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.

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 intra peritoneal 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 53.5% (range, 20.0%–100%). Two randomized prospective trials on intravenous versus intraperitoneal chemotherapy were included, and there were 440 patients receiving intraperitoneal chemotherapy.
At the bivariate level, there was a strong positive correlation between the proportion of patients in each cohort undergoing optimal cytoreductive surgery and the proportion of patients undergoing complete cytoreductive surgery (r = 0.82, p = 0.0002). Model 1 multivariate linear regression analysis, using the surgical outcome criteria of no gross residual disease, revealed that each 10% increase in the proportion of patients receiving intraperitoneal chemotherapy was associated with a 3.9-month increase (95%CI = 1.1–6.8 months, p = 0.008) in median survival, and the proportion of patients undergoing complete cytoreduction was associated with a 2.3-month increase (95%CI = 0.6–4.0 months, p = 0.01) in median cohort survival time (Table 3). These were the only predictor variables significantly associated with, and independently predictive of survival. Substituting optimal residual disease as the surgical outcome criteria in the multivariate linear regression analysis (model 2) yielded similar directionality effects on the change in median cohort survival for all predictor variables; however, the relative magnitude of surgical outcome and intraperitoneal chemotherapy were attenuated compared to model 1. In model 2, each 10% increase in the proportion of patients left with optimal residual disease was associated with a statistically significant 1.8-month increase (95%CI = 0.6–3.0 months, p = 0.004) in median cohort survival time. Although each 10% increase in the proportion of patients receiving intraperitoneal chemotherapy was accompanied by a 2.7-month increase (95%CI = (−)0.1–5.4 months, p = 0.057) in median cohort survival, this effect was not statistically significant (Table 4).

Discussion

Meigs first described cytoreductive surgery for advanced ovarian cancer in 1934 [36]. Forty years later, Griffiths published a landmark study that conclusively demonstrated an inverse relationship between...
residual tumor diameter and patient survival [37]. Nearly every retrospective study and prospective study since then has demonstrated that the extent of residual disease and the use of platinum-based chemotherapy are key factors impacting survival in women with advanced stage ovarian cancer. In 1994, Hoskins et al., reporting for the GOG, definitively demonstrated the prognostic importance of a three-tiered classification system for residual disease: complete resection to no gross residual disease, optimal but visible (0.1 cm to ≤ 1 or 2 cm) residual disease, and suboptimal (> 1 or 2 cm) residual disease, with the most favorable survival associated with complete resection [10]. The introduction of taxane chemotherapy into the frontline treatment regimen and the re-emergence of regional therapeutics (intraperitoneal chemotherapy) have further improved the expected survival outcome for women with advanced-stage ovarian cancer [22]. However, the relative survival impact of complete gross resection within the context of this more contemporary treatment paradigm has been difficult to define. Therefore, the objective of the current study was to examine the available literature using the technique of meta-analysis to quantify the effect on survival of surgical outcome criteria, and other prognostic variables, among patients with advanced-stage ovarian cancer treated during the platinum-taxane era.

The current analysis indicates that the two predictor variables associated with the largest effect on cohort survival were the proportion of patients in whom minimal residual disease was achieved and the proportion of patients receiving intraperitoneal chemotherapy. Although both no gross residual disease and optimal residual disease were significant and independent predictors of improved cohort survival, each 10% increase in the proportion of patients undergoing complete gross resection was associated with a 28% incremental improvement in the expected median survival time (2.3 months) compared to the proportion of patients left with optimal residual disease (1.8 months). These data offer an overarching population-based perspective on the magnitude of survival benefit associated with a progressively increasing percentage of patients with advanced-stage ovarian cancer achieving no gross residual disease prior to initiating chemotherapy.

The current data also validate and quantify the intuitive correlation between the specified surgical outcome criterion and the relative magnitude of the survival advantage associated with intraperitoneal chemotherapy. Applying the surgical outcome criterion of no gross residual disease, while controlling for the effects of other variables, was associated with a statistically significant and independent 3.9-month increase in median cohort survival for each 10% increase in the proportion of patients receiving intraperitoneal chemotherapy. When optimal residual disease was used as the surgical outcome criterion, each 10% incremental change in the proportion of patients receiving regional treatment was reflected as a statistically non-significant 2.7-month increase in median cohort survival, after controlling for other variables. In other words, substituting optimal residual disease for no gross residual disease as the surgical outcome criterion resulted in a 44% reduction in the relative survival impact of each 10% incremental change in the proportion of patients receiving regional treatment. This observation underscores a GOG ancillary data analysis of protocols 114 and 172 recently reported by Landrum et al. [38]. In this dataset of patients with Stage III epithelial ovarian cancer treated with intraperitoneal chemotherapy, complete resection of disease to microscopic residual was associated with a median overall survival time of 110 months, compared to

### Table 3

Model 1: multiple linear regression analysis of selected predictor variables versus median cohort survival time using no gross residual disease as the surgical outcome criteria.

<table>
<thead>
<tr>
<th>Increment</th>
<th>Change in median survival (months)</th>
<th>95%CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study year accrual midpoint (+) 1 year</td>
<td>0.5</td>
<td>(−) 0.4 to 1.3</td>
<td>0.246</td>
</tr>
<tr>
<td>Median age (years) (+) 1 year</td>
<td>−1.5</td>
<td>(−) 3.5 to 0.4</td>
<td>0.116</td>
</tr>
<tr>
<td>Percent taxane therapy (+) 10%</td>
<td>−0.4</td>
<td>(−) 1.5 to 0.8</td>
<td>0.494</td>
</tr>
<tr>
<td>Percent IP therapy (+) 10%</td>
<td>3.9</td>
<td>1.1 to 6.8</td>
<td>0.008</td>
</tr>
<tr>
<td>Percent 6 cycles of therapy (+) 10%</td>
<td>3.4</td>
<td>(−) 2.3 to 9.1</td>
<td>0.242</td>
</tr>
<tr>
<td>Percent stage IV disease (+) 10%</td>
<td>−1.0</td>
<td>(−) 2.2 to 1.1</td>
<td>0.339</td>
</tr>
<tr>
<td>Percent no gross residual disease (+) 10%</td>
<td>2.3</td>
<td>0.6 to 4.0</td>
<td>0.011</td>
</tr>
</tbody>
</table>

### Table 4

Model 2: multiple linear regression analysis of selected predictor variables versus median cohort survival time using optimal residual disease as the surgical outcome criteria.

<table>
<thead>
<tr>
<th>Increment</th>
<th>Change in median survival (months)</th>
<th>95%CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study year accrual midpoint (+) 1 year</td>
<td>0.2</td>
<td>(−) 0.7 to 1.1</td>
<td>0.645</td>
</tr>
<tr>
<td>Median age (years) (+) 1 year</td>
<td>−0.6</td>
<td>(−) 2.4 to 1.2</td>
<td>0.494</td>
</tr>
<tr>
<td>Percent taxane therapy (+) 10%</td>
<td>0.1</td>
<td>(−) 1.0 to 0.9</td>
<td>0.903</td>
</tr>
<tr>
<td>Percent IP therapy (+) 10%</td>
<td>2.7</td>
<td>0.1 to 5.4</td>
<td>0.057</td>
</tr>
<tr>
<td>Percent 6 cycles of therapy (+) 10%</td>
<td>2.1</td>
<td>(−) 3.6 to 7.8</td>
<td>0.457</td>
</tr>
<tr>
<td>Percent stage IV disease (+) 10%</td>
<td>−0.4</td>
<td>(−) 2.8 to 2.0</td>
<td>0.721</td>
</tr>
<tr>
<td>Percent optimal residual disease (+) 10%</td>
<td>1.8</td>
<td>0.6 to 3.0</td>
<td>0.004</td>
</tr>
</tbody>
</table>
55 months for patients with optimal but visible residual disease. Although the current analysis of collective data suggests that the positive survival effect of intraperitoneal chemotherapy is of greater magnitude when the more stringent residual disease criterion of complete gross resection is employed, the small number of patients receiving intraperitoneal chemotherapy may limit the robustness of this conclusion. A critical review of the data presented must take into consideration the methodological limitations of a meta-analysis of this nature. First, every effort was made to include as many studies as possible while preserving the study selection criteria initially set forth. Nevertheless, the potential for selection bias, both with regard to studies selected for inclusion in the analysis as well as inclusion of patients within each individual study, must be considered. A second potential limitation is that the necessary imprecision of our predictor measurements may have affected our ability to discriminate between statistically and clinically meaningful differences. A third limitation is that the variety of chemotherapeutic agents and administration schedules precluded an analysis of total drug dose-intensity or cumulative drug dose. Similar meta-analyses of advanced ovarian cancer have not found these factors to have a significant effect on survival. A fourfold limitation of the current study is that we did not examine additional prognostic factors, such as surgical sub-stage for Stage III disease and performance status, that might have influenced either survival or the proportion of patients undergoing complete or optimal cytoreductive surgery. Expansion of the study selection criteria to include these factors would have markedly reduced the number of eligible studies. Finally, this study was limited to patient cohorts undergoing a standard therapeutic approach of initial surgery followed by adjuvant chemotherapy and was not intended to examine the clinical utility of primary surgery versus neoadjuvant chemotherapy. Despite these limitations, there are several conclusions that can be drawn from the current analysis. First, for patients with advanced-stage ovarian cancer treated during the platinum–taxane era, the proportion of patients left with no gross residual disease is associated with an incremental survival advantage of greater magnitude compared to the proportion of patients left with optimal residual disease. Second, the proportion of patients receiving intraperitoneal chemotherapy is a significant and independent predictor of cohort survival time. And finally, the relatively greater survival benefit associated with intraperitoneal chemotherapy in the context of no gross residual disease highlights the dependency of regional therapeutic efficacy on the completeness of surgical resection.

Conflict of interest statement
The authors do not have any potential conflicts of interest.

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References


