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)

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Objective. The recent EORTC-NCIC randomized trial comparing primary debulking surgery (PDS) to neoadjuvant chemotherapy (NACT) in advanced epithelial ovarian carcinoma (EOC) reported a median progression-free survival (PFS) of 12 months and overall survival (OS) of 30 months for both arms. Due to the equivalent survival and decreased morbidity with NACT, many now consider it the preferred approach. We analyzed the outcomes of patients treated with PDS at our institution during the same time period in which the EORTC-NCIC trial was conducted, using identical inclusion criteria.

Methods. We identified all patients undergoing primary treatment for advanced EOC at our institution from 9/98-12/06. Study inclusion and exclusion criteria were identical to those of the EORTC-NCIC trial. Standard statistical tests were used.

Results. Of 316 eligible patients, 285 (90%) underwent PDS and 31 (10%) received NACT due to extra-abdominal disease, medical comorbidities, and/or advanced age (>85 years). Of the 285 patients who underwent PDS, most had carcinoma of ovarian origin (248, 87%); stage IIIC disease (249, 87%); grade 3 tumors (237, 83%); and serous histology (249, 87%). Optimal cytoreduction (≤1 cm residual) was achieved in 203 patients (71%). Postoperative platinum-based chemotherapy was given to 281 of 285 patients (99%). The median PFS and OS were 17 and 50 months, respectively.

Conclusion. PDS should continue to be the preferred initial management for patients with bulky stages IIIC–IV ovarian carcinoma. NACT should be reserved for those who cannot tolerate PDS and/or for whom optimal cytoreduction is not feasible.

Introduction

Of the estimated 22,000 cases of ovarian cancer diagnosed in the United States each year, approximately 62% present at an advanced stage [1]. It is well established that optimal primary cytoreduction followed by combination taxane and platinum chemotherapy is associated with the highest progression-free survival (PFS) and overall survival (OS) for this population; patients who are not optimally cytoreduced prior to chemotherapy have decreased survival [2–4]. Neoadjuvant chemotherapy (NACT) prior to surgical debulking proposes to increase the proportion of patients who may be optimally cytoreduced, while decreasing surgical morbidity and mortality.

The recently published European Organization for Research and Treatment of Cancer—National Cancer Institute of Canada Clinical Trials Group (EORTC-NCIC) randomized trial comparing primary debulking surgery (PDS) to NACT in patients with FIGO stages IIIC–IV ovarian carcinoma demonstrated equivalent survival and lower toxicity in the NACT arm, leading some in the gynecologic oncology community to conclude that NACT should be the preferred approach for these patients. However, the PFS and OS for patients randomized to the PDS arm were substantially lower than those reported in previous studies, including prospective trials of the Gynecologic Oncology Group (COG) [3–6]. This dichotomy raises an important question concerning the possibility of inter-institutional variation in the adequacy of surgical debulking and/or selection bias in choosing patients to enroll in this large multicenter randomized trial. The objective of this study was to analyze the PFS and OS of patients who underwent PDS at our institution during the same...
Methods

Study group and inclusion criteria

After obtaining Institutional Review Board approval, we used a Gynecology Service Database to identify all patients with International Federation of Gynecology and Obstetrics (FIGO) stages IIIC and IV ovarian, fallopian tube, or primary peritoneal carcinoma who received their primary treatment at our institution between September 1998 and December 2006. As in the EORTC-NCIC study, we excluded all patients with borderline, germ cell, and stromal tumors, patients with advanced disease based solely on microscopic nodal metastases, and those without evidence of abdominal metastasis ≥ 2 cm preoperatively [5].

During the study period, 342 patients with bulky stages IIIC and IV disease [7] presented for primary management at our institution (Fig. 1). Twenty-six of these patients would not have met eligibility criteria for the EORTC-NCIC randomized trial due to poor performance status and/or refusal of primary surgical management. Of the remaining 316 eligible patients, 31 (10%) did not have PDS and were treated with NACT. In our institution, the decision to treat with NACT is never made by a medical oncologist alone but only after consultation with a gynecologic oncologist. The remaining 285 (90%) eligible patients were managed by PDS followed by postoperative taxane and platinum-based chemotherapy.

Data collection and statistical analysis

Medical records for all patients were reviewed, and pertinent demographic, clinical, surgical, pathologic, and follow-up information obtained. Our operative report is standardized, and required fields include quantitative reporting of residual disease. Optimal cytoreduction was defined as no residual disease measuring greater than 1 cm in maximal dimension at the end of surgery. Pelvic and/or para-aortic lymphadenectomy was performed at the discretion of the primary surgeon if it was felt that it would aid in the cytoreductive outcome. Surgical complications were graded according to a previously published institutional grading system [8]. Briefly, grade 1 complications were those managed by oral medications; grade 2 complications required intravenous management; grade 3 complications included those that required major organ resection, interventional radiology, and/or re-operation for correction; grade 4 complications were those that resulted in permanent impairment; and grade 5 complications were those that resulted in patient death within 30 days of the primary surgery [9].

Date of progression was determined by serum CA-125 levels and/or computed tomography (CT) scan. When determined by CT scan, the date of progression was taken as the first appearance of one or more new lesions or increased size of existing lesions. When CA-125 level was utilized, date of progression was defined as the first date the CA-125 level was greater than or equal to two times the nadir value or upper limit of normal, as applicable [10,11]. When a subsequent CT scan confirmed that the rise in CA-125 indicated progression, the date of progression was defined as the date of CA-125 rise.

PFS was defined as the time interval from the date of surgery to the date of the documented first recurrence or progression of disease. If there was no documented recurrence, PFS was calculated from the date of surgery to the date of last follow-up or death, whichever occurred first. Overall survival was defined as the time interval from date of surgery to the date of death or last follow-up. The Kaplan–Meier method was used to estimate survival curves [12,13].

Results

Table 1 demonstrates the characteristics of the 285 patients treated with PDS and the same characteristics of the 336 patients randomized to the PDS arm of the EORTC trial. In our patient cohort, the median age was 60 years (range, 25–88). The majority of patients had FIGO stage IIIC disease (87%), grade 3 tumors (83%), and serous carcinoma histology (87%). The median preoperative CA-125 level was 610 U/dL, the median preoperative platelet count was 365 × 10^3/ul, and the median preoperative serum albumin was 4.1 g/dL.

Of the 285 patients, 93 (33%) underwent extensive upper abdominal surgical procedures, including diaphragm peritonectomy and/or resection, splenectomy, distal pancreatectomy, partial liver resection, cholecystectomy, and resection of tumor from the porta hepatitis, as deemed necessary by the primary surgeon in order to achieve optimal cytoreduction. Residual disease status after cytoreduction was as follows: no gross residual, 69 patients (24%); residual ≤ 1 cm, 134 patients (47%); and residual > 1 cm, 82 patients (29%). Postoperatively, 24 patients (8%) had a grade 3 complication; 1 patient (0.4%) had a grade 4 complication; and 2 patients (0.7%) died (grade 5), for a total of 27 patients (9%) with grade 3–5 complications. In the EORTC trial, 60 grade 3 or 4 complications were reported, but these figures were not included in Table 1 since it is not clear from the paper if all 60 complications occurred in different patients or if more than one occurred in individual patients. Eight patients (2.5%) died within 28 days of the PDS.

Postoperatively, the intent was to treat all patients with platinum and taxane-based chemotherapy. Of the 285 patients, 281 (99%) went on to receive platinum and taxane-based chemotherapy. Chemotherapy records were unavailable for 2 of the 4 patients who were recorded as not having received platinum-based chemotherapy, while the other 2 patients were unable to receive chemotherapy due to surgical complications.

The median PFS for PDS-treated patients was 17 months (95% CI, 14.9–18.5), and the median OS was 50 months (95% CI, 43.5–55.6) (Fig. 2). The median PFS by residual disease status was as follows: no gross residual, 24 months; residual ≤ 1 cm, 17 months; and residual > 1 cm, 13 months. The median OS by residual disease status was as follows: no gross residual, 78 months; residual ≤ 1 cm, 50 months; and residual > 1 cm, 36 months.

Fig. 1. Study design. During the study period, 342 patients with advanced-stage ovarian, fallopian tube, or peritoneal cancer were identified. Twenty-six of these patients would not have met eligibility criteria for the EORTC-NCIC randomized trial due to poor performance status and/or refusal of primary surgical management. Of the remaining 316 eligible patients, 31 (10%) did not undergo PDS but were treated with neoadjuvant chemotherapy (NACT) instead.
Of the 316 patients evaluated at our institution during the study period who would have been eligible for the EORTC-NCIC randomized trial, 31 (10%) did not undergo PDS but were treated with NACT instead. The reported reasons for primary therapy with NACT were: extra-abdominal disease in 18 patients (5 diagnosed during video-assisted thoracic surgery); extensive intra-abdominal disease deemed unresectable by the primary surgical team in 11 cases; and advanced age (>85) in 2 patients. The median age of this subgroup was 60 years (range, 40–87). Interval cytoreduction was performed on 28 of these patients (90%), with no gross residual disease in 15 patients (54%) and residual disease ≤1 cm in 24 patients (79%). The median PFS for this group was 13 months (95% CI, 8.6–16.4), and the median OS was 37 months (95% CI, 13.4–59.8).

Discussion

The benefit of primary debulking or cytoreductive surgery in advanced-stage ovarian, fallopian tube, or primary peritoneal cancer is well established. Over the past 4 decades, several studies have confirmed an inverse relationship between survival and the maximum diameter of residual disease [3,14]. Studies by the GOG and others have demonstrated that patients left with no macroscopic evidence of disease after primary cytoreduction have median survivals of up to 106 months, while those left with residual disease >1 cm do not derive a survival benefit from cytoreduction and have median survivals of 30–36 months [2–4,6]. Patients left with gross but ≤1 cm residual disease have decreased median survivals compared to patients with no macroscopic residual disease; however, they have a significant survival advantage over those left with >1 cm residual disease [3,4].

The biological framework to explain the survival advantage conferred by primary cytoreduction is based on the fractional cell kill hypothesis of Skipper, which presumes that a constant proportion of tumor cells is killed with each cycle of chemotherapy. Provided that the tumor cells are not resistant to therapy, this hypothesis suggests that it is possible to completely eradicate the tumor as long as the absolute number of cells at the initiation of chemotherapy is low [5]. It has also been postulated that NACT administration, while tumor burden is large and heterogeneous, may select for chemotherapy-resistant clones within the tumor mass, reducing overall response and survival [6].

The percentage of advanced-stage ovarian cancer patients who are able to undergo optimal cytoreduction varies in the literature from 15 to 85%. As a result, some institutions have implemented a more extensive surgical approach to increase the percentage of patients who are optimally cytoreduced, as well as improve PFS and OS [17–22]. This approach has been associated with acceptable overall morbidity and mortality [21,23,24].

By contrast, a number of other institutions have addressed the same issue by administration of NACT followed by attempted cytoreductive surgery (usually after three cycles of chemotherapy). In theory, decreased tumor burden prior to surgical debulking should be associated with decreased surgical morbidity, as less extensive surgery will be needed to achieve optimal cytoreduction. If survival is not compromised by neoadjuvant chemotherapy, then this clearly would be the preferred approach. However, a mathematical model proposed by Goldie and Coldman over 30 years ago suggested that the likelihood of mutations resulting in drug resistance is dependent upon the amount of cancer present when the chemotherapy is initiated [16]. It follows that patients who are given chemotherapy with a large tumor burden may have a higher chance of developing drug resistance and consequently shorter PFS and OS. Numerous clinical studies have supported this hypothesis, and a meta-analysis of all NACT studies in ovarian cancer published between 1989 and 2005 confirmed a mean weighted OS of only 24.5 months for patients treated with this approach [25].

The EORTC-NCIC trial stands as the only published randomized control trial comparing these two distinct management approaches. The study randomized 718 patients with stage IIC and IV ovarian, fallopian tube, or primary peritoneal cancers to PDS versus NACT. Optimal cytoreduction (≤1 cm residual disease) was achieved in 41.6% of patients in the PDS arm and 80.6% in the NACT arm. PFS and OS for both arms were 12 and 30 months, respectively [5]. While the PFS and OS in the NACT arm were consistent with other studies in the literature, the PFS and OS for the PDS arm were comparatively low given an optimal cytoreduction rate of greater than 40%.

It is the strikingly low PFS and OS in the PDS arm of the EORTC-NCIC trial that led us to perform our study. While chemotherapy regimens can be standardized in the different arms of a study, surgical expertise and outcomes can vary between different countries, institutions, and surgeons [19,21–23]. In our current study, we selected a similar population to that of the EORTC-NCIC trial over an identical time period to compare our survival outcomes using a generally more extensive surgical approach to PDS than is thought to have been used by the majority of centers participating in the randomized trial. Although this is a retrospective study, with its usual limitations, it is unique in that it offers the experience of a single institution where surgical care is standardized. While our reported median PFS and OS by residual disease were in precise alignment with the contemporary literature, including international and prospective studies of the GOG, the survival outcomes are substantially better than those in the PDS arm of the EORTC-NCIC trial [4,5,22,26,27].

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Our study group (N = 285)</th>
<th>PDS arm of EORTC trial (N = 336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>60 (25–88)</td>
<td>62 (25–86)</td>
</tr>
<tr>
<td>FIGO surgical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIC</td>
<td>249 (87%)</td>
<td>257 (76.5%)</td>
</tr>
<tr>
<td>IV</td>
<td>36 (13%)</td>
<td>77 (22.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 (2.5%)</td>
<td>14 (4.2%)</td>
</tr>
<tr>
<td>2</td>
<td>34 (12%)</td>
<td>57 (17%)</td>
</tr>
<tr>
<td>3</td>
<td>237 (83%)</td>
<td>145 (43%)</td>
</tr>
<tr>
<td>4</td>
<td>7 (2.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0%)</td>
<td>120 (35.7%)</td>
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<tr>
<td>Histology</td>
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<td></td>
</tr>
<tr>
<td>Serous</td>
<td>249 (87%)</td>
<td>220 (65.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>36 (13%)</td>
<td>90 (34.5%)</td>
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<tr>
<td>Median preoperative serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA-125, U/dl (range)</td>
<td>610 (16–14,512)</td>
<td>1130 (16–27,185)</td>
</tr>
<tr>
<td>Median preoperative platelets,</td>
<td></td>
<td></td>
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<tr>
<td>U×10^3/ul. (range)</td>
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<tr>
<td>Median preoperative serum</td>
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<td>albumin, g/dl (range)</td>
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<td>Upper abdominal procedures</td>
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<td>Yes</td>
<td>93 (33%)</td>
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</tr>
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<td>No</td>
<td>192 (67%)</td>
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<tr>
<td>Size of residual disease</td>
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<td></td>
</tr>
<tr>
<td>No gross</td>
<td>69 (24%)</td>
<td>61 (19.4%)</td>
</tr>
<tr>
<td>≤1 cm</td>
<td>134 (47%)</td>
<td>70 (22.2%)</td>
</tr>
<tr>
<td>&gt;1 cm</td>
<td>82 (29%)</td>
<td>167 (53%)</td>
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<td>0 (0%)</td>
<td>17 (5.4%)</td>
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<td>Postoperative complications</td>
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<tr>
<td>Grade 5</td>
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<td>8</td>
</tr>
<tr>
<td>Total Grade 3–5</td>
<td>27 (10%)</td>
<td>N/A</td>
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improved survival could be in part due to our higher rate of optimal cytoreduction (71% vs 42%); however, even with an optimal cytoreduction rate of 42%, one would expect a higher median survival than 30 months [4,17]. For example, in a study from our institution that evaluated all patients treated with PDS for bulky stages IIIC and IV ovarian cancer, in which the optimal cytoreduction rate was similar at 46%, the overall median survival was 43 months [17]. A median survival of 30 months is what one would expect if 100% of the PDS arm underwent suboptimal cytoreduction, not 58% as in the EORTC-NCIC trial. Moreover, the notion that NACT increases the proportion of patients who can undergo optimal and complete gross resection is confounded by the fact that these surgical outcomes do not carry the same favorable prognosis after NACT as they do with PDS. In the EORTC-NCIC trial, even with a complete gross resection at interval cytoreduction, patients who received NACT had a median survival of only 38 months (similar to a suboptimally cytoreduced cohort), further collaborating the Goldie Coldman hypothesis of a higher likelihood of mutations and drug resistance if chemotherapy is initiated with a larger tumor burden [16].

There are numerous possible factors and explanations for the comparatively low survival seen in the PDS arm of the EORTC-NCIC trial, including tumor extent, surgical expertise, and patient selection. In fact, there was a higher percentage of stage IV patients in the PDS arm of the EORTC-NCIC trial than in our study (23% vs 13%), and the median preoperative CA-125 level was also higher (1130 vs 610). So it is possible that only the most advanced and/or medically infirm patients were offered enrollment in the EORTC-NCIC trial. However, while this may explain the poor survival outcomes seen in the trial,
these results then cannot and should not be extrapolated to all patients with stages IIIC and IV disease.

In conclusion, given the comparatively superior survival observed in the literature and in our study with a primary cytoreductive approach, attempted PDS should continue to be the preferred initial management for patients with bulky advanced stage ovarian, fallopian tube, or peritoneal carcinoma. Although NACT-based approaches have been associated with decreased surgical morbidity, the median OS seen with this approach is consistently 30–36 months, comparable to that of patients who are suboptimally cytoreduced during attempted PDS. The GOG is working on the concept of another trial to compare NACT vs PDS. Until the GOG trial and/or other confirmatory studies are performed that demonstrate the superiority or at least the lack of inferiority of the NACT approach, NACT should be reserved for patients who do not have access to a well-trained gynecologic or surgical oncologist, cannot tolerate the procedure, and/or for whom optimal cytoreduction is deemed not feasible by an experienced cytoreductive team.

Conflict of interest statement
Dennis S. Chi: no conflicts.
Fernanda Musa: no conflicts.
Fanny Dao: no conflicts.
Oliver Zivanovic: no conflicts.
Yukio Sonoda: no conflicts.
Mario M. Leitao: speaker, Genzyme Bureau; proctor, Surgical Intuitive.
Douglas A. Levine: no conflicts.
Ginger J. Gardner: no conflicts.
Nadeem R. Abu-Rustum: no conflicts.
Richard R. Barakat: no conflicts.

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