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Centralized primary care of advanced ovarian cancer improves complete cytoreduction and survival - A population-based cohort study

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HIGHLIGHTS

- Centralized primary surgery of advanced ovarian cancer increases complete cytoreduction
- Centralized advanced ovarian cancer care shortens time interval from surgery to chemotherapy
- Survival improves significantly when primary care of advanced ovarian cancer is centralized

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ABSTRACT

Objective. To evaluate centralized primary care of advanced ovarian and fallopian tube cancers in a complete population cohort in relation to complete cytoreduction, time interval from surgery to chemotherapy and relative survival.

Methods. A regional population-based cohort study of women diagnosed with primary ovarian and fallopian tube cancers and included in the Swedish Quality Registry (SQR) during 2008–2013 in a region where primary care of advanced stages was centralized in 2011. Surgical, oncological characteristics, outcomes, follow-ups and relative survivals were analyzed.

Results. There were 817 women diagnosed with ovarian and fallopian tube cancers during 2008–2013 and 523 were classified as FIGO stage III-IV and further analyzed. Primary debulking surgery (PDS) was performed in 81% and neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) in 11%. Complete cytoreduction at PDS was performed in 37% before compared to 49% after centralization ($p < 0.03$). The chemotherapy protocols were identical in the cohorts and they received and completed the planned chemotherapy equally. The time interval between PDS and chemotherapy was 36 days (median) before compared to 24 days after centralization ($p < 0.01$). The relative 3-year survival rate in women treated by PDS was 44% compared to 65% after centralization and the estimated excess mortality rate ratio (EMRR) was reduced (RR 0.58; 95% CI 0.42–0.79). Comparing the complete cohorts before and after centralization, regardless primary treatment, the relative 3-year survival rate increased from 40% to 61% with reduced EMRR (RR 0.59; 95% CI 0.45–0.76).

Conclusion. Centralized primary care of advanced ovarian and fallopian tube cancers increases complete cytoreduction, decreases time interval from PDS to chemotherapy and improves relative survival significantly.

1. Introduction

Ovarian cancer has the highest mortality rate of all gynecological cancers and the majority is diagnosed in an advanced stage [1]. The standard treatment of care of advanced ovarian cancer has been a combination of surgery, taxane- and platinum-based chemotherapy and during the last decade adding new target therapies [2–4]. Throughout the last decade there has been a debate concerning optimal primary care and whether that is primary debulking surgery (PDS) with adjuvant chemotherapy or neadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) [2,5–7]. Nevertheless, it has been established that complete primary cytoreduction, resulting in no residual disease (0 mm), is associated with the highest progression-free survival (PFS) and overall survival (OS) in women with advanced ovarian cancer [8–10], but all women with advanced ovarian cancers are not suitable or feasible for primary extensive cytoreduction due to age,

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comorbidities, tumor burden or other reasons such as patient or family requests.

Primary care of advanced ovarian cancer performed by experienced gynecological oncologist [12–14] at high-volume centers has been shown to have better outcome in PFS and OS than treated by general gynecologists or surgeons at low-volume centers [6,15–18]. Centralized primary care of ovarian cancer has been suggested to increase overall outcome [12–14]. The recommended minimal volume of PDS in women with ovarian cancer at one center or hospital has been internationally discussed [19] and retrospective studies have shown improved outcome when centers treat more than 10–26 cases per year [16,18,20].

There have been multiple studies performed retrospectively, at single or defined institutions but there is a lack of prospective randomized studies probably due to the complexity of the ovarian cancer disease, the heterogenic patient selection, the difference in skilled surgical experience and referral centers. Furthermore, few reports exist analyzing complete population cohorts and outcome in ovarian cancer in relation to primary care. In the era of the promising results of primary complete cytoreduction centralization to high-volume centers has been discussed to be promising to optimize and increase patient outcome [13,16].

The aim of this study was to evaluate the relative survival impact of centralized primary care of advanced ovarian and fallopian tube cancers in a complete population cohort and to further analyze the ratio of; complete primary cytoreduction, neoadjuvant chemotherapy followed by debulking surgery and the time interval from primary surgery to start of adjuvant chemotherapy.

2. Method

The study was designed as a retrospective regional population-based cohort study of primary ovarian or fallopian tube cancers diagnosed and registered in the Swedish Quality Registry for Gynecological Cancer (SQRGC) during 2008–2013. All patients, aged 18 or older at the time of diagnosis were included in the study and patient consent were obtained for registration. Patients were followed until December 31, 2015 or to death. The regional ethical review board of Gothenburg (Dnr: 946-14) approved the study.

In the western Sweden health care region (1.8 million inhabitants) there is one university hospital (tertiary center) and 4 regional hospitals offering diagnostics and selective surgical treatments for women diagnosed with gynecologic cancers. In January 2011, after years of discussions, the region centralized primary care of all advanced stages of ovarian and fallopian tube cancers to the university hospital that performed primary extensive debulking surgery including upper abdominal surgery with diaphragm peritonectomies, full-thickness diaphragm resections, resections of the lesser omentum, splenectomies, liver resections, cholecystectomies and resections of tumor on the surface of parenchymatous organs among others. The university hospital has operational subspecialists in gynecological oncological surgery, according to the national guidelines, and medical gynecological oncologists who plan all schedules for chemotherapy for gynecological cancers in the region. All patients that underwent PDS, regardless before or after centralization, were scheduled identical primary adjuvant chemotherapy protocols by the medical gynecological oncologist; carboplatin (AUC 5) and paclitaxel 175 mg/m^2 intravenously every third week for six cycles and evaluation regarding response at cycle number 3 and 6. The chemotherapy protocols for NACT was identical to the adjuvant chemotherapy and IDS planned after 3 or 4 cycles. Bevacizumab, additional to adjuvant chemotherapy, was not implemented until 2013 and exclusively for women undergoing PDS with residual disease.

In Sweden all citizens are assigned a personal identification number facilitating official registries and reporting to the Swedish National Cancer Registry (SNCR), which started 1958, is mandatory. The Swedish Quality Registry for Gynecological Cancer (SQRGC) for primary cancers of the ovary and fallopian tube was introduced in 2008 where among other parameters surgical and oncological outcomes, follow-ups and mortality are registered. The gynecological oncologists performing the surgeries or oncological therapies report data prospectively and consecutively. The SQRGC coverage in the western Swedish health care region has been 100% compared to the SNCR (coverage 99% in western Sweden) since the beginning in 2008. The validity of the recorded data in the SQRGC has been assessed and agreement between the review and registered data has been shown to be between 70%–96% (unpublished data). The International Statistical Classification of Diseases and Related Health Problems (ICD-10) based on the World Health Organization's (WHO) Criteria was used for tumor location (C56.9, C57.0). Surgical staging was performed according to the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) classification from 1988 [21] since the new classification [22] was not implemented in Sweden until January 2014. In Sweden all gynecological cancer treatments are given by the state-owned hospitals, including oncology surgery and medical oncology such as chemo- and radiotherapy and all therapy protocols are decided by the medical gynecological oncologist at the seven university hospitals and so also in the western Sweden health care region.

The outcome of women diagnosed with ovarian and fallopian tube cancers with advanced stages (FIGO stages III–IV) treated by all hospitals in the western Sweden health care region between 2008–2010 was compared to women diagnosed with equivalent cancer disease between 2011–2013 following the centralization in 2011. The main outcome variables were primary treatment, type of surgery, residual disease after PDS and cytoreduction was defined by macroscopic residual disease (registered at the time of surgery), time interval from PDS to start of adjuvant chemotherapy and relative survival rates. Residual disease was defined as cytoreduction of the tumor to complete cytoreduction (0 cm), ≤0.5 cm, >0.5- ≤1 cm, >1–≤2 cm and >2 cm. The residual disease was evaluated as macroscopically visual disease at the end of surgery by the gynecological oncologist performing the surgery. Explanatory variables included patient and tumor characteristics such as age, FIGO stage, histology and tumor grade.

Relative survival rate was defined as the time from diagnosis to follow up or to death. Clinical follow-ups of the patients were done at fixed time-points; every third to fourth month during the first year and every six months up to three years post primary treatment, according to the regional and national guidelines. Information about death was collected from the Swedish national population register.

2.1. Statistics

Relative survival was computed using the Ederer II method [23]. Mortality data for the general population in Sweden were used to estimate expected survival rates for the study populations. The mortality data comprised the probability of death for single-year age groups in 1-year calendar periods. Survival time was calculated from date of diagnosis to December 31, 2015 or to date of death if occurred before that date. Relative risk between different groups was estimated by Poisson regression. Pearson's Chi-square test was used for testing the difference between proportions within the groups, while a Kruskal-Wallis and Fisher's exact tests were conducted to compare population characteristics. A P-value of <0.05 was considered to be statistically significant. R statistical software (version: 3.1.3) was used for all statistical analyses and the "relsurv" package version 2.0.6 for the relative survival and Poisson estimation.

3. Results

A total of 817 women diagnosed with ovarian or fallopian tube cancers (all stages) were identified in the western Swedish health care region during the time period between January 1, 2008 and December 31, 2013. The median age at diagnosis was 65 years (range 21–95 years) and 523 women (64%) had Stage III or IV disease ($n = 396$ and $n = 127$ respectively). The median follow-up time (from diagnosis to the