Primary Cytoreduction in Advanced Ovarian Cancer: ‘Biologic and Surgical Aggressiveness’

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As outlined in the comprehensive review by Dr. Schwartz, cytoreductive surgery followed by platinum-based chemotherapy is considered the standard of care in the initial management of patients with advanced ovarian cancer. Considering prognostic factors for patients with advanced disease, residual disease after primary surgery is still considered to be the most important modifiable prognostic factor influencing survival. This has again been recently confirmed by a large retrospective study including six different Gynecologic Oncology Group (GOG) studies.[1]

Optimal and Complete Debulking

Our unfortunate use of the term “optimal debulking” belies the consistent observation that wide differences in survival exist between patients with no residual disease vs residual disease < 1 cm vs residual disease < 2 cm. The concept of “optimal cytoreduction” was intended as a prognostic indicator but has led to a false impression that “optimal” equates with best: At times it has become a goal.

The true optimal scenario is complete cytoreduction of visible disease, as outlined by several studies included in the review. This should be the objective of cytoreductive surgery for ovarian cancer when feasible and mitigated primarily by the limits of resectability and morbidity. Unfortunately, no data support the use of CA-125 levels, computed tomography (CT) scan imaging, or gene-expression data to a priori predict resectability. In general, the data suggest that models are center-specific and not reproducible.[2-7]

Tumor Dissemination and Surgical Resectability

Differences in the surgical management of advanced ovarian cancer can partially be attributed to differing philosophies regarding the impact of initial volume of disease on outcome. The first considers the “biologic behavior” of the tumor to be the primary determinant of prognosis in most advanced cases. Accordingly, proponents believe that the ability to render a patient optimally cytoreduced (and the ultimate outcome after such surgery) is directly linked to the biology of the tumor. Thus, the inherent biologic properties of the cancer will dictate ultimate outcome, and extraordinary efforts to debulk patients will not appreciably improve survival.

While it cannot be denied that patients with more advanced-stage cancer have a poorer prognosis, as outlined by Schwartz in the referenced Hoskins study, the subsequent conclusions attributed to that study are flawed and repeatedly taken out of context.[8] On the other hand, the observations from GOG 52 are not inconsistent with a benefit from cytoreductive surgery in advanced cases. Specifically, if a patient with stage IIIC disease has been debulked to the equivalent of stage IIIA but does not have equal survival, that does not diminish the improved survival observed relative to a stage IIIC case that was not cytoreduced,

Unnecessary and morbid surgery should be avoided in patients who cannot be debulked. As described earlier, however, we are unable to preoperatively predict who will be optimally resected.
As outlined in the review, the SCOTROC-1 trial tried to answer this question,[9] but unfortunately two major limitations preclude any conclusions: (1) residual disease < 2 cm was used as the definition of optimal, and (2) few patients underwent extensive surgery to achieve such a goal. Thus, there is little relevance to aggressive surgical cytoreduction and its impact on survival.

The alternative philosophy asserts that extraordinary surgical efforts can mitigate biology and can be safely performed.[10-12] The survival benefit observed in such cases is generally quite large when measured against other morbid forms of treatment (eg, new therapies, new modalities of administration). Undoubtedly, the reality lies somewhere in between these two views, with unavoidable interplay between them. It cannot be stressed enough that while the aggressive biology of the tumor cannot be altered, in nearly all studies to date, residual disease continues to affect survival even in the most aggressive cases. Indeed, it should not be lost on us that residual disease is the only modifiable prognostic factor we have.

**Residual Disease and Survival**

Resectability of advanced disease, with acceptable morbidity, reflects upon surgical experience, technique, excellence in anesthesia, critical care, and nursing. A strong correlation between initial extent of disease and tumor resectability supports the notion that such tumor behavior modulates the ability to achieve effective tumor reduction.

In his excellent review, Dr. Schwartz questions whether patients debulked to no macroscopic residual disease are the only cases to benefit from such surgery. He also questions whether the utilization of more radical procedures such as splenectomy, bowel resection, liver resection, or intensive stripping might be helpful in cytoreducing patients to no macroscopic residual disease, since the rates of complete debulking are quite similar in the GOG studies and in the consecutive cohorts of patients from centers that routinely utilize “radical procedures.”

A discrepancy between the two cohorts lies in the fact that patients from the GOG studies[8] are randomized after surgery but before chemotherapy is administrated, as opposed to the consecutive cohorts that include all the patients referred to a single institution.[10-12]. It might be argued that patients randomized for chemotherapy are already a “selected” group with better performance status, as opposed to patients referred to tertiary centers who might have more disseminated disease. Each analysis should take into consideration patient characteristics and tumor dissemination in order to be reliable.

Regarding the impact of residual disease on survival, patients with a very low amount of residual disease still experience a benefit, although not of the same magnitude as patients debulked to no macroscopic disease.[10,13,14] This reinforces the concept that the goal of cytoreduction should be no gross residual disease, not “optimal” residual disease. Though it would be ideal, an optimal “individualized” strategy for patients with advanced ovarian cancer has not been discovered: Withholding a treatment with known benefits (cytoreductive surgery) seems unwarranted.

The main article can be found here:

**Cytoreductive Surgery in the Management of Ovarian Cancer**

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