Review

Evolution of surgical treatment paradigms for advanced-stage ovarian cancer: Redefining ‘optimal’ residual disease

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Abstract

Over the past 40 years, the survival of patients with advanced ovarian cancer has greatly improved due to the introduction of combination chemotherapy with platinum and paclitaxel as standard front-line treatment and the progressive incorporation of increasing degrees of maximal cytoreductive surgery. The designation of “optimal” surgical cytoreduction has evolved from residual disease ≤1 cm to no gross residual disease. There is a growing body of evidence that patients with no gross residual disease have better survival than those with optimal but visible residual disease. In order to achieve this, more radical cytoreductive procedures such as radical pelvic resection and extensive upper abdominal procedures are increasingly performed. However, some investigators still suggest that tumor biology is a major determinant in survival and that optimal surgery cannot fully compensate for tumor biology. The aim of this review is to outline the theoretical rationale and historical evolution of primary cytoreductive surgery, to re-evaluate the preferred surgical objective and procedures commonly required to achieve optimal cytoreduction in the platinum/taxane era based on contemporary evidence, and to redefine the concept of “optimal” residual disease within the context of future surgical developments and analysis of treatment outcomes.

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Introduction

Worldwide, approximately 225,500 women are diagnosed with ovarian cancer every year and about 140,200 women die from this disease [1]. In the United States, ovarian cancer remains the leading cause of death from gynecological cancers, with 21,990 new cases and 15,460 deaths in 2011 [2]. The International Federation of Gynecology and Obstetrics (FIGO) stage of the disease is the strongest predictor of survival. Unfortunately, the majority of patients will have advanced-stage disease at initial diagnosis and this is intimately linked with the poor prognosis of the disease [3,4]. Most patients with advanced-stage disease will experience relapse, and only 20–25% of patients can be expected to be long-term survivors despite a good response to primary treatment [5].

Although the impact of chemotherapy on survival of advanced ovarian cancer patients is substantial, the evolution of primary cytoreductive surgical techniques to minimize the amount of residual
Historical evolution of primary cytoreductive surgery

Cytoreductive surgery for advanced ovarian cancer was advocated as early as 1934 by Meigs, who suggested that as much tumor as possible should be removed to enhance the effectiveness of postoperative radiation therapy [19]. A single-institution observational study published by Griffiths in 1975 provided a more definitive demonstration of the inverse correlation of the amount of residual disease and subsequent overall survival in patients with advanced ovarian cancer [20]. In this study of 102 patients with stage II and III ovarian cancer, Griffiths found that after tumor bulk resection, survival was inversely correlated with residual tumor size under 1.6 cm and surgery improved survival relative to increasing reduction of tumor size below this limit. On multivariate analysis, the most important factors predicting survival were the tumor grade and the size of the largest residual tumor mass after primary surgery. Multiple retrospective series published during the 1980s validated the findings from the Griffiths’ study, and firmly established primary cytoreduction followed by platinum-based chemotherapy as the standard management for advanced ovarian cancer [21-31].

In 1992 and 1994, Hoskins et al. conducted ancillary data studies on two previous GOG studies (GOG 52 and 97) designed to assess the efficacy of chemotherapy, to evaluate the correlation between the maximal diameter of residual disease after primary cytoreduction and survival in patients with advanced ovarian cancer [6,7]. These two reports included 349 advanced ovarian cancer patients with optimal residual disease (≤ 1 cm) and 294 patients with suboptimal residual disease (> 1 cm) receiving cisplatin/cyclophosphamide chemotherapy. These data demonstrated that survival of patients incrementally improved as the diameter of the largest residual disease decreased from 2 cm to microscopic. Patients with no gross residual disease had a 5-year survival rate of 60%, those with 0.1–1 cm or 1–2 cm residual disease had a 5-year survival rate of 35%, and those with residual disease > 2 cm had the worst 5-year survival rate (≤ 20%). The maximal diameter of residual disease was found to be an independent predictor of overall survival after controlling other variables.

In 2002, Bristow et al. reported a meta-analysis of 6885 patients with stage III or IV ovarian cancer to evaluate the effect of maximal cytoreductive surgery and other prognostic factors on survival among cohorts of patients treated during the platinum era [32]. These investigators demonstrated a significant association between the proportion of patients in any given cohort undergoing maximal cytoreduction and overall survival after adjusting other variables. Each 10% increase in the proportion of patients undergoing maximal cytoreduction was associated with a concomitant 5.5% increase in median cohort survival time. Survival of patient cohorts with > 75% maximal cytoreduction increased by 50% compared with that of cohorts ≤ 25% maximal cytoreduction (median survival time of 33.9 months versus 22.7 months). This study introduced the concept of “population-based cytoreduction” – the correlation between an increasing proportion of patients left with minimal residual disease in a given population and improved overall survival of the group as a whole. The authors concluded that among various clinical characteristics associated with survival in advanced ovarian cancer, the strongest clinician-driven factor was the performance of maximal cytoreductive surgery.

Although these landmark studies demonstrated a survival benefit associated with minimal residual disease and maximal cytoreductive surgical efforts in advanced ovarian cancer patients, some investigators have still advocated that improved survival is possibly due to less advanced initial disease rather than more aggressive surgical cytoreduction [33-35]. For example, Crawford et al. retrospectively analyzed the Scottish Randomized Trial in Ovarian Cancer (SCOTROC-1) trial data on 889 patients with FIGO stage IC-IV ovarian cancer and reported that optimal debulking was associated with increased progression-free survival mainly for patients with less extensive disease [35]. These investigators proposed that the surgical cytoreduction was associated with the favorable prognosis in less extensive disease and optimal debulking could not fully make up for tumor biology.

However, a number of contemporary studies from experienced centers and cooperative groups have improved on attempts to account for the initial disease burden and indicate that so-called ‘radical’ cytoreductive surgery can at least partly compensate for the inherent tumor biology and is associated with extended overall survival via the synergistic effects of minimizing residual disease and improvements in adjuvant chemotherapy.

The impact of platinum/taxane chemotherapy and regional therapeutics

Subsequent to the seminal reports by Hoskins et al., advances in chemotherapy and regional therapeutics have accentuated the survival outcomes for patients with advanced-stage epithelial ovarian cancer according to residual disease, with a disproportionately more favorable outcome for patients with no gross residual disease compared to those patients left with residual disease measuring 0.1–1 cm and > 1 cm.

In 1996 and 2000, McGuire et al. and Piccart et al. reported the survival benefit of paclitaxel/cisplatin (TP) combination chemotherapy compared to cisplatin/cyclophosphamide (PC) combination (the median survival times of 38 versus 24 months and 36 versus 26 months, respectively) in patients with advanced ovarian cancer, respectively [36,37]. Results of two randomized controlled trials comparing TP and paclitaxel/carboplatin (TC) combinations were published in 2003 [38,39]. Since then, TC has been the standard regimen in first-line adjuvant treatment. Of special interest is the data from GOG 158 [38]. Although the trial was not designed to evaluate cytoreductive surgery and all eligible patients had optimally debulked stage III disease, it is noteworthy that patients with microscopic residual disease had significantly longer survival than those with optimal but macroscopic residual disease (median survival times of > 60 versus 45 months in TC arm and > 60 versus 41 months in TP arm). More recently, Bookman et al. reported the results of an international cooperative group study of 4312 patients with stage III and IV ovarian cancer, of which the
objective was to evaluate whether incorporation of an additional cytotoxic agent improves survival for women who receive TC combination chemotherapy [40]. The addition of a new cytotoxic agent provided no survival benefit. For patients with suboptimal (> 1 cm), gross-optimal (≤ 1 cm), and microscopic residual disease, however, the median overall survival times were 33, 40, and 68 months, respectively.

The re-emergence of regional therapeutics has had a similar impact on improving the expected overall survival time for patients with advanced-stage ovarian cancer as well as accentuating the proportionally greater extension in median survival time for patients left with no gross residual disease. Two important phase III randomized trials on the clinical utility of intraperitoneal chemotherapy for advanced ovarian cancer patients with small residual disease after maximal cytoreductive surgery revealed a statistically significant improvement in overall survival associated with intraperitoneal chemotherapy in optimally debulked patients [41,42]. The study conducted by the Southwest Oncology Group (SWOG) and the GOG yielded important data relevant to the correlation between survival and residual disease [41]. Alberts et al. published the results of this intergroup study comparing intraperitoneal and intravenous chemotherapy for stage III ovarian cancer. Among 546 patients with optimal residual disease (≤ 2 cm), 139 (25.5%) patients had microscopic residual disease, 254 (46.5%) had residual disease ≤ 0.5 cm, and 153 (28.0%) had residual disease > 0.5–2.0 cm. The median overall survival time was significantly longer in patients with no gross residual disease relative to patients with larger residual disease diameters (74 versus 41 versus 34 months, respectively).

In 2006, a seminal phase III trial on optimal cytoreduction and post-operative intraperitoneal chemotherapy was published [43]. Armstrong et al. reported that intravenous paclitaxel plus intraperitoneal TP chemotherapy improved survival in 429 patients with optimally debulked (≤ 1 cm) stage III ovarian cancer comparing with intravenous TP. Adverse effects were more common in the intraperitoneal chemotherapy group than in the intravenous chemotherapy group and only 42% of the patients receiving intraperitoneal chemotherapy could complete the planned 6 treatment cycles. However, the survival benefit outweighed these limitations. There were statistically significant improvement in progression-free (18.3 versus 23.8 months) and overall survival times (49.7 versus 65.6 months) associated with the combined intravenous and intraperitoneal regimen. Especially relevant from the standpoint of surgically achievable residual tumor was the difference in survival among patients with optimal residual disease. Although the median overall survival had not yet been reached, patients with no gross residual disease had a longer progression-free survival time than those with residual disease of 0.1–1 cm in both intraperitoneal and intravenous chemotherapy groups (38 versus 18 months and 35 versus 15 months, respectively). These results highlight the more pronounced differential in survival benefit associated with complete cytoreduction or no gross residual disease versus optimal but visible (0.1–1 cm) residual disease as a result of more efficacious adjuvant therapy.

The potential impact of aggressive locoregional therapy in extending the survival advantage associated with no gross residual disease is further highlighted by recently published results of a phase II study by Deraco et al. [44]. These investigators treated 26 patients with advanced-stage ovarian cancer with up-front cytoreductive surgery, of which 58% had no gross residual disease, and intraoperative hyperthermic intraperitoneal chemotherapy with cisplatin and doxorubicin followed by 6 cycles of intravenous carboplatin and paclitaxel chemotherapy. In this study, after a median follow-up of 25 months, the median progression-free survival time was 30 months and the median overall survival time had not yet been reached; 5-year overall survival and progression-free survival rates were 60.7% and 15.2%.

The above studies suggest that as regional therapy has advanced to extend survival times overall, the separation of survival times between patients with no gross residual disease and with residual disease of 0.1–1 cm has widened. In other words, the more effective the better adjuvant therapy is given, the larger the relative impact of complete cytoreduction versus optimal but visible is much more noticeable. In connection with this issue, we will analyze the impact of complete cytoreduction on survival in advanced ovarian cancer patients drawing from the review of the literature.

Impact of complete cytoreduction on survival

Since the landmark GOG studies reported by Hoskins et al., a number of studies have confirmed that overall survival is significantly improved in advanced ovarian cancer patients with optimal residual disease after maximal cytoreductive surgery [6–18,32,36–43,45–56]. Although these studies demonstrated a strong association between survival improvement and maximal cytoreductive surgery, the majority of these included patients who did not receive the paclitaxel–platinum combination chemotherapy and did not conduct a survival analysis for patients with no gross or microscopic residual disease. The more recent literature does, however, offer several single institution studies and collective reports of cooperative group trials that directly address the impact of complete cytoreduction on survival in patients receiving paclitaxel and platinum as first-line chemotherapy after primary cytoreductive surgery.

Single institution studies

Results of two retrospective studies were published from the Memorial Sloan–Kettering Cancer Center and the Mayo Clinic in 2006 [11,12]. In 2006, Chi et al. analyzed 465 patients with bulky stage IIIC disease from the Memorial Sloan–Kettering Cancer Center [11]. All patients underwent attempted maximal cytoreductive surgery, with extensive upper abdominal surgery (diaphragm stripping/resection, splenectomy, distal pancreatectomy, liver resection, and resection of tumor from porta hepatitis) in a significant proportion of patients followed by a minimum of 6 cycles of postoperative platinum-based systemic chemotherapy. The authors demonstrated that patients with no gross residual disease after primary cytoreduction had median survival of 106 months and proposed that resection of all visible disease significantly improved survival and should be the surgical goal of primary cytoreductive surgery.

Also in 2006, Aletti and coworkers from the Mayo Clinic reported their experience with 194 patients with stage IIIC epithelial ovarian cancer and analyzed the impact of radical cytoreductive surgical procedures (diaphragm surgery, splenectomy, liver resection, extensive peritonectomy) on residual disease and the associated survival outcome [12]. All patients received adjuvant platinum-based chemotherapy (including paclitaxel or cyclophosphamide) for 6–8 cycles after primary surgery. Overall, 131 (67.5%) patients had residual disease ≤ 1 cm in maximal diameter. The median survival times of patients left with no gross residual disease and optimal but visible residual disease (0.1–1 cm) were ≥ 84 months and 34 months, respectively. The amount of residual disease was the only independent predictor of survival outcome after adjusting for clinical and pathological variables on multivariate analysis. To further examine the potential survival advantage associated with radical surgical resection, the authors conducted a subgroup analysis of 144 patients with the most extensive disease — those with documented peritoneal carcinomatosis. Multivariate survival analysis of this subgroup revealed that the performance of radical surgery and the status of residual disease were the only independent prognostic factors for 5-year disease-specific overall survival. Specifically, overall survival of patients who underwent radical procedures was significantly improved compared to those who did not undergo radical procedures (38% versus 9%, p < 0.001). In perhaps the most compelling aspect of this study, the authors also evaluated whether patient outcomes were affected by an individual surgeon’s tendency to utilize radical procedures as
part of maximal cytoreductive surgery. Surgeons were classified into two groups — those that performed radical procedures in more than 70% of patients and those that performed radical procedures in fewer than 40% of patients. In comparing the clinical outcomes according to the surgeon’s tendency to employ radical cytoreductive procedures, the authors found that there were no differences in clinical and tumor characteristics between patients of the two groups; however, patients treated by surgeons who frequently utilized radical procedures had a significantly longer median overall survival time compared to patients treated by surgeons who infrequently performed radical surgery (42 months versus 24 months, respectively; \( p < 0.001 \)). Three important conclusions can be drawn from these data: 1) complete cytoreduction to no gross residual disease is associated with significantly longer overall survival, 2) radical cytoreductive surgery is able to at least partly counteract the effect of tumor burden, and 3) the survival outcome of patients with advanced ovarian cancer is strongly influenced by the individual surgeon’s ability and willingness to undertake radical surgical procedures to achieve minimal residual disease.

Collective analysis of cooperative group trials

Recently, the collected experience from cooperative group trials from both the GOG and AGO have been reported in an attempt to further clarify the role of complete cytoreduction to no gross residual disease in patients receiving contemporary platinum/taxane-based adjuvant chemotherapy [13–15]. Winter III et al. published the GOG experience, which analyzed data from previous GOG clinical trials evaluating the efficacy of chemotherapy [13,14]. These investigators identified 1895 stage III and 360 stage IV ovarian cancer patients, who participated in one of seven trials (GOG 111, 114, 132, 152, 158, 162, and 172). All patients underwent primary cytoreductive surgery followed by six cycles of intravenous cisplatin and paclitaxel combination chemotherapy. In patients with stage III disease, optimal (<1 cm) and no gross residual disease were achieved in 64.7% and 23.1% of cases, respectively. The comparable rates for patients with stage IV disease were 29.8% and 8.1%. The status of residual disease was one of the independent predictors of prognosis in both studies. Among patients with stage III disease, microscopic residual disease was associated with the longest median survival compared with residual disease ≤1 cm and residual disease >1 cm (71.9 versus 42.4 versus 35.0 months). Similar findings were observed in study of stage IV disease, which demonstrated that microscopic residual disease had the most favorable survival outcome compared with residual disease 0.1–1 cm, 1–5 cm and >5 cm (median survival of 64.1 versus 29 versus 31 versus 19 months). Although complete resection was only achievable in a minority of patients in these analyses, the wide differential in survival outcome between no gross residual and optimal but visible residual disease is noteworthy. The authors proposed that the traditional concept of optimal residual disease ≤1 cm should be re-evaluated and radical cytoreductive procedure might be justified even in stage IV disease if complete cytoreduction to microscopic residual disease can be achieved.

In a similar approach, du Bois et al. retrospectively analyzed 3126 patients from 3 prospective randomized trials conducted by the AGO (AGO-OVAR 3, 5, and 7) of patients with stage III–IV ovarian cancer receiving at least 6 cycles of platinum/taxane-based chemotherapy following primary surgery [15]. Overall, patients with no gross residual disease had significantly longer median overall survival than those with residual disease 0.1–1 cm and >1 cm (99.1 versus 36.2 versus 29.6 months, respectively) after stratification by stage of disease.

Although these are not prospective randomized trials comparing surgical cytoreductive efforts among advanced-stage ovarian cancer patients, these collective analyses do offer large and homogenous study populations that at the very least underscore the important prognostic value of complete cytoreduction in the era of platinum/taxane chemotherapy.

Collected single-institutional series and combined cooperative group trial data published since 2003 are listed in Table 1. These 14 studies included a total of 13,949 patients and specifically reported survival time associated with cytoreductive surgery to no gross residual disease, with varying gradations of larger volume residual disease. An examination of the three major residual disease categories reveals a marked inverse correlation between the maximal diameter of residual tumor and overall survival. Specifically, the weighted median overall survival for 3593 patients with no gross residual disease is 77.8 months compared to 39.0 months for the 4780 patients with 0.1–1 cm residual disease and 31.1 months for the 3518 patients with residual tumor >1 cm in maximal diameter. The magnitude of the incremental improvement in overall survival associated with no gross residual disease compared to optimal but visible (0.1–1 cm) residual disease strongly suggests that complete resection should be the surgical objective whenever feasible (Fig. 1).

Feasibility of radical cytoreductive procedures

Primary cytoreductive surgery for ovarian cancer can be categorized into simple and radical surgical procedures. Simple cytoreductive procedures consist of total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, limited excision of pelvic/para-aortic lymph nodes, peritoneal excision, and segmental resection of bowel. These procedures can be accomplished in most patients with minimal risk of complications. To achieve optimal cytoreduction, surgery for advanced ovarian cancer frequently requires the addition of radical procedures such as radical oophorectomy, rectosigmoid colectomy, multiple bowel resections, diaphragm peritoneectomy or resection, liver resection, porta hepatitis surgery, splenectomy, distal pancreatectomy, gastric resection, extensive nodal debulking, and intrathoracic surgery, and these procedures accompany some degree of complications. However, many series have shown that radical cytoreductive procedures are highly effective for complete cytoreduction with survival benefit and can be safely performed with acceptable morbidity and mortality (Table 2).

Advanced-stage ovarian cancer often extends to pelvic peritoneum and rectosigmoid colon and obliterates the cul-de-sac. Many investigators have shown that radical pelvic resection — radical oophorectomy, en bloc rectosigmoid colectomy, or modified posterior pelvic exenteration — is feasible and effective to completely remove the per-pelvic disease without significant morbidity [57–67]. In addition to rectosigmoid colectomy, extensive bowel resections are performed as part of cytoreductive procedures [55,68–74]. Hoffman et al. reported reviewed 144 advanced ovarian cancer patients who underwent primary optimal cytoreductive surgery that included bowel resection [69]. Thirty-six percent had extensive involvement of colon segments separate from the rectosigmoid colon and only 9 patients (6%) experienced a major complication in their series. Salani et al. demonstrated that multiple (>2) bowel resections are warranted to achieve an optimal, or ideally complete, residual disease state in advanced ovarian cancer [55].

To accomplish optimal cytoreductive surgery, the need for extensive upper abdominal procedures increases in management for advanced ovarian cancer patients with widespread upper abdominal disease [75–96]. Guido et al. evaluated 30 patients who underwent radical pelvic and upper abdominal cytoreductive surgery, and 23 (76.7%) patients had optimal cytoreduction [91]. Scholz et al. analyzed the surgical outcomes of 101 patients undergoing extensive multivisceral cytoreductive surgery for FIGO stage IIIb and IV ovarian cancer — 55 patients had primary surgery and 46 patients had interval debulking surgery. They reported that complete cytoreduction was possible in 84 (83%) patients [93].
The report by Chi et al. clearly illustrated the impact of such a paradigm shift in surgical approach with the incorporation of extensive upper abdominal debulking procedures on the rates of optimal primary cytoreduction in patients with advanced ovarian cancer [94]. The authors' institution has incorporated extensive upper abdominal procedures as a part of primary cytoreductive surgical strategy since 2000. A total of 378 stage IIIC and IV ovarian cancer patients who were treated at the institution between 1996 and 2004 were identified and classified into two groups based on the date of surgery: group 1 consisted of 168 patients who underwent primary cytoreductive surgery and did not have extensive upper abdominal surgery from 1996 to 1999, and group 2 consisted of 210 patients who underwent primary cytoreduction in patients with advanced ovarian cancer [94].

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Age, yr</th>
<th>FIGO stage</th>
<th>No of Pts</th>
<th>Chemo agents*</th>
<th>Chemo route</th>
<th>Outcomes</th>
<th>OS, mos</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single institution study</strong></td>
<td></td>
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</tr>
<tr>
<td>Eisenkop [10]</td>
<td>Retrospective</td>
<td>63</td>
<td>IIC</td>
<td>408 (100%)</td>
<td>PC, TP</td>
<td>IV</td>
<td>0 (Reference)</td>
<td></td>
<td>Completeness of cytoreduction and ranking system according to extent of disease</td>
</tr>
<tr>
<td>Chi [11]</td>
<td>Retrospective</td>
<td>60</td>
<td>IIC</td>
<td>465 (100%)</td>
<td>NA</td>
<td>IV</td>
<td>0 (Reference)</td>
<td></td>
<td>Age, ascites, RD</td>
</tr>
<tr>
<td>Aletti [12]</td>
<td>Retrospective</td>
<td>64</td>
<td>IIC</td>
<td>194 (100%)</td>
<td>NA</td>
<td>IV</td>
<td>0 (Reference)</td>
<td></td>
<td>Age, ASA, ascites, carcinoma, diaphragm involvement, bowel mesentery involvement, bowel resections, and RD</td>
</tr>
<tr>
<td>Salani [55]</td>
<td>Retrospective</td>
<td>63</td>
<td>III</td>
<td>97 (78%)</td>
<td>PC, TP</td>
<td>IV</td>
<td>0 (Reference)</td>
<td></td>
<td>Age, stage, ascites, number of bowel resections, and RD</td>
</tr>
<tr>
<td>Peiretti [16]</td>
<td>Retrospective</td>
<td>58</td>
<td>IIC</td>
<td>199 (76%)</td>
<td>NA</td>
<td>IV</td>
<td>0 (Reference)</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Komnoss [18]</td>
<td>Retrospective</td>
<td>64</td>
<td>IIIB</td>
<td>23 (9%)</td>
<td>NA</td>
<td>IV</td>
<td>0 (Reference)</td>
<td></td>
<td>Age, ECOC performance status, stage, histology, tumor grade, and RD</td>
</tr>
<tr>
<td><strong>Cooperative group trial</strong></td>
<td></td>
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</tr>
<tr>
<td>Ozols [38]</td>
<td>Prospective</td>
<td>56</td>
<td>III</td>
<td>792 (100%)</td>
<td>TP, TC</td>
<td>IV</td>
<td>0 (Reference)</td>
<td></td>
<td>Age, race, histology, tumor grade, GOG performance status, and RD</td>
</tr>
<tr>
<td>Armstrong [43]</td>
<td>Prospective</td>
<td>56</td>
<td>III</td>
<td>415 (100%)</td>
<td>TP, IV, IP</td>
<td></td>
<td></td>
<td></td>
<td>History, site, and RD</td>
</tr>
<tr>
<td>Wimberger [56]</td>
<td>Retrospective</td>
<td>NA</td>
<td>IIIB-IV</td>
<td>213 (28%)</td>
<td>PC, TP</td>
<td>IV</td>
<td>0 (Reference)</td>
<td></td>
<td>Age, performance status, stage, grade, histology, ascites, and RD</td>
</tr>
<tr>
<td>Winter III [13]</td>
<td>Retrospective</td>
<td>57</td>
<td>III</td>
<td>1895 (100%)</td>
<td>TP, TC</td>
<td>IV</td>
<td>0 (Reference)</td>
<td></td>
<td>Histology, disease site, and RD</td>
</tr>
<tr>
<td>Winter III [14]</td>
<td>Retrospective</td>
<td>59</td>
<td>IV</td>
<td>360 (100%)</td>
<td>TP, TC</td>
<td>IV</td>
<td>0 (Reference)</td>
<td></td>
<td>Histology, disease site, and RD</td>
</tr>
<tr>
<td>du Bois [15]</td>
<td>Retrospective</td>
<td>59</td>
<td>IIIB-IV</td>
<td>814 (26%)</td>
<td>TP, TC</td>
<td>IV</td>
<td>0 (Reference)</td>
<td></td>
<td>Histology, disease site, and RD</td>
</tr>
<tr>
<td>Bookman [40]</td>
<td>Prospective</td>
<td>59</td>
<td>III</td>
<td>3681 (85%)</td>
<td>TC-TOP, TCE</td>
<td></td>
<td></td>
<td></td>
<td>Histology, disease site, and RD</td>
</tr>
<tr>
<td>Wimberger [17]</td>
<td>Retrospective</td>
<td>59</td>
<td>IV</td>
<td>573 (100%)</td>
<td>TP, TC</td>
<td>IV</td>
<td>0 (Reference)</td>
<td></td>
<td>Age, ECOG performance status, stage, histology, disease site, and RD</td>
</tr>
</tbody>
</table>

* PC, cisplatin/cyclophosphamide; TP, paclitaxel/cisplatin; TC, paclitaxel/carboplatin; TC-TOP, TC-Topotecan; TCE, TC-epirubicin; IV, intravenous; IP, intraperitoneal; HR, hazard ratio; RR, risk ratio; CI, confidence interval; RD, residual disease; NA, not available.
43 months, \( p = 0.03 \)). These investigators concluded that the incorporation of extensive upper abdominal procedures increased optimal cytoreduction rates and significantly improved survivals.

A recent European study addresses the similar issue of the introduction of quality management programs regarding the surgical therapy in advanced ovarian cancer. Harter et al. demonstrated in this study of 396 stage IIIB–IV ovarian cancer patients that since the program was employed in management of patients, the rate of extended surgical procedures have increased from 0% up to 42%. The percentage of patients with complete cytoreduction to microscopic residual disease has increased from 33% to 62%, while the number of patients with residual disease > 1 cm decreased from 35% to 14%. The median overall survival time during the study period significantly increased from 26 months to 45 months after adoption of the program, and the median survival time was 69 months for patients with no gross residual disease.

These studies support that the incorporation of extensive upper abdominal procedures into the maximal cytoreductive surgery for advanced ovarian cancer can considerably increase the complete cytoreduction rates and improve survival. Furthermore, the experience of the investigators at the Mayo Clinic, Memorial Sloan-Kettering Cancer Center, and others indicate that the proportion of patients that are able to be successfully cytoreduced to optimal or no gross residual disease within a given clinical practice is not static. On the contrary, with institutional support and a concerted multidisciplinary effort significant improvement in a program’s optimal and complete cytoreduction rates is an achievable goal.

### Neoadjuvant chemotherapy and interval cytoreduction

Interval cytoreductive surgery for advanced ovarian cancer is a term with two meanings: 1) secondary cytoreductive surgery after primary suboptimal debulking followed by induction chemotherapy and 2) primary cytoreductive surgery after the short course of neoadjuvant chemotherapy. This review will focus on the latter.

Table 3 details recently published studies on neoadjuvant chemotherapy and interval cytoreduction [97–103]. In these studies, there were no significant differences in rate of optimal cytoreduction and overall survival between patients who had primary cytoreductive surgery and neoadjuvant chemotherapy followed by interval cytoreduction. The most relevant take home point, however, is that the longest overall survival times are observed in patients with no gross residual disease, which suggested that complete cytoreduction to no gross residual disease would be the most important prognostic determinant in patients who underwent neoadjuvant chemotherapy followed by interval cytoreduction as well as those who underwent primary cytoreduction.

Recently, the results of a randomized, controlled, prospective trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) were published [103]. Six hundred and seventy patients with stage IIIC and IV ovarian cancer were randomly assigned to primary cytoreductive surgery group or neoadjuvant chemotherapy group. There were no significant differences in overall survival (29 months for primary cytoreductive surgery group versus 30 months for neoadjuvant chemotherapy group) between the two groups. Complete cytoreduction with no gross residual disease was possible in 20% of patients who underwent primary cytoreduction and 52% of those who had neoadjuvant chemotherapy. On multivariate analysis, the strongest independent predictor of prolonged survival was the absence of residual tumor after surgery (\( p < 0.001 \)). The authors concluded that neoadjuvant chemotherapy followed by interval debulking surgery has similar efficacy compared with primary debulking surgery followed by chemotherapy for patients with stage IIIC or IV ovarian cancer and complete resection of all gross lesions remains the objective of the cytoreductive surgery whether performed as primary or after neoadjuvant chemotherapy.

A recent report from the Memorial Sloan-Kettering Cancer Center contradicts the findings of the EORTC study and suggests that the strategy of neoadjuvant chemotherapy requires further investigation. A total of 316 stage IIIC–IV ovarian cancer patients who were treated at the institution during the same period in which the EORTC-NCIC trial were evaluated, using identical inclusion criteria [104]. The optimal cytoreduction rate was 71% and the median overall survival time was 50 months. This study suggested that primary cytoreductive surgery should be considered as the preferred initial management strategy for patients with this disease.

It seems that neoadjuvant chemotherapy should not be performed routinely in patients with advanced ovarian cancer and be done in selected patients who are at risk of morbidity associated with primary surgery and likely to have optimal cytoreduction.
Literature on neoadjuvant chemotherapy and interval cytoreductive surgery for primary advanced epithelial ovarian cancer.

Table 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Age, yr</th>
<th>Stage</th>
<th>Control</th>
<th>Neoadjuvant</th>
<th>RD</th>
<th>Related to surgery</th>
<th>OS, mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuhn [97]</td>
<td>64</td>
<td>IIIIC</td>
<td>31</td>
<td>32</td>
<td>TC</td>
<td>3</td>
<td>32 (100%)</td>
</tr>
<tr>
<td>Monroe [98]</td>
<td>56</td>
<td>IIIIC</td>
<td>23</td>
<td>40</td>
<td>TP, TC</td>
<td>3</td>
<td>30 (98%)</td>
</tr>
<tr>
<td>Fanti [99]</td>
<td>57</td>
<td>IIIIC</td>
<td>111</td>
<td>10</td>
<td>TP, TC</td>
<td>3</td>
<td>62 (85%)</td>
</tr>
<tr>
<td>Hegazy [100]</td>
<td>56</td>
<td>IV</td>
<td>14</td>
<td>11</td>
<td>PC</td>
<td>3</td>
<td>18 (66%)</td>
</tr>
<tr>
<td>Hou [101]</td>
<td>64</td>
<td>IV</td>
<td>18</td>
<td>16</td>
<td>PC</td>
<td>3</td>
<td>36 (97%)</td>
</tr>
<tr>
<td>Vergate [103]</td>
<td>62</td>
<td>IV</td>
<td>257</td>
<td>253</td>
<td>NA</td>
<td>3</td>
<td>253 (88%)</td>
</tr>
</tbody>
</table>

PC, cisplatin/cyclophosphamide; TP, paclitaxel/cisplatin; TC, paclitaxel/carboplatin; RD, residual disease; NA, not available.

Conclusion

In advanced ovarian cancer, a number of retrospective and prospective studies suggest that survival is inversely proportional to the amount of residual disease — patients with residual disease ≤ 1 cm after cytoreductive surgery have significant survival benefit comparing with patients who have residual disease > 1 cm. Moreover, among residual disease ≤ 1 cm, those with no gross residual disease have the best prognostic outcomes comparing with those who have optimal but visible residual disease (0.1–1 cm). Therefore, the surgical objective of primary cytoreduction should be toward removing all macroscopic lesions.

There is now compelling evidence supporting not only a change in the definition of “optimal” residual disease to reflect contemporary...
Acknowledgment

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References


Chi DS, Musa F, Dao F, Zivanovic O, Sonoda Y, Leitao MM. An analysis of patients with bulky advanced stage ovarian, tubal, and peritoneal carcinoma treated with primary debulking surgery (PDS) during an identical time period as the randomized EORTC-NCIC trial of PDS vs neoadjuvant chemotherapy (NACT). Gynecol Oncol 2012;124:10–4.