Re: Systematic Aortic and Pelvic Lymphadenectomy Versus Resection of Bulky Nodes in Optimally Debulked Advanced Ovarian Cancer: A Randomized Clinical Trial

We read with great interest the article by Benedetti Panici et al. (1) on the results of systematic lymphadenectomy in advanced-stage ovarian cancer. We also read the editorial about this trial by Chambers (2), but we do not totally agree with her conclusions.

This trial confirms the high rate of nodal involvement in advanced-stage ovarian cancer (70% of patients in the lymphadenectomy arm versus 42% in the no lymphadenectomy arm). Given this rate, nodal spread would have been misdiagnosed in approximately half of the patients with nodal metastases if only bulky nodes had been removed. Such a result is consistent with data in the literature, which show that half of advanced-stage ovarian cancer patients with nodal involvement have no suspicious nodes during macroscopic examination at the time of the surgical procedure (3).

The quality of the surgical resection of disseminated disease is critical for optimizing the survival of patients treated for this disease. The size of residual disease at the end of debulking surgery is a powerful prognostic factor (4). Recent series suggest that the aim of debulking surgery is not simply to achieve optimal surgery (i.e., residual disease <1 cm) but rather complete removal of all macroscopic disease (3). If a surgical effort is expended to achieve complete resection of peritoneal disease, this effort should also theoretically include retroperitoneal areas. If only bulky nodes are removed, half of the patients with nodal spread would be undertreated, and complete resection would therefore not be achieved in such patients (even if all peritoneal disease is removed).

Chambers concludes that systematic lymphadenectomy should be abandoned because, although optimal debulking improves disease-free survival, it does not have an impact on overall survival. However, important information that was not included in the article by Benedetti Panici et al. should be considered before firm conclusions are drawn—namely, the second-line chemotherapy modalities used and the surgical debulking procedures used (which reflect the extent of peritoneal disease). But above all, an issue not mentioned in the article by Benedetti Panici et al. is the impact on survival of lymphadenectomy in the subgroup of patients in whom this procedure may be the most useful, i.e., the group of 159 patients who underwent complete surgical resection.

Chambers underlined the higher rate of complications in the lymphadenectomy arm. The surgical procedure was longer; however, the number of intraoperative complications was similar in the two arms. The rates of blood loss and transfusion were higher in the lymphadenectomy arm. However, these increases were related to the use of an additional procedure and should not be questioned if the procedure added is considered essential to optimize the survival of patients. Furthermore, there was no impact of lymphadenectomy on the duration of hospitalization. Finally, the rate of late complications directly related to lymphadenectomy was very low (14/221 or 6%). The authors did not differentiate lymphocysts from lymphoedema, but if the majority of late complications were lymphocysts then the existence of these late complications should not put into question the use of lymphadenectomy because they are easily curable.

Finally, like Benedetti Panici et al., we believe that lymphadenectomy should be integrated into the surgical procedure for advanced stage ovarian cancer (provided complete removal of peritoneal disease is feasible). At any rate, although we are still waiting for data that could demonstrate the therapeutic value of lymphadenectomy in terms of overall survival, this trial at least confirms its prognostic value because the survival of patients with nodal involvement was different from that of patients without nodal spread. Systematic lymphadenectomy could therefore help to optimize the treatment of patients with nodal involvement by identifying the subgroup of patients with the worst prognosis (patients with nodal involvement).

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Notes

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Benedetti Panici et al. (1) should be commended for having tried to address the controversial issue of the therapeutic value of lymph node dissection in patients with optimally or completely debulked stage IIIC ovarian carcinoma. They conclude—and this finding could be considered from now on as the current state of the art—that node dissection does not improve survival rates, although it does increase the disease-free interval.

The design of the study, however, raises questions about the validity of conclusions. The conclusions would have been clearer if randomization had taken place after palpation. This approach would have eliminated from the control group the subgroup of patients with enlarged nodes that require at least selective removal and impact prognosis. As the number and specific outcome of these patients are not available, a separate comparative analysis of patients with enlarged nodes in both groups should be provided. As a consequence, the results of the analysis of the remaining patients, with no enlarged nodes, may be altered.

The most disputable conclusions are not in the original article, however, but rather in the statements in the associated editorial (2)—in particular, the statement that “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.” Considering the dismal long-term prognosis of advanced ovarian cancer and the adverse effects on quality of life of recurrences and their medical management, interval-free survival is a most relevant endpoint that must not be neglected. In this regard, the Benedetti Panici et al. study can be read as a strong argument to perform node dissection in optimally or completely debulked patients, provided that their general condition at the end of surgical cytoreduction is good enough. Indeed, the additional risks of node dissection affect mainly the operative period and do not worsen the postoperative period, as evidenced by the finding that hospital stay is not increased in the group of patients with node dissection.

In addition, Chambers’ disputable statement that node dissection is useless in advanced ovarian cancer will inevitably be exploited by surgeons without adequate training in surgical oncology, who may apply the same conclusion to patients with early ovarian cancer. The risk is that the proportion of patients managed by surgeons without adequate experience in aortic dissection will consequently increase. This may result in a lowering of the standard of care for all ovarian cancer patients, including the group of patients who still require debulking of enlarged nodes by experienced surgeons.

Management of malignancies should be directed not only at lengthening life but also at improving quality of life. Disease-free interval is an essential component of enjoying life for advanced ovarian cancer patients. Most adjuvant therapies in oncology, such as radiation therapy in patients with breast cancer or with cervical or endometrial carcinoma with positive pelvic nodes, do not increase survival. They are still widely used, notwithstanding a long-term complication rate comparable to the long-term complication rate of node dissection in ovarian cancers. We therefore suggest that node dissection remain a standard of care in patients with optimally debulked advanced ovarian cancers. Careful operative technique may reduce intraoperative blood loss, which is the main complication observed in the Benedetti Panici et al. study, and modify the balance of risk-benefit in favor of node dissection.

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RESPONSES

We thank Morice et al. and Querleu and Ferron for their interesting comments and questions. Morice et al.’s observation of the risk of underestimating the tumor spread of advanced ovarian cancer in patients not undergoing systematic lymphadenectomy is certainly an important motivation for performing this procedure. In recent years, most gynecologic oncologists have come to believe that the optimal diameter of the residual tumor after cytoreduction is zero (i.e., no residual tumor). This view is fundamental to understanding the importance of aggressive retroperitoneal dissection.
Concerning their question about second-line chemotherapy, our protocol did not provide any restriction on this therapy, and specific analyses were not possible. But the question is interesting, and we plan to retrieve and analyze this information.

To address their question about the impact of systematic lymphadenectomy on survival in patients with no residual tumor, we have performed a further analysis, adding an interaction term (therapy * residual disease) to the Cox multivariable analysis. The interaction term was not statistically significant for either progression-free or overall survival (hazard ratio [HR] = 0.92, 95% confidence interval [CI] = 0.56 to 1.51, \( P = .75 \), and HR = 1.07, 95% CI = 0.59 to 1.94, \( P = .83 \), respectively). Although the power of an interaction test is limited, these results seem to rule out the hypothesis that lymphadenectomy would be most useful in patients with no residual tumor.

Querleu and Ferron question the timing of the randomization in our study, suggesting that randomization after palpation of lymph nodes would have been more appropriate. However, doing so would have been difficult. Eliminating the subgroup of patients with enlarged nodes from the control group, as proposed by the authors, would have introduced a systematic bias, and eliminating all patients with bulky nodes would have slowed accrual. It is important to remember that, in our study, patients assigned to the no-lymphadenectomy arm underwent removal of bulky nodes as part of the cytoreductive procedure. We also believe that had we performed the randomization after palpation of enlarged nodes, we would have not observed differential detection of bulky nodes between arms. In fact, 87/211 (41.2%) of patients in the no-lymphadenectomy arm and 52/216 (24.1%) patients in the systematic lymphadenectomy arm had bulky nodes (\( P < .001 \)). Because nodes in the lymphadenectomy group had to be removed anyway, the exploratory surgical step may have been less accurate in these patients. However, we are confident that the randomization procedure ensured a similar distribution of enlarged nodes between arms.

We do agree with Querleu and Ferron that progression-free survival in patients with a “chronic disease” such as ovarian cancer is very important. Therefore, we reiterate our belief that systematic lymphadenectomy should always be considered for advanced ovarian cancer patients who have undergone optimal cytoreduction. We also agree that appropriate surgical training is mandatory for treating patients with ovarian cancer.

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We thank Morice et al. and Querleu and Ferron for their interest in the recent editorial by Chambers (1) on the article by Benedetti Panici et al. (2). These letters raise several points: 1) the second-line chemotherapy modalities used in the trial, 2) the extent of nodal involvement, 3) the impact of the study on the surgical management of early ovarian cancer, and 4) issues of complications and quality of life.

As far as the first point goes, the outcome of this trial was unlikely to have been affected by the fact that the first- and second-line chemotherapy regimens were not strictly controlled. Initial platinum-based chemotherapy was given to 93% of the patients. As with all adequately powered phase III trials, the randomization procedure should have eliminated biases between the two study arms. Second-line taxanes and/or platinum are effective salvage treatments for ovarian cancer patients who had not received these drugs as first-line therapy (3). In the trial reported by Benedetti Panici et al., the effectiveness of modern chemotherapy largely contributed to the lack of survival advantage for systematic lymphadenectomy. If the tumors are initially drug sensitive, as 80% of them are, then tumors involving lymph nodes 1 cm in size can be eradicated (4).

Turning to the second point, it is certainly true that removal of more lymph node-bearing tissue will lead to the discovery of more lymph node metastases, which is a prognostic factor. But is this finding clinically significant? It is known that removal of microscopically positive lymph nodes does not influence survival (5). In the study by Benedetti Panici et al., there are no data to suggest that removal of positive lymph nodes by systematic lymphadenectomy leads to improved outcome compared with debulking grossly positive lymph nodes only. The ovarian cancer literature is replete with both clinical and molecular prognostic variables. We do not feel that added surgery and toxicity for prognostication indications is either needed or appropriate.

The third point concerns the impact of this study on the surgical management of early ovarian cancer. Querleu and Ferron suggest that patients with advanced ovarian cancer should be treated with systematic lymphadenectomy, in part because some surgeons may interpret the results of this study as the reason not to perform necessary staging lymphadenectomy of apparent early ovarian cancer. The appropriate response is to educate our colleagues adequately rather than to perform a morbid procedure on a different group of patients.

The last point concerns complications and quality of life. Improved progression-free survival, in the absence of an improvement in overall survival, does not automatically translate into an improved quality of life. This is particularly true for this study in that no quality-of-life measures were performed, and there was an increase in overall reportable complications from 25.6% (54/211) in the control arm to an impressive 35.7% (77/216) with the added systematic lymphadenectomy. Moreover, these figures do not take into account the substantial increase in blood loss, transfusions, and operative time with the added procedure. The patients were not followed systematically for detection of complications, and details were not presented. Hence, the complications identified, including those of lymphocysts/lymphedema, were likely to have been symptomatic.
Any discussion on risk–benefit ratio is best held after analysis of complete data on severity, duration, number, and type of complications, as well as standardized quality-of-life measures. In this case, duration of disease-free interval is insufficient as a marker on its own to make the case that the added procedure has benefit sufficient to outweigh the risks.

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