The magnitude of the role surgical exploration and extirpation play in the contemporary management of patients with advanced ovarian cancer is hard to overstate. Beyond diagnostic confirmation, the aggressive posture taken to remove bulk disease provides—among other benefits—symptomatic relief, theoretically enhanced immunologic integrity, chemosensitivity, and improved survival characteristics.

Despite consensus in this regard, however, the vast evidence base to support the approach is admittedly circumstantial, as phase III interrogation of the hypothesis has yet to be formally done in most settings, with the exception of interval cytoreduction. Unfortunately, even in this setting, universal acceptance of the magnitude of effect is debated, based on cited variances between the randomized trials in terms of stage of the patients accrued, extent of surgical intent offered, the study’s statistical design and power, chemotherapy used, frequency of secondary assessment of response, and allowance of maintenance therapy following primary treatment.

‘Biology vs Brawn’

A common cogitation further confounding the issue, and as yet unanswered, is the “biology vs brawn” contention. Simply put, is it the innate characteristics of the tumor that provide a disease distribution that affords more complete tumor excision or is it the skills of the surgeon that render a biologically antagonistic tumor more responsive to therapy because it was aggressively resected? The debate has fostered further data-mining, such as the description of a unique microarray gene signature representing patients with bulky postoperative residuum. In contrast, recent reports have proposed that a differential effect in survival exists even within the category of “optimal” (no visible vs < 1 cm residual disease), while others have suggested that improved outcomes can be produced in patients with the poorest preoperative disease distribution once aggressive upper abdominal cytoreduction renders them disease-free.
Women with recurrent ovarian, peritoneal primary or fallopian tube cancer and a treatment-free interval greater than or equal to 6 months

- Surgical candidate?
  - Yes
    - Randomize
      - Surgery
      - No surgery
  - No
    - Randomize
      - Carboplatin Paclitaxel
      - Carboplatin Paclitaxel Bevacizumab
      - Maintenance bevacizumab
Surgical Cytoreduction for Ovarian Cancer: Issues Awaiting Formal Clarification
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Figure1: GOG 213 Trial—The treatment schema for Gynecologic Oncology Group (GOG) 213, a phase III randomized, controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, primary peritoneal, and fallopian tube cancer.

The complexities of the issues involved in this dialogue are problematic, interrelated, and unlikely to be settled soon. It is clear that the effectiveness of chemotherapy influences this discussion, and as such, distinguishes the disease from other intra-abdominal malignancies. Fortunately, studies such as the soon-to-be-reported European Organisation for Research and Treatment of Cancer-Gynaecological Cancer Cooperative Group (EORTC-GCCG) 55971 trial, which randomized advanced-stage ovarian, fallopian tube, and primary peritoneal cancer patients to either primary surgery or induction chemotherapy followed by surgery, will formally initiate the illumination of this debate.

Peripheral Issues

Several somewhat peripheral (but no less important) issues will remain, even if the aforementioned approach is codified. Dr. Schwartz poignantly raised some of these issues. First, while we may agree that 100% removal of disease is our stated goal of surgery, determining in whom this can be reasonably achieved will require validation not only of preoperative imaging but also of what and where disease should be searched in order to provide confidence that the patient is truly “optimal.” Previous attempts at exporting an individual institution’s imaging assessment have largely failed.[6] Currently, a joint study from Memorial Sloan-Kettering and M.D. Anderson Cancer Center is prospectively evaluating the utility of preoperative computed tomography (CT) scan and CA-125 on the ability to determine success of optimal tumor reduction.

A second, related consideration is the extent to which we can standardize extirpative surgical acumen among gynecologic oncologists so that the probability for complete resection will reach parity. It is suspected that wide variances exist, as reported rates of complete resection (even in selected patients) across trials and within the same institution differ. A recent survey showed that many gynecologic oncologists are unfamiliar with procedures that could improve their patients’ surgical outcomes and increase the proportion of optimal cytoreductions.[7] This same survey demonstrated that 84% of responders favored continuing education emphasizing surgical technique and strategy. It is not inconceivable that in the absence of parity, a call for centralized surgical management could be a featured solution.

Finally, a responsive investigative process will need discriminating development to address the ever-changing adjuvant therapy domain, as the question of surgical merit will undoubtedly be raised in the context of “new and improved” nonsurgical therapy. We applaud the worldwide cooperative group clinical research mechanism for enabling this process.

Recurrent Disease

Addressing cytoreduction for recurrent ovarian cancer, Dr. Schwartz again succinctly highlights several clinicopathologic factors that have led to some empiric “consensus” about the procedure’s merit and in whom it should be undertaken. More than two dozen reports in the literature have discussed the topic, and about half of these included multivariate analyses to interrogate independent prognosticators of survival. While the message is clear—no visible postoperative residuum and effective adjuvant chemotherapy—our ability to a priori predict either is dreadful.

Imaging is insensitive (with typically one-third of explored patients with “isolated disease” found to harbor multiple sites of tumor or diffuse carcinomatosis) and institution-dependent (represented by lack of cross-trial validation of scoring algorithms).[8] Similarly, prediction of chemotherapy sensitivity is largely inferred from long treatment-free intervals following completion of primary therapy—but how long is long enough? Of the mentioned reports in this setting, criteria from “greater than 6 months” to “greater than 24 months” have been identified from evaluation of the heterogeneous and highly selected patients being offered surgery at recurrence.

Further, while a treatment-free interval of “X” months is usually highlighted as a discriminator for
survival, we are often left pondering whether chemotherapy alone (which is statistically more likely to be active in patients with longer disease-free survivals) could have produced the same results. In a study by Dizon et al, 84 patients with recurrent platinum-sensitive (median treatment-free interval: 22 months) ovarian cancer were evaluated for response to combination platinum and paclitaxel.[9] In this study, 21 patients were also cytoreduced, with 86% achieving no visible residuum. While there was a 6 month advantage in progression-free survival for those undergoing surgery (11 vs 17 months, P = .04), the 3-year overall survival was no different.

Looking Ahead

We are fortunate that the completion of one trial (EORTC 55963, closed January 21, 2003), the initiation of another (GOG 213, opened December 6, 2007, Figure 1), and the planned AGO-DESKTOP OVAR 3 trials will ultimately produce results for clinicians to make a sound recommendation about the role of secondary cytoreduction in patients with recurrent ovarian cancer. These phase III studies are absolutely necessary, as information from further retrospective or single-institution prospective trials will do little more than add to the battle cry that we address this topic formally.

The main article can be found here: Cytoreductive Surgery in the Management of Ovarian Cancer

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References: References

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