ORIGINAL ARTICLE

A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms

P. Harter, J. Sehouli, D. Lorusso, A. Reuss, I. Vergote, C. Marth, J.-W. Kim, F. Raspagliesi, B. Lampe, G. Aletti, W. Meier, D. Cibula, A. Mustea, S. Mahner, I.B. Runnebaum, B. Schmalfeldt, A. Burges, R. Kimmig, G. Scambia, S. Greggi, F. Hilpert, A. Hasenburg, P. Hillemanns, G. Giorda, I. von Leffern, C. Schade-Brittinger, U. Wagner, and A. du Bois

ABSTRACT

BACKGROUND

Systematic pelvic and paraaortic lymphadenectomy has been widely used in the surgical treatment of patients with advanced ovarian cancer, although supporting evidence from randomized clinical trials has been limited.

METHODS

We intraoperatively randomly assigned patients with newly diagnosed advanced ovarian cancer (International Federation of Gynecology and Obstetrics stage IIB through IV) who had undergone macroscopically complete resection and had normal lymph nodes both before and during surgery to either undergo or not undergo lymphadenectomy. All centers had to qualify with regard to surgical skills before participation in the trial. The primary end point was overall survival.

RESULTS

A total of 647 patients underwent randomization from December 2008 through January 2012, were assigned to undergo lymphadenectomy (323 patients) or not undergo lymphadenectomy (324), and were included in the analysis. Among patients who underwent lymphadenectomy, the median number of removed nodes was 57 (35 pelvic and 22 paraaortic nodes). The median overall survival was 69.2 months in the no-lymphadenectomy group and 65.5 months in the lymphadenectomy group (hazard ratio for death in the lymphadenectomy group, 1.06; 95% confidence interval [CI], 0.83 to 1.34; P=0.65), and median progression-free survival was 25.5 months in both groups (hazard ratio for progression or death in the lymphadenectomy group, 1.11; 95% CI, 0.92 to 1.34; P=0.29). Serious postoperative complications occurred more frequently in the lymphadenectomy group (e.g., incidence of repeat laparotomy, 12.4% vs. 6.5% [P=0.01]; mortality within 60 days after surgery, 3.1% vs. 0.9% [P=0.049]).

CONCLUSIONS

Systematic pelvic and paraaortic lymphadenectomy in patients with advanced ovarian cancer who had undergone intraabdominal macroscopically complete resection and had normal lymph nodes both before and during surgery was not associated with longer overall or progression-free survival than no lymphadenectomy and was associated with a higher incidence of postoperative complications. (Funded by Deutsche Forschungsgemeinschaft and the Austrian Science Fund; LION ClinicalTrials.gov number, NCT00712218.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Harter at the Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, Evang. Huyssens-Stiftung/Knappschaft, Henricistr. 92, 45136 Essen, Germany, or at p.harter@gmx.de.

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The mainstay of treatment of advanced ovarian cancer is primary surgery with the aim of macroscopically complete resection of all visible tumor, followed by chemotherapy that includes carboplatin and paclitaxel.[1] More recently, systemic therapy with bevacizumab, an anti–vascular endothelial growth factor antibody, combined with chemotherapy and thereafter used as maintenance therapy has been proposed.[2,3] Surgical outcomes in ovarian cancer are classified according to the size of the largest residual tumor present after surgery, which is one of the most important prognostic factors.[4] Resection of the tumor is regarded as complete if no macroscopically visible tumor remains.[5] Lymphatic spread has been reported to be a common feature and an important prognostic factor in both early and advanced ovarian cancer. Studies of unselected case series including patients with disease in all International Federation of Gynecology and Obstetrics (FIGO) stages have shown a 44 to 53% rate of lymph-node metastasis detected by systematic lymphadenectomy.[6,7]

Some retrospective analyses have suggested a potential survival benefit from systematic pelvic and paraaortic lymphadenectomy in patients with macroscopically completely resected advanced ovarian cancer,[8-12] although a prospectively randomized trial did not show an overall survival benefit.[13] However, the latter trial evaluated only the extent of lymphadenectomy (systematic removal vs. removal of enlarged lymph nodes only) and included both patients with macroscopically complete resection and those with residual tumors of up to 1 cm in diameter after surgery. A more precise and homogeneous selection of both the trial population (only patients with macroscopically complete resection) and the procedure (systematic lymphadenectomy vs. no lymphadenectomy) and inclusion of a quality-of-life evaluation should help to balance the potential additional treatment burden of this surgical procedure with its potential benefits. Here, we present the results of the Lymphadenectomy in Ovarian Neoplasms (LION) trial, a prospectively randomized, controlled trial of systematic pelvic and paraaortic lymphadenectomy in patients with macroscopically completely resected primary ovarian cancer.

METHODS

PATIENTS

Patients were eligible for participation in the trial if they had a histologically proven primary diagnosis of advanced epithelial ovarian cancer of FIGO stage IIB through IV (in FIGO stage IIB through III disease, the cancer has not spread outside the peritoneal cavity; patients with metastases outside the peritoneal cavity [FIGO stage IV] were included if resectable metastases were present in the pleura, liver, spleen, or abdominal wall), if macroscopically complete resection seemed feasible, if they were between 18 and 75 years old and had a good Eastern Cooperative Oncology Group (ECOG) performance status score (0 or 1; scores range from 0 to 5, with higher scores reflecting greater disability), and if they had provided written informed consent. The trial protocol and statistical analysis plan are available with the full text of this article at NEJM.org. Patients could undergo randomization only if macroscopically complete resection had been achieved, the patient was still in good condition, and clinically positive nodes were not present. To evaluate the lymph-node status, it was recommended that the retroperitoneal space be opened from the inguinal ligament to the renal vein. If there were any nodes that appeared macroscopically to the surgeon to be involved with tumor, the patient did not fulfill the eligibility criteria, and further treatment was performed according to local standards.

TRIAL DESIGN

Patients who met the presurgical eligibility criteria were registered with the central randomization office no later than 1 day before surgery. Treatment assignments were concealed from the surgical team. The central randomization office did not disclose the assignment until a telephone call was received from the surgical team stating that the patient met the intraoperative eligibility criteria. Hence, the assessors of intraoperative eligibility were not aware of the treatment assignments until they had confirmed eligibility. Patients were randomly assigned in a 1:1 ratio to undergo either systematic lymphadenectomy or no lymphadenectomy. We applied a covariate-adaptive randomization procedure as described

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by Rosenberg and Lachin,[14] which combines elements of the minimization approach with a biased coin technique. The stratification factors were trial center, patient age (<60 or ≥60 years), and ECOG performance status score (0 or 1).

Participating centers had to qualify before participation in the trial. The first and last authors evaluated anonymous surgical and pathological reports that included a systematic pelvic and paraaortic lymphadenectomy performed within the preceding 12 months at every center. To qualify, at least 12 operations in the previous year had to fulfill the quality criteria as described in the protocol (chapter 6.4).

The trial was performed in accordance with European Network of Gynecologic Oncology Trialists model A.[15] The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

TRIAL END POINTS AND ASSESSMENTS

The primary end point was overall survival calculated from the date of randomization to death. Secondary end points included progression-free survival (calculated from randomization to disease progression or death, whichever occurred first), quality of life (measured with the European Organization for Research and Treatment of Cancer [EORTC] 30-item Quality of Life Questionnaire [QLQ-C30] and its ovarian cancer module [QLQ-OV28]), and the number of resected lymph nodes.

STATISTICAL ANALYSIS

The primary efficacy analysis of overall survival was performed with a two-sided stratified log-rank test with a significance level of 0.05. On the basis of previous studies, we assumed a 3-year overall survival rate of 76% in the no-lymphadenectomy group and planned for the trial to show a hazard ratio for death of 0.7 in the lymphadenectomy group as compared with the no-lymphadenectomy group, corresponding to a 3-year overall survival rate of 82.5% in the lymphadenectomy group. With a planned enrollment period of 3 years and a 6-year follow-up phase, and accounting for a potential dropout rate of 10%, we calculated that 640 patients would need to be enrolled in order to record 247 deaths, which ensured a power of 80%.

The primary efficacy analysis was performed in the intention-to-treat population. A sensitivity analysis was performed in the per-protocol population, which consisted of patients without major protocol violations (Fig. S1 in the Supplementary Appendix, available at NEJM.org). To compare event time distributions, we used Kaplan–Meier methods, as well as log-rank tests (stratified according to age and ECOG performance status) and Cox regression models.

RESULTS

PATIENTS AND PROCEDURES

From December 2008 through January 2012, a total of 1895 patients gave written informed consent and were preoperatively registered, and 650 patients (34.3%) met the intraoperative criteria for randomization. Because 3 patients were excluded, 647 patients made up the intention-to-treat population, with 323 patients in the lymphadenectomy group and 324 patients in the no-lymphadenectomy group (Fig. 1). The characteristics of the patients were well balanced between the groups (Table 1). Surgical procedures beyond basic procedures such as bilateral salpingo-oophorectomy, hysterectomy, and omentectomy included parietal peritonectomy in approximately 90% and gastrointestinal tract resection in more than 50% of the patients in both groups. The randomly assigned intervention was performed in 99.1% of patients in the lymphadenectomy group and 96.6% of patients in the no-lymphadenectomy group. A median of 57 resected lymph nodes was reported in the lymphadenectomy group, including 22 paraaortic and 35 pelvic nodes. Pathological diagnosis revealed microscopic lymph-node metastases in 55.7% of the patients in the lymphadenectomy group.

SURVIVAL

In the overall population of patients, median progression-free and overall survival were 25.5 months (95% confidence interval [CI], 21.9 to 28.6) and 67.2 months (95% CI, 61.2 to 74.8), respectively. The median overall survival was 65.5 months in the lymphadenectomy group and 69.2 months in the no-lymphadenectomy group (hazard ratio for death in the lymphadenectomy group, 1.06; 95% CI, 0.83 to 1.34; P=0.65 by stratified log-rank test with stratification according to age and performance status). The analysis of the secondary end point, progression-free survival, also did not show a significant between-

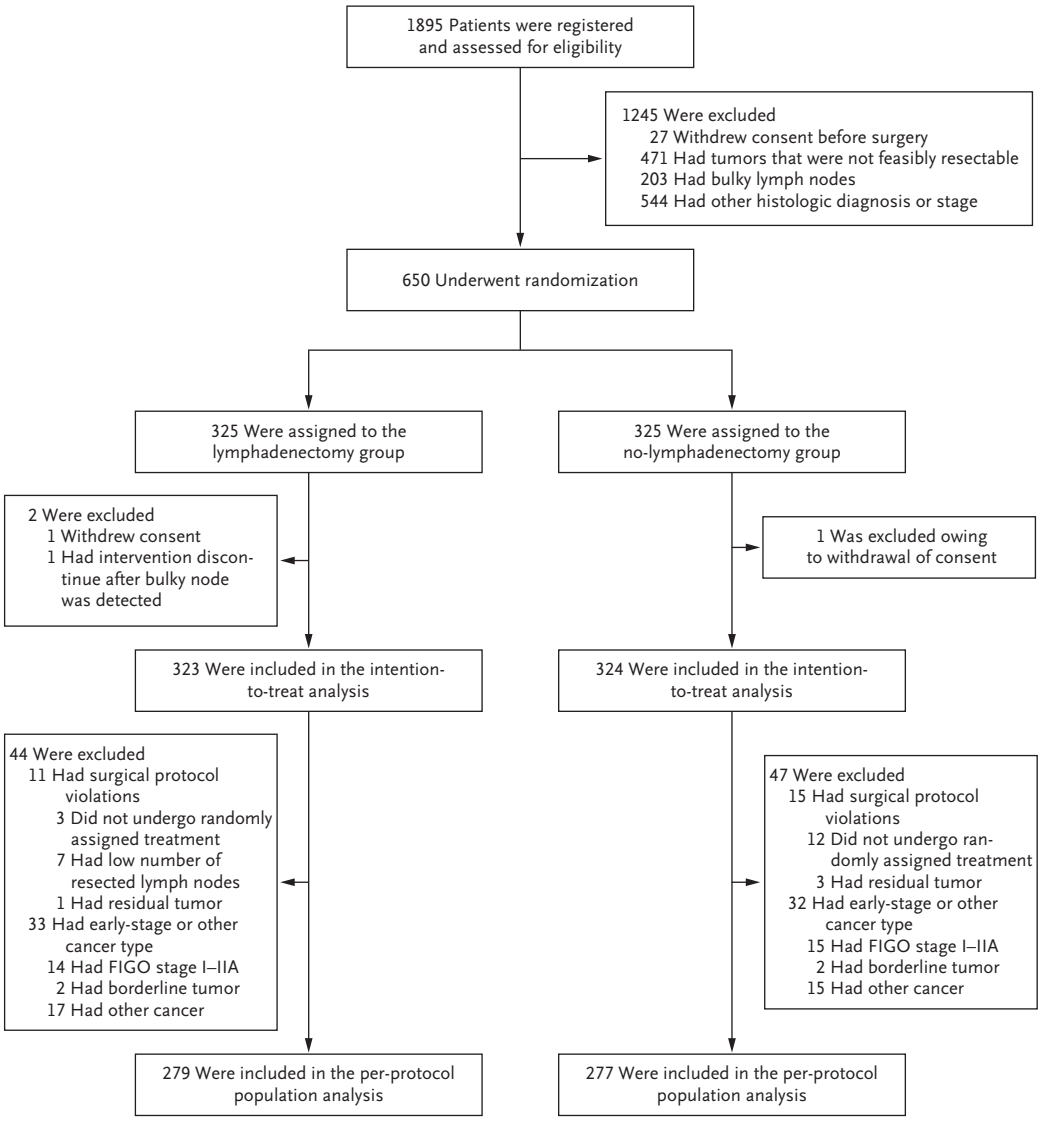

Figure 1. Enrollment, Randomization, and Treatment.

group difference in benefit, with a median of 25.5 months in both groups (hazard ratio for death or progression in the lymphadenectomy group, 1.11; 95% CI, 0.92 to 1.34; P=0.29) (Fig. 2). The sensitivity analysis in the per-protocol population confirmed these results (Fig. S1 in the Supplementary Appendix).

QUALITY OF LIFE AND COMPLICATIONS

Clinically meaningful differences in global health status and subdomains of quality of life were not found between the groups, although there were significant between-group differences at some time points in subdomain scores of the quality-of-life measures. However, all differences in these scores were less than 10 points and therefore were regarded as not clinically relevant (see the "Quality of Life Methods" section and Figs. S2 through S8 in the Supplementary Appendix).

The addition of open lymphadenectomy to the debulking surgery had a significant effect on the median duration of surgery (340 vs. 280 minutes, P<0.001), median blood loss (650 vs. 500 ml, P<0.001), the percentage of patients receiving

Table 1. Characteristics of the Patients at Baseline and the Surgical Procedures.*

Characteristic	Lymphadenectomy Group (N=323)	No-Lymphadenectomy Group (N=324)
Median age (range) — yr	60 (21–83)	60 (23–78)
Median CA-125 level before surgery (IQR) — U/ml	416 (138–1276)	347 (122–1025)
ECOG performance status score — no. (%)†		
0	272 (84.2)	280 (86.4)
1	51 (15.8)	44 (13.6)
Histologic diagnosis available before registration — no. (%)	106 (32.8)	106 (32.7)
Final histologic diagnosis — no. (%)		
Ovarian, fallopian tube, or peritoneal cancer	306 (94.7)	307 (94.8)
Other diagnosis, including borderline tumor	17 (5.3)	17 (5.2)
Final FIGO stage — no. (%)‡		
I to IIA	15 (4.6)	17 (5.2)
IIB to IIIA	41 (12.7)	52 (16.0)
IIIB to IV§	261 (80.8)	244 (75.3)
Missing data	6 (1.9)	11 (3.4)
Surgical procedure — no. (%)		
Bilateral salpingo-oophorectomy¶	319 (98.8)	320 (98.8)
Hysterectomy¶	321 (99.4)	322 (99.4)
Omentectomy	319 (98.8)	322 (99.4)
Parietal peritonectomy	291 (90.1)	291 (89.8)
Pelvis	276 (85.4)	278 (85.8)
Paracolic region	193 (59.8)	208 (64.2)
Diaphragm	173 (53.6)	196 (60.5)
Gastrointestinal tract resection	169 (52.3)	167 (51.5)
Stoma placement	34 (10.5)	24 (7.4)
Splenectomy	62 (19.2)	56 (17.3)
Surgery involving porta hepatis or lesser omentum	61 (18.9)	69 (21.3)
Partial pancreatectomy	7 (2.2)	7 (2.2)
Partial hepatectomy	27 (8.4)	28 (8.6)
Pleurectomy	20 (6.2)	24 (7.4)
Complete resection performed — no. (%)	321 (99.4)	322 (99.4)
Randomly assigned procedure performed — no. (%)	320 (99.1)	313 (96.6)

* None of the characteristics differed significantly between the groups with the exception of Randomly assigned procedure performed (P=0.03). CA-125 denotes cancer antigen 125, and IQR interquartile range.
† Eastern Cooperative Oncology Group (ECOG) performance status scores range from 1 to 5, with higher scores indicating greater disability.
‡ Cancer stages were assigned in accordance with the International Federation of Gynecology and Obstetrics (FIGO) 2009 classification. FIGO stages I through IIA indicate early disease limited to the inner genital tract, stages IIB through IIIA advanced disease without macroscopic spread beyond the pelvis, and stages IIIB through IV advanced disease with macroscopic spread beyond the pelvis or distant metastasis.
§ Seven patients in the lymphadenectomy group and six patients in the no-lymphadenectomy group had cancer of histopathological stage T1 through T2a, N1 (early disease limited to the inner genital tract but with regional lymph-node metastasis, classified as FIGO stage IIIC at the time of enrollment).
¶ This category includes earlier procedures — for example, hysterectomy for a benign histologic abnormality.

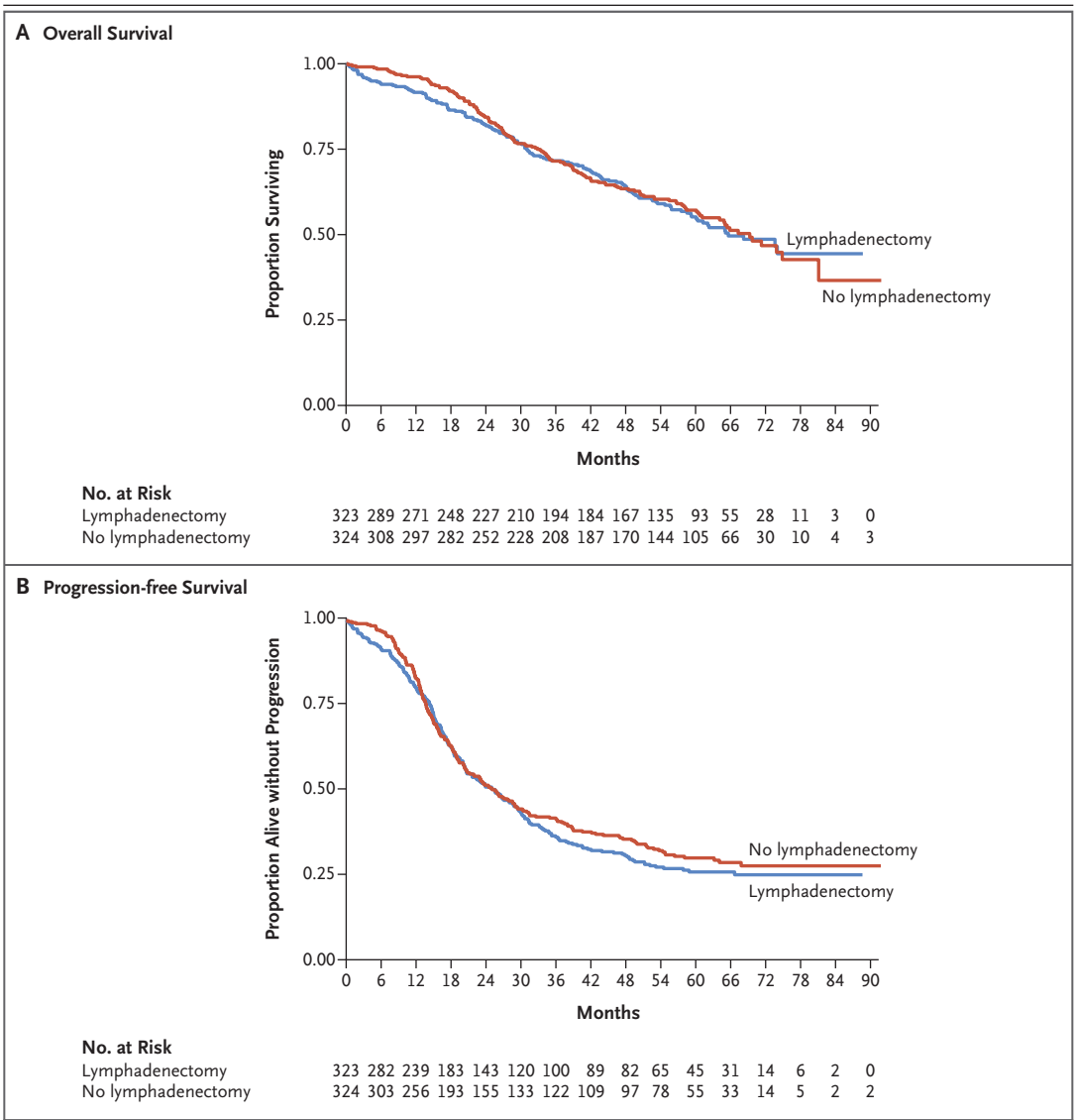

Figure 2. Overall Survival and Progression-free Survival.

transfusions (63.7% [205 of 322 patients] vs. 56.0% [181 of 323 patients], P=0.005) or fresh-frozen plasma (36.3% [117 of 322] vs. 29.7% [96 of 323], P=0.07), and the percentage of patients with postoperative admission to an intermediate or intensive care unit (77.6% [250 of 322] vs. 69.0% [223 of 323], P=0.01) — all in favor of the no-lymphadenectomy group. We also found that the lymphadenectomy group had a higher incidence of infections treated with antibiotics (25.8% [83 of 322 patients] vs. 18.6% [60 of 323 patients], P=0.03), lymph cysts at discharge (asymptomatic cysts: 4.3% [14 of 322] vs. 0.3% [1 of 323], P<0.001; symptomatic cysts: 3.1% [10 of 322] vs. 0, P=0.001), and repeat laparotomies for complications (12.4% [40 of 323] vs. 6.5% [21 of 324], P=0.01), as well as a significantly higher 60-day mortality (3.1% [10 of 323] vs. 0.9% [3 of 324], P=0.049) (Table 2). The main reason for repeat laparotomy in both groups was bowel leakage or fistula, with 22 events in the lymphadenectomy group and 8 events in the no-lymphadenectomy group. Independent predictive risk factors for repeat laparotomy were a longer

Table 2. Postsurgical Complications and Primary Systemic Treatment.

Complication or Treatment	Lymphadenectomy Group (N=323)	No-Lymphadenectomy Group (N=324)	P Value
	number of patients (percent)		
Complication			
Infection treated with antibiotics*	83 (25.8)	60 (18.6)	0.03
Fever with body temperature >38.0°C*	41 (12.7)	32 (9.9)	0.26
Sepsis†	6 (1.9)	3 (0.9)	0.31
Thrombosis*	7 (2.2)	5 (1.6)	0.56
Pulmonary embolism†	12 (3.7)	15 (4.6)	0.56
Secondary wound healing*	31 (9.6)	19 (5.9)	0.12
Prolonged ileus, conservative management*	15 (4.7)	17 (5.3)	0.72
Peripheral sensory neurologic event*	7 (2.2)	7 (2.2)	0.99
Peripheral motor neurologic event*	10 (3.1)	8 (2.5)	0.63
Lymph cysts*			
Asymptomatic	14 (4.3)	1 (0.3)	<0.001
Symptomatic	10 (3.1)	0	0.001
Lymphedema‡	13 (4.0)	6 (1.9)	0.10
Fistula†	5 (1.5)	7 (2.2)	0.56
Readmission†	40 (12.4)	27 (8.3)	0.09
Repeat laparotomy for complications†	40 (12.4)	21 (6.5)	0.01
Death†§	10 (3.1)	3 (0.9)	0.049
Primary systemic therapy			0.29
Platinum, taxane, and bevacizumab	23 (7.1)	14 (4.3)	
Platinum and taxane	237 (73.4)	258 (79.6)	
Platinum single agent	10 (3.1)	9 (2.8)	
Platinum and other agents¶	4 (1.2)	6 (1.9)	
Other systemic treatment‖	14 (4.3)	14 (4.3)	
No systemic treatment	5 (1.5)	7 (2.2)	
Died before systemic treatment	15 (4.6)	6 (1.9)	
No follow-up about systemic treatment	15 (4.6)	10 (3.1)	

* Complication was recorded at discharge after the original surgery. Data were missing for one patient in each group.
† Complication was recorded within 60 days after surgery.
‡ Complication was recorded at any time during follow-up.
§ All deaths included here occurred within the first 30 days after surgery.
¶ Other nontaxane combination partner drugs were gemcitabine (in four patients in the lymphadenectomy group and one patient in the no-lymphadenectomy group), pegylated liposomal doxorubicin (two patients in the no-lymphadenectomy group), bevacizumab (one patient in the no-lymphadenectomy group), cyclophosphamide (one patient in the no-lymphadenectomy group), and cisplatin–fluorouracil (one patient in the no-lymphadenectomy group).
‖ Category includes treatment mostly for cancer other than ovarian, tubal, or peritoneal cancer, with the exception of two patients with ovarian cancer in the no-lymphadenectomy group, one of whom received pegylated liposomal doxorubicin and one of whom received doxorubicin–ifosfamide.

duration of surgery (>340 minutes in the lymphadenectomy group and >280 minutes in the no-lymphadenectomy group), a higher American Society of Anesthesiologists score (III vs. I or II; scores range from I to VI, with higher scores reflecting greater baseline dysfunction), and randomly assigned treatment group (lymphadenectomy vs. no-lymphadenectomy) (Tables S1 and S2 in the Supplementary Appendix). No lymph cysts were found 3 months after the end of chemotherapy in the no-lymphadenectomy group, but in the lymphadenectomy group the percentage of patients with asymptomatic lymph cysts increased (to 8.6%) and the percentage of those with symptomatic lymph cysts decreased (to 1.2%) relative to the percentages at the discharge visit. Chyle leaks were not reported.

With regard to postoperative systemic treatment, 80.5% of the patients in the lymphadenectomy group and 83.9% of those in the no-lymphadenectomy group were treated with platinum and taxane with or without bevacizumab. The corresponding percentages in the per-protocol analysis were 86.0% and 87.4% (Table S3 in the Supplementary Appendix).

We also investigated the role of the level of treatment-center patient recruitment on overall survival in the intention-to-treat population. At 52 centers, at least 1 patient underwent randomization. At the largest center, 78 patients (12% of 647) underwent randomization. We evaluated the effect of lymphadenectomy as compared with no lymphadenectomy within high-recruiting centers (defined as those with ≥21 patients undergoing randomization) and low-recruiting centers (those with ≤20 patients undergoing randomization). Approximately 55% of patients underwent randomization in high-recruiting centers, and 45% underwent randomization in low-recruiting centers. No significant treatment effect was found in either subgroup.

DISCUSSION

In this trial, patients with advanced ovarian cancer who underwent macroscopically complete resection did not benefit from systematic lymphadenectomy. In contrast, lymphadenectomy resulted in treatment burden and harm to patients.

The results of this prospectively randomized, adequately powered, international, multicenter trial add level 1 evidence to the long-standing discussion about the role of lymphadenectomy in advanced ovarian cancer and once more underline the importance of the use of proper research methods in generating clinical evidence. Many of the retrospective analyses including large numbers of patients have suggested a benefit of lymphadenectomy, and accordingly, patients have been exposed to this procedure over the decades. However, evaluations of lymphadenectomy as compared with no lymphadenectomy in nonrandomized studies are prone to several biases. Lymphadenectomy is a procedure with a considerable treatment burden, and the surgeon's decision as to whether to perform such a procedure may depend not only on disease characteristics such as stage or histology but also on the patient's age, performance status, or coexisting conditions. Consequently, patients with poor performance status would find themselves in a no-lymphadenectomy group, whereas younger and fitter patients may undergo lymphadenectomy more commonly. It is difficult to account for such a bias even if the surgeon is aware of the pitfalls of retrospective analyses.

A previously reported prospectively randomized international trial of lymphadenectomy also did not show a significant effect on overall survival among patients with advanced ovarian cancer.[13] However, the trial was criticized for several reasons, including the fact that centers had not been assessed for quality before participation in the trial, and it did not lead to the abandonment of the procedure in advanced ovarian cancer.

To avoid heterogeneous surgical quality as a potential weakness in our trial, we performed prospective evaluation of all centers. All centers had to prove their proficiency in performing a complete lymphadenectomy before being qualified to participate in the trial. Accordingly, the quality of surgery and the numbers of resected lymph nodes were higher than in previous gynecologic oncologic clinical trials analyzing this issue.

Another criticism regarding the above-mentioned trial of lymphadenectomy was that more

than two thirds of the included patients had residual postoperative intraabdominal tumor.[13] Resection of lymph nodes in patients with residual tumor may remove some tumor in the lymph nodes but will not change the status of residual tumor in the abdomen. Consequently, the prognostic effect of residual tumor in advanced ovarian cancer may mask the potential benefit of lymphadenectomy. We accounted for this assumed shortcoming by recruiting only patients who had undergone macroscopically complete resection. We knew on the basis of previous data that patients with clinically negative nodes often have histologically diagnosed lymph-node metastases.[6] Our assumption was that removing these tumor cells could further reduce residual tumor burden to such an extent that it would affect prognosis (turning an assumed macroscopically complete — but actually incomplete — resection into an "authentic" complete resection). However, this procedure did not provide a benefit, even though 55.7% of the patients in the lymphadenectomy group in our trial had positive nodes. We have to conclude that a macroscopically complete resection may not be improved by increasing the radicality of the procedure.

Another criticism of the previous trial was that the patients in both groups underwent lymph-node resection, because resection of bulky nodes was allowed in the no-lymphadenectomy group. We accounted for this pitfall by excluding all patients with bulky nodes, and we did not allow any lymphadenectomy to be performed in the no-lymphadenectomy group. Despite our efforts to prospectively address the concerns raised about the previous trial, we also did not find a beneficial role of lymphadenectomy. Moreover, our data indicated that substantial additional morbidity was associated with this procedure.

The relatively high morbidity and mortality in the lymphadenectomy group in our trial may be questioned. In a similar trial involving patients with early ovarian cancer, morbidity was lower than in our trial.[16] However, although the lymphadenectomy in early-stage ovarian cancer is technically the same procedure as it is in advanced ovarian cancer, the clinical perspective is different. In early disease, lymphadenectomy adds approximately 1 hour to a short overall surgery. Furthermore, patients with early disease commonly do not have symptoms or a large amount of ascites and are generally healthier than patients with more advanced disease. Lymphadenectomy in advanced disease also adds only 1 hour of surgery, but this is after a long and much more complex operation. The latter factor explains, for example, the higher incidence of repeat laparotomies in the lymphadenectomy group resulting from complications that at first glance were not directly associated with the removal of lymph nodes.

Overall, the cohort in our trial had relatively favorable outcomes, with a median progression-free survival of 25 months and a median overall survival of more than 5 years, as compared with outcomes in other surgical phase 3 trials involving patients with advanced ovarian cancer.[17] In part, this finding may be related to the fact that treatment was performed in specialized surgical centers, which have several positive factors that have been associated with better outcomes, including high surgical volume,[18,19] frequent study participation,[20] and high rates of macroscopically complete resection.[21,22] However, the patients who underwent randomization were highly selected, as indicated by the number of registered patients relative to the number of patients who underwent randomization. The number of registered patients reflected all comers with suspected advanced ovarian cancer. We did not allow randomization without registration at least 1 day before surgery, to avoid an intraoperative selection bias. The registered population comes very close to reflecting standard practice. This approach led to a high percentage of patients (65.7%) not undergoing randomization, for several reasons. One of the reasons for nonrandomization was incomplete resection intraabdominally. Thus, the poorest prognostic group was not included — a group of patients who were unlikely to benefit from lymphadenectomy. The results in the no-lymphadenectomy group in our trial show that macroscopically complete resection is feasible in a substantial proportion of patients and — if lymphadenectomy is omitted — is not associated with excessive morbidity and is associated with a short-term mortality of less than 1%.

In conclusion, in this trial involving patients

with macroscopically complete resection of advanced ovarian cancer and clinically negative lymph nodes, systematic pelvic and paraaortic lymphadenectomy was not associated with better outcomes than no lymphadenectomy and was associated with a higher incidence of postoperative complications.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' full names and academic degrees are as follows: Philipp Harter, M.D., Ph.D., Jalid Sehouli, M.D., Ph.D., Domenica Lorusso, M.D., Alexander Reuss, M.Sc., Ignace Vergote, M.D., Ph.D., Christian Marth, M.D., Ph.D., Jae-Weon Kim, M.D., Ph.D., Francesco Raspagliesi, M.D., Ph.D., Björn Lampe, M.D., Ph.D., Giovanni Aletti, M.D., Werner Meier, M.D., Ph.D., David Cibula, M.D., Ph.D., Alexander Mustea, M.D., Ph.D., Sven Mahner, M.D., Ph.D., Ingo B. Runnebaum, M.D., Ph.D., Barbara Schmalfeldt, M.D., Ph.D., Alexander Burges, M.D., Ph.D., Rainer Kimmig, M.D., Ph.D., Giovanni Scambia, M.D., Ph.D., Stefano Greggi, M.D., Ph.D., Felix Hilpert, M.D., Ph.D., Annette Hasenburg, M.D., Ph.D., Peter Hillemanns, M.D., Ph.D., Giorgio Giorda, M.D., Ingo von Leffern, M.D., Carmen Schade-Brittinger, B.Sc., Uwe Wagner, M.D., Ph.D., and Andreas du Bois, M.D., Ph.D.

The authors' affiliations are as follows: the Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, Essen (P. Harter, A. du Bois), Department of Gynecology, Charité–Universitätsmedizin Berlin, Berlin (J.S.), the Coordinating Center for Clinical Trials, Philipps University Marburg (A.R., C.S.-B.), and the Department of Gynecology and Obstetrics, University Hospital Giessen and Marburg (U.W.), Marburg, the Department of Gynecology and Obstetrics, Kaiserswerther Diakonie (B.L.), and the Department of Obstetrics and Gynecology, Heinrich-Heine-University Düsseldorf (W.M.), Düsseldorf, the Department of Gynecology and Obstetrics, University Medicine Greifswald, Greifswald (A.M.), the Department of Gynecology, University Medical Center Hamburg-Eppendorf (S.M.), and the Department of Gynecology and Obstetrics, Albertinen Krankenhaus (I.L.), Hamburg, University Women's Hospital, Department of Gynecology and Reproductive Medicine and Center for Gynecologic Oncology, Jena University Hospital, Jena (I.B.R.), the Department of Obstetrics and Gynecology, University Munich rechts der Isar (B.S.), and the Department of Obstetrics and Gynecology, University Hospital, Ludwig-Maximilians-Universität München (A. Burges), Munich, West German Cancer Center, Department of Gynecology and Obstetrics, University of Duisburg-Essen, Duisburg (R.K.), the Department of Gynecology and Obstetrics, University Hospital Kiel, Kiel (F.H.), University Medical Center Freiburg, Freiburg (A.H.), University Medical Center Mainz, Department of Gynecology and Obstetrics, Mainz (A.H.), and the Department of Gynecology and Obstetrics, Hannover Medical School, Hannover (P. Hillemanns) — all in Germany; the Gynecologic Oncology Unit, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Nazionale Tumori (D.L., F.R.), and the Department of Gynecologic Oncology, European Institute of Oncology, University of Milan (G.A.), Milan, the Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Rome (G.S.), Gynecologic Oncology, Istituto Nazionale per lo Studio e la Cura dei Tumori di Napoli, IRCCS Fondazione G. Pascale, Naples (S.G.), and the Cancer Reference Center, Centro di Riferimento Oncologico, Aviano (G.G.) — all in Italy; the Department of Gynecological Oncology, University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium (I.V.); the Department of Obstetrics and Gynecology, Medical University Innsbruck, Innsbruck, Austria (C.M.); the Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, South Korea (J.-W.K.); and the Gynecologic Oncology Center, Department of Obstetrics and Gynecology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic (D.C.).

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