Gynecologic Oncology 133 (2014) 454–459

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Is it possible to define an optimal time for chemotherapy after surgery for ovarian cancer?

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HIGHLIGHTS

- Time from primary surgery to initiation of chemotherapy in ovarian cancer
- Survival time for patients with early initiation and late initiation of adjuvant chemotherapy in ovarian cancer

ARTICLE INFO

Article history:
Received 29 January 2014
Accepted 2 April 2014
Available online 12 April 2014

Keywords:
Ovarian cancer
Surgery
Chemotherapy
Time interval
Survival
Prognosis

ABSTRACT

Objective. The aims of this study are to investigate the actual time from primary surgery for epithelial ovarian cancer (OC) to initiation of chemotherapy (TI) amongst Danish women in 2005–2006, and to compare the survival for groups with early initiation (≤median TI) and late initiation of adjuvant chemotherapy (>median TI).

Methods. All Danish women who underwent surgery for OC in the period 1 January 2005 to 31 December 2006 and recorded in the Danish Gynaecological Cancer Database (DGCD) were included. The five-year survival was estimated overall and by TI exposure. The Cox proportional hazard regression analysis was used to compute the adjusted hazard ratio (HR).

Results. The median TI was 32 days (25–75% quartile: 24 days; 41 days). The strongest prognostic factors for death were residual tumour and the International Federation of Obstetrics and Gynecology (FIGO) stage. The unadjusted HR for death in patients with TI > 32 days compared with TI ≤ 32 days was 0.85 (95% CI: 0.70; 1.04), *p*-value 0.12. When adjusted for residual tumour and FIGO-stage the HR was 1.13 (95% CI: 0.92; 1.39), *p*-value 0.26. The overall five-year survival was 42.8%, (95% CI: 38.9%; 46.5%).

Conclusions. This nationwide population-based cohort study revealed a non-significant increased risk of death for patients with TI > 32 days compared with the reference TI ≤ 32 days. The strongest prognostic factors were residual tumour after surgery and FIGO-stage. The overall five-year survival was 42.8% (95% CI: 38.9%; 46.5%).

Introduction

Epithelial ovarian cancer (OC) is the fifth most frequent cause of cancer-related death and the leading cause of death among women diagnosed with gynaecological cancers in the western world [1,2]. In general, the prognosis for OC is poor, because tumours due to few and unspecific symptoms often are diagnosed in an advanced stage. Five-year survival independent of the International Federation of Obstetrics and Gynecology (FIGO) stage was 40% in Denmark during the period 1998–2009 [3,4].

Residual-tumour after surgery, FIGO-stage, degree of differentiation and histology are well established prognostic factors for OC. Furthermore age, performance status and presence of ascites have been pointed at as prognostic factors [5–13].

The main treatment for OC is radically intended surgery with adjuvant, such as carboplatin and paclitaxel [14,15]. Today it is unclear when adjuvant chemotherapy should be initiated for maximum effect, *i.e.* survival. The current Danish Guidelines from 2012 recommends a time interval from primary surgery to initiation of chemotherapy (TI) of maximum 28 days for OC patients [16]. The timing of the initiation of adjuvant chemotherapy is essential for the prognosis for patients with *i.e.* colorectal cancer [17]. Previous studies on OC with smaller numbers of patients and conflicting results do not give a clear answer to the association between TI and the prognosis for patients with OC [5–7,10–12,18,19]. Some of the studies suggested a negative effect of prolonged TI. *In vivo* studies have shown an increase in angiogenesis and growth acceleration in residual tumour after primary tumour resection suggesting an association between survival and the TI.

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http://dx.doi.org/10.1016/j.ygyno.2014.04.004
0090-8258/

Our aims were to investigate the actual time for initiation of chemotherapy amongst Danish women who have undergone primary surgery for OC, and to compare the survival for groups with early initiation and late initiation of adjuvant chemotherapy.

Materials and methods

Setting

A nationwide population-based study was conducted in Denmark, which has approximately 5.6 million inhabitants. The Danish National Health Service is tax-supported and provides universal, equal and unlimited access to medical care, including hospitalization. No OC patients were treated in private hospitals during the study period.

Study population

The Danish Gynaecological Cancer Database (DGCD) was used to identify all women in Denmark who underwent surgery for OC between 1 January 2005 and 31 December 2006.

The DGCD contains data on all Danish patients diagnosed with gynaecological cancer from 1 January 2005. The DGCD contains validated data sufficient for quality monitoring in gynaecological oncology [20]. From DGCD data on FIGO stage, residual tumour after surgery, the Eastern Cooperative Oncology Group (ECOG) performance status, differentiation grade, tumour histology, and presence of ascites were extracted and used in the calculations.

By use of the unique Danish Civil Registry Number assigned to each Danish citizen at birth or immigration, data from the DGCD were linked with data from hospital records. The Danish Civil Registry Number and the Danish Civil Registry System were established in 1968 and contain complete information on death date, emigrations date *etc.* [21]. According to the outcome being survival, information on deaths and emigration was obtained from the Danish Civil Registry System.

To obtain information on the date of initiation of chemotherapy, chemotherapy regimen and numbers of chemotherapy series the medical files were used. Medical files on the included patients were collected from the hospitals or accessed electronically.

Exclusion

Exclusion criteria were: age <18 years, no surgery performed, no chemotherapy given, lack of information on chemotherapy administration, neoadjuvant chemotherapy given and chemotherapy initiated more than 100 days after surgery.

Patients initiating chemotherapy more than 100 days after surgery were excluded because in these cases there were special reasons why the chemotherapy had not been initiated earlier *e.g.* very poor general condition and treatment refrained on patient's request.

Statistics

Each patient was monitored from the date of surgery until the date of death or end of follow up, 1 January 2013. Survival time was the time from the initiation date of chemotherapy until death or end of follow up, whichever came first.

The patients were divided into two groups according to the TI: the early group and the late group. The cut-off, 32 days, is the median TI. Thus, the early group received chemotherapy ≤32 days after primary surgery (TI ≤ 32 days), and the late group received chemotherapy >32 days after primary surgery (TI > 32 days).

Subgroups according to age were defined using the age quartiles; age group 1: <56 years of age, age group 2: 56–63 years of age, age group 3: 64–70 years of age, age group 4: >70 years of age.

OC is staged using FIGO-stages. By means of FIGO-stage all cases were divided into 4 groups containing FIGO IA–IIA, FIGO IIB–IIIB, FIGO IIIC and FIGO IV [5].

Subgroups according to surgical outcome were defined as patients with complete resection, and patients with any residual tumour.

To visualize the crude survival and to compare the unadjusted survival for the groups with TI ≤ 32 days and TI > 32 days Kaplan–Meier curves were constructed. The five-year survivals were estimated for the entire study population and for the two TI-groups. Log rank estimate was used to compare the number of deaths in the two TI-groups.

The Cox Proportional Hazards analysis was used with TI ≤ 32 days as the reference to compare the mortality between the TI-groups and to detect statistical correlations between TI and well known clinical prognostic parameters; residual tumour after surgery, age at surgery, FIGO-stage (IIB–IIIB, IIIC, IV), tumour differentiation grade, histology, more or less than 500 ml ascites and the ECOG performance status [8,9,22].

The hazard ratio (HR) was adjusted for potential confounders based on the 10 per cent-change-in-estimate method, *i.e.* including variables, which altered the unadjusted HR estimate in the Cox-analysis with more than 10% [23].

Identical analyses on groups with TI ≤ 14 days and > 14 days were performed as a supplement to the analyses on the groups with TI ≤ 32 days and TI > 32 days.

All statistical calculations were performed using Stata software version 12. A p value less than 0.05 was considered significant.

Results

Characteristics of the study population

A total of 1223 women were registered in the DGCD. Of these, 46.9% were excluded from the study after reviewing the medical records thus leaving a total of 650 patients to be included in the study population. The reasons for exclusion were age <18 years ($n = 4$), no surgery performed ($n = 1$), no chemotherapy given ($n = 473$), lack of information on chemotherapy administration ($n = 12$), neoadjuvant chemotherapy given ($n = 69$), and chemotherapy initiated more than 100 days after surgery ($n = 14$). In the 473 cases where no chemotherapy was given, it was due to low stage OC ($n = 57$), borderline tumour ($n = 261$), sex-cord-stromal cancer ($n = 14$), germ cell cancer (3), poor general condition/high age/death/after patients wish ($n = 100$), other cancer types ($n = 17$), and unknown reason ($n = 21$).

For the entire study population the median age was 63.1 years (Table 1) and the median observation period after initiation of adjuvant chemotherapy was 82.1 months (25–75% quartile: 76.1 months; 88.3 months) (Table 2), the median TI was 32 days (25–75% quartile: 24 days; 41 days). The group with TI ≤ 32 days had a median observation period of 83.6 months (25–75% quartile: 77.5 months; 89.7 months) and the group with TI > 32 days had a median observation period of 84.9 months (25–75% quartile: 78.8 months; 90.5 months) (Table 2).

At the time of surgery the ECOG performance status for the majority of patients was “fully active” (62.6%) or “with minor signs of illness” (29.4%). Residual tumour after primary surgery was found in 54.3% of the patients. More than half of the patients had advanced stage of OC, *i.e.* FIGO-stage IIIC (44.6%) and IV (12.0%). The oncological treatment was mainly combination therapy with Carboplatin–Taxol (69.2%) and Carboplatin–Taxotere (11.5%). Some patients who were in a poor performance status were treated with mono therapy Carboplatin (8.8%) or another less aggressive chemotherapeutic regimen (10.5%).

The distribution of TI is shown in Fig. 1. Detailed baseline characteristics are listed in Table 1.

TI, survival and mortality

Of the 650 patients in the cohort, 64.9% died during the study period (Table 2). The median survival from initiation of adjuvant