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Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: A meta-analysis

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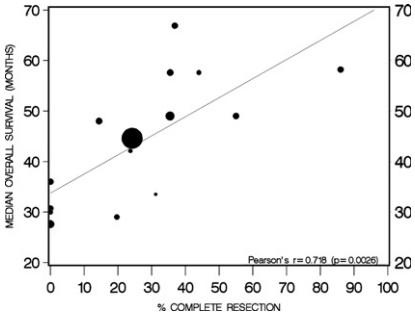
HIGHLIGHTS

- The proportion of patients left with no gross residual disease is independently predictive of survival.
- The proportion of patients receiving intraperitoneal chemotherapy is a significant predictor of cohort survival time.
- These data underscore the synergy between regional therapeutic efficacy and the completeness of surgical resection.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective. To quantify the impact of complete cytoreduction to no gross residual disease on overall survival among patients with advanced-stage ovarian cancer treated during the platinum–taxane era.

Methods. PubMed and Cochrane Library databases were searched for all articles on primary cytoreductive surgery for advanced-stage ovarian cancer published from 1/1996 to 7/2011. A total of 18 relevant studies (13,257 patients) were identified for analysis. Simple and multiple linear regression analyses, with weighted correlation calculations, were used to assess the effect on median survival time of clinical and treatment-related factors.

Results. The mean weighted median overall survival time for all cohorts was 44.4 months (range, 27.6–66.9 months). Simple linear regression analysis revealed that residual disease, stage IV disease, and use of intraperitoneal chemotherapy were significantly associated with median survival time. After controlling for other factors on multiple linear regression analysis, each 10% increase in the proportion of patients undergoing complete cytoreduction to no gross residual disease was associated with a significant and independent 2.3-month increase (95%CI = 0.6–4.0, p = 0.011) in cohort median survival compared to a 1.8-month increase (95%CI = 0.6–3.0, p = 0.004) in cohort median survival for optimal cytoreduction (residual disease ≤ 1 cm). Each 10% increase in the proportion of patients receiving intraperitoneal chemotherapy was associated with a significant and independent 3.9-month increase (95%CI = 1.1–6.8, p = 0.008) in median cohort survival time.

Conclusions. For advanced-stage ovarian cancer treated during the platinum–taxane era, the proportions of patients left with no gross residual disease and receiving intraperitoneal chemotherapy are independently significant factors associated with the most favorable cohort survival time.

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Introduction

Worldwide, approximately 225,000 women are diagnosed with ovarian cancer and 140,000 women die from this disease annually [1]. In the United States, ovarian cancer remains the leading cause of death from gynecological malignancy, with 21,990 new cases and 15,460 deaths in 2011 [1]. The majority of ovarian cancer patients are initially diagnosed with tumor metastases beyond the ovary, which results in diminished chances of long-term survival [2]. Surgical cytoreduction and adjuvant chemotherapy are the cornerstones of management for advanced ovarian cancer. Since the mid-1990s, primary cytoreductive surgery followed by platinum and taxane-based combination chemotherapy has been the standard treatment regimen for advanced-stage disease [3–6].

Residual disease after cytoreductive surgery for advanced-stage ovarian cancer is estimated as the largest diameter of remaining tumor and is one of the most important prognostic factors [7,8]. Paradoxically, universal consensus regarding the definition of "optimal" residual disease has been lacking. The Gynecologic Oncology Group (GOG) has defined optimal residual disease as residual tumor ≤ 1 cm in the largest diameter [9,10]. However, optimal residual disease has been variously defined as ranging from no gross residual disease to remaining tumor nodules measuring ≤ 2 cm [11–14]. More contemporary data suggest that the most favorable survival outcomes are associated with complete cytoreduction to no gross residual disease [15–22]. Despite this observation the relative impact of complete cytoreduction, as opposed to "optimal but visible residual disease", within the context of contemporary platinum–taxane-based adjuvant therapy has been difficult to determine. Therefore, the objective of the current study was to quantify the impact of complete cytoreduction to no gross residual disease on overall survival among patients with advanced-stage ovarian cancer treated during the platinum–taxane era using the technique of meta-analysis.

Methods

Study selection and data extraction

Potential articles for analysis were identified from a literature search of the National Library of Medicine (PubMed) and the Cochrane Library for all English-language publications between January 1, 1996 and July 31, 2011. The keywords used were "ovarian neoplasm," "ovarian carcinoma," "ovarian cancer," and "surgery." Two authors (S.J.C. and R.E.B.) independently reviewed the titles and abstracts of publications searched, and excluded the unrelated articles. A full-text audit of identified articles was performed, and publications that fulfilled selection criteria were included in the study.

Study inclusion criteria for meta-analysis were as follows: 1) primary epithelial ovarian, fallopian tube, or peritoneal carcinoma; 2) International Federation of Gynecology and Obstetrics (FIGO) stages IIB to IV disease; 3) primary cytoreductive surgery; 4) adjuvant chemotherapy administered when both taxane and platinum agents were available; 5) residual disease reported using the criteria of no gross (microscopic) residual disease, residual disease 0–1.0 cm, residual disease of 0.1–1.0 cm, or residual disease > 1 cm; and 6) survival analysis according to the aforementioned residual disease criteria. Optimal residual disease was defined as residual tumor size ≤ 1.0 cm in the largest diameter based on the GOG criteria. In cases of multiple publications with overlapping cohort data, the most relevant study satisfying the above criteria was selected for analysis. In the case of ancillary studies analyzing previously published data, only the original study was included for meta-analysis. For each eligible study cohort the following information was recorded: study design (randomized controlled trial, prospective trial, retrospective review), year of publication, the temporal midpoint of study accrual time period, number of study subjects, median patient age at diagnosis, the proportion of patients with stage IV disease, the proportion of patients receiving taxane chemotherapy, the proportion of patients receiving intraperitoneal chemotherapy, the proportion of patients completing a planned 6-cycles of chemotherapy, the proportion of patients undergoing complete cytoreduction to no gross residual disease, the proportion of patients left with optimal (≤1 cm) residual disease, and the reported median overall survival time.

Statistical analysis

Simple linear regression models were generated to examine the effect on median cohort survival time of the predictor variables. Each regression model was weighted by the number of patients in each cohort. Multiple linear regression analyses were used to derive the independent effects of the aforementioned variables on log median survival time, using an imputed dataset to account for missing values, simultaneously controlling for other measured variables that could potentially affect survival. Because the surgical outcome criteria of no gross residual and optimal residual disease are not mutually exclusive, separate multiple linear regression analyses were performed using no gross residual disease (model 1) or optimal residual disease (model 2) as the surgical outcome criteria. All results reflect a two-sided p-value, and a p-value < 0.05 was considered statistically significant. All analyses were carried out using SAS 9.2 statistical software package.

Results

Study characteristics

The initial electronic search yielded 1203 articles. The full-length published reports of 104 studies were formally reviewed, and 15 studies were identified as containing the minimum study inclusion criteria [5,15–21,23–29]. Of these 15 studies, 4 studies [18–21] were ancillary data studies which retrospectively reanalyzed the data collected for 9 previous randomized prospective trials [5,6,23,30–35], and these ancillary data studies included overlapping data with two other studies [5,23]. Therefore, the original randomized trials were included in the meta-analysis instead of the 4 ancillary data studies. Ultimately, 18 studies were selected for inclusion in the meta-analysis (Table 1) [3,5,6,15–17,23–35]. Seventeen studies were published after 2000 and one study was published in 1996. Six studies were retrospective observational series from single institution and 12 studies were randomized controlled trials investigating the efficacy of adjuvant chemotherapy regimens.

The clinical characteristics of the final study population cohorts (13,257 patients) are summarized in Table 1. There were no missing values for the predictor variables of study accrual time period midpoint, median cohort age at diagnosis, proportion of patients receiving intraperitoneal chemotherapy, and proportion of patients undergoing optimal cytoreductive surgery. For the remaining predictor variables, the percentage of all patients with missing values was 11.1% for receipt of 6 cycles of chemotherapy, 16.7% for complete cytoreduction, and 27.8% for proportion receiving taxane chemotherapy.

The mean weighted median overall survival time for all cohorts was 44.4 months (range, 27.6–66.9 months), and the median age was 59 years (range, 56–64 years). The mean weighted proportion of patients in each cohort with residual disease ≤ 1 cm in maximal diameter was 62.3% (range, 0%–100%). The mean weighted proportion of patients in each cohort undergoing complete cytoreduction was 25.9% (range, 0%–86.0%). All cohorts received platinum-based chemotherapy, and the weighted mean proportion of patients in each cohort receiving taxane chemotherapy was 65.9% (range, 20.0%–100%). Two randomized prospective trials on intravenous versus intraperitoneal chemotherapy were included, and there were 440 patients receiving intraperitoneal chemotherapy.