# EDITORIALS

## Systematic Lymphadenectomy in Advanced Epithelial Ovarian Cancer: Two Decades of Uncertainty Resolved

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The overall long-term survival rates for patients with advanced epithelial ovarian cancer remain poor, despite modern advances in both surgery and chemotherapy. Maximal surgical cytoreduction *(1)* and primary platinum-based chemotherapy are powerful determinants of survival. For two decades, however, there has been a debate on the value of including systematic aortic and pelvic lymphadenectomy as part of the initial ovarian cancer debulking procedure in patients with advanced disease *(2)*. It is clear that more than 50% of such patients will have positive lymph nodes and that the more extensive the intraperitoneal tumor burden, the higher the chance of retroperitoneal lymph node positivity. Although many investigators feel that it is the intrinsic biologic aggressiveness of the tumor (of which nodal metastasis represents just one marker), coupled with its chemosensitivity, that largely determines outcome, other investigators have raised the possibility that the retroperitoneal space may represent a sanctuary for chemoresistance *(3–5)*. If so, systemic lymphadenectomy could improve survival. Indeed, several retrospective studies have shown that there may be a survival advantage to including systemic lymphadenectomy in the primary surgery *(2,5–7)*. However, retrospective studies have many recognized inherent flaws, including the fact that the decision to proceed with this procedure intraoperatively is dependent on many factors, potentially leading to substantial bias.

Hence, the report by Benedetti Panici et al. in this issue of the Journal *(8)* of the first randomized control trial focusing on this important issue has been long awaited. The authors should be commended on their massive effort, which spanned over 12 years and 13 centers, accrued 427 eligible patients, and had a long median follow-up (68.4 months). The trial design was rigorous and well thought out. All advanced ovarian cancer patients underwent optimal surgical debulking (96% had residual disease ≤1 cm), including removal of clinically suspicious lymph nodes larger than 1 cm. They were then randomly assigned to systematic lymphadenectomy or not. After surgery, approximately 88% of patients received adjuvant platinum-based chemotherapy. Although there could be some minor critiques about the conduct and analysis of the trial, by and large the two arms were quite balanced, and the analysis was appropriately performed on an intent-to-treat basis. The authors found a progression-free survival advantage of 5–7 months (depending on the statistical model applied) with systematic lymphadenectomy but no overall survival advantage to the procedure.

Several important conclusions can be drawn from this study. First, this report confirms the high morbidity from systematic lymphadenectomy. The intraoperative complications, which are well detailed by the authors, confirm that blood loss, transfusions, and operative time are all statistically significantly prolonged by the addition of systematic lymphadenectomy. In addition, the incidence of perioperative and late morbidity underwent a statistically significant increase, from 18% in the control arm to 28% in the lymphadenectomy arm, although the authors provide less detail about the nature of these complications. They do confirm the increased incidence of lymphocysts and lymphedema among patients who underwent lymphadenectomy. However, little information is provided about their severity or the nature of the other late complications. Such information is very important to any discussion of the quality of life that accompanies the prolonged time to progression. For example, lymphedema can be a major lifelong problem from the patient's point of view.

Second, the fact that there is no overall survival advantage from systematic lymphadenectomy, coupled with the excess toxicity of the procedure, is valuable information because it will discourage the routine use of this procedure and hence its attendant toxicity. Indeed, many oncologists would conclude from this large trial that there is no role for systemic lymphadenectomy as part of initial ovarian cancer debulking.

Third, the retroperitoneal lymph nodes do not appear to be a sanctuary for chemoresistance. The authors have confirmed in this large trial that patients who underwent removal of positive lymph nodes with systematic lymphadenectomy still had a higher risk of dying from the disease than patients who underwent extensive resection of what turned out to be negative lymph nodes. Further, a recent retrospective review by Isonishi et al. *(9)* showed that the potential survival value of systematic lymphadenectomy in a similar group of patients was restricted to those with platinum-resistant disease. The possibility of the retroperitoneal space being a pharmacologic sanctuary is also not in line with the large body of evidence in the literature showing the consistent effect of platinum-based neoadjuvant chemotherapy on lymph node positivity in patients with high-risk cervical cancer *(10)*. Finally, the lack of impact of systematic lymphadenectomy on overall survival is probably due, in part, to the effectiveness of modern chemotherapy. Even if the patients had not received platinum and/or taxane treatment up front, they may have been salvaged by these or other effective therapies later.

There are other questions for which the results of Benedetti Panici et al. do not provide clear answers. First, neither the percentage of micrometastases nor the size of the positive lymph nodes was detailed. Did the systematic lymphadenectomy end up being part of the debulking effort aimed at a residual disease of 1 cm or less? Or did the procedure serve in large part to remove

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some of the micrometastases that existed in the lymph node chain? Removal of micrometastases would not be expected to have an impact on survival *(6)*.

Second, the authors did not address the possibility that the procedure may interfere with timely computed tomography (CT) detection of recurrent disease. Such interference is possible because CT scanning is not particularly sensitive for the detection of small peritoneal disease and is more discriminatory for retroperitoneal disease. In fact, this potential confounding factor may explain why later detection of recurrence in the lymphadenectomy arm did not have an effect on overall survival. However, the sites of initial recurrence detailed in the report would argue against the possibility that lymphadenectomy interferes with timely detection of recurrent disease.

Third, the authors suggest that the quality of life gained from the enhanced median progression-free survival of 5–7 months with avoidance of chemotherapy for that time may outweigh the acute and chronic morbidity from the procedure and the lack of impact on overall survival. However, only the inclusion of quality-of-life measures would tell us that answer. Even when randomized control trials have shown that a treatment for advanced ovarian cancer increases overall survival, as is the case for intraperitoneal chemotherapy, such treatments are far from being universally adopted as front-line treatment, in part due to excess toxicity *(11)*.

Finally, this report does not provide us with the important progression-free and overall survival analysis of impact of resection of positive lymph nodes as part of systematic lymphadenectomy. The authors show that, among those who underwent systematic lymphadenectomy, patients with positive lymph nodes had a statistically significant, 1.6-fold increase in the risk of death compared with those with negative lymph nodes. Other investigators have noted that those who undergo resection of positive nodes as part of a systematic lymphadenectomy may have a better outcome than patients who do not undergo the procedure at all *(7)*. However, such retrospective studies likely differed from this trial in that the control arms may not have included debulking of suspicious lymph nodes, as it did in the trial reported by Benedetti Panici et al. In this study, how did resection of positive lymph nodes by systematic lymphadenectomy compare with only plucking out clinically suspicious nodes (a relatively minor procedure without attendant undue toxicity)? What, if any, was the difference in median progression-free or overall survival in this comparison?

This pivotal trial should be considered definitive, and the findings used to dictate clinical management. Because of the trial's design, the large numbers of patients, the long follow-up, and the balance between the two arms, we now have the answer to a question that has been debated for many years. As disappointing as the result may be to some gynecologic oncologists, the body of evidence does not favor including systematic lymphadenectomy as part of front-line maximal surgical debulking in the management of advanced ovarian cancer.

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