Systematic Pelvic Lymphadenectomy vs No Lymphadenectomy in Early-Stage Endometrial Carcinoma: Randomized Clinical Trial

Pierluigi Benedetti Panici, Stefano Basile, Francesco Maneschi, Andrea Alberto Lissoni, Mauro Signorelli, Giovanni Scambia, Roberto Angioli, Saverio Tateo, Giorgia Mangili, Dionyssios Katsaros, Gaetano Garozzo, Elio Campagnutta, Nicoletta Donadello, Stefano Greggi, Mauro Melpignano, Francesco Raspagliesi, Nicola Ragni, Gennaro Cormio, Roberto Grassi, Massimo Franchi, Diana Giannarelli, Roldano Fossati, Valter Torri, Mariangela Amoroso, Clara Crocè, Costantino Mangioni

Background Pelvic lymph nodes are the most common site of extrauterine tumor spread in early-stage endometrial cancer, but the clinical impact of lymphadenectomy has not been addressed in randomized studies. We conducted a randomized clinical trial to determine whether the addition of pelvic systematic lymphadenectomy to standard hysterectomy with bilateral salpingo-oophorectomy improves overall and disease-free survival.

Methods From October 1, 1996, through March 31, 2006, 514 eligible patients with preoperative International Federation of Gynecology and Obstetrics stage I endometrial carcinoma were randomly assigned to undergo pelvic systematic lymphadenectomy (n = 264) or no lymphadenectomy (n = 250). Patients' clinical data, pathological tumor characteristics, and operative and early postoperative data were recorded at discharge from hospital. Late postoperative complications, adjuvant therapy, and follow-up data were collected 6 months after surgery. Survival was analyzed by use of the log-rank test and a Cox multivariable regression analysis. All statistical tests were two-sided.

Results The median number of lymph nodes removed was 30 (interquartile range = 22–42) in the pelvic systematic lymphadenectomy arm and 0 (interquartile range = 0–0) in the no-lymphadenectomy arm ($P < .001$). Both early and late postoperative complications occurred statistically significantly more frequently in patients who had received pelvic systematic lymphadenectomy (81 patients in the lymphadenectomy arm and 34 patients in the no-lymphadenectomy arm, $P = .001$). Pelvic systematic lymphadenectomy improved surgical staging as statistically significantly more patients with lymph node metastases were found in the lymphadenectomy arm than in the no-lymphadenectomy arm (13.3% vs 3.2%, difference = 10.1%, 95% confidence interval [CI] = 5.3% to 14.9%, $P < .001$). At a median follow-up of 49 months, 78 events (ie, recurrence or death) had been observed and 53 patients had died. The unadjusted risks for first event and death were similar between the two arms (hazard ratio [HR] for first event = 1.10, 95% CI = 0.70 to 1.71, $P = .68$, and HR for death = 1.20, 95% CI = 0.70 to 2.07, $P = .50$). The 5-year disease-free and overall survival rates in an intention-to-treat analysis were similar between arms (81.0% and 85.9% in the lymphadenectomy arm and 81.7% and 90.0% in the no-lymphadenectomy arm, respectively).

Conclusion Although systematic pelvic lymphadenectomy statistically significantly improved surgical staging, it did not improve disease-free or overall survival.

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Affiliations of authors: Department of Obstetrics and Gynecology, La Sapienza University, Rome, Italy (PBP, SB, MA); S. Maria Goretti Hospital, Latina, Italy (FM); S. Gerardo Hospital, Monza, Italy (AAL, MS, CM); Gemelli Hospital, Rome, Italy (GS); Department of Obstetrics and Gynecology, Campus Biomedico University, Rome, Italy (RA); Fondazione Policlinico S. Matteo di Pavia, Pavia, Italy (ST); S. Raffaele Hospital, Milan, Italy (GM); S. Anna Hospital, Turin, Italy (DK); Department of Obstetrics and Gynecology, Catania University, Catania, Italy (GG); Aviano Hospital, Aviano, Italy (EC); Department of Obstetrics and Gynecology, University of Varese, Varese, Italy (ND); Istituto Nazionale Tumori, Fondazione G. Pascale, Naples, Italy (SG); Department of Obstetrics and Gynecology, Parma University, Parma, Italy (MM); INT, Milan, Italy (FR); Department of Obstetrics and Gynecology, Genova University, Genova, Italy (NR); Department of Obstetrics and Gynecology, University of Bari, Bari, Italy (GC); Treviglio Hospital, Treviglio, Italy (RG); Department of Obstetrics and Gynecology, University of Verona, Verona, Italy (MF); IFO-Istituto Regina Elena, Rome, Italy (DG); Mario Negri Institute, Milan, Italy (RF, VT); Jackson Memorial Hospital, Miami, FL (CC).

Correspondence to: Pierluigi Benedetti Panici, Professor, Department of Obstetrics and Gynecology, La Sapienza University of Rome, Viale del Policlinico 155, 00161 Rome, Italy (e-mail: pierluigi.benedettipanici@uniroma1.it).

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CONTEXT AND CAVEATS

Prior knowledge

The most common site for the spread of early-stage endometrial cancer is the pelvic lymph nodes, but randomized trials have not assessed the impact of pelvic systematic lymphadenectomy in addition to standard hysterectomy with bilateral salpingo-oophorectomy on overall and disease-free survival.

Study design

Phase 3 randomized trial among patients with early-stage endometrial carcinoma who were randomly assigned to standard surgery for endometrial cancer with or without lymphadenectomy.

Contribution

Systematic pelvic lymphadenectomy did not improve disease-free or overall survival of patients with early-stage endometrial cancer, but the added information obtained from the pelvic lymph nodes removed during lymphadenectomy helped to more accurately determine the stage of the disease.

Implications

Lymph node status of patients with early-stage endometrial cancer was confirmed to be of prognostic value that only partly overlaps with other prognostic factors for endometrial cancer and may be of value in tailoring adjuvant therapies. However, it had no discernible therapeutic impact.

Limitations

The lymphadenectomy used did not systematically include some types of lymph nodes. The protocol lacked strict criteria for adjuvant therapies.

From the Editors

Endometrial cancer is the most frequent malignancy of the female genital tract in Western countries and accounts for approximately 6% of all newly diagnosed cancer and for approximately 3% of cancer deaths in women in the United States. An estimated 40 100 new cases of endometrial cancer are expected to be diagnosed in 2008 in the United States, with 7470 cancer-related deaths (1). Because vaginal bleeding is commonly associated with the presence of disease, more than 75% of patients with endometrial cancer are diagnosed at an early stage, resulting in overall favorable prognosis, with a 5-year overall survival rate of 80% to 85% and a cancer-specific survival rate of 90% to 95% (2,3).

Pelvic lymph nodes represent the most common site of extrauterine disease in patients with clinical early-stage disease, and in 1988 the International Federation of Gynecology and Obstetrics (FIGO) revised the staging system of endometrial cancer to mandate surgical dissection and evaluation of lymph nodes (4). The staging role of lymph node resection is widely recognized, and lymphadenectomy is considered the most accurate way to assess lymph nodes in the retroperitoneum and, therefore, to detect the presence or absence of lymph node metastases. The incidence of metastases to the pelvic lymph nodes in patients with corpus-confined endometrial cancer who undergo lymphadenectomy varies between 5% and 18% (5–11). Retroperitoneal lymph node involvement, including either pelvic or para-aortic lymph nodes, results in a worse prognosis in that patients with lymph node metastases may have 5-year survival rates as low as 44%–52% (12).

Although several authors (7,13–16) have suggested that complete lymphadenectomy may be associated with improved survival outcomes, particularly for patients with lymph node metastases, results of most of these studies (7,13,16) have been equivocal, because they were retrospective analyses, did not include control groups, and the results could have been biased by stage migration. Traditionally, surgical staging protocols for endometrial cancer have dictated that grossly enlarged lymph nodes be excised or evaluated in biopsy specimens (5). Because gross residual disease in the lymph nodes is a highly statistically significant predictor of disease-specific survival, Bristow et al. (16) extended the concept of cytoreductive surgery for patients with advanced endometrial carcinoma to patients with macroscopic metastases to the retroperitoneal lymph nodes and concluded that resection of all grossly evident adenopathy is a reasonable therapeutic objective for patients with stage IIIC disease. In fact, among patients with clinically suspicious adenopathy, those undergoing complete resection of all macroscopic disease had a fourfold reduction in the risk of disease-related death compared with patients who had gross residual lymph node disease after surgery (16). Therefore, lymphadenectomy might have therapeutic value by itself by reducing the number of tumor cells or disrupting lymphatic pathways for cancer spread.

To date, no definitive results from well-designed randomized trials comparing the outcome of systematic pelvic lymphadenectomy with standard hysterectomy and bilateral adnexectomy alone have been published. Extensive lymphadenectomy is not devoid of adverse effects, because it may lengthen the time in surgery and increase perioperative complications. Consequently, more reliable evidence to help clinicians make proper use of lymphadenectomy is warranted (7,17). We conducted a prospective multicenter randomized clinical trial to investigate whether the addition of systematic pelvic lymphadenectomy to standard hysterectomy with bilateral salpingo-oophorectomy improved overall survival and disease-free survival in patients with preoperative stage I endometrial cancer.

Patients and Methods

Patient Eligibility

Patients with histologically proven endometrioid or adenosquamous endometrial carcinoma clinically confined to uterus (preoperative FIGO stage I disease) were evaluated for the trial. All patients with proven endometrial cancer with myometrial invasion were deemed eligible for the trial, with the exception of patients whose intraoperative pathological assessment showed a well-differentiated tumor whose depth of myometrial invasion was less than 50% (FIGO stage IB with grading 1). Additional eligibility criteria were age 75 years or younger, Karnofsky performance status of 80 or more, no previous chemotherapy or radiation therapy, and no previous malignant neoplasia other than basal cell carcinoma or nonmelanoma skin cancer. The study protocol was revised and accepted by local ethics committees, and appropriate written informed consent was obtained from all patients.

Randomization Procedures

At the end of endoperitoneal surgical procedures and after confirming myometrial invasion, grading, and tumor histology by frozen section analysis, patients were randomly assigned to one of the two trial arms by a block arrangement that balanced the treatment assignment within each site. Intraoperative random assignment was performed centrally by telephone at the Mario Negri Institute, Milan. From October 1, 1996, through March 31, 2006, 514 eligible patients with preoperative FIGO stage I endometrial carcinoma were randomly assigned to undergo pelvic systematic lymphadenectomy (n = 264) or no lymphadenectomy (n = 250).

Patient Characteristics and Follow Up

Patients' clinical data, pathological tumor characteristics, and operative and early postoperative data were recorded soon after surgery. Late postoperative complications, adjuvant therapy, and follow-up data were collected 6 months after surgery. Follow-up examinations were performed every 3–4 months during the first 2 years after surgery, every 6 months for the next 3 years, and then annually. To optimize the logistics of data flow, this study was conducted by two distinct networks of hospitals with coordinating data centers at La Sapienza University of Rome and the Mario Negri Institute in Milan.

Surgical Procedures

For both the lymphadenectomy arm and the no-lymphadenectomy arm, primary surgery included standard hysterectomy with bilateral salpingo-oophorectomy. Patients in the pelvic systematic lymphadenectomy arm received pelvic systematic lymphadenectomy that included the removal of the lympho-fatty tissue located above the external iliac vessels between the iliac bifurcation, the inferior epigastric vessels, and psoas muscle laterally; these lymph nodes were the external iliac lymph nodes. The dissection continued with the removal of the lymph nodes located below the external iliac vessel and above the obturator nerve, between the iliac bifurcation, the psoas muscle laterally, the obturator muscle caudally, and the virtual plane passing through the umbilical artery and bladder medially; these lymph nodes were the superficial obturator lymph nodes and included the interiliac lymph nodes. The lymphadenectomy was completed with the removal of the lymph nodes located above and laterally to the common iliac lymph nodes between the aortocaval bifurcation and the iliac bifurcation; these were named common iliac lymph nodes. Pelvic systematic lymph node dissection was considered to have been performed appropriately and according to protocol when at least 20 pelvic lymph nodes were removed and analyzed by the pathologist. Single or multiple aortic lymph node samplings or systematic lymphadenectomy was performed at the discretion of the surgeon. In the no-lymphadenectomy arm, at the end of primary surgery, no lymphatic tissue in the retroperitoneal region was removed other than bulky (>1 cm) lymph nodes, if they were detected at gross intraoperative inspection by palpation of lymph node sites.

Adjuvant Therapy

After surgery, patients at higher risk of recurrence on the basis of the histopathologic analysis of surgical specimen (ie, patients with different combination of risk factors such as FIGO stage IIB–IVB, poorly differentiated tumors, and positive surgical margins) could be administered adjuvant therapy at the discretion of the treating physician. Platinum- or taxol-based chemotherapy, pelvic radiotherapy with possible extended field therapy to aortic lymph nodes, and brachytherapy, either alone or in combination, were considered suitable adjuvant approaches. Adjuvant regimens had to be initiated within 1 month from surgery.

Statistical Analysis

The primary outcome of this trial was overall survival (defined as the time from random assignment to death from any cause). Secondary endpoints were disease-free survival (defined as the time from random assignment to the earliest occurrence of relapse or death from any cause) and surgical morbidity (defined as intraoperative and early and late postoperative complications).

The trial was designed with a power of 80% and a statistical significance level of 5% (two-tailed test); a total of 524 patients were required to detect an improvement difference of 8% in 5-year overall survival, from 80% to 88% (which corresponds to a hazard ratio [HR] of 0.52).

Survival curves were estimated by the Kaplan–Meier method and were compared by use of the log-rank test. Survival analysis was performed with the Cox proportional hazards model with adjustment for multiple baseline characteristics, including age, tumor grade, myometrial invasion, and stage, provided that these variables were statistically significantly associated with survival in a univariate model. Proportional hazard assumptions were checked by plotting $\log\{-\log[S(t)]\}$ against $\log t$ for each group and were found to be satisfied. Data from all eligible patients were analyzed for survival on an intention-to-treat basis. Disease-free survival and overall survival were also analyzed only among patients who underwent the appropriate surgical procedure to which they had been randomly assigned (ie, per trial protocol, presented in the CONSORT trial flow diagram, see Figure 1). In this per-protocol analysis, survival analysis was performed on 459 patients (226 in the pelvic systematic lymphadenectomy arm and 233 in the control arm).

Comparison of proportions between groups was performed by use of a χ^2 test. Continuous variables such as number of resected lymph nodes, operating time, and hospital stay were expressed as medians with their interquartile range and were compared by use of a Mann–Whitney test. All statistical tests were two-sided.

Results

Patient Accrual

From October 1, 1996, through March 31, 2006, 537 patients were enrolled at 31 centers (30 in Italy and 1 in Chile). There were 23 violations to eligibility criteria and all 23 patients were deemed ineligible. The trial flow diagram and detailed reasons for patient ineligibility are shown in Figure 1.

Patient Characteristics

The clinical and tumor characteristics of eligible patients are listed in Table 1. General characteristics of patients and their tumors were well balanced across treatment arms. The higher proportion

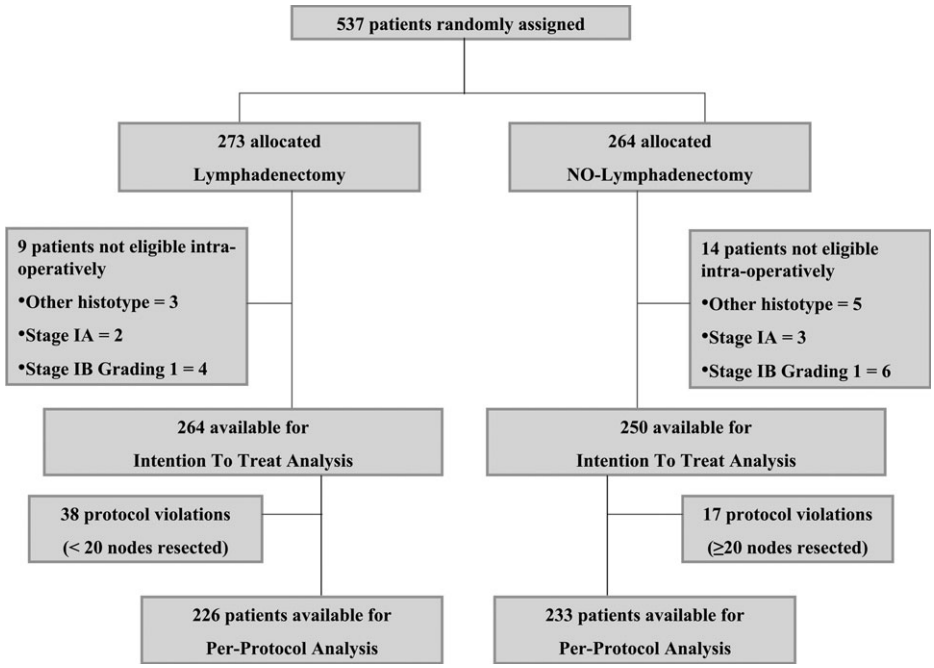

Figure 1. CONSORT trial flow diagram for patients with clinical early-stage endometrial cancer who were accrued into the trial. Protocol violations in the no-lymphadenectomy (control) arm were 20 or more lymph nodes resected and in the systematic lymphadenectomy arm were fewer than 20 lymph nodes resected.

of patients with FIGO stage IIIC endometrial cancer in the lymphadenectomy arm was related to the lymph node dissection itself, which increases the detection of lymph node metastases.

At definitive histopathologic examination, eight patients were downstaged to stage IA disease and six patients had tumors with histological types other than endometrioid or adenosquamous: we have retained these patients in the analysis because at frozen section examination they seemed to meet the eligibility criteria (myometrial infiltration and endometrioid or adenosquamous only histotype). The tumor grades, as determined by frozen section analysis in the operating room in the eligible patients, were distributed between the lymphadenectomy and no-lymphadenectomy

Table 1. Patients' clinical characteristics and tumor data by treatment arm

Characteristics	Lymphadenectomy arm (n = 264)	No-lymphadenectomy arm (n = 250)	Total (n = 514)
Median age (IQR), y	63 (56–68)	61 (55–68)	62 (56–68)
Median body mass index (IQR), kg/m²	26.6 (23.7–30)	26.9 (23.8–30)	26.8 (23.7–30)
FIGO stage*, No. (%)			
IA	0 (0)	8 (3.2)	8 (1.6)
IB	87 (33)	107 (42.8)	194 (37.7)
IC	104 (39.4)	80 (32)	184 (35.8)
IIA	12 (4.5)	6 (2.4)	18 (3.5)
IIB	10 (3.8)	15 (6)	25 (4.9)
IIIA	9 (3.4)	19 (7.6)	28 (5.4)
IIIC	35 (13.3)	8 (3.2)	43 (8.4)
IVB	3 (1.1)	3 (1.2)	6 (1.2)
Missing	4 (1.5)	4 (1.6)	8 (1.5)
Tumor grade†, No. (%)			
1 (well differentiated)	19 (7.2)	19 (7.6)	38 (7.4)
2 (moderately differentiated)	150 (56.8)	148 (59.2)	298 (58)
3 (poorly differentiated)	91 (34.5)	78 (31.2)	169 (32.9)
Missing	4 (1.5)	5 (2)	9 (1.7)
Tumor histotype†, No. (%)			
Endometrioid	246 (93.2)	228 (91.2)	474 (92.2)
Adenosquamous	16 (6)	17 (6.8)	33 (6.4)
Papillary serous	1 (0.4)	2 (0.8)	3 (0.6)
Clear cell	1 (0.4)	0	1 (0.2)
Mullerian mixed malignant tumor	0	2 (0.8)	2 (0.4)
Tumor not found	0	1 (0.4)	1 (0.2)

* International Federation of Gynecology and Obstetrics (FIGO) stage was determined by pathological analysis. IQR = 25th–75th percentiles or interquartile range.

† After a definitive histopathologic examination.

arms, respectively, as follows: for tumor grade 1, 8% and 8%; for grade 2, 58% and 61%; and for grade 3, 33% and 30% (data not shown). The depth of myometrial invasion, as assessed by frozen section analysis in the operating room, was less than one half of the myometrium in 44% of the patients in the lymphadenectomy arm and 55% of the patients in the no-lymphadenectomy arm (data not shown). In each arm, 1% of patients had missing values for the frozen section data (data not shown).

Surgical Procedures

A median number of 26 pelvic lymph nodes (interquartile range = 21–35) were removed from patients in the lymphadenectomy arm and a median number of 0 pelvic lymph nodes (interquartile range = 0–0) were removed from patients in the no-lymphadenectomy arm ($P < .001$) (Table 2). Aortic lymphadenectomy was performed in 69 (26%) of the 264 patients in the lymphadenectomy arm and in five (2%) of the 250 patients in the no-lymphadenectomy arm. Overall, the median number of total lymph nodes removed was 30 (interquartile range = 22–42) in the lymphadenectomy arm and 0 (interquartile range = 0–0) in the no-lymphadenectomy arm ($P < .001$).

In the no-lymphadenectomy arm, 194 (78%) of the 250 patients had no lymph nodes removed and 56 (22%) patients had enlarged lymph nodes and underwent pelvic lymph node sampling or lymphadenectomy: 16 (6%) had five pelvic lymph nodes or fewer removed; 12 (5%) had 6–10 removed; 11 (4%) had 11–19 removed; and 17 (7%) had 20 or more pelvic lymph nodes removed. Only eight (14.3%) of the 56 patients with bulky lymph nodes had metastatic lymph nodes at pathological examination.

In the pelvic systematic lymphadenectomy arm, 38 patients had fewer than 20 pelvic lymph nodes resected. In the no-lymphadenectomy arm, 17 patients had 20 pelvic lymph nodes or more resected. All 55 patients were excluded from the per-protocol survival analysis for inappropriate surgical treatment.

As a direct consequence of the higher number of lymph nodes recovered in the systematic lymphadenectomy arm, a higher number of lymph node metastases were detected at pathological analysis in this arm than in the no-lymphadenectomy arm (13.3% vs 3.2%, difference = 10.1%, 95% confidence interval [CI] = 5.3% to 14.9%, $P < .001$). In the lymphadenectomy arm, seven of the 69 patients who underwent extended aortic lymphadenectomy had aortic lymph node mestastases (and five had also pelvic lymph node involvement). Of these 69 patients, 11 had solely pelvic lymph node involvement and two had solely aortic lymph node involvement. Although systematic pelvic lymphadenectomy was associated with statistically significantly longer median operating time than no-lymphadenectomy (180 vs 120 minutes, respectively, $P < .001$), median estimated blood loss and the rate of patients undergoing a blood transfusion were similar in the two arms (Table 3). Patients in the systematic pelvic lymphadenectomy arm had a median hospital stay of 6 days and those in the control arm had a stay of 5 days ($P = .001$).

A similar number of severe intraoperative complications were reported across the trial arms. In the lymphadenectomy arm, one brain stroke, one anesthesiologic complication, and one vascular injury were reported. In the no-lymphadenectomy arm, one vascular injury and one bowel injury were reported. Both early and late postoperative complications occurred statistically significantly more frequently in patients who had received pelvic systematic lymphadenectomy (81 patients in the lymphadenectomy arm and 34 patients in the no-lymphadenectomy arm, $P = .001$). Most of the difference in morbidity was due to lymphocysts and lymphedema that occurred in 35 patients in the lymphadenectomy arm and four patients in the no-lymphadenectomy arm. Deep venous thrombosis occurred in four patients (two in each arm), and pulmonary embolism occurred in two patients undergoing lymphadenectomy. Two cases of bladder-vaginal fistula occurred in the lymphadenectomy arm, and bowel obstruction occurred in four patients in each arm. No surgical procedure-related deaths occurred.

Adjuvant Therapy

Details of adjuvant treatments are shown in Table 4. Treatment options (ie, radiation therapy, chemotherapy, and both chemotherapy and radiation therapy) did not differ statistically significantly between the two arms ($P = .07$). Most women in both arms received no adjuvant therapy (ie, 68.9% in the lymphadenectomy arm and 64.8% in the no-lymphadenectomy arm). When primary surgery was followed by adjuvant therapy, radiation therapy was the most frequently administered treatment in both arms. In the lymphadenectomy arm, among the 59 patients who received radiation therapy, 41 patients received pelvic external beam irradiation, 10 received extended aortic field irradiation, 11 received brachytherapy (three as a single treatment and eight in association with pelvic external beam irradiation), and five patients had unspecified radiation therapy. In the no-lymphadenectomy arm, among the 74 patients who received radiation therapy, 58 patients received pelvic external beam irradiation, five received extended aortic field irradiation, 13 received brachytherapy (one as a single treatment and 12 in association with pelvic external beam irradiation), and 10 patients had unspecified radiation therapy.

Disease-free and Overall Survival

At a median follow-up of 49 months (interquartile range = 27–79 months), 78 events had been observed. Endometrial cancer had

Table 2. Median number (25th–75th percentiles) of resected lymph nodes by treatment arm*

Lymph node site	Lymphadenectomy arm (n = 264)	No-lymphadenectomy arm (n = 250)
Median No. of pelvic lymph nodes recovered (IQR)	26 (21–35)	0 (0–0)†
Median No. of total lymph nodes recovered‡ (IQR)	30 (22–42)	0 (0–0)†

* Results for both pelvic and total lymph nodes were statistically significantly different between arms ($P < .001$, Mann–Whitney test). All statistical tests were two-sided. IQR = 25th–75th percentiles or interquartile range.

† The interquartile range 0–0 indicates that less than 25% of patients assigned to the no-lymphadenectomy arm had at least one lymph node removed.

‡ Aortic lymphadenectomy was performed in 69 (26%) of the 264 patients in the lymphadenectomy arm and in five (2%) of the 250 patients in the no-lymphadenectomy arm.

Table 3. Perioperative data by treatment arm

Perioperative data	Lymphadenectomy arm (n = 264)	No-lymphadenectomy arm (n = 250)	*P*
Median operating time (IQR), min	180 (140–240)	120 (90–155)	<.001*
Missing data, No. of patients	38	41	
Patients transfused, No. (%)	26 (9.8)	19 (7.6)	.45†
Missing data, No. of patients	0	0	
Median hospital stay (IQR), days	6 (5–8)	5 (4–7)	<.001*
Missing data, No. of patients	39	43	

* Mann–Whitney test. All statistical tests were two-sided. IQR = 25th–75th percentiles or interquartile range.

† χ^2 test.

recurred in 67 (13.0%) of the 514 patients—in 34 (12.9%) of the 264 patients in the lymphadenectomy arm and 33 (13.2%) of the 250 patients in the no-lymphadenectomy arm (Table 5). Fifty-three (10.3%) of the 514 patients had died—42 (8.2%) from endometrial cancer and 11 (2.1%) from other causes, without evidence of relapse. Median time to relapse was 14 months in lymphadenectomy arm and 13 months in no-lymphadenectomy arm.

Sites of first recurrences were similar between treatment arms (Table 5). Four patients in each arm had disease recurrence in the lymph nodes. Site-specific lymph node involvement in the lymphadenectomy arm included two external iliac lymph nodes, one common iliac lymph node, and one para-aortic lymph node. All iliac lymph node relapses occurred in patients without lymph node metastases at primary surgery and the patient with a para-aortic relapse had stage IV disease at primary surgery. Site-specific lymph node involvement in the no-lymphadenectomy arm included two external iliac lymph nodes, one common iliac lymph node, and one para-aortic lymph node. Two of the three patients with iliac lymph node recurrence did not have bulky lymph nodes at primary surgery (stage IB), whereas the third patient had positive bulky lymph nodes at primary surgery. The patient with para-aortic recurrence had bulky but negative pelvic lymph nodes at primary surgery (stage IC). Twelve of the 67 (17.9%) patients whose cancer relapsed (three to the lung, four to lymph nodes, and five to vagina) underwent potentially curative salvage surgery.

Disease-free and overall survival, respectively, for all eligible patients from an intention-to-treat analysis are shown in Figures 2 and 3. The rate of 5-year disease-free survival was 81.0% in the lymphadenectomy arm and 81.7% in the no-lymphadenectomy arm (HR for relapse = 1.10, 95% CI = 0.70 to 1.71, $P = .68$ by the log-rank test, when the lymphadenectomy arm was compared with the no-lymphadenectomy arm). The rate of overall survival at 5 years was 85.9% in the lymphadenectomy arm and 90.0% in the no-lymphadenectomy arm (HR for death from any cause = 1.20, 95% CI = 0.70 to 2.07, $P = .50$ by the log-rank test, when the lymphadenectomy arm was compared with the no-lymphadenectomy arm).

In univariate analysis, covariates associated with disease-free survival included age, tumor grade, myometrial invasion, and stage, whereas only age, tumor grade, and stage were associated with overall survival (Table 6). A multivariable analysis of survival that was adjusted for these covariates yielded essentially identical estimated risks of relapse between arms (HR for relapse = 1.20, 95% CI = 0.75 to 1.91, and HR for death = 1.16, 95% CI = 0.67 to 2.02, when the lymphadenectomy arm was compared with the no-lymphadenectomy arm) (Table 6).

In a per-protocol analysis, we also evaluated the outcome of pelvic systematic lymphadenectomy on disease-free and overall survival among the 459 women who received the appropriate randomly assigned surgical procedure (226 in the systematic lymphadenectomy arm and 233 in the control arm) (Figure 1). In this analysis, the 5-year disease-free survival rate was 80.0% in the lymphadenectomy arm and 83.3% in the no-lymphadenectomy arm (HR for relapse = 1.26, 95% CI = 0.78 to 2.03, $P = .34$ by the log-rank test, when the lymphadenectomy arm was compared with the no-lymphadenectomy arm) (data not shown). In the per-protocol analysis, the rate of overall survival at 5 years was 85.9% for the lymphadenectomy arm and 90.6% for the no-lymphadenectomy arm (HR for death from any cause = 1.20, 95% CI = 0.67 to 2.13, $P = .55$, by the log-rank test, when the lymphadenectomy arm was compared with the no-lymphadenectomy arm) (data not shown).

Finally, the prognostic value of lymph node involvement was evaluated in all 264 patients assigned to the lymphadenectomy arm. In these patients, lymph node status was associated with survival (HR for death = 2.38, 95% CI = 1.06 to 5.39, when patients with positive lymph nodes were compared with patients with negative lymph nodes).

Table 4. Adjuvant therapies by treatment arm*

Type of adjuvant therapy	Lymphadenectomy arm (n = 264)	No-lymphadenectomy arm (n = 250)	Total (n = 514)
No adjuvant therapy, No. (%)	182 (68.9)	162 (64.8)	344 (66.9)
Radiation therapy, No. (%)	44 (16.7)	63 (25.2)	107 (20.8)
Chemotherapy, No. (%)	23 (8.7)	14 (5.6)	37 (7.2)
Chemotherapy and radiation therapy, No. (%)	15 (5.7)	11 (4.4)	26 (5.1)

* $P = .07$, by the χ^2 test for the whole tabular values. No single comparison was done.

Table 5. Site of disease recurrence by treatment arm*

Recurrence site	Lymphadenectomy arm (n = 264)	No-lymphadenectomy arm (n = 250)
No recurrence, No. (%)	231 (87.5)	217 (86.8)
Recurrence, No. (%)	34 (12.9)	33 (13.2)
Lung	8 (3)	8 (3.2)
Intraperitoneum	8 (3)	7 (2.8)
Vagina	7 (2.6)	6 (2.4)
Lymph node	4 (1.5)	4 (1.6)
Bone	4 (1.5)	3 (1.2)
Liver	2 (0.7)	3 (1.2)
Missing data	3 (1.1)	3 (1.2)

* Sum of the recurrences does not equal 100% because some patients suffered from concurrent multiple-site recurrences.

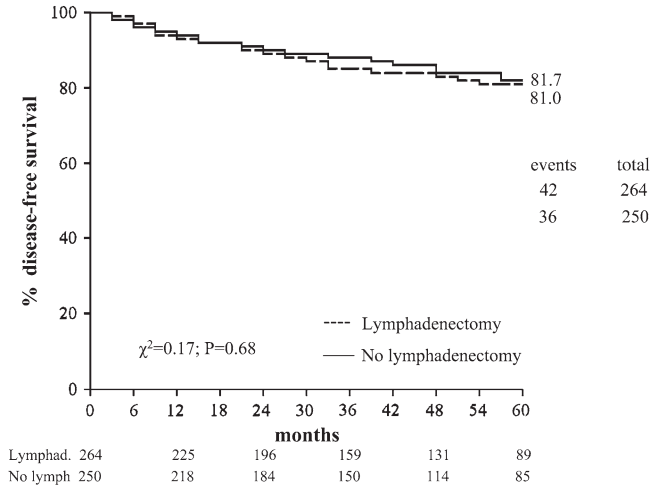

Figure 2. Disease-free survival for patients with clinical early-stage endometrial cancer undergoing systematic pelvic lymphadenectomy (Lymphad.) vs those undergoing resection of bulky lymph nodes only (No lymph). All statistical tests were two-sided.

Discussion

The results of our study provide, to our knowledge, the first direct and fully reported survival comparison of systematic pelvic lymphadenectomy with no lymphadenectomy after conventional surgery in patients with what was suspected preoperatively to be stage I endometrial carcinoma. Specifically, we found that 1) the addition of pelvic systematic lymphadenectomy to total hysterectomy and bilateral salpingo-oophorectomy did not improve disease-free or overall survival in intention-to-treat and according-to-protocol analyses, compared with no lymphadenectomy; 2) patients undergoing systematic pelvic lymphadenectomy had a higher likelihood of being upstaged to FIGO stage IIIC disease, thus allowing a more accurate prognostic profile than those not undergoing lymphadenectomy; and 3) patients undergoing pelvic systematic lymphadenectomy had a higher rate of postoperative complications than those who received only conventional surgery.

Since FIGO introduced surgical staging of endometrial carcinoma in 1988, various questions have remained, including what constitutes an optimal lymphadenectomy, which patients may benefit from lymphadenectomy, and whether it is a really safe procedure (4). Evidence on the effects of lymphadenectomy among patients with endometrial cancer comes from studies (18–20) of retrospective series of patients that have the potential limitation of selection bias inherent in the nature of retrospective analyses. Therefore, comparisons of patients who have received systematic lymphadenectomy with patients who have not received lymphadenectomy are largely indirect, with some studies from single institutions tending to favor lymphadenectomy (18–20), and others finding no survival advantage (21,22).

In a recent large retrospective analysis, Chan et al. (23) reviewed outcomes of 39 396 patients treated for endometrial cancer from 1988 to 2001, whose data are in the US National Cancer Institute's database (Surveillance, Epidemiology, and End Results program). The authors compared the outcomes of 12 333 patients who received a lymphadenectomy with those of 27 063 who did not receive a lymphadenectomy and found that the extent of lymph node resection was associated with improved survival among women with intermediate- or high-risk endometrial cancer (23,24). However, because patients undergoing surgical staging have from one to more than 20 lymph nodes removed, the adequacy of staging among patients varied widely, and the authors suggested that the observed survival difference could result from stage migration (eg, comparing patients with true stage I disease after a thorough staging procedure with inaccurately staged patients with true stage IIIC disease).

In another retrospective analysis of 565 patients with apparent early-stage endometrial cancer who were treated with conventional surgery and selective lymphadenectomy, Cragun et al. (7) found that a more extensive lymphadenectomy (>11 pelvic lymph nodes evaluated), compared with a less extensive lymphadenectomy, was associated with improved survival in women with grade 3 cancers. This statistically significant interaction between number of lymph nodes removed and grade persisted after controlling for administration of adjuvant radiation in a multivariable analysis,

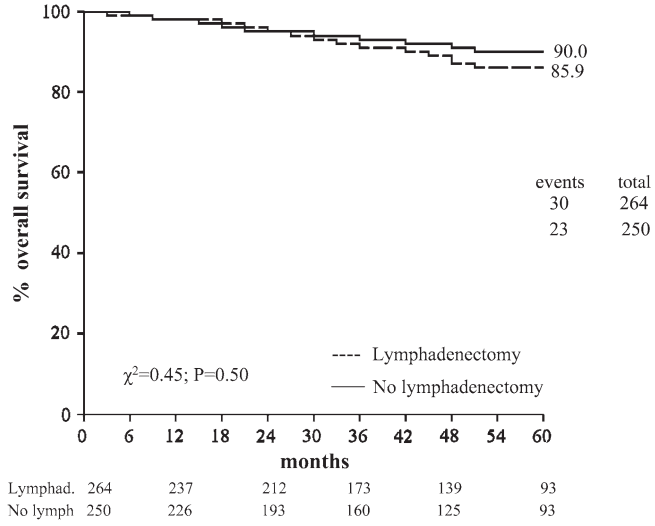

Figure 3. Overall survival for patients with clinical early-stage endometrial cancer undergoing systematic pelvic lymphadenectomy (Lymphad.) vs those undergoing resection of bulky lymph nodes only (No lymph). All statistical tests were two-sided.

Table 6. Univariate and multivariable analysis of disease-free survival and overall survival data by different prognostic factors*

	Univariate				Multivariable			
	Disease-free survival		Overall survival		Disease-free survival		Overall survival	
Prognostic factor	HR (95% CI)	P†	HR (95% CI)	P†	HR (95% CI)	P†	HR (95% CI)	P†
Treatment arm								
No lymphadenectomy	1.0 (referent)	.68	1.0 (referent)	.50	1.0 (referent)	.41	1.0 (referent)	.59
Lymphadenectomy	1.10 (0.70 to 1.71)		1.20 (0.70 to 2.07)		1.20 (0.75 to 1.91)		1.16 (0.67 to 2.02)	
Age, y								
≤65	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
>65	1.74 (1.12 to 2.73)	.02	2.69 (1.57 to 4.63)	<.001	1.49 (0.93 to 2.38)	.09	2.85 (1.65 to 4.92)	<.001
Tumor grade								
1–2	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
3	1.75 (1.12 to 2.73)	.01	2.04 (1.19 to 3.50)	.01	1.44 (0.90 to 2.31)	.13	2.03 (1.17 to 3.52)	.01
Myometrial invasion, %								
≤50	1.0 (referent)		1.0 (referent)		1.0 (referent)			
>50	1.66 (1.03 to 2.68)	.03	1.31 (0.74 to 2.34)	.36	1.35 (0.82 to 2.22)	.24	Not included	
Tumor stage								
I–II	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
III–IV	2.56 (1.56 to 4.19)	<.001	2.44 (1.34 to 4.45)	.007	2.03 (1.18 to 3.50)	.01	2.14 (1.17 to 3.93)	.01

* HR = hazard ratio; CI = confidence interval.

† The Wald test was used to estimate *P* values. All statistical tests were two-sided.

thus indicating that the survival benefit could not be attributed solely to adjuvant therapy. In this series from a single institution, the median number of lymph nodes removed increased statistically significantly over time, from nine in the period from 1973 to 1987 to 14 in the period from 1988 to 2002. It is well known that in retrospective analyses, no matter how large the sample size is, many biases may interfere in the correct evaluation of the results. Consequently, randomized clinical trials to assess the value of lymphadenectomy have been eagerly awaited by the oncologic community.

The preliminary results of the randomized A Study in the Treatment of Endometrial Cancer (ASTEC) trial from the UK Medical Research Council which assessed the therapeutic value of lymphadenectomy in clinical early-stage endometrial cancer, have been reported (25). That study recruited 1408 patients and found that recurrence-free survival was slightly shorter among women who underwent lymphadenectomy than among those who did not (HR = 1.32, 95% CI = 1.01 to 1.73) and that lymphadenectomy did not improve overall or disease-specific survival. These preliminary findings appear to support ours, although the extent of the lymph node dissection was rather different between the ASTEC trial and our trial because approximately 60% of patients randomly assigned to the lymphadenectomy arm of the ASTEC trial had fewer than 14 lymph nodes recovered.

Our prospective randomized trial consisted of an unselected group of patients with endometrial cancer enrolled from 31 gynecology departments and this process should reduce selection and surveillance biases that are often associated with clinical trials from a single institution. Although systematic lymphadenectomy is a major surgical procedure, we provided evidence that the procedure itself was feasible in the framework of a multicenter randomized trial and that the median number of lymph nodes resected in the lymphadenectomy arm was high, showing a satisfactory level of surgical performance in Italian gynecology departments. Our results confirmed the longer operation times and higher postoperative complication rates associated with systematic pelvic lymphadenectomy than with hysterectomy alone (7,21).

Limitations of our trial must be acknowledged and relate to the extent of lymphadenectomy which did not systematically include para-aortic lymph nodes, to the absence of a registry of all potentially eligible patients, and to the lack of strict criteria for adjuvant therapies. We know that the expected rate of para-aortic involvement in the presence of metastatic pelvic lymph nodes can be as high as 30%–50% (10,16), which is in keeping with our finding that five of the 16 patients with pelvic involvement who underwent extended lymphadenectomy had also aortic involvement. Nonetheless, only four patients relapsed at the overall lymph node level in each arm (notably, only one at aortic level in each arm). Among the 38 patients with lymph node involvement in the lymphadenectomy arm, 35 had FIGO stage IIIC disease and three had FIGO stage IVB disease. Because lymph node status was used to identify most patients who should receive adjuvant therapy (ie, 33 of the 38 patients in the lymphadenectomy arm) and lymph node relapse was uncommon in the no-lymphadenectomy arm, adjuvant therapy appears to have been adequate to prevent lymph node relapse. The number of potentially eligible patients and also the number of patients who gave their consent were not recorded by the centers in this study. However, the intraoperative randomization greatly reduced the number of patients who were preoperatively eligible for the study but were then deemed ineligible after surgical staging, and any exclusion before randomization did not jeopardize the internal consistency of the study.

When this study was launched, the role of adjuvant radiotherapy in stage I disease was controversial. Therefore, the use of adjuvant radiotherapy was left to the discretion of the treating physicians who tried to identify a subgroup of patients at high risk for relapse by use of prognostic features such as tumor grading or depth of myometrial infiltration. During the period of active random assignment to treatment of our trial, two seminal randomized

clinical trials were published and showed that adjuvant radiotherapy, although decreasing the incidence of local recurrence, was not associated with survival (2,26), thus limiting the relative importance of this bias on the primary outcome of our trial, which was overall survival.

There was no statistically significant difference in the pattern of adjuvant therapies between the two arms of our study, although the lymphadenectomy arm was associated with a non–statistically significant trend toward higher use of postoperative systemic therapy (chemotherapy alone or in combination with radiation therapy). This result was related to the statistically significant difference in the proportions of patients undergoing systematic lymphadenectomy who were upstaged to FIGO stage IIIC disease, which warrants treatment with adjuvant systemic therapy. Given that the majority of patients did not undergo any adjuvant therapy and that there was a substantial balance in postsurgical management between arms, our study can be deemed as a model to explore the therapeutic value of systematic lymphadenectomy. Our data do not support any positive effect of lymphadenectomy on the survival. Although several studies (7,23,24) indicate a specific benefit of lymphadenectomy in patients with a grade 3 tumor, our data were not in keeping with these findings (HR for death = 1.8, 95% CI = 0.83 to 4.19).

Pelvic systematic lymphadenectomy did not change the natural history of the disease as can be inferred from the pattern of disease recurrence, which was similar between the two groups. However, pelvic lymphadenectomy did allow for an accurate prognosis on the basis of a pathological lymph node assessment and, in our trial, provided for approximately 10% of the upstaging to surgical stage IIIC ($P < .001$). In our study, lymph node status (which was evaluated only in the lymphadenectomy arm) was statistically significantly associated with both disease-free ($P = .005$) and overall ($P = .04$) survival, regardless of the fact that involved lymph nodes had been removed. Lymph node status, thus, was confirmed to be of prognostic value and to be an important marker of tumor aggressiveness that only partly overlaps with other well-known prognostic factors, such as depth of myometrial invasion and tumor grading. Therefore, lymphadenectomy maintained its importance in determining a patient's prognosis and in tailoring adjuvant therapies. Consequently, studies are warranted that are aimed at elucidating the relationships, if any, between the content of lymphoangiogenic and angiogenic factors in the tumor cells and stroma (eg, vascular endothelial growth factor [VEGF] C, D, and A and their receptors VEGFR3 and VEGFR2) and lymphatic spread (27). Better insight into the molecular mechanisms involved in the process of lymphoangiogenesis and lymphatic spread could open up new therapeutic avenues in which lymphoangiogenic inhibitor or immunologic therapies could inhibit cancer dissemination.

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Other trial collaborators, listed alphabetically by name: Marco Atlante, IFO-Istituto Regina Elena, Rome; Carlo Belloni, Valduce Hospital, Como; Alessandro Buda, Bassini Hospital, Cinisello Balsamo; Piergiorgio Fornara, Borgomanero Hospital, Novara; Eugenio Fusco, General Hospital, Urbino; Giorgio Giardina, S. Anna Hospital, Torino; Tiziano Maggino, General Hospital, Mirano; Antonino Monaco, General Hospital, Biella; Fabio Parazzini, Mario Negri Institute, Milan; Raul Puente, Valdivia University of Chile, Chile; Riccardo Rolli, General Hospital, Carpi; Sonia Rota, Bolognini Hospital, Seriate; Claudio Scarabelli, General Hospital, Voghera; Paolo Scollo, Cannizzaro Hospital, Catania; Paolo Zola, Mauriziano Hospital, Torino.

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