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A B S T R A C T

Introduction: The care for patients with epithelial ovarian cancer(EOC) is organised in eight different geographical regions in the Netherlands. This situation allows us to study differences in practice patterns and outcomes between geographical regions for patients with FIGO stage IIIC and IV.
Methods: We identified all EOC patients who were diagnosed with FIGO stage IIIC or IV between 01.01.2008 and 31.12.2015 from the Netherlands Cancer Registry. Descriptive statistics were used to summarize treatment and treatment sequence(primary cytoreductive surgery(PCS) or neoadjuvant chemotherapy and interval cytoreductive surgery(NACT-ICS)). Moreover, outcome of surgery was compared between geographical regions. Multilevel logistic regression was used to assess whether existing variation is explained by geographical region and case-mix factors.
Results: Overall, 6,741 patients were diagnosed with FIGO IIIC or IV disease. There were no differences in the percentage of patients that received any form of treatment between the geographical regions(range 80–86%, $P = 0.162$). In patients that received cytoreductive surgery and chemotherapy, a significant variation between the geographical regions was observed in the use of PCS and NACT-ICS(PCS: 24–48%, $P < 0.001$). The percentage of complete cytoreductive surgeries after PCS ranged from 10 to 59%($P < 0.001$) and after NACT-ICS from 37 to 70%($P < 0.001$). Moreover, geographical region was independently associated with the outcome of surgery, also when adjusted for treatment sequence($P < 0.001$).
Conclusion: We observed a significant variation in treatment approach for advanced EOC between geographical regions in the Netherlands. Furthermore, the probability to achieve no residual disease differed significantly between regions, regardless of treatment sequence. This may suggest that surgical outcomes can be improved across geographical regions.

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Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynaecological cancer worldwide, and long-term overall survival did not change over the last twenty years [1,2]. Most patients are diagnosed with advanced stage disease, which requires extensive treatment consisting of maximal cytoreductive surgery (CRS) and platinum-based chemotherapy.

The outcome of CRS is one of the few amendable factors in EOC patients, and is directly linked to survival rates [3]. Patients with no macroscopic residual disease after surgery (complete CRS) have the best survival [4]. Extensive surgical procedures, including bowel surgery and diaphragm stripping, are often required to obtain a complete CRS. It is suggested that surgical outcomes can be improved through several factors. First of all, neoadjuvant chemotherapy (NACT) may reduce intra-abdominal tumour load, which diminishes the complexity of the surgical procedure, in order to increase the likelihood to successful surgery [5,6]. Furthermore, centralizing surgical care, and thus increasing the surgical volume of hospitals and individual gynaecologic-oncologists, contributes to improved (surgical) outcomes [7–9]. Finally, discussing all patients in (regional) multidisciplinary tumour board meetings, including adequate preoperative diagnostics (imaging, pathology review and in selected patient diagnostic laparoscopy), ensures that every patient undergoes the most optimal treatment strategy [10,11].

The most optimal treatment strategy, however, is subject to a lively debate among experts. Over the last years, NACT followed by interval cytoreductive surgery (ICS) became an attractive treatment alternative with non-inferior long-term outcome in randomised studies and reduced morbidity in Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage IIIC and IV patients [5,6]. However, since survival of patients after a complete primary cytoreductive surgery (PCS) is higher when compared to a complete ICS, variation between believers and non-believers exists in adopting NACT-ICS [5,12–14].

Patients with ovarian cancer are treated within different geographical regions in the Netherlands. In these regions, specialised gynaecologic-oncologic centres organise regional multidisciplinary tumour board meeting, in which patients from the whole region are discussed. Moreover, these meetings facilitate referral for CRS, as the performance of CRS is restricted to specialised gynaecologic-oncologic centres that perform a minimum of twenty cytoreductive surgeries annually. This situation allows us to study differences in practice patterns between geographical regions for all FIGO stage IIIC and IV patients, including those who undergo limited or no therapy at all. Therefore, the aim of our study is to describe variation between geographical regions in the Netherlands in primary treatment for advanced EOC patients, and its effect on patient outcome.

Methods

We identified all consecutive patients that were diagnosed with EOC, including fallopian tube and primary peritoneal cancer (International Classification of Diseases for Oncology (ICD-O) C56.9, C57.0, C48.2), from the Netherlands Cancer Registry (NCR) [15]. Thoroughly trained registration clerks routinely extract information on patient and tumour characteristics, diagnostic procedures and treatment from medical records. For this study, complementary data were obtained for patients who underwent chemotherapy and/or cytoreductive surgery. Follow-up is obtained by annual linkage with the municipal demography registries (GBA). The study design, data abstraction process and storage protocols were approved by the NCR review board.

Study population

We included all patients who were diagnosed with FIGO IIIC and IV disease between 01.01.2008 and 31.12.2015. Patients were divided into groups according to their treatment; either no therapy (i.e. neither chemotherapy nor cytoreductive surgery), chemotherapy only, or a combination of cytoreductive surgery and chemotherapy. Moreover, patients were categorised according to treatment sequence in PCS, NACT-ICS, or PCS + NACT-ICS. The latter category was used for patients who underwent an exploratory laparotomy followed by NACT and ICS, or when initial PCS resulted in a suboptimal cytoreduction and secondary ICS was performed.

Geographical regions

In the Netherlands, patients with ovarian cancer are treated within eight different geographical regions. Over time, the number of hospitals that perform cytoreductive surgery decreased as a result of formal surgical volume norms. Every region contains at least one academic/specialized referral centre. The treatment hospital defined the specific geographical region for patients. In case hospitals of surgery and chemotherapy differed, the hospital of surgery was chosen as treatment hospital. In addition, when patients did not undergo surgery or chemotherapy, the hospital of initial diagnosis was chosen.

Definitions

The outcome of cytoreductive surgery was defined as complete in case of no macroscopic residual disease, as optimal in case of residuals of 0–1 cm in maximal diameter, and as suboptimal in case of >1 cm of residual disease. In case patients underwent multiple (attempts to) cytoreductions (PCS + NACT-ICS, the last cytoreductive surgery was used to determine the outcome of cytoreductive surgery.

For patients who underwent chemotherapy and/or cytoreductive surgery, CA125 at diagnosis, American Society of Anaesthesiologists (ASA) scores, and present comorbidities were extracted from medical records. The latter were used to calculate the Charlson Comorbidity Index (CCI) [16]. In patients with limited or no therapy, socioeconomic status (SES) was used as proxy for comorbidity, since concomitant medical conditions are more common in patients with low SES [17,18]. SES was based on a patients postal area according to the Netherlands Institute for Social Research [19].

Statistical analyses

Descriptive statistics were used to summarize treatment, treatment sequence (PCS, NACT-ICS or PCS + NACT-ICS) and outcomes of cytoreductive surgery in each geographical region and over the study period (in two-year intervals). In order to gain insight into crude differences between regions (i.e. not adjusted for patient- and tumour characteristics), chi-square tests were used. Multilevel logistic regression was used to account for differences in case mix between geographical regions. We adjusted our models for age, FIGO stage, histologic subtype, differentiation grade, year of diagnosis and SES. In patients who underwent cytoreductive surgery and/or chemotherapy multilevel models were adjusted for performance score and CCI, rather than SES. In addition, CA125 at diagnosis ($\log_e$-transformed) was also added in these models.

Kaplan-Meier survival curves and log-rank tests were used to analyse overall survival (OS) and event-free survival (EFS). OS was defined as the date from diagnosis until date of death or last follow-up date in case patients were still alive (01.02.2018), which was available for all included patients. EFS was only available for patients who underwent chemotherapy and/or cytoreductive surgery. In these patients; EFS was defined as the date from last treatment until date of recurrence, progression or death (whichever occurred first). Progression was defined as clinical signs of tumour growth, i.e. increase in CA125 and/or visible lesions on imaging techniques (either regrowth of pre-existing lesions or new lesions), combined with the clinical judgment of the treating physician (medical oncologist or gynaecologists). In case patients had no signs of progression and were still alive, they were censored at their last hospital visit. For multivariable cox-regression models, we adjusted survival outcomes for age at diagnosis, FIGO stage, histologic subtype, differentiation grade, CCI, CA125 at diagnosis and treatment sequence. A *P*-value <0.05 was considered statistically significant, and analyses were performed using STATA/SE (version 14.1; STATA CORP., College Station, Texas, USA).

Results

Overall, 6,741 patients were diagnosed with FIGO IIIC or IV disease between 01.01.2008 and 31.12.2015. We categorized patients into eight different geographical regions, which ranged in number of patients from 515 to 1,572 patients over the total study period. Baseline characteristics of all patients and stratified by region were presented in the appendix (S1).

Variation in treatment over time and between geographical regions

The number of patients that underwent CRS in combination with chemotherapy decreased over time in our total population (from 70% in 2008–2009 to 62% in 2014–2015). Simultaneously the number of patients that received solely chemotherapy increased, and the number of patients that received neither chemotherapy nor surgery increased as well (S2a). Changes over time were mainly observed in case of FIGO stage IIIC, while therapy did not significantly change in FIGO IV patients ($P = 0.899$). Over time, median age at diagnosis increased from 67 years (interquartile range (IQR) 59–76) to 69 years (IQR 61–77, $P < 0.001$). Changes in therapy regimen were not observed in patients aged younger than 65 ($P = 0.710$), but did change significantly in patients over 65 years ($P = 0.028$).

We observed no difference in the number of patients that received no therapy between geographical regions (Fig. 1a, range 14–20%, $P = 0.134$). This did not change when we adjusted our analyses for patient- and tumour characteristics (LR test ICC 0.4%, $P = 0.162$). The number of patients that underwent cytoreductive surgery in combination with chemotherapy did differ between the geographical regions (range 61–71%, $P < 0.001$), also when adjusted for patient- and tumour characteristics (LR test ICC 1.4%, $P < 0.001$).

Variation in the use of PCS and NACT-ICS over time and between geographical regions

In patients that underwent the combination of cytoreductive surgery and chemotherapy, we observed a significant decrease in the use of PCS over time (41% in 2008–2009 to 27% in 2014–2015, $P < 0.001$, S2b). Simultaneously, the number of patients that underwent PCS followed by NACT-ICS decreased over time as well (11% in 2008–2009 to 6% in 2014–2015, $P < 0.001$, S2b). Furthermore, there was a significant variation in initial treatment sequence between the geographical regions (PCS: 24–48%, NACT-ICS: 44–70% and PCS + NACT-ICS: 5–13%, $P < 0.001$, Fig. 1b).

The variation in use of initial NACT-ICS could not be explained by differences in patient characteristics, while treatment region contributed to the variation in used treatment sequence (LR test ICC 5.7%, $P < 0.001$). Factors that were associated with a higher likelihood towards initial NACT-ICS were higher age, FIGO IV disease, poor performance score and a high CA125 at diagnosis (Table 1).

Variation in the outcome of surgery over time and between geographical regions

The probability of a complete cytoreductive surgery was higher when patients were treated with NACT (41% after PCS, 50% after NACT-ICS), also when adjusted for patient- and tumour characteristics (OR 1.56, 95%CI 1.33–1.82). Therefore, the outcomes of surgery are presented stratified by the treatment sequence. Surgical outcomes improved over time, for both PCS and NACT-ICS patients (S3a and S3b respectively). There was a significant variation, however, in surgical outcomes between geographical regions. For patients who underwent PCS, the percentage of complete surgery ranged between 10 and 59% ($P < 0.001$, Fig. 2a). When adjusted for patient- and tumour characteristics, there was still a significant variation between geographical regions (LR test $P < 0.001$, ICC 19.3%). The same patterns were observed for patients who received NACT and ICS, but smaller variation existed between the geographical regions (37–70%, LR test $P < 0.001$, ICC 3.7%, Fig. 2b).

When treatment sequence was incorporated in our multilevel model, the probability of complete CRS was still influenced by the geographical region where patients were treated (24–67%, LR test $P < 0.001$, ICC 6.5%).

Survival outcomes

OS was significantly influenced by treatment sequence and outcome of CRS. OS was the highest in patients with no residual disease after PCS (S4). Survival of patients who underwent PCS + NACT-ICS was similar to patients that underwent initial NACT-ICS (5-year survival both 23%, $P = 0.741$).

In all patients together, including those with no or limited therapy, there was no significant difference in OS between geographical regions (five-year OS range 17–22%, $P = 0.059$, Fig. 3a). In patients who underwent chemotherapy and cytoreductive surgery survival rates did differ significantly (five-year OS range 24–30%, $P = 0.030$, Fig. 3b). In addition, EFS (only known for patients undergoing cytoreductive surgery and chemotherapy) also differed significantly between regions (five-year EFS range 9–13%, $P = 0.030$, Fig. 3c). Patients who were treated in the region with the lowest number of complete cytoreductive surgeries (region 5), experienced significantly worse EFS and OS (adjusted HRE_{FS} 1.28(1.14–1.44) and HR_{OS} 1.18(1.04–1.34) compared to all other regions). However, as stated above, the OS of all patients (including those with no or limited therapy) in this region was comparable to the other regions (adjusted HR_{OS} 1.07(0.97–1.18)).

Discussion

In this large population-based study, we gained insight in the variation between geographical regions in the primary treatment for EOC patients. The use of PCS and NACT-ICS differed significantly between regions and could not be (fully) explained by differences in patient populations. Moreover, the probability of complete cytoreductive surgery differed among the regions, even when accounting for possible confounders (including treatment sequence).

A considerable number of patients did not undergo any treatment in our population (16%), and this was not associated with

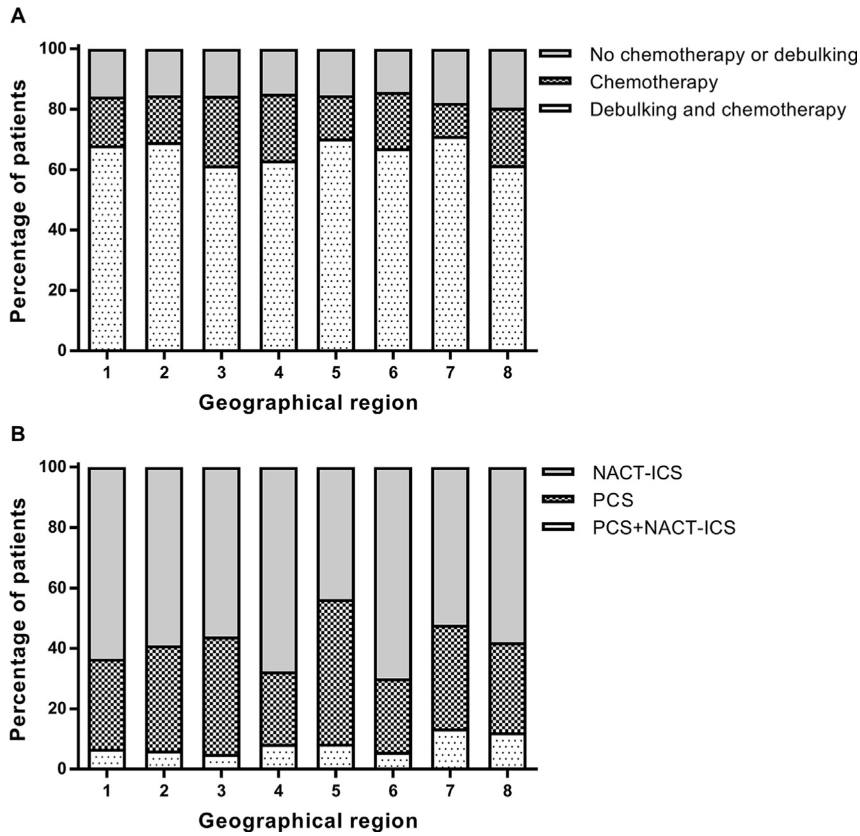

Fig. 1. Treatment approach (A) and treatment sequence (B) in advanced stage EOC patients by geographical region.

Table 1
Prognostic factors that are associated with NACT-IDS in advanced EOC patients.

	OR (95%CI)[a]
Age	
<65	Reference
65-75	**1.27 (1.07–1.49)**
>75	1.22 (0.98–1.52)
FIGO stage	
IIIC	Reference
IV	**2.93 (2.44–3.52)**
Histologic subtype	
Serous	Reference
Mucinous	**0.37 (0.22–0.63)**
Endometrioid	**0.61 (0.40–0.92)**
Clear-cell	**0.23 (0.15–0.36)**
Adenocarcinoma NOS	**2.25 (1.66–3.04)**
Other	**0.41 (0.22–0.76)**
Differentiation grade	
I	Reference
II	**1.46 (1.21–1.76)**
III	**1.71 (1.60–2.84)**
ASA score	
ASA I	Reference
ASA II	**1.46 (1.21–1.76)**
ASA ≥3	**2.13 (1.60–2.84)**
CCI score*	
0	Reference
1	0.93 (0.75–1.14)
≥2	0.93 (0.76–1.15)
CA125 at diagnosis	**1.41 (1.33–1.48)**
Year of diagnosis	**1.16 (1.12–1.21)**

Bold values are significant p<0.05.
[a] All OR's are adjusted for the listed variables, all unknown variables were included in the model but not listed in this table.

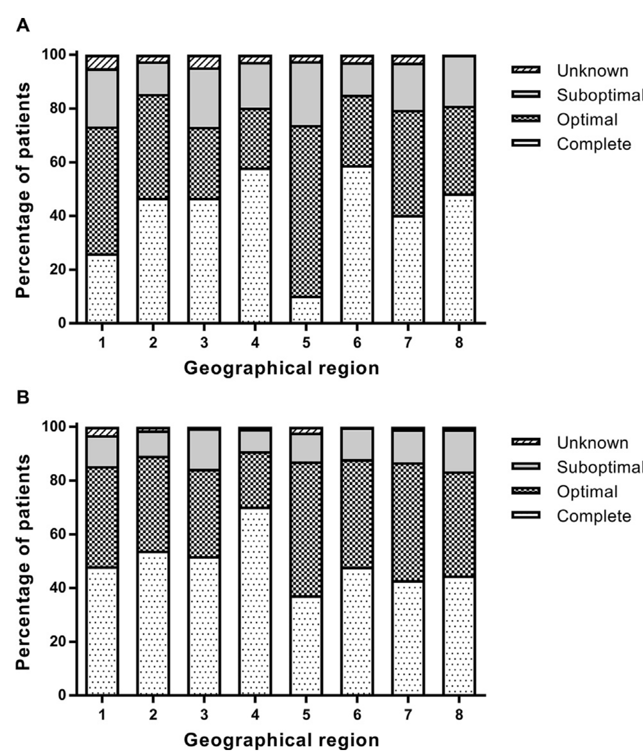

Fig. 2. Surgical outcomes after PCS (a) and NACT-ICS (b) in advanced stage EOC patients by geographical region.

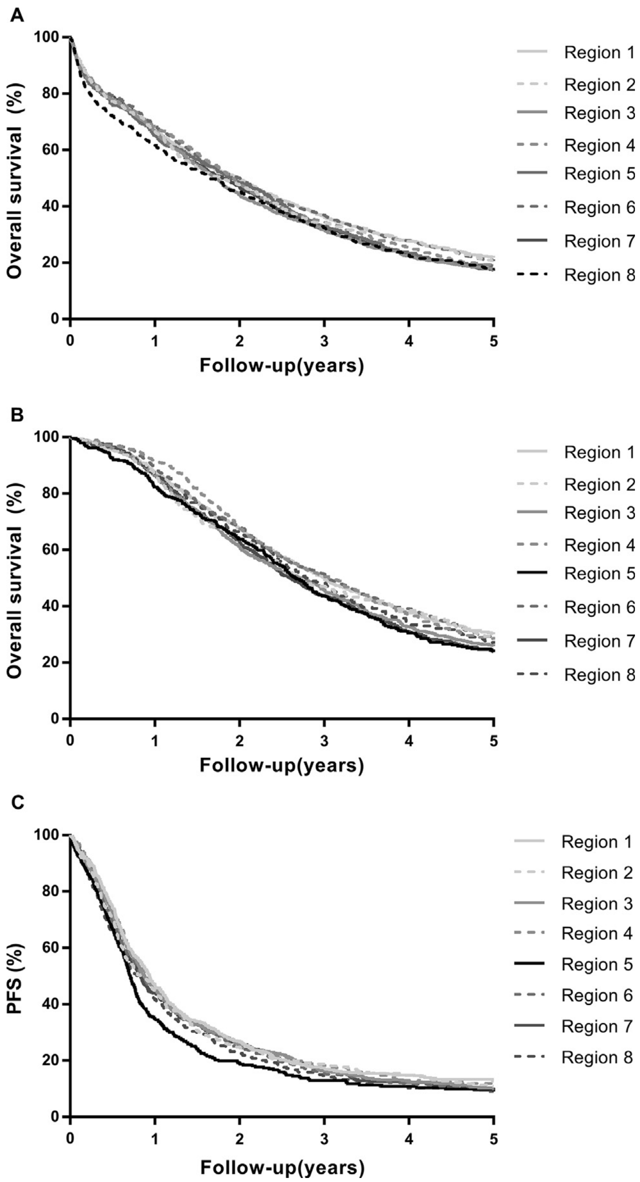

Fig. 3. Kaplan-Meier survival curves stratified by geographical region. A) Overall survival for all patients B) Overall survival for patients who underwent cytoreductive surgery and chemotherapy C) Progression-free survival for patients who underwent cytoreductive surgery and chemotherapy.

geographical region. Over time, the number of patients that did not undergo any treatment increased, and was (partly) explained by an increasing age at diagnosis. Age is a strong predictor of receiving treatment [20–23]. This phenomenon could be explained by more comorbidity at higher age, and also by patients' wishes. Proper selection of patients who undergo treatment is of paramount importance, as some studies showed that the effect of age on survival disappears when standard treatment is applied [22,24]. A standardised geriatric assessment may help to identify those patients who benefit from surgery and platinum-based combination chemotherapy, and those who may not complete this aggressive therapy [25–27]. In the latter, (palliative) chemotherapy may increase survival in combination with symptom control and better quality of life. The effect of single-agent or standard combination chemotherapy should be studied in this fragile population as well, considering the increasing number of patients that is diagnosed at an older age.

In patients that underwent the combination of chemotherapy and cytoreductive surgery, the timing of surgery is based on (inter) national guidelines, in which a wide range of advices exists. The Dutch guideline (2012) and the NICE guideline (2011) both suggest that the aim of cytoreductive surgery should be complete resection, for which PCS and NACT-ICS can both be used [28,29]. The Belgian guideline (2016) prefers PCS when complete resection seems feasible, but NACT-ICS could be considered as alternative treatment approach (predominantly when lesions are larger than 5 cm) [30]. The American guideline prefers PCS when complete cytoreductive surgery is deemed feasible, but prefers NACT-ICS over PCS in case of a high perioperative risk profile or a low likelihood to optimal cytoreduction (<1 cm) [31]. The German guideline (2013), however, states that patients obtain no benefit from NACT-ICS, and PCS is thus the preferred treatment option with no macroscopic residual disease as goal [32]. The discrepancy between guidelines reflects the ongoing debate about the subject, and the absence of clear advice in the Dutch guideline explains the observed variation between geographical regions.

A previously published meta-analysis concluded that NACT-ICS was inferior to PCS, and comprised retrospective data [13]. In our study, which is also based on retrospective data, patients with no residual disease after PCS experienced the best survival. Retrospective studies on PCS versus NACT-ICS are exposed to confounding by severity, which refers to the situation where physicians alter their treatment according to patient- and tumour characteristics [33]. Especially in earlier years, where NACT-ICS was an exception in the treatment for advanced EOC, patients who underwent this treatment sequence were probably older and had a higher tumour load, which explains the inferior survival of NACT-ICS patients in these series. Two landmark randomized clinical trials found no differences in survival outcomes between PCS and NACT-ICS [5,6]. The most important limitation of both studies is the low rate of complete cytoreductive surgeries, predominantly in the PCS group (19% and 17% in the EORTC and CHORUS trial respectively), which may limit external validity. Upcoming RCTs try to overcome this limitation by setting surgical requirements, as it has been argued that surgical interventions can only be properly studied in RCTs with adequate surgical quality [34,35].

It is agreed that the outcome of surgery is one of the most important prognostic factor for prolonged survival [3,4]. Our study showed that the geographical region influences the probability of leaving no macroscopic residual disease, independent of treatment approach (PCS vs. NACT-ICS). Patient related factors and tumour biology are known to affect surgical outcome, but are hardly amendable [36–38]. Centralisation of care, however, may improve surgical outcomes and survival in ovarian cancer patients [7–9]. A national consensus was reached in 2012 to restrict the performance of surgery to hospitals that carried out a minimum of twenty cytoreductive surgeries on an annual basis in the Netherlands. This consensus, in combination with increased use of NACT-ICS, resulted into more favourable surgical outcomes over time. The differences between geographical regions were, however, also present in the period after 2012 (data not shown). Previous studies already showed that a considerable number of hospitals involved in the surgical treatment of ovarian cancer patients, did not meet the minimal requirement of twenty cytoreductive surgeries annually in the Netherlands (56% in 2013 and 31% in 2015) [9,39]. Although the most optimal treatment strategy is a subject of a lively debate, the goal of cytoreductive surgery should be no macroscopic residual disease. Further optimisation of surgical outcomes could be achieved through adequate patient selection, and adequate centralisation of surgical care to ensure the most optimal treatment regimen for all patients. These findings suggest opportunities for improvement to ensure that the likelihood towards no macroscopic residual disease is equal in patients with similar extent of disease.

In the present study, we observed variation in survival between geographical regions. This may be related to the variation in surgical outcomes, as OS and EFS were the lowest in the region with the lowest number of complete cytoreductive surgeries. However, when all patients were analysed together (including those with no or limited therapy), survival was comparable between all regions. Patient selection to those who benefit from cytoreductive surgery and chemotherapy may explain this discrepancy, and this may differ between regions. Moreover, the impact of the observed variation in clinical outcome is susceptible to a variety of biases. Earlier studies showed that initial disease burden at diagnosis influenced OS, while patients had the same amount of residual disease after surgery [36,38]. In addition, we observed that EFS was more affected than OS by the treatment region. This may be explained by other differences between geographical regions. Long-term overall survival is not only influenced by the primary treatment, but also by a patient's response to treatment for recurrent disease. Data about treatment after recurrence is lacking, however, in our database. Finally, the judgement of residual disease between geographical regions probably differs between gynaecologists, and may have influenced our results [40,41].

Our study has some limitations. The amount of intra-abdominal disease at diagnosis (besides FIGO stage) as well as the location of the tumour bulk (upper or lower abdomen) were unknown in our database. These factors are inherently associated with successful surgery, and may explain (some) variation between regions. Moreover, a substantial number of patients did not undergo any treatment, but the rationale for omitting treatment in individual patients was not recorded. At last, our multivariable models were not adjusted for the use of (hyperthermic) intraperitoneal chemotherapy, and could have potentially biased our results since this is associated with improved survival in selected patient populations [42,43]. Strengths of our study are the population-based character, complete follow-up status, and additional data in treated patients (such as comorbidity, CA125 at diagnosis and performance status) for which we could adjust our models.

In conclusion, we observed significant variation in the treatment approach between geographical regions, and in the probability to reach no macroscopic residual disease. This variation resulted in survival differences in the treated population, but not when all patients were analysed together. As the results of upcoming RCTs are eagerly awaited for the optimal treatment approach, stricter compliance to surgical guidelines may improve outcome of surgery.

Conflicts of interest

None.

Author contributions

Study design/concepts: MT, GS, BS, KV, RK, MA.

Data acquisition: MT.

Quality control of data and algorithms: MT, MA.

Data analysis and interpretation: MT, GS, BS, AB, RB, GF, CG, AK, ER, PZ, KV, RK, MA.

Manuscript preparation: MT.

Manuscript editing and review: MT, GS, BS, AB, RB, GF, CG, AK, ER, PZ, KV, RK, MA.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.04.009.

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