Improving quality of care for patients with ovarian and endometrial cancer

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CHAPTER 2

Improved outcomes due to changes in organization of care for patients with ovarian cancer in the Netherlands

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ABSTRACT

Objectives

Objectives of this study were to evaluate the effect of changes in patterns of care, for example centralization and treatment sequence, on surgical outcome and survival in patients with epithelial ovarian cancer (EOC).

Methods

Patients diagnosed with FIGO stage IIB-IV EOC (2004-2013) were selected from the Netherlands Cancer Registry. Primary outcomes were surgical outcome (extent of macroscopic residual tumor after surgery) and overall survival. Changes in treatment sequence (primary cytoreductive surgery and adjuvant chemotherapy (PCS+ACT) or neo-adjuvant chemotherapy and interval cytoreductive surgery (NACT+ICS)), hospital type and annual hospital volume were also evaluated.

Results

Patient and tumor characteristics of 7987 patients were retrieved. Most patients were diagnosed with stage III-IV EOC. The average annual case-load per hospital increased from 8 to 28. More patients received an optimal cytoreduction (tumor residue ≤ 1cm) in 2013 (87%) compared to 2004 (55%, $p<0.001$). Complete cytoreduction (no macroscopic residual tumor), registered since 2010, increased from 42% to 52% (2010 and 2013, respectively, $p<0.001$). Optimal/complete cytoreduction was achieved in 85% in high volume (≥20 cytoreductive surgeries annually), 80% in medium (10-19 surgeries) and 71% in small hospitals (<10 surgeries, $p<0.001$). Within a selection of patients with advanced stage disease that underwent surgery the proportion of patients undergoing NACT+ICS increased from 28% (2004) to 71% (2013). Between 2004 and 2013 a 3% annual reduction in risk of death was observed (HR 0.97, $p<0.001$).

Conclusion

Changes in pattern of care for patients with EOC in the Netherlands have led to improvement in surgical outcome and survival.

INTRODUCTION

Epithelial ovarian cancer is the leading cause of death in gynecological malignancies (1), and the seventh most common cancer in women worldwide (2). In 2013 there were over 1200 new cases and around 1000 deaths as a result of ovarian cancer in the Netherlands (3). Due to a lack of specific symptoms, the majority of patients presents with advanced stage disease, resulting in a poor prognosis. Current treatment of advanced stage ovarian cancer consists of a combination of platinum-based chemotherapy and cytoreductive surgery.

In the past decade, changes in the organization of care for patients with ovarian cancer have been implemented in the Netherlands. Traditionally, patients were staged and treated in the hospital of diagnosis. Consequently, less than 20% of ovarian cancer patients were treated in specialized hospitals between 1996 and 2003 (4). Over the past decade increasing evidence has shown that complete cytoreduction is strongly correlated with improved disease free and overall survival, and that the likelihood of achieving this is higher when cytoreductive surgery is performed by a specialized gynecologic oncologist in a high-volume hospital (5–14). These insights emphasized the need for improved regional collaboration and a larger ovarian cancer case load for a smaller number of hospitals and practitioners (9–11). Centralization initiatives undertaken by the Dutch Society of Obstetrics and Gynecology resulted in a nationwide consensus in 2011. Additionally, national standards for general and specialized cancer care were compiled. An important criterion in these national standards is that surgical cytoreduction for ovarian cancer should only be performed by specialized gynecologic oncologists in institutions in which a minimum of 20 cytoreductive surgeries take place annually.

Increasing awareness of the importance of achieving complete cytoreduction has led to alterations in the therapy regimen for patients with advanced ovarian cancer (5–8,13). Administration of neoadjuvant chemotherapy to reduce tumor load and increase the chance of achieving complete cytoreduction was introduced after the publication of the EORTC-NCIC trial in 2010 (15). Comparison of standard therapy (primary cytoreductive surgery followed by adjuvant chemotherapy (PCS+ACT)) with the alternative regimen (neoadjuvant chemotherapy followed by interval cytoreductive surgery (NACT+ICS)) demonstrated equal progression free and overall survival chances (15–22). Additionally, reduced per- and postoperative complications following NACT+ICS were demonstrated (16–22). In several other publications, not being randomized controlled trials, less favorable outcomes such as inferior overall survival and increased toxicity due to chemotherapy, were depicted (23–25). Despite these variations in outcome however, the proportion of ovarian cancer patients treated with NACT+ICS has increased in recent years(16,18,20,26).

The aim of the current study was to evaluate whether the changes in pattern of care for ovarian cancer patients, which have taken place in the Netherlands in the past decade, have led to improved surgical outcome and survival.

MATERIALS AND METHODS

Data collection

Population-based data were retrieved from the Netherlands Cancer Registry (NCR), which is maintained by the Netherlands Comprehensive Cancer Organization. The NCR contains data of all cancer patients in the Netherlands, and relies on notifications of newly diagnosed malignancies from the automated nationwide pathology archive. Trained medical registrars use standardized forms to collect patient information from medical records and the national registry of hospital discharge diagnoses. Information regarding vital status and date of death is obtained through Statistics Netherlands, an agency responsible for the official Dutch statistics. Regular consistency checks are performed to ensure the quality of data in the NCR.

Patients

Data from all consecutive patients diagnosed with FIGO stage IIB – IV ovarian cancer between January 1st 2004 and January 1st 2014 in the Netherlands were retrieved. In total, 452 patients were excluded from analysis. These patients underwent unilateral or bilateral salpingo-oophorectomy (BSO) or hysterectomy with BSO only, and were excluded from analysis as these could not be classified as having had an attempt to achieve maximal cytoreduction, and patients that underwent staging only. Patient-, tumor- and treatment characteristics of 7987 patients were retrieved. Surgery performed within 9 months of the date of diagnosis was considered related to ovarian cancer.

To avoid understaging of patients undergoing neoadjuvant chemotherapy, determination of the stage of disease was dependent on the sequence of received treatments. Stage of disease was determined using the pathological TNM stage for patients who underwent PCS+ACT. For patients receiving NACT+ICS, stage of disease was determined before initiation of primary therapy and was based on the clinical TNM stage. After careful consideration and consultation by an experienced pathologist it was decided to view serous and adenocarcinoma not otherwise specified (NOS) subtypes as one entity.

Hospitals

Hospitals were categorized into three groups: academic hospitals, specialized hospitals, and general hospitals. Academic hospitals are tertiary referral hospitals that deliver highly specialized care, and are related to a university. Specialized hospitals are teaching hospitals that are not related to a university. General hospitals are non-teaching hospitals and are usually smaller than specialized hospitals. Hospital volume was defined as the average annual number of cytoreductive surgeries performed for ovarian cancer between 2004 and 2013. Annual volumes of 1-3 cytoreductive surgeries were considered to be incidents, and were not included in the volume-analysis.

Outcomes

Primary outcomes were surgical outcome and overall survival. During the study period several alterations in definitions of cytoreductive outcome occurred within the NCR registration (table 1). The term complete cytoreduction was introduced in the NCR in 2009 and fully implemented by 2010. Comparison of complete cytoreductive outcomes is therefore only possible between 2010 and 2013. To allow comparison of outcomes within the whole study period (2004-2013), optimal and complete results of cytoreductive surgery were compiled into one variable. Treatment sequence (PCS+ACT or NACT+ICS), type of treatment hospital and annual number of cytoreductive surgeries per hospital were also evaluated.

Table 1. Definitions utilized by NCR for result of cytoreductive surgery

Term	Definition in 2004-2006	Definition in 2007-2009	Definition in 2010 onwards
Incomplete	Residual tumor >2cm	Residual tumor >1cm	Residual tumor >1cm
Optimal	Residual tumor ≤2cm	Residual tumor ≤1cm	Residual tumor ≤1cm
Complete	-	-	No macroscopic residual tumor

Within the selection of patients fulfilling all in- and exclusion criteria, patients in whom ovarian cancer was detected by coincidence without an attempt to remove macroscopic tumor tissue, and patients who underwent surgery that was not further specified, were all categorized as having received incomplete cytoreduction.

Data analysis

Data analysis was performed using STATA data analysis and statistical software (StataCorp, College Station, TX). Comparison between unpaired groups was done using the Chi^2 test. Overall survival was used as primary survival outcome measure, and estimated using Kaplan Meier analyses. To correct for possible confounders such as age, stage, type of tumor, grade and treatment sequence, multivariable survival analyses were performed using Cox regression. Year of diagnosis was entered into these analyses as a continuous variable. To avoid immortal time bias when comparing survival rates between the patients that received PCS and the patients that received NACT-ICS, conditional survival analysis was used. It was assumed that all patients underwent cytoreductive surgery and the first 3 chemotherapy cycles within 6 months after diagnosis. Thus, survival analyses were performed with a landmark at 6 months. Differences were considered statistically significant at $p<0.05$.

RESULTS

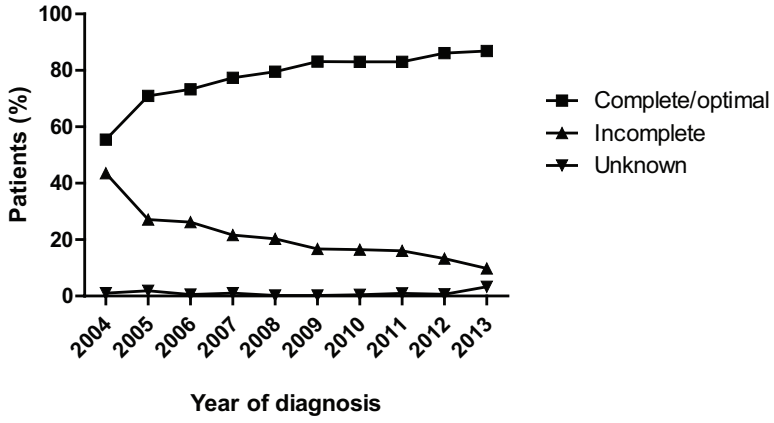
Data from 7987 patients were retrieved for this study. Clinicopathological characteristics are shown in table 2. Within the study-population, most patients were diagnosed with stage IIIC (60%) and serous type (86%) ovarian cancer. Primary cytoreductive surgery was the most frequently chosen therapeutic regimen. Overall, 73% of patients underwent surgery and 27% did not. The proportion of patients that did not undergo surgery increased from 21% in 2004 to 32% in 2013. Of the patients who did not receive surgery, 52% underwent chemotherapy, 5% had hormonal therapy or other palliative treatment, and in 43% further treatment was unknown or not indicated. In general, patients that did not receive surgery were older than those who did receive surgical treatment (75 years and 63 years respectively, P<0.001, data not shown). Between 2004 and 2013, the average age of patients increased from 65 years (95%CI 64-65) to 68 years (95%CI 67-69).

The number of hospitals performing cytoreductive surgery for ovarian cancer patients decreased from 90 hospitals in 2004 to 34 hospitals in 2013. As a consequence, the average annual caseload per hospital increased from 8 cases in 2004 to 28 cases in 2013. In total, 15 out of the 34 hospitals (44%) involved in cytoreductive surgery for ovarian cancer in 2013 met the minimal requirement of 20 cytoreductive surgeries per hospital per year (data not shown).

Surgical outcomes

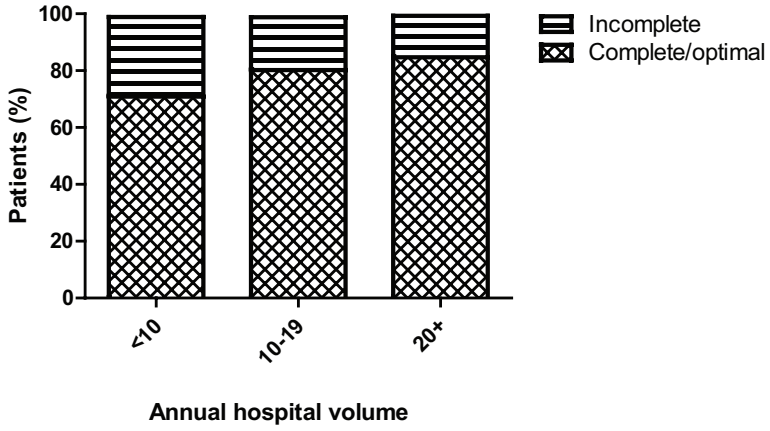
Within the study period an increase in the amount of complete/optimal cytoreductions was achieved: 55% in 2004 compared to 87% in 2013 (p<0.001 with test for trend, figure 1). Between 2010 and 2013 an increase in the rate of complete cytoreduction was seen from 42% to 52% (p<0.001, data not shown). Patients in whom a complete cytoreduction was achieved had a favorable survival compared to those who underwent an optimal or incomplete cytoreduction (data not shown).

Figure 1. Surgical outcome between 2004 and 2013



A correlation was found between hospital volume and the number of patients who underwent a complete cytoreduction. Hospitals with an annual volume of ≥20 cytoreductive surgeries achieved better cytoreductive outcomes than hospitals with annual volumes of 10-19 and <10 surgeries. Complete/optimal cytoreduction was achieved in 85%, 80% and 71% respectively (P<0.001, figure 2). Between 2010 and 2013, complete cytoreduction was achieved in 57%, 45% and 44% in hospitals that performed >20, 10-19 and <10 cytoreductive surgeries annually (p<0.001). Hospitals that performed ≥30 cytoreductive surgeries annually attained more complete cytoreductions compared to those that performed 20-29 cytoreductive surgeries (59% and 50% respectively between 2010 and 2013 (p=0.003, data not shown).

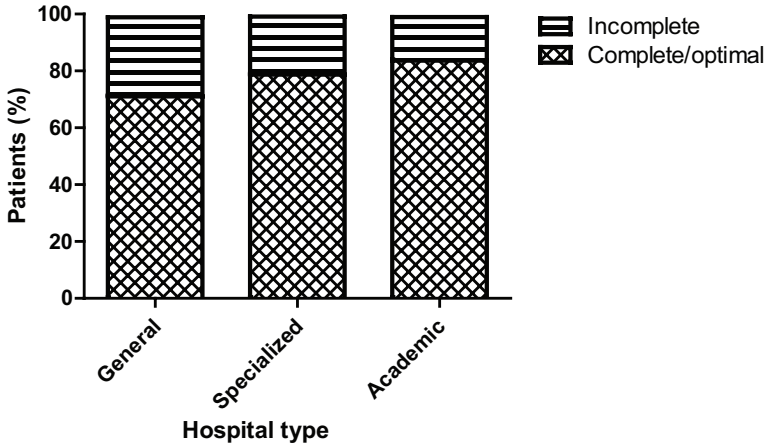
Figure 2. Surgical outcome for annual hospital volumes between 2004 and 2013



In hospitals that performed ≥20 cytoreductive surgeries annually, an optimal/complete cytoreduction was achieved in 69% of patients in 2004, compared to 89% in 2013. Likewise, in hospitals with an annual volume of <10 cytoreductive surgeries, optimal/complete cytoreduction was achieved in 43% of patients in 2004, compared to 83% in 2013. An unfavorable survival was found in patients that were treated in hospitals with an annual volume of < 10 cytoreductions, compared to hospitals with an annual volume of 10-19 or ≥20 cytoreductive surgeries (data not shown).

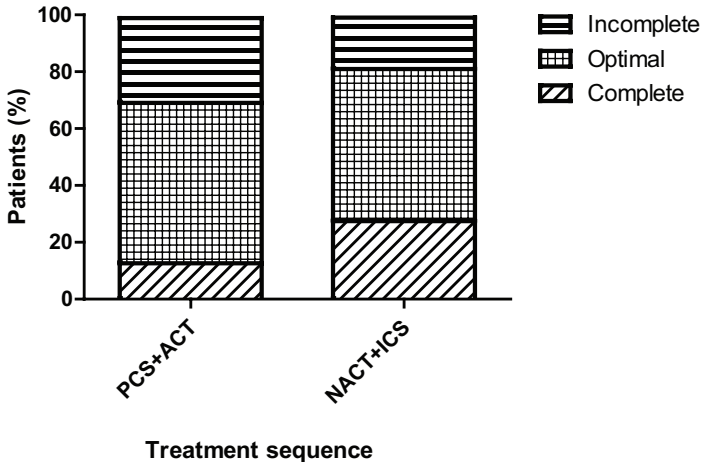
Academic hospitals achieved better surgical outcomes than specialized and general hospitals. Complete/optimal cytoreduction was achieved in 84%, 79% and 71% respectively (p<0.001 with chi^2 test, figure 3). Between 2010 and 2013, complete cytoreduction was achieved in 53%, 48% and 42% respectively (p=0.002, data not shown). There were no differences in the number of patients with FIGO stage IIIC or IV between the three hospital types (p=0.227, data not shown).

Figure 3. Surgical outcome for hospital types between 2004 and 2013



In patients with advanced stage disease who received NACT+ICS a complete/optimal cytoreduction was reached in 81%, compared to 69% in patients who received PCS+ACT (p<0.001, figure 4). Between 2010 and 2013, 47% of patients with advanced stage disease that underwent NACT+ICS received a complete cytoreduction versus 43% of patients that underwent PCS+ACT (p=0.028). In patients receiving ICS after initial PCS+ACT surgical outcome was poor (data not shown). PCS+ACT followed by ICS is not part of standard therapy for patients with ovarian cancer in the Netherlands, as illustrated by the small number of patients involved (table 2). Patients who underwent PCS+ACT+ICS were generally younger and more frequently diagnosed with high stage serous ovarian cancer than those who underwent standard PCS+ACT therapy (data not shown).

Figure 4. Surgical outcome per treatment sequence between 2004 and 2013



PCS: primary cytoreductive surgery, ACT: adjuvant chemotherapy, NACT: neoadjuvant chemotherapy, ICS: interval cytoreductive surgery.

Table 2. Clinicopathological characteristics of total patient population

	Total (n=7987)	
	n	**%**
FIGO Stage		
IIB	306	4
IIC	332	4
IIIA	210	2
IIIB	534	7
IIIC	4769	60
IV	1836	23
Type of tumor		
Serous	6856	86
Mucinous	281	4
Endometrioid	432	5
Clear cell	222	3
Other	196	2
Grade		
I	304	4
II	889	11
III	3004	38
Anaplastic	38	0
Undefined	3752	47
Treatment		
Surgery	5870	73
PCS +ACT	3004	51
NACT+ICS	2635	45
PCS+ACT+ICS	231	4
No surgery	2117	27
Age at diagnosis (years)		
Mean (range)	66 (20-97)	

FIGO: International Federation of Gynecology and Obstetrics; PCS: primary cytoreductive surgery; ACT: adjuvant chemotherapy; NACT: neoadjuvant chemotherapy; ICS: interval cytoreductive surgery.

Survival

Within the group of patients diagnosed with stage IIB-IV ovarian cancer, a small improvement in five year overall survival was demonstrated between patients diagnosed in 2004-2006 (24%) and 2010-2013 (25%, HR 0.91, 95% CI 0.84-0.99, p=0.031). One year overall survival increased from 82% (95% CI 0.78-0.85) in 2004 to 90% (95% CI 87-92, p<0.001) in 2013 (p<0.001). Additionally, a 2% annual reduction in risk of death was demonstrated between 2004 and 2013 (HR 0.983, 95% CI 0. 970-0.995, p=0.007, univariable analysis). Multivariable analysis, correcting for age, stage, type of tumor and grade, demonstrated a 3% annual reduction in risk of death (HR 0.974, 95% CI 0.962 – 0.987, p<0.001, Table 3).

Table 3. Multivariate analysis of overall survival between 2004 and 2013

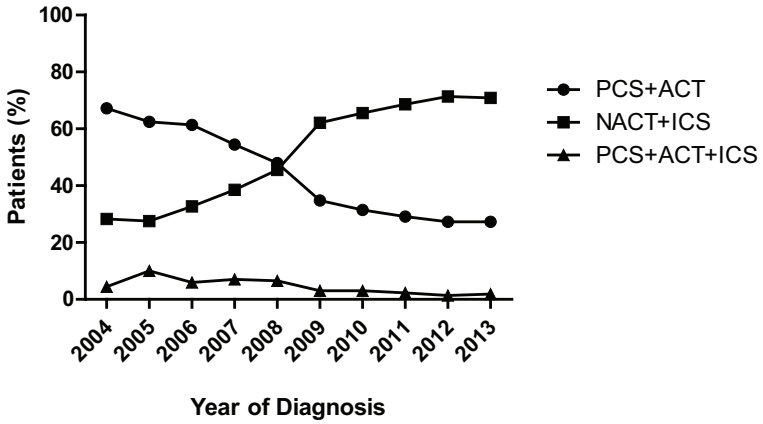
	HR	**95% CI**		**p-value**
Year of diagnosis	0.974	0.962	0.987	<0.001
Age	1.020	1.017	1.023	<0.001
Stage				
IIB	ref	ref	ref	ref
IIC	1.275	0.959	1.700	0.094
IIIA	2.456	1.832	3.292	<0.001
IIIB	2.325	1.819	2.971	<0.001
IIIC	3.348	2.702	4.149	<0.001
IV	4.503	3.611	5.616	<0.001
Grade				
I	ref	ref	ref	ref
II	1.480	1.220	1.795	<0.001
III	1.412	1.177	1.695	<0.001
Anaplastic	1.883	1.096	3.233	0.022
Unknown	1.414	1.175	1.701	<0.001
Type of tumor				
Serous	ref	ref	ref	ref
Mucinous	2.083	1.770	2.451	<0.001
Endometrioid	0.882	0.766	1.015	0.081
Clearcell	1.392	1.162	1.667	<0.001
Undefined	1.246	0.946	1.641	0.118

HR: hazard risk; CI: confidence interval.

Treatment regimens

A total of 5870 patients underwent cytoreductive surgery for ovarian cancer in the Netherlands between 2004 and 2013. Within this timeframe, the proportion of patients receiving PCS+ACT decreased considerably, whereas the proportion of patients receiving NACT+ICS showed a steady increase (figure 5). Patients receiving NACT+ICS were more frequently diagnosed with advanced stage and serous disease compared to patients receiving PCS+ACT (p<0.001 in both cases, data not shown). Within the selection of patients with advanced stage disease (FIGO IIIC-IV) who underwent complete/optimal cytoreduction, patients receiving PCS+ACT had a 5-year overall survival of 39% (95% CI 36-42) compared to 26% (95% CI 23-28) in those receiving NACT+ICS.

Figure 5. Choice of treatment between 2004 and 2013



PCS: primary cytoreductive surgery, ACT: adjuvant chemotherapy, NACT: neoadjuvant chemotherapy, ICS: interval cytoreductive surgery.

The treatment sequence of NACT followed by interval cytoreductive surgery was introduced earlier in academic hospitals compared to specialized and general hospitals. In 2004, 38% of patients treated in academic hospitals received NACT+ICS compared to 20% in specialized and 21% in general hospitals. By 2013 all hospital types routinely performed NACT+ICS (64%, 59% and 63% of patients treated in academic, specialized and general hospitals, respectively).

DISCUSSION

To our knowledge, this is the largest population-based study analyzing the changes in pattern of care for ovarian cancer patients within the past decade. A unique feature of the current study is that within the study period all patients were treated with the standard first line platinum based chemotherapy. We observed an increase in the rate of complete/optimal cytoreduction and simultaneously a small decrease in annual risk of death.

Improvement in surgical outcomes may be related to the organizational changes that have been implemented during recent years. Implementation of national standards has enforced regional collaboration and the presence of specialized gynecologic oncologists during cytoreductive surgeries. Both of these factors are associated with favorable surgical outcomes and survival (9–11,14). Furthermore, rapid implementation of new guidelines and the presence of specialized personnel and state of the art facilities in high volume and specialized hospitals contribute strongly to the high standards of care within these institutions.

Our results demonstrate an association between the type and volume of treatment hospital and the outcome of cytoreductive surgery. Although surgical outcomes improved in both low and high volume hospitals between 2004 and 2013, hospitals that met the volume requirements (≥20 surgeries annually) attained better surgical outcomes than hospitals with lower annual volumes.

Furthermore, academic hospitals and specialized hospitals reported better cytoreductive outcomes than general hospitals. In 2013, 44% of the hospitals that performed cytoreductive surgeries for ovarian cancer in the Netherlands met the annual volume requirements of ≥20 cytoreductive surgeries. Considering the association between high annual surgical volumes, centralization of care and improvement of surgical outcomes, stricter implementation of national standards is deemed essential.

An unfavorable survival was found in patients that were treated in hospitals with an annual volume of <10 cytoreductive surgeries, compared to hospitals with an annual volume of 10-19 or ≥20 cytoreductive surgeries. Analysis of volume effects on survival may require a longer follow up time than is currently available. Although centralization initiatives started in 2005, the official implementation of centralization of care in the Netherlands took place in 2013.

A previous Dutch study demonstrated that patients undergoing surgery by high volume surgeons (the definition of high volume ranging between performing >10 and >12 cytoreductive surgeries for ovarian cancer annually) have lower operative mortality rates. Furthermore, an association was found between surgery performed by high volume surgeons and higher rates of adherence to treatment guidelines (27–30). Nevertheless, no volume requirements currently exist for individual gynecologic oncologists in the Netherlands (10,31).

Besides the changes in the organization of care, alterations in the therapeutic regimens themselves have contributed to the improvement seen in surgical outcomes. While the effect of cytoreductive outcome on survival is undisputed, the timing of cytoreductive surgery has been, and still is, subject of debate. Our nationwide study depicts the increased implementation of NACT+ICS in the Netherlands during recent years, a trend that was previously described by Van Altena *et al* (26). Though there are no official guidelines, patients deemed unsuitable candidates for primary surgery are selected for NACT+ICS to downstage the tumor, facilitate subsequent cytoreduction and reduce damage to surrounding tissue. Women receiving NACT+ICS are often older, have more comorbidity and generally have tumors of higher grade and stage(32). A complete/optimal cytoreduction was achieved in 81% of women with advanced stage disease who received NACT+ICS, compared to 69% of those who underwent PCS+ACT.

Favorable surgical outcomes following NACT+ICS were previously reported in a randomized clinical trial by Vergote *et al*, in which residual tumor of ≤1cm was achieved in 81% with ICS and 42% with PCS (15). Similarly, a Cochrane review reported favorable cytoreductive outcome in the NACT+ICS group compared to the PCS+ACT group (RR 2.56; 95% CI 2.00-3.28)(21).

In the current study 27% of patients did not undergo any cytoreductive surgery. This is consistent with similar data from the Dutch population between 1996 and 2004 (26). Furthermore, a recent analysis of 9491 stage III/IV ovarian cancer patients in the population-based Surveillance, Epidemiology and End Results (SEER)-database from the United States, also showed that 27% of patients did not undergo surgery. (33). It may be expected that the proportion of patients that is unable to undergo cytoreductive surgery will rise as the age of patients with ovarian cancer slowly increases.

Within the current study, a minority (4%) of patients received ICS after initial PCS+ACT. It has previously been demonstrated that the addition of secondary cytoreductive surgery to postoperative platinum-based chemotherapy does not improve survival in patients with a residual tumor exceeding 1 cm after having a maximal effort during primary cytoreductive surgery, supporting the fact that this regimen is not standard practice in the Netherlands (34).

Within our retrospectively selected study population, patients who underwent PCS+ACT had favorable survival outcomes compared to patients who underwent NACT+ICS. Patients were selected for NACT+ICS based on initial unfavorable prognostic characteristics such as advanced stage disease and severe comorbidity. The unfavorable long term survival seen in patients who underwent NACT+ICS is therefore most likely a reflection of the selection bias within this retrospective study. This bias may readily explain the fact that our findings greatly differ from the results of two large randomized controlled trials (EORTC-NCIC and CHORUS) in which non inferiority of survival following NACT+ICS was demonstrated (15,22). Importantly, the EORTC-NCIC trial has been criticized for the short median survival rates (29-30 months) and the disappointing surgical outcomes (optimal cytoreduction was achieved in only 42% of patients randomized to PCS+ACT) that were reported.

Of note, patients were categorized in the NACT+ICS group under the condition that ICS was performed, implying that they must have survived the NACT. For patients categorized as PCS+ACT, no such conditions were in place. As this may have led to an immortal time bias, a landmark analysis was used as described above.

A small but significant improvement in five-year overall survival was demonstrated between the periods 2004-2006 and 2010-2013, and one year overall survival increased from 82% to 90% between 2004 and 2013. Furthermore, the decrease in annual risk of death, as demonstrated in the current study, remained significant when correcting for, stage, type of tumor and grade, suggesting that other factors than these played a role in this association. The increasing proportion of complete cytoreductions attained within recent years is thought to be an important factor for the improved survival, but centralization may have played an important role as well(6–8,13).

The fact that we observed an improvement in five-year survival is encouraging, as previous survival analyses failed to show improvement. A study by Van Altena *et al* on the influence of regional collaboration in treatment for ovarian cancer in the Netherlands did not show a significant improvement in five-year overall survival rates between 1996 (36%) and 2010 (39%) (9). Similarly, the CONCORD-2 study estimated stable five-year net survival rates in the Netherlands between 1995-1999 (39%), 2000-2004 (37%) and 2005-2009 (38%)(35). The EUROCARE-5 study recently published survival data from ovarian cancer patients in individual European countries between 1999 and 2007. Within that period, five-year net survival of Dutch patients with ovarian cancer was 39.9 (95%CI 38.7-41.1)(36). Survival in the CONCORD-2-study and EUROCARE-5 study was adjusted for background mortality by age, sex, and calendar year. Importantly, survival rates in the current study are lower than those reported by Van Altena *et al* and in the CONCORD-2 and EUROCARE-5 studies due to inclusion of patients with early stage ovarian cancer in those studies.

The importance of reaching an optimal or complete cytoreduction has become increasingly evident. Chang and colleagues demonstrated a 2.3-month increase in cohort median survival time for each 10% increase in patients that received a complete cytoreduction as compared to a 1.8-month improvement for each 10% increase in patients that received an optimal cytoreduction(8). Additionally, a recent analysis of GOG 182 showed a significant improvement in survival between optimal cytoreduction and complete cytoreduction (progression free survival of 15 versus 29 months, and overall survival of 41 and 77 months, respectively, P=0.01 for both)(13). It is important to note that as a relatively short follow-up was available for patients diagnosed within the most recent years of our study, the effects of the changes implemented in recent years may not have been fully appreciated.

The retrospective nature of this study has some inevitable limitations. First of all, this study was based on data from the NCR, and thus relies on the data that are available in this registration. In this database no information was registered about the specific chemotherapy regimens that were

used. As national guidelines regarding chemotherapy for EOC patients did not change within the study period, we assume all patients were treated with the same standard first line platinum based chemotherapy. However, we cannot exclude that there may have been some minor variations in chemotherapy regimens.

Our study also relies on the accuracy of the NCR. Patient registration in the NCR is performed by trained and dedicated registrars and the data are regularly checked to ensure optimal quality of the database. It is important to note that registrars depend on the integrity of information available in local medical records. Nonetheless, the NCR is currently the most reliable nationwide source of information on cancer patients in the Netherlands.

Furthermore, the comparison of cytoreductive results is complicated by variation in definitions used worldwide. During the study period changes also occurred within the definitions used for registration in the NCR (table 1). Complete cytoreduction was registered from 2010 onward. Compilation of complete and optimal cytoreductive outcomes enabled comparison throughout the study period, though changes within optimal cytoreduction that occurred within this timeframe were not taken into account.

Finally, the nature of the study precludes the determination of the individual contribution of factors such as centralization and changes in therapy regimes on the improvement in survival.

In conclusion, in this study, regarding 7987 patients diagnosed with ovarian cancer FIGO stage IIB and higher, changes in pattern of care for ovarian cancer patients between 2004 and 2013 were evaluated. A combination of centralization initiatives and changes in therapy regimens has led to improvements in surgical outcome and survival. Continuing centralization of oncological care and implementation of stricter guidelines may lead to further improvement of survival for patients with ovarian cancer in the Netherlands.

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