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

Maite Timmermans^{a,b,c,*}, Melinda S. Schuurman^a, Vincent K.Y. Ho^a, Leon F. Massuger^d, Hans W. Nijman^e, Toon van Gorp^{b,c}, Gabe S. Sonke^f, Roy F.P.M. Kruitwagen^{b,c}, Maaïke A. van der Aa^a

^a Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, The Netherlands

^b Department of Obstetrics and Gynecology, Maastricht University Medical Centre, Maastricht, The Netherlands

^c GROW, School for Oncology and Developmental Biology, Maastricht, The Netherlands

^d Department of Obstetrics and Gynecology, Radboud University Medical Center, Nijmegen, The Netherlands

^e Department of Obstetrics and Gynecology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

^f Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

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.

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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-

* Corresponding author at: Godebaldkwartier 419, 3511 DT Utrecht, The Netherlands.
E-mail address: m.timmermans@iknl.nl (M. Timmermans).

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

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