



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



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HIGHLIGHTS

- In the past decade patterns of care for ovarian cancer patients have changed.
- High volume hospitals achieve the best cytoreductive outcomes.
- The majority of Dutch ovarian cancer patients receive neo-adjuvant chemotherapy.
- Surgical outcomes and overall survival have improved within the past ten years.

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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 debulking surgery and adjuvant chemotherapy (PDS + ACT) or neo-adjuvant chemotherapy and interval debulking surgery (NACT + IDS)), 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 ≤ 1 cm) 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 + IDS 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.

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1. 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, <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 debulking surgery followed by adjuvant chemotherapy (PDS + ACT)) with the alternative regimen (neoadjuvant chemotherapy followed by interval debulking surgery (NACT + IDS)) demonstrated equal progression free and overall survival chances [15–22]. Additionally, reduced per- and postoperative complications following NACT + IDS 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 + IDS 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.

2. Materials and methods

2.1. 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.

2.2. 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 PDS + ACT. For patients receiving NACT + IDS, 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.

2.3. 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.

2.4. 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 (PDS + ACT or NACT + IDS), type of treatment hospital and annual number of cytoreductive surgeries per hospital were also evaluated.

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.

2.5. 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 χ^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 PDS and the patients that received NACT-IDS, 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

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