Survival Effect of Maximal Cytoreductive Surgery for Advanced Ovarian Carcinoma During the Platinum Era: A Meta-Analysis

By Robert E. Bristow, Rafael S. Tomacruz, Deborah K. Armstrong, Edward L. Trimble, and F.J. Montz

Purpose: To evaluate the relative effect of percent maximal cytoreductive surgery and other prognostic variables on survival among cohorts of patients with advanced-stage ovarian carcinoma treated with platinum-based chemotherapy.

Materials and Methods: Eighty-one cohorts of patients with stage III or IV ovarian carcinoma (6,885 patients) were identified from articles in MEDLINE (1989 through 1998). Linear regression models, with weighted correlation calculations, were used to assess the effects on log median survival time of the proportion of each cohort undergoing maximal cytoreduction, dose-intensity of the platinum compound administered, proportion of patients with stage IV disease, median age, and year of publication.

Results: There was a statistically significant positive correlation between percent maximal cytoreduction and log median survival time, and this correlation remained significant after controlling for all other variables (P < .001). Each 10% increase in maximal cytoreduction was associated with a 5.5% increase in median survival time. When actuarial survival was estimated, cohorts with ≤25% maximal cytoreduction had a mean weighted median survival time of 22.7 months, whereas cohorts with more than 75% maximal cytoreduction had a mean weighted median survival time of 33.9 months—an increase of 50%. The relationship between platinum dose-intensity and log median survival time was not statistically significant.

Conclusion: During the platinum era, maximal cytoreduction was one of the most powerful determinants of cohort survival among patients with stage III or IV ovarian carcinoma. Consistent referral of patients with apparent advanced ovarian cancer to expert centers for primary surgery may be the best means currently available for improving overall survival.


I N THE UNITED STATES, approximately 14,000 women are diagnosed with advanced epithelial ovarian carcinoma annually. Standard therapy consists of primary surgical cytoreduction followed by platinum-based chemotherapy. Although the positive effect of platinum-based chemotherapy on the survival of patients with advanced ovarian carcinoma is widely accepted, the relative effect of aggressive surgical intervention on long-term outcome has been more difficult to quantify. Proponents of surgery refer to the large body of retrospective data consistently showing that prognosis and survival are strongly correlated with the amount of postoperative residual disease. On the other hand, critics of surgery argue that the survival advantage associated with minimal residual disease has more to do with the inherent biologic predisposition of the tumor than with the predisposition and skill of the surgeon.

Large meta-analyses of studies involving patients with advanced ovarian carcinoma, and selected reports of series of such patients, are often cited as providing evidence that the effect of primary platinum-based therapy on survival is proportionally much greater than any effect of the degree of surgical debulking. However, survival comparisons of platinum- and nonplatinum-treated patients are largely of historical interest. Because virtually all patients now receive initial platinum-based chemotherapy, the first objective of the current study was to determine the relative effect on survival of maximal cytoreductive surgery and other prognostic variables in patients with advanced-stage ovarian carcinoma treated during the platinum era.

From a population-based perspective, the compiled literature on primary cytoreduction for ovarian carcinoma reveals a wide disparity in surgical success rates, which depend on the experience, skill, and philosophical approach of the operating surgeons. For practical purposes, health care delivery centers can be divided into two groups: those with a particular interest and expertise in cytoreductive surgery (in these centers, optimal resection rates of more than 75% are common); and those with comparatively less experience (optimal resection rates are frequently 25% or less). Although gynecologic oncologists are significantly more likely to achieve optimal cytoreduction than are other...
surgical subspecialists, studies of care patterns have shown that only 20% to 40% of ovarian cancer patients have initial access to such care. With this in mind, our second objective was to quantify the effect on survival of a significant difference in the proportion of patients undergoing maximal cytoreductive surgery. Such comparisons may have important implications with respect to the current patterns of surgical care for women with suspected ovarian cancer.

MATERIALS AND METHODS

Study Selection and Data Abstraction

Using the headings and keywords “ovarian neoplasms,” “ovarian carcinoma,” “ovarian cancer,” and “surgery,” we performed a MEDLINE search for English-language articles published between January 1, 1989, and December 31, 1998. Publications were selected for initial review if the research subjects were predominantly (> 90%) patients with stage III or IV epithelial ovarian cancer who were undergoing initial cytoreductive surgery followed by chemotherapy that included either cisplatin or carboplatin. Maximal cytoreduction was considered to have occurred if residual disease measured ≤ 3 cm in largest diameter. We excluded articles that did not include the median survival time of individual patient cohorts, the definition of maximal cytoreductive surgery, the proportion of patients with stage IV disease, or the dosing schedule of the platinum agent. The bibliography of each selected article was reviewed for other potentially relevant citations. In the case of studies whose results were published more than once, data from the most recent article were used for statistical analysis.

Two of the authors (R.E.B. and R.S.T.) reviewed the formal published versions of all eligible studies for content and screened them according to the aforementioned inclusion criteria. The following information was recorded for each eligible study cohort: study design (randomized prospective trial, prospective trial, retrospective review), year of publication of the study, number of patients, median patient age, percentage of patients with stage IV disease, specified definition of maximal cytoreductive surgery and the percentage of patients achieving it, chemotherapy agents administered, dosage and prescribed administration schedule of the platinum compound used, and reported median survival time.

Calculation of Platinum Dose-Intensity

Platinum dose-intensity was considered the dose in milligrams per meter squared (or, in the case of carboplatin, area under the concentration time curve) administered during a conventional treatment cycle (every 3 or 4 weeks). To approximate a weighted mean platinum dose-intensity of 1.00, we selected the following baseline dose-intensities: cisplatin administered at a dosage of 75 mg/m² every 3 or 4 weeks (or 25 mg/m² administered every week) and carboplatin administered at a dosage of 350 mg/m² (or area under the concentration time curve equal to 5) every 3 or 4 weeks. These baseline dosages yielded a weighted mean platinum dose-intensity for the entire study population of 0.98 and are consistent with the threshold platinum dose that could potentially affect survival. All results are quoted as two-sided P values and 95% confidence intervals (CIs). P < .05 was considered statistically significant. The analysis was carried out using the STATA statistical software package (STATA Corp, College Station, TX).

RESULTS

Study Characteristics

The initial MEDLINE search yielded 3,305 articles. We reviewed the formal published reports of 69 of these studies (108 patient cohorts and 9,161 patients). Ultimately, 53 studies (81 patient cohorts and 6,885 patients) were identified as meeting all study inclusion criteria (Table 1).

Fifty-five cohorts were extracted from randomized prospective trials, 24 were from nonrandomized prospective trials, and two were from retrospective reviews. In the majority of studies, the investigative focus was on the efficacy of novel chemotherapeutic agents, combination regimens, or administration schedules, not on surgical outcome. The mean number of patients in each cohort was 85 (median, 64; range, 20 to 306), and the reported median survival time ranged from 12.0 to 62.0 months. For all patient cohorts taken together, the mean weighted median survival time was 29.0 months.

Maximal Cytoreductive Surgery

Maximal cytoreductive surgery was defined according to the largest diameter of residual disease, with the following distribution among selected study cohorts: less than 2 cm in 40.7%, ≤ 2 cm in 38.3%, ≤ 1 cm in 12.3%, less than 1 cm in 3.7%, less than 3 cm in 2.5%, ≤ 1.5 cm in 1.2%, and less than 0.5 cm in 1.2%. Ninety-five percent of studies used either 1 or 2 cm as the discriminating criterion. The weighted
<table>
<thead>
<tr>
<th>Reference</th>
<th>Publication Year</th>
<th>No. of Patients</th>
<th>Median Age (years)</th>
<th>Percent Stage IV Disease</th>
<th>Maximal Cytoreduction %</th>
<th>Maximal Diameter (cm)</th>
<th>Chemotherapy Agents</th>
<th>Platinum Dose-Intensity Median Survival Time (months)</th>
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<td>13.2</td>
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<td>CDDP/CYC</td>
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Abbreviations: CBDCA, carboplatin; CDDP, cisplatin; CHLOR, chlorambucil; CYC, cyclophosphamide; DOX, doxorubicin; EPI, epirubicin; ETO, etoposide; HMM, hexamethylmelamine; IFO, ifosfamide; IP, intraperitoneal; MEI, melphelan; MTZ, mitoxantrone; NA, not available; PTX, paclitaxel.

*Randomized prospective trial.
†Survival time used for statistical analysis; median not yet reached.
‡Prospective trial.
§Retrospective trial.
mean percentage of maximal cytoreductive surgery for all cohorts was 41.9%, with a range from 0% to 100%.

Simple linear regression analysis of percent maximal cytoreductive surgery versus log median survival time for the 81 patient cohorts is shown in Fig 1. The regression line was computed weighted by the number of observations in each study, and the effects of other variables were ignored. Each 10% increase in the proportion of patients in each cohort undergoing maximal cytoreductive surgery was associated with a 6.3% increase in log median survival time (95% CI, 4.7% to 7.8%). There were too few studies with cytoreductive surgical outcome criteria other than less than 2 cm or ≤ 2 cm to evaluate any potential effect on median survival of variations in this criterion.

From these data, it seems that incremental changes in percent maximal cytoreductive surgery have a relatively minor effect on the median survival times of patient cohorts. For example, an increase in the percentage of maximal cytoreductive surgery from 20% to 30% is associated with an increase in median survival time of only 1.5 months (24.1 months to 25.6 months). However, these data can also be interpreted within the conceptual framework of the more commonly observed disparity between centers experienced in ovarian tumor reductive surgery (with optimal resection rates usually in excess of 75%) and centers with comparatively less expertise (with optimal resection rates frequently in the range of 25% or less). To demonstrate more fully the potential effect of a significant change in percent maximal cytoreductive surgery between patient cohorts, we plotted the de-logged values of weighted median survival against proportional increases in percent maximal cytoreduction (Fig 2). When the data are examined in this fashion, it is evident that an increase in the percentage of maximal cytoreductive surgery within a cohort from ≤ 25% to more
than 75% is associated with a significant extension of median survival time. For patient cohorts having a maximal cytoreductive surgery rate of \( \leq 25\% \), the mean weighted median survival time was 23.0 months. In contrast, cohorts in which maximal cytoreductive surgery was achieved in more than 75% of patients had a mean weighted median survival time of 36.8 months, an increase of 60% (13.8 months).

**Platinum Dose-Intensity and Cumulative Platinum Dose**

Twelve chemotherapeutic agents were used in a variety of combinations, yielding 24 distinct treatment regimens. Because of the large number of individual chemotherapeutic agents and the wide variety of combination regimens reported during the study period, calculation of the total dose-intensity and total cumulative dose for all agents combined was impractical.

The platinum dose-intensity ranged from 0.57 to 3.71, with a weighted mean of 0.98. Figure 3 shows log median survival time plotted against platinum dose-intensity for all cohorts, ignoring the effects of other variables. The regression line, again weighted by the number of observations in each study, reveals no statistically significant relationship between platinum dose-intensity and median survival time \((P = .896)\). For each 10% increase (0.10) in platinum dose-intensity, median survival time increased by only 0.9% (95% confidence limits [CL], \(-0.4\%, 2.2\%)\).

The weighted mean cumulative platinum dose prescribed was 7.6 U (range, 3.4 to 28.8 U). Simple linear regression model analysis showed no statistically significant association between cumulative platinum dose and median survival time \((P = .377)\). Each increase of 1 U in cumulative platinum dose was associated with a 1.5% increase in median survival time (95% CL, \(-1.9\%, 4.9\%)\).

**Year of Publication**

The median (and mean) number of study cohorts included per year of publication was eight. Figure 4 shows log median survival time plotted against year of publication for all 81 patient cohorts. The effects of other variables were ignored. By simple linear regression, there was a statistically significant association between the year of publication...
and median survival time ($P < .009$). The passage of 1 year was associated with an estimated 3.3% increase in median survival time (95% CI, 0.8% to 5.8%). Simple linear regression analysis revealed no statistically significant interactions between year of publication, percent maximal cytoreductive surgery, percent stage IV disease, platinum dose-intensity, or cumulative platinum dose. There was, however, a negative association between year of publication and the number of prescribed chemotherapy cycles, going from a median of 10 cycles in 1989 to a median of six cycles in 1998 ($P < .002$).

**Median Cohort Age and Percent Stage IV Disease**

Median age was not reported for eight patient cohorts. For the remaining 73 cohorts, the mean weighted median age was 57 years (range, 47.0 to 72.0 years). Simple linear regression analysis revealed no statistically significant relationship between age and median survival time ($P = .371$). With weighted calculations, each 1-year increase in median age was associated with an estimated 0.9% decrease in median survival time (95% CI, −3.1%, 1.2%).

The weighted mean percentage of patients with stage IV disease per cohort was 19.9% (range, 0% to 46.2%). Simple linear regression analysis revealed a significant relationship between percent stage IV disease and median survival time. Each 10% increase in the proportion of patients with stage IV disease was associated with a 13.7% decrease in median survival time (95% CI, −18.5%, −8.9%). There was also a highly significant negative interaction between percent stage IV disease and percent maximal cytoreductive surgery ($-0.52$, $P < .001$). In other words, there was a strong inverse relationship between increasing percent stage IV disease and decreasing percent maximal cytoreductive surgery.

**Table 2. Multiple Linear Regression Analysis**

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<th>% Increase</th>
<th>95% CI or CL</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
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<td>Percent maximal cytoreduction</td>
<td>5.5%</td>
<td>3.3-7.8%</td>
<td>.001</td>
</tr>
<tr>
<td>Year of publication</td>
<td>2.8%</td>
<td>0.9-4.6%</td>
<td>.004</td>
</tr>
<tr>
<td>Platinum dose-intensity</td>
<td>0.8%</td>
<td>−0.7, 2.3%</td>
<td>.911</td>
</tr>
<tr>
<td>Cumulative platinum dose</td>
<td>1.4%</td>
<td>−1.9, 4.7%</td>
<td>.377</td>
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<tr>
<td>Percent stage IV disease</td>
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<td>−8.5, 4.1%</td>
<td>.495</td>
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<tr>
<td>Median age</td>
<td>−0.9%</td>
<td>−3.1, 1.2%</td>
<td>.371</td>
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</tbody>
</table>

Abbreviations: CI, confidence interval; CL, confidence limits.

Multiple linear regression analysis was used to derive the independent effect on log median survival time of each variable while controlling for the other measured factors that could potentially affect survival time (Table 2). After controlling for other factors, percent maximal cytoreductive surgery continued to be the strongest predictor of median survival time ($P < .001$). Each 10% increase in percent maximal cytoreductive surgery was associated with a 5.5% increase in median survival time (95% CI, 3.3% to 7.8%). The magnitude of this effect is only minimally attenuated compared with that seen on simple regression analysis. After controlling for the effects of all other measured variables, the mean weighted median survival time for patient cohorts with maximal cytoreductive surgery ≥ 25% was 22.7 months. The mean weighted median survival time for patient cohorts with more than 75% maximal cytoreductive surgery was 33.9 months, an increase of 50% (11.2 months).

More recent studies had on average statistically significantly longer median survival times. The passage of 1 year was associated with an increase in median survival time of 2.8%. After controlling for maximal cytoreductive surgery, the effect of percent stage IV disease was no longer significant. Each 10% increase in percent stage IV disease was associated with only a 2.2% decrease in median survival time. As in the simple regression models, there was no statistically significant relationship between median survival time and platinum dose-intensity or cumulative platinum dose.

An analysis of data from all available cohorts, irrespective of which individual publication they were extracted from, assumes that after controlling for median age, percent maximal cytoreduction, percent stage IV disease, platinum dose-intensity, cumulative platinum dose, and year of publication, two cohorts from the same study are as alike or
different as two cohorts from different studies. To validate this assumption, the multiple linear regression analysis was repeated using only the largest cohort from each publication, for a total of 55 cohorts. Analyzing the data in this fashion yielded no meaningful changes in either the magnitude or significance of the initial findings. Percent maximal cytoreductive surgery again had the strongest independent effect, with each 10% increase associated with a 5.9% increase in median survival time (95% Cl, 4.1% to 7.8%; P < .001). Neither platinum dose-intensity nor cumulative platinum dose was significantly associated with median survival time.

**DISCUSSION**

Cytoreductive surgery for advanced ovarian carcinoma was first championed by Meigs\(^67\) in 1934. Meigs suggested that to enhance the effects of postoperative radiation therapy, as much tumor as possible should be removed. In 1975, 41 years after Meigs’ initial proposition, Griffiths\(^68\) published a landmark study that conclusively demonstrated an inverse relationship between residual tumor diameter and patient survival. Since that time, multiple retrospective studies have confirmed this observation.\(^6,65,69-75\) Although surgery remains the cornerstone of diagnosis and initial therapy for patients with advanced ovarian carcinoma, questions persist regarding the relative effect of aggressive surgical cytoreduction on survival. Critics of surgery argue that intrinsic tumor biology, rather than surgical intervention, determines not only prognosis and survival but the feasibility of surgical debulking as well.\(^76\)

To clarify the independent contribution of both surgery and platinum-based chemotherapy to the overall survival of patients with advanced ovarian carcinoma, several investigators have conducted meta-analyses, whereby multiple individual studies are evaluated collectively to provide a more expansive database. Perhaps the most widely cited of such reports was published by Hunter et al\(^2\) in 1992. This study, involving 6,962 patients with ovarian carcinoma treated between 1967 and 1989, found that each 10% increase in maximal cytoreductive surgery was associated with a 4.1% increase in median survival time. The use of platinum chemotherapy produced an estimated 53% increase in median survival time. The authors concluded that surgery has only a minor effect on the survival of women with advanced ovarian cancer. Additional studies have supported the view that platinum-based chemotherapy has a proportionally much greater effect on patient survival than does surgical debulking.\(^3,4\) In contrast, other investigators have shown that surgical outcome is also an independent predictor of survival, but they have had difficulty quantifying the comparative magnitude of this effect.\(^77-80\)

The meta-analysis literature clearly demonstrates that platinum-based primary chemotherapy is associated with prolonged survival in patients with advanced ovarian carcinoma. However, the current standards of care make comparisons of platinum- and nonplatinum-treated patients less relevant. The first objective of the current study, therefore, was to examine the relative effect of maximal cytoreductive surgery and other prognostic factors on survival among patients treated during the era of universal primary platinum-based chemotherapy. Our results indicate that in this setting, the strongest predictor of improved median survival time was the proportion of patients in a given cohort undergoing maximal cytoreductive surgery. Even after controlling for the effects of other variables, the proportion of maximal cytoreductive surgery was the most powerful independent determinant of cohort survival. That neither platinum dose-intensity nor cumulative platinum dose was a statistically significant predictor of survival does not undermine the critical importance of platinum-based chemotherapy in the primary treatment of advanced ovarian carcinoma. Rather, our data confirm the findings of Ben-David et al\(^79\) and simply suggest that when all patients do receive a platinum-based regimen, minor alterations in dose-intensity and cumulative dose are relatively less important.

The observation that more recent studies were associated with a statistically significant extension of median survival time has been previously described. Balvert-Locht et al\(^81\) and Bjorge et al\(^82\) also found that the period of diagnosis is an independent predictor of improved survival for patients with ovarian carcinoma. The reason or reasons for this finding are not immediately evident from the variables examined in the present study. Although the observed effect may have been due to improvements in cancer care, the potential contribution of other unmeasured factors must also be considered. The survival advantage associated with increasing year of study publication seems not to be due to the introduction of taxanes into front-line clinical practice, because only two studies in our analysis incorporated paclitaxel in this fashion. This does not discount the possibility that with the passage of time, an increasing number of patients may have received taxanes, or other active second-line agents (eg, topotecan), in the setting of salvage treatment. The finding of a significant negative correlation between year of publication and the number of chemotherapy cycles prescribed (median of 10 cycles in 1989 v median of six cycles in 1998) would argue against a higher cumulative chemotherapy dose accounting for the improvement in median survival over time.

A critical review of the data presented requires an appreciation of the methodological limitations of a meta-analysis of this nature. First, we made every effort to
include as many studies as possible, while continuing to use the selection criteria initially set forth. Nevertheless, the potential for selection bias, with regard to both studies selected for our analysis and the inclusion of patients within each individual study, must be considered. The overall rate of maximal cytoreductive surgery for all study cohorts is consistent with those reported in other large meta-analyses.

A second limitation is that the necessary imprecision of our measurement tools may have affected our ability to discriminate between statistical and clinically meaningful differences. We believe that increasing the precision of data measurement would likely accentuate the observed effects.

A third limitation is that the baseline dosages used for calculating platinum dose-intensity may be seen as somewhat arbitrary. However, the mean weighted platinum dose-intensity of 0.98 indicates that the selected baseline dosages closely approximated the standard of care during the period under study. The literature also supports the concept that these dosages meet the level required to achieve significant chemotherapeutic efficacy, with increases above these levels not being accompanied by substantial increases in survival.

A fourth limitation is that the large variety of different chemotherapeutic agents and administration schedules used during the study period precluded an analysis of total drug dose-intensity or total cumulative drug dose. Although this omission may be a potential source of confounding, similar meta-analyses of advanced ovarian carcinoma studies have not found these factors to affect survival significantly. In analyzing total drug dose-intensity and total cumulative drug dose, Ben-David et al\textsuperscript{79} and Hunter et al\textsuperscript{7} found that dose increases above contemporary practice standards were unlikely to have a measurable effect on survival.

A fifth limitation of the current study is that we did not examine additional prognostic factors, such as surgical substage and performance status, that might have influenced either survival or the proportion of patients undergoing maximal cytoreductive surgery. At least one meta-analysis has found that performance status, in addition to optimal surgery and the use of platinum chemotherapy, had a measurable effect on survival.\textsuperscript{77} Although such data would likely attenuate the risk of confounding effects, expanding the selection criteria to include additional variables would have markedly reduced the number of eligible studies.

Lastly, although the majority of studies (79\%) used a criterion of \(\leq 2.0\) cm to define maximal cytoreductive surgery, this number ranged from less than 0.5 cm to less than 3.0 cm. Consequently, maximal cytoreductive surgery should be viewed as a relative measure of surgical outcome. Unfortunately, there were too few studies using criteria other than \(\leq 2.0\) cm to provide for a meaningful analysis of the possible survival effect associated with variations in this parameter.

Despite these limitations, the data from the current study have important implications with regard to a concept we term population-based cytoreduction. Population-based cytoreduction is based on the premise that among women with advanced ovarian carcinoma, the survival outcome of an entire cohort can be significantly influenced by the proportion of patients undergoing a maximal surgical effort. The two key elements within this conceptual framework are surgical outcomes analysis and patterns of care.

A review of surgical outcomes data reveals a wide disparity in success rates of cytoreductive surgery for advanced ovarian carcinoma.\textsuperscript{6,7,43,46,65,69-72,75,84-93} In many areas or centers, surgeons who do not have extended formal training in cytoreductive techniques perform the initial surgery for patients with suspected advanced ovarian cancer. In such instances, rates of optimal surgical resection, although variably defined, are often 25\% or less.\textsuperscript{43,72,84-90} An illustrative report was published in 1992 by Unzelman,\textsuperscript{88} who described the experience of 101 women with stage III or IV ovarian carcinoma undergoing surgery at two community hospitals. All surgeries were performed by either general gynecologists or general surgeons. In this series, only 43 patients underwent complete removal of the ovaries and uterus, and no patient underwent lymph node biopsy. In addition, optimal (\(\geq 2\) cm) surgery was accomplished in just 20.2\% of the 84 patients with stage IIIC or IV disease. At the other end of the spectrum are the so-called expert centers, where surgeons with the necessary skill and philosophical approach achieve optimal resection rates far superior to those achieved at centers with less experienced surgeons.\textsuperscript{6,7,43,46,65,69-71,75,91-93} The suggested requirement for an “expert center” is an optimal resection rate of at least 75\%.\textsuperscript{69,70,94} Consistent with this figure, it has been demonstrated that gynecologic oncologists, an integral component of such centers, achieve optimal cytoreduction in 71\% to 76\% of patients with advanced ovarian carcinoma initially thought to be unresectable by less experienced surgeons.\textsuperscript{70,74}

Ultimately, the clinical relevance of disparate surgical success rates hinges on the potential survival benefit associated with a consistent and concerted effort to achieve maximal cytoreductive surgery. As early as 1968, Mun nell\textsuperscript{95} suggested that the survival rate of an entire cohort of patients with advanced ovarian carcinoma could be improved by increasing the intensity of the initial surgical procedure. In 1992, Eisenkop et al\textsuperscript{6} specifically examined the effect of surgeons’ specialty training on the outcome of primary cytoreductive surgery in 263 patients with advanced stage ovarian carcinoma. Gynecologic oncologists
performed optimal (≤ 1 cm) surgery in 81.7% of cases, compared with only 29.2% for other surgical specialties. Not surprisingly, optimal surgery was associated with improved overall survival. More importantly, however, multivariate analysis revealed that surgery performed by a gynecologic oncologist was also a significant and independent predictor of median survival time (35 months), compared with surgery performed by a nongynecologic oncologist (median survival time, 17 months). Similar findings have been reported by other authors.6,7 On a larger scale, population-based outcomes analyses have consistently demonstrated that the specialty of the operating surgeon is an independent determinant of survival for women with ovarian carcinoma.85,87,97,98 These data mirror the well-known relationship between cancer care outcomes for patients with malignancies treated with technologically complex surgical procedures and hospital volume or physician specialty.99-102

The aforementioned studies provide a backdrop for interpreting the findings of the current report. Incremental changes in the proportion of patients undergoing maximal cytoreduction, although statistically significant, lack clinical effect. However, the second major objective of the present study was to quantify the effect on survival of a major difference in percent maximal cytoreductive surgery, akin to a comparison of expert centers and centers with less experienced surgeons. After controlling for the effects of all other measured variables, cohorts with ≥ 75% maximal cytoreductive surgery had a median survival time that was 50% longer than that of cohorts with less than 25% maximal cytoreductive surgery (33.9 vs 22.7 months). To put this into perspective, one can consider the findings of Gynecologic Oncology Group protocol 111, which led to the adoption of the combination of cisplatin and paclitaxel as front-line treatment for advanced ovarian carcinoma.59,103 In this landmark study, the substitution of paclitaxel for cyclophosphamide resulted in a comparable increase in median survival time of 54% (37.5 vs 24.4 months).

In addition to surgical outcomes analysis, the concept of population-based cytoreduction is dependent on cultivating the necessary patterns of care for women with suspected ovarian carcinoma. In the United States, the extended formal training of gynecologic oncologists translates into optimal resection rates that are 50% to 60% higher than in other surgical specialties.5,6 Unfortunately, widespread initial access to such care has been an elusive goal. Several reports underscore the gradual evolution of practice patterns. McGowan8 reported that between 1978 and 1981, only 12% of patients with ovarian carcinoma in the Washington, DC, metropolitan area had a gynecologic oncologist present at the time of initial surgery. Nguyen et al10 collected data on 12,316 patients from the National Survey of Ovarian Carcinoma from 1983 through 1988. In this group, only 21% of patients received care from a gynecologic oncologist. Similarly, Averette et al8 reported the experience of the American College of Surgeons National Cancer Survey of cancer hospitals and found that gynecologic oncologists cared for just 25% of ovarian carcinoma patients during 1988. This trend has improved at a marginal rate; in Utah, only 39% of such patients had access to gynecologic-oncologist care between 1992 and 1998.11 The proposed concept of population-based cytoreduction dictates that current surgical practice patterns conform to the definition of high-quality cancer care offered by the Institute of Medicine: "Quality care is the degree to which health services for individuals and populations increase the likelihood of desired outcome and are consistent with current professional knowledge."99

In conclusion, the current data suggest that in the setting of universal primary platinum-based therapy for advanced ovarian carcinoma, the strongest clinician-driven predictor of survival is optimal surgical outcome. Consistent referral of patients with advanced ovarian carcinoma to expert centers for initial surgery may be the best means currently available for improving overall survival. Only by assuring that the majority of women with advanced ovarian carcinoma have access to a maximal primary surgical effort can we expect to realize the population-based survival benefits of cytoreductive surgery.

REFERENCES


