Centralization of ovarian cancer in the Netherlands

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Centralization of ovarian cancer in the Netherlands: Hospital of diagnosis no longer determines patients' probability of undergoing surgery

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HIGHLIGHTS

- Hospital of diagnosis influenced the probability of undergoing cytoreductive surgery.
- Surgical outcomes and overall survival improved in the Netherlands.
- Centralization of surgical care resolved variation between hospitals.

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ABSTRACT

Objective. Surgical care for advanced stage epithelial ovarian cancer (EOC) patients has been centralized in the Netherlands since 2012. We evaluated whether the likelihood for patients to undergo surgery depends on the hospital of initial diagnosis before and after centralization of surgical care.

Methods. Patients with EOC FIGO stage IIB–IV, diagnosed in the Netherlands between 2000 and 2015, were identified from the Netherlands Cancer Registry. Multilevel multivariate logistic regression was used to study the association between hospital of diagnosis and patients' likelihood of undergoing surgery in subsequent time periods. Furthermore, changes in overall survival were analyzed by multivariable Cox regression models.

Results. 15,314 EOC patients were selected from the NCR. Hospital of diagnosis was identified as a significant level for patients' likelihood of undergoing surgery in 2000–2005 (LR test $p < 0.001$), as well as in 2006–2011 (LR test $p = 0.002$) but not in 2012–2015 (LR test $p = 0.127$). Patients who underwent surgery in 2012–2015 had a better survival when compared to 2006–2011 (HR 0.90(0.84–0.96)).

Conclusion. This study shows that centralization of surgical care resolved the variation between hospitals in the probability to undergo cytoreductive surgery for patients with advanced EOC. Since centralization was established in 2012, the decision to operate patients seems solely attributable to patient and tumor characteristics. This supports the growing evidence in favor of centralizing (surgical) treatment for complex and heterogeneous diseases such as EOC.

1. Introduction

Epithelial ovarian cancer (EOC) is the seventh most common cancer in women worldwide and the most lethal gynecologic cancer [1,2]. Due to the non-specific symptoms of this malignancy the majority of patients are diagnosed with advanced staged disease. This results in poor prognosis with five-year survival rates of 25–35% [3,4]. The mainstay of therapeutic management consists of platinum based chemotherapy in addition to cytoreductive surgery. Patient survival depends (among others) on the ability to minimize residual disease during surgery [5, 6]. This suggests an amendable role for cytoreductive surgery in the primary treatment for EOC.

The efforts to improve care for EOC patients should emphasize on minimizing the amount of residual disease by extensive surgery. Research has shown that cytoreductive surgery performed in high-

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volume hospitals by experienced gynecologic-oncologists leads to improved outcome rates [7–15]. In the Netherlands, EOC patients were traditionally staged and treated in all hospitals, regardless of patients- or tumor characteristics. Consequently the level of surgical expertise was suspected to differ considerably across hospitals. In the last decade, a gradual centralization process was initiated in several stages. In the first stage, gynecologists in smaller hospitals consulted registered gynecological-oncologists to perform surgery together in these smaller hospitals. In 2012, a national consensus was reached to restrict the performance of surgery to hospitals which carried out a minimum of twenty cytoreductive surgeries on an annual basis. Furthermore, more emphasis was placed on regional multidisciplinary tumor board (MDT) meetings. All patients diagnosed with ovarian cancer are discussed with gynecological-oncologists, medical oncologists, pathologists and radiotherapists, prior to treatment. Overall, these developments led to improved surgical outcomes and improved survival in the Netherlands [8,16].

Although surgical care is increasingly centralized and outcomes improved for EOC patients, the initial diagnosis is made in virtually all Dutch hospitals. Most studies focus on the outcome rates of cytoreductive surgery and overall survival with respect to the success of centralization. However, the diagnostic process and possible variation in treatment decisions between diagnosing hospitals is not a widely studied subject for ovarian cancer patients. In order to improve outcome rates for EOC patients, treatment decisions should be based on tumor- and patient characteristics and not be influenced by the hospital where patients are initially diagnosed. The present study examined whether the likelihood for EOC patients to undergo surgery depends on the hospital of initial diagnosis in an era of gradual centralization of surgical care.

2. Methods

2.1. Data collection

Patients were identified from the Netherlands Cancer Registry (NCR). The NCR is a population-based registry based on notification by the automated nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) and the National Registry of Hospital Discharge Diagnosis (LMR). It covers all newly diagnosed malignancies in the Netherlands. Dedicated registration clerks routinely extract patient information from medical records within the hospitals.

The hospital and date of diagnosis is recorded for all patients in this study. In addition, hospitals and dates of provided treatments are recorded for patients from 2005 onwards. Treatment information includes the type of surgery (exploratory laparotomy, staging or cytoreductive surgery) and systemic treatment. Outcome of cytoreductive surgery was registered from 2004 onwards (optimal (≤1 cm) versus incomplete (>1 cm)). Complete cytoreduction, defined as no macroscopic residual disease, is registered from 2010.

As for patient characteristics, data were obtained on patients' age at diagnosis and socioeconomic status. Information on vital status and date of death are obtained through linkage with the municipal demography registries. Regarding tumor characteristics, information is available on histological subtype according to the International Classification of Disease-Oncology (ICD-O), differentiation grade and both clinical and pathological TNM (tumor-node-metastasis) stage [17,18]. Staging according to the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) 2009 system was derived from the TNM.

2.2. Study population

All consecutive patients diagnosed with advanced stage EOC, including peritoneal and fallopian tube cancer (ICD-O codes C48.1, C48.2, C56.9 and C57.0), between 2000 and 2015 were selected from the NCR. Advanced stage EOC was defined as FIGO stage IIB or higher based on operative findings and final pathology. In case patients did not undergo surgery or when patients underwent interval cytoreductive surgery after neoadjuvant chemotherapy (NACT), clinical tumor stage was used to avoid down-staging. Patients with an unknown FIGO stage were included as well, but only if they were diagnosed with peritoneal EOC (C48.1 and C48.2) because TNM stage was not registered for these patients until 2010.

2.3. Hospital of diagnosis and surgery

Diagnosis was assigned to the hospital that was visited first by each patient for her disease. If hospitals merged within one of the specific time periods, these hospitals were analyzed as a single institution for that particular period. For calculating patient's probability of undergoing surgery, surgery was defined as any attempt to perform cytoreductive surgery, regardless of residual disease, timing of surgery and hospital of surgery. Thus, patients who underwent explorative surgery that did not result in tumor removal were regarded as patients who underwent surgery.

2.4. Statistical analyses

Multilevel statistical techniques have been developed to analyze data arranged in a natural hierarchy [19,20]. Hence, to assess whether hospital level influenced decision-making processes, multilevel logistic regression was performed, thereby adjusting for case mix factors [21,22]. We included age, FIGO stage, histological type, differentiation grade and SES in the model, based on basic multivariable logistic regression models, and predicted the probability of undergoing surgery for each individual hospital expressed as an odds ratio (OR) accompanied by a 95% confidence interval (CI). The likelihood ratio test (LR test) was used to assess the influence of hospital level on the probability of undergoing surgery for the whole period. To study effects over time, a comparison was made between three time periods. The period before national consensus on centralization took place was divided in two equal periods (2000–2005 and 2006–2011) and these were compared to the last period (2012–2015).

The impact of centralization on overall survival was explored using multivariable Cox regression models for the three individual time periods. These periods were analyzed for all patients combined and stratified by surgical treatment (yes or no). Overall survival time was defined as the date of diagnosis until death or if patients were still alive to the last follow-up date (1 February 2017). For all analyses a p-value < 0.05 was considered statistically significant. Statistical analyses were performed using STATA/SE (version 14.1; STATA CORP., College Station, Texas, USA).

3. Results

Between 2000 and 2015, 15,314 EOC patients were diagnosed with advanced stage disease. Mean age at diagnosis was 66.3 years (standard deviation (SD) 12.4 years) and increased over time (from 65.1(12.5) in 2000–2005 to 67.8(12.0) in 2012–2015, $p < 0.001$). Most patients were diagnosed with a high grade serous tumor and had FIGO stage III disease. The number of patients with an unknown FIGO stage decreased over time, while the number of patients with FIGO IV disease increased (Table 1). A substantial number of our patients did not receive any therapy (12%) or received single therapy only (19%).

3.1. Hospital of diagnosis and hospital of surgery

Due to merges, patients were diagnosed in 96 hospitals in 2000–2005, 92 hospitals in 2006–2011 and 90 hospitals in 2012–2015. Consequently, the mean annual number of diagnoses per

Table 1
Baseline characteristics of EOC patients diagnosed in the Netherlands by period of diagnosis (n = 15,314).

	2000–2005 n (%)	2006–2011 n (%)	2012–2015 n (%)	p-Value
Age				<0.001[a]
18–59	1723 (33.0)	1689 (28.4)	969 (23.4)	
60–74	2156 (41.4)	2598 (43.6)	1865 (45.0)	
>75	1335 (25.6)	1669 (28.0)	1310 (31.6)	
Mean (SD)	65.1 (12.5)	66.2 (12.4)	67.8 (12.0)	<0.001[b]
FIGO stage				<0.001[a]
IIB–IIC	447 (8.6)	465 (7.8)	359 (8.7)	
IIIA–IIIC	3085 (59.2)	3387 (56.9)	2477 (59.8)	
IV	1163 (22.3)	1515 (25.4)	1303 (31.4)	
Unknown	519 (9.9)	589 (9.9)	5 (0.1)	
Type of tumor				<0.001[a]
High grade serous	4044 (77.6)	4782 (80.3)	3356 (81.0)	
Low grade serous	143 (2.7)	170 (2.9)	121 (2.9)	
Other	1027 (19.7)	1004 (16.8)	667 (16.1)	
Socioeconomic status				0.042[a]
High	1562 (29.9)	1776 (29.8)	1262 (30.4)	
Medium	2142 (41.1)	2397 (40.3)	1581 (38.2)	
Low	1510 (29.0)	1783 (29.9)	1301 (31.4)	
Total	5214	5956	4144	

[a] Chi-square test.
[b] ANOVA test.

hospital increased from 9 (interquartile range (IQR) 6–11) in 2000–2005 to 12 (IQR 7–15) in 2012–2015.

Within the study period the number of patients who underwent surgical treatment decreased from 77% in 2000–2005 to 73% in 2012–2015 ($p < 0.001$, Table 2). The number of hospitals that performed cytoreductive surgery decreased from 77 in 2006–2011 to 39 in 2012–2015 (unknown for 2000–2005 as hospital of surgery was not registered at that time). Despite of the overall decrease in surgical treatment, the mean annual number of cytoreductive surgeries per hospital increased from 9 (IQR 3–12) in 2006–2011 to 17 (IQR 5–20) in 2012–2015. More patients were referred to a specialized hospital to undergo cytoreductive surgery in the last period (35% in 2006–2011 compared to 71% in 2012–2015, $p < 0.001$). Furthermore, the number of hospitals that met the minimum requirement of 20 cytoreductive surgeries annually increased from 8% in 2006–2011 to 26% in 2012–2015. In addition, in 2015 69% of the hospitals that performed cytoreductive surgery met this requirement.

The percentage of patients who underwent an incomplete cytoreduction, indicating macroscopic residual tumor of >1 cm, decreased from 23% in 2006–2011 to 13% in 2012–2015 ($p < 0.001$). For patients treated with primary cytoreductive surgery or neoadjuvant chemotherapy these percentages decreased from 23% to 16% ($p < 0.001$) and from 22% to 12% ($p < 0.001$), respectively. Over the total study period, patients who were treated with primary cytoreductive surgery had a higher probability of an incomplete cytoreductive surgery compared to patients who received neoadjuvant chemotherapy (OR 1.37(1.23–1.52)).

Table 2
Hospital characterizations by period of diagnosis (n = 15,314).

	2000–2005 n (%)	2006–2011 n (%)	2012–2015 n (%)
Diagnosing hospitals	96	92	90
1–10 annually	66 (68.7)	46 (50.0)	43 (47.8)
≥10 annually	28 (29.2)	42 (45.7)	39 (43.3)
≥20 annually	2 (2.1)	4 (4.3)	8 (8.9)
Mean diagnosis annually (IQR)	9.1 (6.1–11.1)	10.8 (6.5–14.2)	11.5 (7.1–14.8)
Debulking hospitals	N.A.	77	39
1–10 annually	N.A.	52 (67.5)	18 (46.2)
≥10 annually	N.A.	19 (24.7)	11 (28.2)
≥20 annually	N.A.	6 (7.8)	10 (25.6)
Mean surgeries annually (IQR)	N.A.	9.1 (3.3–12.2)	16.9 (5.3–19.5)
Surgical treatment	4022 (77.1)	4622 (77.6)	3012 (72.7)
Referral for debulking surgery[a]	N.A.	1067 (35.4)	1324 (71.1)
Total	5214	5956	4144

[a] Patients who were diagnosed in specialized centers were excluded from this analysis.

3.2. Probability of undergoing surgery

Prognostic factors for undergoing surgery are high socioeconomic status and younger age at diagnosis. Compared to those with FIGO III disease, patients with FIGO IV had a lower probability of undergoing surgery (OR 0.27(0.24–0.29)) and patients with FIGO IIb–IIc had a higher probability (OR 2.09 (1.68–2.60)). Furthermore, patients with a low-grade serous tumor were more likely to undergo surgery compared to those with high-grade serous tumors (S1).

In addition to these patient-related factors, multilevel multivariate logistic regression identified the hospital of diagnosis as a significant level for patients' likelihood of undergoing surgery in 2000–2005 (LR test $p < 0.001$, intra-class correlation (ICC) 6.1%) as well as in 2006–2011 (LR test $p = 0.002$, ICC 2.5%) (Fig. 1a, b). This effect disappeared in the period 2012–2015, as no association between the hospital of initial diagnosis and probability of undergoing surgery was found in this timeframe (LR test $p = 0.127$, ICC 0.9%, Fig. 1c).

3.3. Survival

Overall, crude five-year survival rates increased over time (23.5% in 2000–2005, 24.4% in 2006–2011 and 25.7% in 2012–2015). When adjusted for patient and tumor characteristics, patients diagnosed in 2000–2005 experienced significant worse survival compared to those diagnosed in 2006–2011 (hazard ratio (HR) 1.15(1.10–1.20)) but there was no difference between patients diagnosed in 2006–2011 and in 2012–2015 (HR 0.98(0.93–1.03)). When stratified by surgical treatment we did see an increase in overall survival for patients who underwent surgery in the last period compared to 2006–2011 (HR 0.90(0.84–0.96), Table 3).

4. Discussion

In this study, we showed that for EOC patients, centralization of surgical care resulted in more coherent treatment policies across Dutch hospitals. Following a number of initiatives, including the national consensus on a volume norm for cytoreductive surgeries, the decision whether or not to operate patients no longer depends on the hospitals of initial diagnosis. Instead, patients and tumor characteristics may now fully explain observed variations in treatment decisions.

Centralization of (surgical) care aims to improve overall survival of EOC patients by, among others, improving the outcome of cytoreductive surgery. The percentage of cytoreductive surgeries that result in no macroscopic residual disease increase when they are performed in high volume hospitals by experienced gynecological-oncologists [14,15,23]. In line with these studies, our study also showed that the percentage of patients with >1 cm of residual disease decreased after centralization was established. Most importantly, our study confirmed the improved survival rates after centralization for patients who underwent (an attempt to) surgical treatment as reported earlier by Eggink et al. [8]. In addition to these favorable outcomes, this study shows a decrease in treatment variation between diagnosing hospitals, suggesting improved awareness about the important role of cytoreductive surgery on patients' prognosis, also in non-surgical centers.

Overall survival rates of the whole study population remained fairly stable around 25%, which is lower when compared to the results reported by the majority of studies [24–26]. However, most of these series concern single or multicenter studies that include a selective group of patients who had primary cytoreduction in combination with chemotherapy (PDS). In contrast, in our population-based study, we included unselected patients by using the NCR database. In this unselected nationwide population, a fair number of patients did not receive any treatment or underwent single therapy only, which translates into lower survival rates. Indeed, the subgroup of patients diagnosed between 2012 and 2015 who underwent PDS had a five-year survival of 53.7%, which is comparable to the rates reported in other studies (data not shown).

Centralization for EOC patients was implemented as anticipated; more patients were referred for surgical treatment and a decrease in surgical centers is noted over time. However, we showed that only 26% of the hospitals met the consensus requirement of performing a minimum of twenty cytoreductive surgeries on an annual basis within the last period. Centralization was formally established in 2012 but implementation of new guidelines take time when covering multiple hospitals [27]. Regarding centralization processes, some hospitals could be identified as 'early adopters' according to Roger's diffusion theory because the provided evidence convinces them. Other hospitals could be identified as 'late majority' or 'laggards' because of deviant beliefs [28]. This theory is exemplified by some hospital that still performed cytoreductive surgery in 2012–2013, and started referring their patients to specialized centers from 2014 onwards. So, in 2015, 69% of the hospitals that performed cytoreductive surgery met the consensus requirement. Moreover, cytoreductive surgeries for recurrent disease are not registered within the NCR, so the annual number per hospital could be slightly higher.

In the second period, 2006–2011, surgical collaboration between registered gynecological-oncologist and general gynecologists enabled smaller hospitals to continue performing cytoreductive surgeries rather than referring to specialized hospitals. These first initiatives to centralization already resulted in a decrease in hospital variation, although the

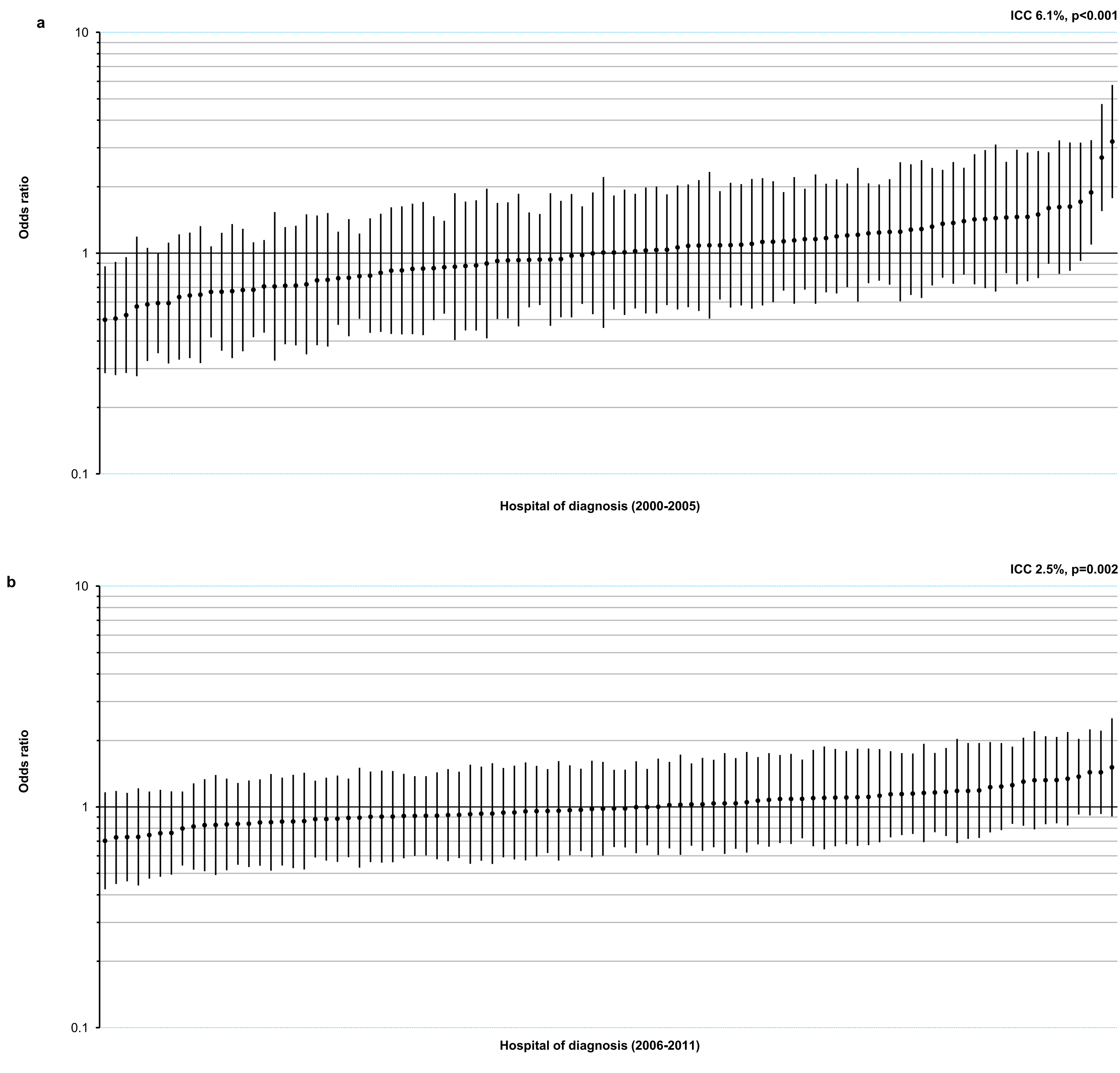

Fig. 1. a: Case-mix adjusted variation in the probability of undergoing surgery for each hospital of diagnosis expressed as an odds ratio and 95% confidence interval on a log scale by a multilevel multivariate regression model. Patients diagnosed in hospitals with an odds ratio less than 1 had a lower likelihood to undergo surgery, hospitals are sorted by their adjusted OR. Adjustment was made for age, FIGO stage, histological type, differentiation grade and socioeconomic status. a) Period 2000–2005, n = 5,214; b) Period 2006–2011, n = 5,956; c) Period 2012–2015, n = 4,144.

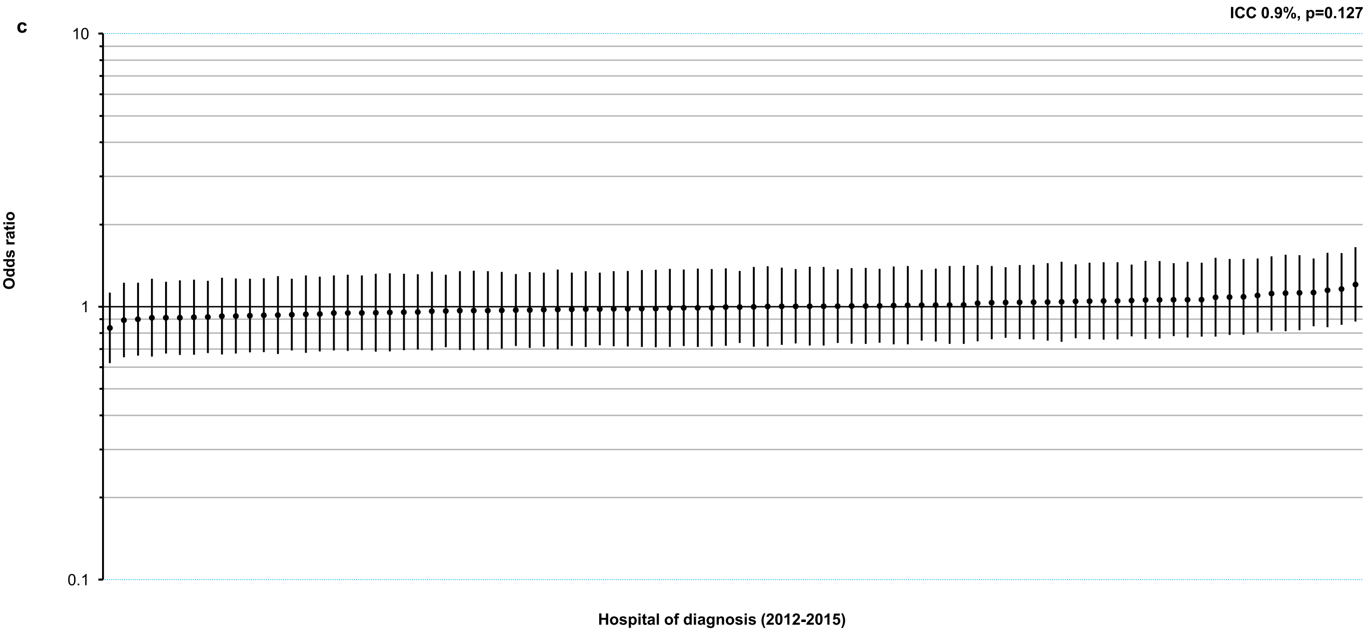

Fig. 1 (*continued*).

initial hospital of diagnosis still significantly influenced treatment decisions. In the last period, centralization also covered the introduction of regional MDTs and a national consensus was reached, which may explain the non-significant association between the hospital of diagnosis and likelihood of undergoing surgery.

The proportion of patients who underwent surgery decreased in the last period. We showed that important predictors for undergoing surgery were younger age, high SES and low FIGO stage, which is consistent with international literature [21,29]. In the last period patients became significantly older and were more often diagnosed with FIGO stage IV disease. This might have contributed to the decreased surgical rate in our population. The rise in FIGO IV disease could be explained by improved diagnostic workup in terms of extended pre-operative imaging and cytological examination of pleural fluid. Furthermore, the percentage of patients with an unknown FIGO stage decreased considerably in the last period as a result of nationwide registration of TNM stage for primary peritoneal cancers within the NCR. The distribution of stage III and IV patients in this group is comparable to primary ovarian cancers, so the rise in FIGO IV patients is probably not based on this registration artifact.

Besides changes in our population, the introduction of neoadjuvant chemotherapy as an alternative approach for advanced stage EOC patients may play a role in the decreased surgical rate [30,31]. The use of neoadjuvant chemotherapy increased in the Netherlands and the majority of advanced stage patients were treated with NACT-IDS in the last period [8]. After two or three cycles NACT, patients are evaluated whether they should undergo interval cytoreductive surgery. When NACT is prematurely stopped due to unacceptable side effects, or response to NACT is low and intraperitoneal tumor load is high, these patients might be considered ineligible for cytoreductive surgery. Consequently, the percentage of patients who undergo cytoreductive surgery decreased.

These alterations in treatment could also contribute to the improved surgical outcomes in the most recent period. The probability of gross residual disease is significantly lower after NACT. The selection of patients who undergo cytoreductive surgery thus altered over time. One could criticize this trend, if only patients with low intraperitoneal tumor load undergo cytoreductive surgery, outcomes will improve without actual improvement in quality of care. Consequently, if quality of care is getting worse, overall survival rates should drop in the most recent years. After all, cytoreductive surgery in combination with chemotherapy is the cornerstone of treatment in advanced ovarian cancer [30]. However, though surgical rates dropped in the last period, overall survival remained comparable and even improved for patients who had an attempt to cytoreductive surgery. This might imply that the selection process improved, and further improving patient selection is therefore of great importance.

The limitations of the study are mainly related to the lack of detailed information about comorbidity, which is regarded as an important factor for initiating surgical treatment [32]. However, the addition of comorbidity to a comparable multilevel model in two studies with gastric and esophageal cancer patients did not reveal major differences in the analyses [33,34]. The initiation of surgery is not only based on the decision of physicians, but also on patients desires. This latter information is not available in our database and could possibly explain some variation between hospitals. Finally, we assumed that changes over

Table 3
Multivariable cox regression models by period of diagnosis (n = 15,314).

	Model I		Model II		Model III	
	Crude OS[a]	HR (95% CI)[b]	Crude OS[a]	HR (95% CI)[b]	Crude OS[a]	HR (95% CI)[b]
2000–2005	23.5	1.15 (1.10–1.20)	29.3	1.17 (1.11–1.23)	3.8	0.95 (0.87–1.03)
2006–2011	24.4	Reference	30.6	Reference	2.7	Reference
2012–2015	25.7	0.98 (0.93–1.03)	34.7	0.9 (0.84–0.96)	N.A.	0.97 (0.89–1.05)

Model I: all patients (n = 15,314), Model II: patient who underwent surgery (n = 11,656), Model III: patients who did not underwent surgery (n = 3658).
[a] 5-year crude overall survival (%).
[b] Adjusted for age, FIGO stage, histological type, differentiation grade and SES.

time were associated with centralization of surgical care and the introduction of MDTs. Although this sounds reasonable, and is supported by the decrease in surgical centers in the last period, we could not establish the cause-effect relationship of centralization and improved outcome rates. Also we had no information about whether patients were truly discussed in MDTs.

5. Conclusion

This study shows that centralization of surgical care resolved the variation between hospitals in the probability to undergo cytoreductive surgery for patients with advanced EOC. Since centralization was established in 2012, the decision to operate patients seems solely attributable to patient and tumor characteristics. This supports the growing evidence in favor of centralizing (surgical) treatment for complex and heterogeneous diseases such as EOC.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2017.11.009.

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