovarian cancer (2008–2016)

with several prior studies.^{23,24} Patients with a higher socioeconomic status are more inclined to prefer to play an active role in the decision-making process,²⁵ and a lower socioeconomic status is associated with a higher prevalence of co-morbidity,²⁶ which may be a reason for deciding for no cancer-directed treatment.

Of the reasons reported for no cancer-directed treatment, patient's choice was the most prevalent reason, which indicates patient involvement in the decision-making process. In the United States National Cancer database (2003–2011), 6.2% of epithelial ovarian cancer patients (all FIGO stages) were known to have decided to forgo recommended surgery.¹⁸ In the United States Surveillance, Epidemiology, and End Results database, 1.4% of advanced epithelial ovarian cancer patients ≥65 years between 1995 and 2005 chose to forgo surgery, but no additional information regarding reasons for this decision was available.²³ Studies dating from the earlier years of this decade show that the involvement of patients in the decision-making process was limited.^{27,28} Since shared decision-making is seen as an essential part of good practice nowadays and may have a beneficial impact on quality of life,²⁹ advances in this area are still ongoing. Although older age appears to increase the preference for a more passive role in the decision-making process,²⁵ patient's choice not to receive cancer-directed treatment was most frequently indicated among elderly patients. Despite under-representation of elderly patients (≥65 years) in clinical trials,³⁰ it has been reported that also for

elderly women with advanced epithelial ovarian cancer, combined surgery and chemotherapy is the preferred treatment and is considered feasible.¹⁶ Nevertheless, a United States study among ovarian cancer patients demonstrated that older women reported being less worried about the consequences of cancer,³¹ which may perhaps influence treatment considerations in this age group. Moreover, older patients seem more focused on the quality of life rather than length of life.^{17,25}

Both from a patient's and physician's perspective, several factors play a role in the decision-making process regarding treatment of ovarian cancer. Patients indicate the need for good information provision regarding diagnosis, treatment, and prognosis.²⁷ Not only rational arguments and medical reasons, but also the personal attitudes of both patient and physician, fears of side effects or metastases, existential issues, and social environment are known factors that influence medical decision-making in patients with ovarian cancer.²⁷ For physicians, as expected, co-morbidity, performance status, and the medical literature are important factors that influence treatment considerations.^{25,32} In addition, the physician's experience with ovarian cancer treatment appears to be an important aspect in the decision-making process. In the Netherlands, centralization of surgical care for patients with ovarian cancer has been formally implemented since 2011, which has increased surgical annual case load per hospital considerably and improved overall patient survival.⁶ Consultation with a

Table 2 Reasons for no cancer-directed treatment 2015–2016, subdivided by age group

Reason	<70 years (n (%))	70–79 years (n (%))	≥80 years (n (%))	Total (n (%))
Co-morbidity	5 (10)	1 (1.1)	2 (1.1)	8 (2.5)
Functional status	15 (31)	26 (28)	52 (29)	93 (29)
Old age	0	0	4 (2.2)	4 (1.2)
Short life expectancy	5 (10)	2 (2.2)	12 (6.7)	19 (5.9)
Patient's choice	11 (23)	41 (45)	77 (43)	129 (40)
Extensive disease	4 (8.3)	10 (11)	14 (7.8)	28 (8.7)
Other	8 (17)	12 (13)	19 (11)	39 (12)
Total	48 (100)	92 (100)	180 (100)	320 (100)

physician specialized and experienced in ovarian cancer treatment is positively associated with receiving guideline-based treatment.³³ Conversely, however, specialized care may not only lead to better outcomes, but more experienced physicians may also have become more skilled in the selection of patients who are fit for, and potentially may benefit most from, cancer-directed treatment, and therefore in some cases, perhaps consciously but appropriately, deviate from guideline-based treatment.

A notable strength of this study is that treatment trends were analyzed in a large cohort of patients with advanced epithelial ovarian cancer on a nationwide population-based level. Not only were we able to study the characteristics of patients not receiving cancer-directed treatment, but also the reasons for this decision, although only in the most recent time period. This information provides valuable insights into treatment patterns for advanced epithelial ovarian cancer in the last decade, and the considerations that play a role when determining treatment. Since a decrease in cancer-directed treatment over time was observed, a comparison of the main reasons for no cancer-directed treatment between different timeframes would be interesting, but unfortunately this information was only evaluated in patients diagnosed in more recent years (2015–2016). Furthermore, the main reason for no cancer-directed treatment was extracted from medical records, which often embody a limited reflection of what is actually considered and discussed in consulting rooms or during multidisciplinary team consultations. Assessment based on medical records may be susceptible to interpretation due to interrelatedness of several reasons to start or withhold treatment. However, the item was registered by experienced and trained administrators and a previous study regarding this item, in which also a quality control was performed, suggests that it is a reliable measure.³⁴ Another limitation of our analysis is that certain clinical parameters that may be valuable in the decision-making process are missing, such as performance status and geriatric assessment. Finally, assessment of socioeconomic status based on the postal code of the patient's area of residence is a rather crude proxy and should be interpreted with care.

An increasing proportion of patients with advanced epithelial ovarian cancer receive no cancer-directed treatment, and a considerable number of such patients appear to be involved in the process leading to this decision. However, we have no information about how decision-making processes have taken place and whether appropriate mutual exchange of information between physician and patient has occurred in order to actually comply with adequate shared decision-making. Furthermore, our study is not focused on the impact of receiving or not receiving cancer-directed treatment on the quality of life and experienced quality of care of patients with advanced epithelial ovarian cancer. Evaluating these perceptions of patients by using patient-reported outcome measures is seen as an increasingly important aspect in determining appropriate oncologic care.³⁵ Therefore, future research into quality of life, experienced quality of care, and decision-making processes in patients with advanced epithelial ovarian cancer, from their perspective, is desirable.

The proportion of patients with advanced epithelial ovarian cancer not receiving cancer-directed treatment has increased in the last decade, particularly in older patients. Patient's choice was the main reason for deciding for no cancer-directed treatment,

which indicates patient involvement in the decision-making process. The second most common reason for no cancer-directed treatment was poor condition of the patient, which might indicate careful selection of patients for treatment. These results suggest that decision-making regarding treatment is well-considered, but more insight into this process is needed, especially from the patient's perspective.

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