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Potential Therapeutic Role of Para-aortic Lymphadenectomy in Node-Positive Endometrial Cancer[1]

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Objective. **The aim of this study was to assess the potential therapeutic role of para-aortic lymphadenectomy (PAL) in high-risk patients with endometrial cancer.**

Methods. **We studied two groups of patients with endometrial cancer who underwent operation at Mayo Clinic (Rochester, MN) during the interval 1984 to 1993: (1) 137 patients at high risk for para-aortic lymph node involvement (myometrial invasion >50%, palpable positive pelvic nodes, or positive adnexae), excluding stage IV disease, and (2) 51 patients with positive nodes (pelvic or para-aortic), excluding stage IV disease. By our definition, PAL required removal of five or more para-aortic nodes.**

Results. **In both groups, no significant difference existed between patients who had PAL (PAL+) and those who did not (PAL−) in regard to clinical or pathologic variables, percentage irradiated, or surgical or radiation complications. Among the 137 high-risk patients, the 5-year progression-free survival was 62% and the 5-year overall survival was 71% for the PAL− group compared with 77 and 85%, respectively, for the PAL+ group ($P = 0.12$ and 0.06, respectively). For the 51 patients with positive nodes, the 5-year progression-free survival and 5-year overall survival for the PAL− group were 36 and 42% compared with 76 and 77% for the PAL+ group ($P = 0.02$ and 0.05, respectively). Lymph node recurrences were detected in 37% of the PAL− patients but in none of the PAL+ patients ($P = 0.01$). Multivariate analysis suggested that submission to PAL was a cogent predictor of progression-free survival (odds ratio = 0.25; $P = 0.01$) and overall survival (odds ratio = 0.23; $P = 0.006$).**

Conclusions. **These results suggest a potential therapeutic role for formal PAL in endometrial cancer.** © 2000 Academic Press

Key Words: **endometrial cancer; lymphadenectomy; management; therapy.**

Adenocarcinoma of the endometrium is the most common malignancy of the female genital tract. It accounts for 6% of all cancers in women and is exceeded in frequency only by breast, lung, and colorectal cancers. In 75% of cases the tumor is clinically confined to the uterus at the time of diagnosis. The estimated number of new cases of endometrial cancer in the United States during 1999 is 37,400, and the estimated number of cancer-related deaths is 6400. The overall survival rate with endometrial cancer is 84% [1].

Since 1988, metastatic involvement of the pelvic or aortic lymph nodes has been classified as stage IIIc [2]. The official guidelines of the International Federation of Obstetricians and Gynecologists (FIGO) do not provide specific details for the surgical assessment of regional lymph nodes. That formal pelvic and aortic lymphadenectomy is not regarded as the standard surgical staging and treatment of endometrial cancer, even among patients at high risk for lymph node metastasis, reflects the sparcity of clinical data documenting clinical efficacy [3]. Many authors have described para-aortic node biopsy as a nontherapeutic procedure [4–6], whereas others [7–9] have described a possible benefit of para-aortic node dissection, especially in cases with grossly enlarged para-aortic nodes submitted to postoperative extended-field radiation therapy.

The aim of this study was to examine the possible therapeutic role of para-aortic lymphadenectomy (PAL), often associated with extended-field radiation therapy, in endometrial cancer.

MATERIALS AND METHODS

From the database of Mayo Clinic (Rochester, MN), we identified 815 patients with endometrial cancer who were treated surgically from 1984 to 1993. We selected 612 patients with epithelial endometrial cancer who satisfied the following inclusion criteria: (1) the patients had been surgically managed with hysterectomy and removal of remaining adnexal structures and (2) the patients had not had another malignancy diagnosed within 5 years before or after the diagnosis of

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endometrial cancer (with the exception of patients with carcinoma *in situ* or with skin cancer other than melanoma). Of the 612 patients, 238 had hysterectomy only and 374 had histologic assessment of regional lymph nodes (at least 1 pelvic or para-aortic node biopsy). The mean number of nodes harvested was 15.9 pelvic (range, 1–55) and 5.9 para-aortic (range, 1–43). Biopsy was done on at least 1 para-aortic lymph node in 104 patients.

From the group of 612 patients with endometrial cancer, we initially reviewed 137 at high risk for para-aortic node involvement (the presence of myometrial invasion >50%, macroscopically positive pelvic nodes, or positive adnexae [10], but excluding stage IV disease). We defined PAL as the removal of five or more lymph nodes from the para-aortic area. We compared the survival and recurrence rates and sites of recurrence (local, distant, local and distant, lymph nodal) in patients who had PAL (PAL+) and those who did not have PAL (PAL−). Furthermore, we performed the same analysis, selecting from the total group of 612 patients with endometrial cancer, in 51 patients with any positive nodes (pelvic or para-aortic), again excluding stage IV disease. Thirty-six of the 51 patients with positive lymph nodes in fact had high-risk features [10] and were part of the first subgroup of 137 women.

Staging was defined according to the FIGO surgical staging system [2]. In patients who had an operation before 1988, stage was retrospectively determined on the basis of postsurgical pathology reports. Histologic classification was performed according to the World Health Organization classification [11]. Histologic grading was based on the degree of glandular differentiation in accordance with Broders' classification [12].

All surgical staging procedures were completed by a gynecologic oncologist. Surgical staging included palpation of all abdominal organs and mesenteric surfaces and cytologic evaluation of the peritoneum. In the absence of macroscopic metastasis, total hysterectomy plus bilateral salpingo-oophorectomy was performed. Additional surgical procedures included omentectomy, appendectomy, and cytoreductive procedures when indicated. Frozen sections were routinely available in all cases. Lymphadenectomy usually was performed in high-risk cases. The extent of lymphadenectomy was determined by the surgeon and was sometimes influenced by the characteristics of patients, such as obesity and age, by the intraoperative histologic evaluation of the tumor at frozen section, and by the desire to include patients in study protocols.

The administration of radiation therapy to the para-aortic area was defined as extended-field radiotherapy. Postoperatively, high-risk patients were submitted to external whole pelvis, whole abdomen, or extended-field irradiation, or brachytherapy, according to risk factors and the characteristics of the patient. Patients whose peritoneal cytologic result was the only sign of extrauterine disease generally were treated with intraperitoneal phosphorus-32.

Complications due to radiotherapy were graded according to the European Organization for Research and Treatment of Cancer—Subjective, Objective, Management, and Analytic (EORTC–SOMA) scale, dividing them on the basis of the anatomical region involved [13]. Surgical complications were defined as those occurring within 1 month from operation. The presence of lymphedema or abdominal hernia was included as a surgical complication even when occurring more than 1 month from operation. As a reflection of surgical morbidity, the preoperative American Society of Anesthesiologists (ASA) Physical Status score [14], operative time, estimated blood loss, febrile morbidity (defined as temperature >38°C, on two different measurements at least 6 h apart, after the first 24 h from operation), intraoperative or postoperative transfusions, day of first flatus, day of first bowel movement, and day of dismissal were evaluated.

Follow-up of patients was performed on the basis of information reported in the clinical histories. When information about survival and recurrence was not sufficiently detailed in the histories, death certificates were obtained or contact was made with the patients or their physicians.

All patients who were alive (with or without disease) at the time of follow-up or patients who died of a cause not related to the disease were considered censored, and only patients who died of disease were considered uncensored.

We considered local failure as a recurrence, diagnosed on physical examination, radiologic imaging, or operation, localized to the pelvis, vagina, vaginal cuff, or pelvic sidewall when located below the pelvic brim. All other recurrences were considered distant. All relapses localized in the pelvic, aortic, inguinal, or scalene node-bearing regions were considered lymph node recurrences. Concomitant recurrences in the pelvic and para-aortic nodes were considered local plus distant.

Statistical analysis was performed with Fisher exact test, χ^2 analysis, and Student *t* test. Survival curves were determined by the Kaplan–Meier product-limit method. Analysis of the differences between survival curves was performed with the log-rank test, and the Cox model was used to assess the effect of prognostic factors on survival. Differences between groups were considered statistically significant at P values <0.05. BMDP statistical software was used for the analysis.

RESULTS

Patients at High Risk for Para-aortic Lymph Node Involvement

Analysis of the 137 patients at risk for para-aortic lymph node involvement showed that 104 cases (75.9%) had biopsy of pelvic lymph nodes, and 35 of them (33.6%) had positive results. Fifty-one patients (37.2%) had para-aortic lymph node biopsy, and 11 of them (21.6%) had pathologically confirmed para-aortic lymph node metastasis.

The mean age of the patients was 66.9 ± 10.6 years (range, 40–90 years). The mean duration of follow-up was 66.1 ± 40.5 months (range, 3–153 months). All censored patients had

TABLE 1
Clinical and Pathologic Characteristics of Different Groups of High-Risk Patients with Endometrial Cancer

	Group					
	137 patients[a]			51 patients[b]		
Characteristics	PAL−	PAL+	*P*	PAL−	PAL+	*P*
Age	67.1 ± 10.9	66.5 ± 9.3	0.78	65.0 ± 11.7	64.2 ± 10.2	0.81
Body mass index	29.6 ± 7.1	30.3 ± 6.1	0.67	30.8 ± 7.7	28.6 ± 4.4	0.34
% High grade	43	54	0.32	63	69	0.69
% Nonendometrioid	14	14	0.91	9	8	1
% Positive adnexa	14	7	0.35	13	0	0.31
% Positive peritoneal cytology	17	14	0.73	42	23	0.22
% Deep MI	83	86	0.71	62	62	0.96
% Cervical invasion	23	25	0.79	39	23	0.28

Note. MI, myometrial invasion; PAL, para-aortic lymphadenectomy (−, without; +, with).

[a] Patients with endometrial cancer at high risk for para-aortic lymph node involvement (myometrial invasion >50%, macroscopically positive pelvic nodes, or positive adnexae) (excluding stage IV disease).

[b] Patients with endometrial cancer and positive lymph nodes (pelvic or para-aortic) (excluding stage IV).

at least a 36-month follow-up. No patients were lost to follow-up. By definition (see Materials and Methods), 109 patients (79%) did not have para-aortic lymphadenectomy (PAL−), and 28 patients (21%) had para-aortic lymphadenectomy (PAL+). The mean number of pelvic lymph nodes identified was 13.7 ± 13.2 in the PAL− patients and 18.3 ± 12.1 in the PAL+ patients ($P = 0.09$). The mean number of para-aortic lymph nodes dissected was 0.52 ± 1.1 in PAL− patients and 9.4 ± 7.4 in PAL+ patients ($P < 0.0001$). Adjuvant radiation therapy was used in 101 patients (73.7%); 22 patients (16%) had extended-field radiotherapy. The mean dose of radiation administered to the para-aortic area was 4293.9 ± 615.1 cGy (range, 3060–5689 cGy). Only 3 patients (1 PAL− and 2 PAL+) received adjuvant chemotherapy, and 7 patients received hormonal therapy. The overall 5-year survival was 74.1%, and the 5-year recurrence-free survival was 65.1% for the entire group.

There were no significant differences between the PAL− and PAL+ patients in regard to the mean age, body mass index, percentage with myometrial invasion >50%, high-grade tumors, nonendometrioid histologic subtype, positive adnexae, positive cervix, positive peritoneal cytologic result, or positive para-aortic nodes (Table 1). Surgical morbidity and complications due to operation and radiotherapy are listed in Tables 2, 3, and 4.

The 5-year overall survival was 71.2% in PAL− patients and 85.1% in PAL+ patients ($P = 0.06$). The 5-year recurrence-free survival was 61.8% in PAL− patients and 77.5% in PAL+ patients ($P = 0.12$).

There was a lymph node recurrence in 20 PAL− patients (18.5%) and 1 PAL+ patient (3.5%) ($P = 0.05$). Recurrences were detected in 13 PAL− patients (12%) in the para-aortic area but in none of the PAL+ patients ($P = 0.05$); 6 PAL− patients (5.5%) had a recurrence along the pelvic sidewall, and only 1 PAL+ patient (3.5%) had such a recurrence ($P = 0.67$).

The analysis stratifying patients by administration of extended-field radiation therapy is summarized in Table 5. Although not significant, there was a difference in the percentage of PAL− and PAL+ patients who died of disease and did not have extended-field radiotherapy. Death from disease was documented in 29 (30.6%) PAL− patients and 2 (10%) PAL+ patients ($P = 0.06$). Among the patients who received extended-field radiotherapy, 10 PAL− patients (71.5%) had recurrences, compared with 2 (25%) PAL+ patients ($P = 0.07$). No PAL+ patient had a para-aortic failure; however, para-aortic failure developed in 12 (12.7%) PAL− patients who did not have extended-field radiotherapy ($P = 0.09$) and in 1 (7.1%) PAL− patient who was given para-aortic radiotherapy ($P = 1$).

Patients with Documented Positive Lymph Nodes

In the group of 51 patients with positive nodes (pelvic or para-aortic), 39 patients had only positive pelvic nodes (25 had no para-aortic lymph node biopsy), 11 had both positive pelvic and aortic nodes, and 1 had positive para-aortic nodes where the pelvic nodes were not biopsied. Twenty patients (39.2%) had palpably positive lymph nodes (10 pelvic only and 10 pelvic and para-aortic), and 31 (60.8%) had microscopically positive lymph nodes. There were 38 (74.5%) PAL− patients and 13 PAL+ patients (25.5%). The mean duration of follow-up was 51.4 ± 42.0 months (range, 3–148 months). All censored patients had at least a 36-month follow-up. No patients were lost to follow-up.

Forty patients (78.4%) received adjuvant radiotherapy; 17

TABLE 2
Surgical Morbidity in Different Groups of High-Risk Patients with Endometrial Cancer

	Group[a]					
	137 Patients[b]			51 Patients[c]		
Morbidity	PAL− (n = 109)	PAL+ (n = 28)	P	PAL− (n = 38)	PAL+ (n = 13)	P
ASA status 3–4, No. (%)[d]	37/92 (41%)	6/25 (24%)	0.13	10/26 (38.4%)	1/11 (9%)	0.11
Blood transfusion, No. (%)	12/100 (12%)	4/25 (16%)	0.59	4/35 (11.4%)	2/13 (15.3%)	0.65
Postoperative febrile morbidity, No. (%)[e]	20/90 (22.2%)	3/21 (14.2%)	0.41	6/34 (17.6%)	1/10 (10%)	1
Mean operative time, min	143.3 ± 50.0	169.7 ± 53.7	0.01	154.5 ± 48.2	162.5 ± 43	0.65
Mean estimated blood loss, mL	472.6 ± 240.9	516.1 ± 221.6	0.51	533.3 ± 200.7	484.3 ± 251.7	0.65
Mean day of first flatus	4.4 ± 1.8	4.3 ± 0.8	0.89	4.3 ± 1.1	4.3 ± 0.8	0.8
Mean day of first bowel movement	5.6 ± 1.9	6.4 ± 3.5	0.29	5.6 ± 1.7	6.8 ± 2.9	0.5
Mean day of dismissal	8.6 ± 2.5	8.8 ± 2.8	0.85	9.1 ± 3.1	8.4 ± 2.7	0.47

Note. ASA, American Society of Anesthesiologists; PAL, para-aortic lymphadenectomy (−, without; +, with).
[a] Data were not available for all patients. Thus, the percentages were calculated according to the total number of patients with available data.
[b] Patients with endometrial cancer at high risk for para-aortic lymph node involvement (myometrial invasion >50%, macroscopically positive pelvic nodes, or positive adnexae) (excluding stage IV disease).
[c] Patients with endometrial cancer and positive lymph nodes (pelvic or para-aortic) (excluding stage IV disease).
[d] Preoperative American Society of Anesthesiologists Physical Status score [14].
[e] Temperature >38°C on two different measurements at least 6 h apart after the first 24 h from operation.

patients (33.3%) had extended-field radiotherapy. The mean dose of radiation administered to the para-aortic area was 4313.4 ± 549.3 cGy (range, 3060–5320 cGy). Four patients received adjuvant chemotherapy (1 PAL− and 3 PAL+), and 5 patients received hormonal therapy. The mean number of pelvic lymph nodes dissected was 17.7 ± 11.3 in PAL−

TABLE 3
Surgical Complications in Different Groups of High-Risk Patients with Endometrial Cancer

	Group							
	137 Patients[a]				51 Patients[b]			
	PAL− (n = 98)[c]		PAL+ (n = 23)[d]		PAL− (n = 35)[e]		PAL+ (n = 11)[f]	
Complication	No.	%	No.	%	No.	%	No.	%
Lymphocyst	3	3	1	4.3	1	2.8		
Wound infection	8	8.1	1	4.3	3	8.5	1	9
Abdominal hernia	4, 2 ST	4	1	4.3	1	2.8		
Lymphedema	2	2	1	4.3	1	2.8	1	9
Obturator nerve lesion	1	1			1	2.8		
Postoperative hemorrhage + ureteral injury	1, 1 ST	1						
Chronic pelvic pain/adhesions					1, 1 ST	2.8		
Postoperative abscess in para-aortic area			1, 1 ST	4.3				
Ureteral injury			2, 2 ST	8.6	1, 1 ST	2.8		

Note. PAL, para-aortic lymphadenectomy (−, without; +, with); ST, complication surgically treated.
[a] Patients with endometrial cancer at high risk for para-aortic lymph node involvement (myometrial invasion >50%, macroscopically positive pelvic nodes, or positive adnexae) (excluding stage IV disease).
[b] Patients with endometrial cancer and positive lymph nodes (pelvic or para-aortic) (excluding stage IV disease).
[c] Eleven patients with no available data.
[d] Five patients with no available data.
[e] Three patients with no available data.
[f] Two patients with no available data.

TABLE 4
Grade 3–4 (EORTC–SOMA Scale) Complications Due to Radiotherapy in Different Groups of High-Risk Patients with Endometrial Cancer

	Group[a]							
	137 Patients[b]				51 Patients[c]			
	PAL− (n = 109; 78 RT)		PAL+ (n = 18; 23 RT)		PAL− (n = 38; 29 RT)		PAL+ (n = 13; 11 RT)	
Complication	No.	%	No.	%	No.	%	No.	%
Hemorrhagic cystitis	3, 1 ST	3.8	1	4.3	1	3.4		
Intestinal and ureteral obstruction	2, 2 ST[d]	2.5			3, 3 ST[d]	10.3		
Lesions to the bone	3, 1 fracture	3.8					1	9
Intestinal obstruction	5, 2 ST	6.4	2, 2 ST	8.6			1	9
Ureteral obstruction			1, 1 ST	4.3	1, 1 ST	3.4	1, 1 ST	9
Symptomatic vaginal stenosis	1, 1 ST	1.2						
Rectovaginal fistula	1, 1 ST	1.2						

Note. PAL, para-aortic lymphadenectomy (−, without; +, with); RT, radiation therapy; ST, complication surgically treated.
[a] The percentages are calculated according to the number of patients who had radiotherapy (pelvic, extended-field, whole abdomen).
[b] Patients with endometrial cancer at high risk for para-aortic lymph node involvement (myometrial invasion >50%, macroscopically positive pelvic nodes, or positive adnexae) (excluding stage IV disease).
[c] Patients with endometrial cancer and positive lymph nodes (pelvic or para-aortic) (excluding stage IV disease).
[d] One death.

patients and 17.3 ± 11 in PAL+ patients ($P = 0.9$). The mean number of para-aortic lymph nodes dissected was 0.83 ± 1.3 in PAL− patients and 13.0 ± 10.0 in PAL+ patients ($P < 0.0001$).

There were no significant differences between PAL− and PAL+ patients in regard to the mean age, body mass index, percentage with myometrial invasion of more than 50%, high-grade tumors, nonendometrioid histologic subtype, positive

TABLE 5
Analysis of Different Groups of High-Risk Patients with Endometrial Cancer, Stratified by the Administration of Extended-Field Radiotherapy

	Group																			
	137 Patients[a]										51 Patients[b]									
	No EFRx					EFRx					No EFRx					EFRx				
	PAL− (n = 95)[c]		PAL+ (n = 20)			PAL− (n = 14)		PAL+ (n = 8)			PAL− (n = 28)		PAL+ (n = 6)			PAL− (n = 10)		PAL+ (n = 7)		
Status	No.	%	No.	%	P	No.	%	No.	%	P	No.	%	No.	%	P	No.	%	No.	%	P
Death rate	29	30.6	2	10	0.06	6	42.9	2	25	0.64	16	57.2	1	16.7	0.09	6	60	2	28.6	0.33
Recurrence rate	33	34.8	5	25	0.4	10	71.5	2	25	0.07	16	57.2	1	16.7	0.09	7	70	2	28.6	0.15
Lymph node recurrence	16	17	1	5	0.4	4	28.5	0	0	0.25	11	39.2	0	0	0.14	3	30	0	0	0.22
Para-aortic recurrence	12	12.7	0	0	0.09	1	7.1	0	0	1	9	32.1	0	0	0.16	1	10	0	0	1
Pelvic sidewall recurrence	5	5.3	1	5	0.95	1	7.1	0	0	1	7	25	0	0	0.3	1	10	0	0	1

Note. EFRx, extended-field radiotherapy; PAL, para-aortic lymphadenectomy (−, without; +, with).
[a] Patients with endometrial cancer at high risk for para-aortic lymph node involvement (myometrial invasion >50%, macroscopically positive pelvic nodes, or positive adnexae) (excluding stage IV disease).
[b] Patients with endometrial cancer and positive lymph nodes (pelvic or para-aortic) (excluding stage IV disease).
[c] Site of recurrence not available in one patient.

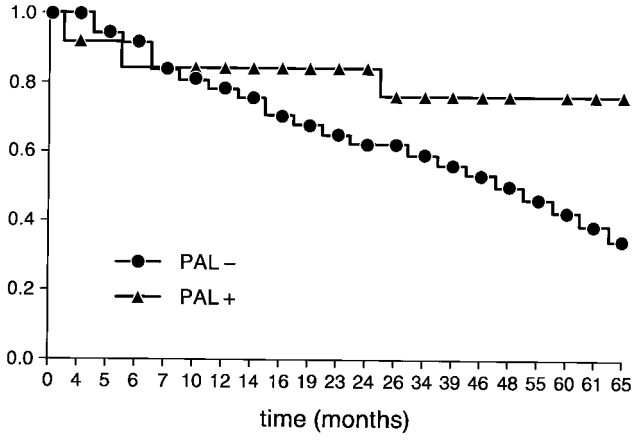

FIG. 1. Overall survival in 51 patients with endometrial cancer harboring node metastasis (excluding stage IV disease), according to the extent of para-aortic lymphadenectomy: without (PAL−, $n = 38$) and with (PAL+, $n = 13$) ($P = 0.05$).

adnexae, positive cervix, positive peritoneal cytologic result, or positive para-aortic nodes (Table 1). Surgical morbidity and complications due to operation and radiotherapy are listed in Tables 2, 3, and 4.

In the entire group, the 5-year overall survival was 51.1%, and the 5-year recurrence-free survival was 46.6%. Lymph node recurrences were found in 14 patients (27.4%), 10 of whom had a component in the para-aortic area and 4 in other lymph node areas (1 along the pelvic sidewall and 3 in the scalene lymph nodes). Of the 10 patients who had a para-aortic recurrence (3 also had involvement of the scalene nodes and 7 also of the pelvic sidewall areas), 9 (90%) died of disease.

The 5-year overall survival was 42% in PAL− patients and 76.9% in PAL+ patients ($P = 0.053$). The 5-year recurrence-free survival was 36.1% in PAL− patients and 76.1% in PAL+ patients ($P = 0.02$) (Figs. 1 and 2). No PAL+ patient experienced a local plus distant recurrence, but 13 (34.2%) PAL− patients had such a recurrence ($P = 0.02$). A distant site of recurrence was found in 50% of the PAL− group and in 15% of the PAL+ group ($P = 0.02$). No PAL+ patient experienced a recurrence in the lymph-node-bearing areas, but 14 PAL− patients (36.8%) had such a recurrence ($P = 0.01$)—10 (26.3%) in the para-aortic area ($P = 0.04$) and 8 (21%) along the pelvic sidewall ($P = 0.09$) (4 cases had concurrent recurrence in both the para-aortic area and on the pelvic sidewall).

Cox models suggested that submission to para-aortic lymphadenectomy was the only significant predictor for both recurrence-free survival (odds ratio [OR] = 0.28, $P = 0.01$) and overall survival (OR = 0.32, $P = 0.03$), whereas adnexal status, peritoneal cytologic result, and submission to extended-field radiotherapy (the other variables tested in the model) were all nonsignificant. When the model included histologic grade and subtype, depth of myometrial invasion, and cervical invasion, submission to para-aortic lymphadenectomy still retained independent significance for both recurrence-free survival and overall survival. In fact, submission to para-aortic lymphadenectomy (OR = 0.25, $P = 0.01$) and histologic grade (OR = 5.25, $P = 0.002$) were independent predictors of survival; submission to para-aortic lymphadenectomy (OR = 0.23, $P = 0.006$) and histologic grade (OR = 4.09, $P = 0.006$) were also independent predictors of recurrence-free survival.

The analyses stratifying patients for the administration of extended-field radiation therapy and for the presence of macroscopically or microscopically positive lymph nodes are summarized in Tables 5 and 6, respectively. For the patients not submitted to extended-field radiotherapy, 1 PAL+ patient (16.7%) had recurrence and died of disease, whereas 16 PAL− patients (57.2%) had recurrence and died of disease ($P = 0.09$). The differences in death and recurrence rates between PAL− and PAL+ patients submitted to radiotherapy were not significant ($P > 0.05$). No PAL+ patient had lymph node failure, whereas 3 PAL− patients (30%) submitted to extended-field radiation ($P = 0.22$) and 11 PAL− patients (39.2%) not submitted to para-aortic radiotherapy had lymph node failure ($P = 0.14$) (Table 5).

In patients with palpable lymph node disease, 2 PAL+ patients (28.6%) had recurrence and died of disease, whereas 9 PAL− patients (69.3%) had recurrence ($P = 0.15$) and 8 (61.6%) died of disease ($P = 0.34$). Of patients with microscopic lymph node disease, 1 PAL+ patient (16.7%) had recurrence and died of disease, whereas 14 PAL− patients (56%) had recurrence and died of disease ($P = 0.17$). No PAL+ patient had a lymph node recurrence, but 7 PAL− patients (53.8%) with palpable lymph node disease ($P = 0.04$) and 7 (28%) PAL− patients with microscopic node disease had lymph node recurrence ($P = 0.29$). Most of the lymph node recurrences were in PAL− patients who did not have extended-field radiotherapy (Table 6).

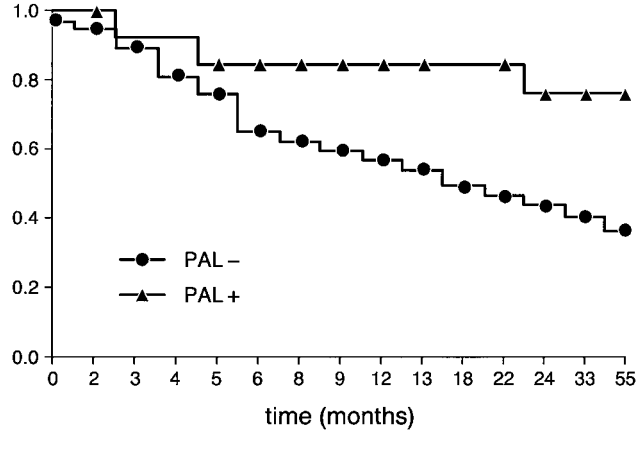

FIG. 2. Recurrence-free survival in 51 patients with endometrial cancer harboring node metastasis (excluding stage IV disease), according to the extent of para-aortic lymphadenectomy: without (PAL−, $n = 38$) and with (PAL+, $n = 13$) ($P = 0.02$).

TABLE 6
Analysis of 51 Patients with Endometrial Cancer and Positive Lymph Nodes (Pelvic or Para-aortic),[a] Stratified by the Presence of Macroscopically or Microscopically Positive Lymph Nodes

	Group									
	Macro[b,c]					Micro[d]				
	PAL− (n = 13)[e]		PAL+ (n = 7)[e]			PAL− (n = 25)[e]		PAL+ (n = 6)[f]		
Status	No.	%	No.	%	P	No.	%	No.	%	P
Death rate	8	61.6	2	28.6	0.34	14	56	1	16.7	0.17
Recurrence rate	9	69.3	2	28.6	0.15	14	56	1	16.7	0.17
Lymph node recurrence	7	53.8[g]	0	0	0.04	7	28[h]	0	0	0.29
Para-aortic recurrence	6	46.1[g]	0	0	0.05	4	16[i]	0	0	0.56
Pelvic side wall recurrence	5	38.4	0	0	0.11	3	12	0	0	1

Note. PAL, para-aortic lymphadenectomy (−, without; +, with).
[a] Excluding stage IV disease.
[b] Palpable lymph nodes (pelvic or para-aortic).
[c] Ten patients had palpable positive para-aortic lymph nodes: 7 in the PAL− group and 3 in the PAL+ group.
[d] Microscopically positive lymph nodes.
[e] Five patients submitted to extended-field radiotherapy.
[f] Two patients submitted to extended-field radiotherapy.
[g] Five recurrences in patients not submitted to extended-field radiotherapy.
[h] Six recurrences in patients not submitted to extended-field radiotherapy.
[i] All four recurrences in patients not submitted to extended-field radiotherapy.

DISCUSSION

Numerous authors have studied the possible therapeutic role of lymph node dissection in endometrial cancer, but they have focused mainly on pelvic lymphadenectomy [15, 16] or have combined low- and high-risk patients and subdivided them according to whether lymph node biopsy was done [4, 6, 17, 18]. It is intuitive that the mere biopsy of one or two nodes is not likely to confer a therapeutic benefit; in fact, even in high-risk patients with positive lymph nodes, this procedure probably will leave residual disease (microscopic or macroscopic) without significantly lessening the tumor burden. Moreover, only a restricted number of high-risk patients are likely to benefit from a complete lymphadenectomy. In fact, patients without tumor spread in the lymph nodes do not need lymph node removal; furthermore, in patients with systemic disease (stage IV), regional surgery has only a limited role. For these reasons, we focused on high-risk patients, excluding those with early-stage and stage IV disease. Patients with apparently negative lymph nodes were also included in the analysis because of the possible presence of occult lymph node metastases not detected at routine histologic evaluation [19, 20].

In the current retrospective review, all patients had an operation at Mayo Clinic Rochester between 1984 and 1993. Frozen section was routinely performed in all cases, providing the grade of neoplasia and the depth of myometrial invasion intraoperatively. This is a possible confounding factor in our analysis, because the surgeon may have modulated the extent of the nodal dissection on the basis of known prognostic factors. However, we did a precise selection of cases, analyzing two groups of patients homogeneous for the presence of clinicopathologic risk factors (Table 1). Moreover, all operations were performed by a small number of experienced surgeons, at the same institution, during a period of 10 years.

In our analysis, although the choice of five or more para-aortic nodes dissected as a discriminator for defining PAL was arbitrary, it reflected more than minimal diagnostic sampling and it is probably a sign of more extensive operation in this lymph node area. The number of pelvic lymph nodes dissected was not significantly different between PAL− and PAL+ patients in the various groups analyzed. This presupposes that any possible therapeutic advantage must be found in the para-aortic part of the procedure.

PAL did not add significant surgical morbidity or complications due to radiotherapy compared with patients not sub-

mitted to PAL (Tables 2, 3, and 4). This observation is in accord with that of other authors [21] who noted that the associated morbidity of lymphadenectomy is minimal in the surgical management of endometrial cancer. Moreover, complete lymphadenectomy does not add any significant extra morbidity to lymph node "sampling" [6].

In the 51 patients with positive lymph nodes at any site analyzed in the current study, 46% of those who had histologic assessment of the para-aortic area had documented tumor metastasis. Moreover, 90% of patients who experienced a para-aortic recurrence died of disease, a result attesting to the importance of minimizing this type of failure. The significant differences in 5-year overall survival and recurrence-free survival and in the percentage of lymph node and distant recurrences are a strong indication of the therapeutic value of PAL in patients with positive lymph nodes (Figs. 1 and 2). Moreover, the finding that PAL was an independent predictor of prognosis further reinforces this observation.

The analysis of women not submitted to extended-field radiotherapy showed a difference in cancer-related death and recurrence rates between PAL− and PAL+ patients. Statistical significance was not reached, presumably reflecting the small number of patients studied (Table 5). The data suggest a possible therapeutic value of PAL by itself, even in the absence of adjuvant radiation. The differences are less evident in patients submitted to extended-field radiotherapy (Table 5). This finding may be explained by the smaller number of patients analyzed or by a possible therapeutic role of extended-field radiotherapy even in patients who did not have PAL. The fact that only 10% of recurrences were in the para-aortic area in PAL− patients submitted to extended-field radiotherapy, compared with 32% in PAL− cases not submitted to extended-field radiotherapy, favors the second hypothesis.

The analysis of patients with macroscopic or microscopic positive lymph nodes showed a difference in death and recurrence rates between PAL− and PAL+ patients, but it did not reach significance (Table 6). PAL+ patients, both those with macroscopic and those with microscopic lymph node disease, did not experience recurrences in the lymph-bearing regions. On the contrary, 46% of PAL− patients with macroscopically positive lymph nodes and 16% of PAL− patients with microscopic disease had para-aortic recurrences. Most recurrences were in patients not submitted to extended-field radiotherapy (Table 6). Again, these observations support the hypothesis of a combined therapeutic role for PAL and extended-field radiotherapy in both patients with macroscopic and patients with microscopic lymph node disease.

Because of the retrospective nature of this study, it can be inferred that patients in the PAL− group had in fact unresectable nodes, which would account for the fewer number of lymph nodes removed and worse outcome. Despite this, there were no other significant differences in risk factors between PAL− and PAL+ patients (Table 1), and this hypothesis underlines the importance of removing all resectable tumor from the para-aortic area.

A recent editorial [22] inferred that removal of positive lymph nodes, thereby lessening the tumor burden, should facilitate adjuvant therapy by sterilizing the node bed and reduce the amount of therapy required to treat residual disease. In contrast, at early stages of disease and when clinically unaffected, regional lymph nodes should be sampled only for prognostic purposes (staging the disease), because the removal of negative lymph nodes may theoretically diminish the immune defenses of the host against tumor. These observations are in accord with our data, in which the possible benefit of PAL is evident only in a selected number of high-risk cases.

CONCLUSION

Our results suggest a possible therapeutic role for PAL in a select group of high-risk patients with endometrial cancer. This role seems particularly relevant in patients with positive nodes (pelvic or para-aortic), in whom PAL is able to improve survival and recurrence rates and lymph node-specific recurrences. Extended-field radiation therapy may contribute to the therapeutic effect of PAL. The hypothesis that a systematic lymphadenectomy (pelvic and para-aortic) is an important step for the treatment of high-risk endometrial cancer requires verification by prospective randomized studies.

REFERENCES

1. Landis SH, Murray T, Bolden S, Wingo PA: Cancer statistics, 1999. CA Cancer J Clin 49:8–31, 1999
2. Announcements: FIGO stages—1988 Revision. Gynecol Oncol 35:125–127, 1989
3. Podratz KC, Mariani A, Webb MJ: Staging and therapeutic value of lymphadenectomy in endometrial cancer. Gynecol Oncol 70:163–164, 1998
4. Belinson JL, Lee KR, Badger GJ, Pretorius RG, Jarrell MA: Clinical stage I adenocarcinoma of the endometrium—analysis of recurrences and the potential benefit of staging lymphadenectomy. Gynecol Oncol 44:17–23, 1992
5. Kim YB, Niloff JM: Endometrial carcinoma: analysis of recurrence in patients treated with a strategy minimizing lymph node sampling and radiation therapy. Obstet Gynecol 82:175–180, 1993
6. Faught W, Krepart GV, Lotocki R, Heywood M: Should selective paraaortic lymphadenectomy be part of surgical staging for endometrial cancer? Gynecol Oncol 55:51–5, 1994
7. Corn BW, Lanciano RM, Greven KM, Schultz DJ, Reisinger SA, Stafford PM, Hanks GE: Endometrial cancer with para-aortic adenopathy: patterns of failure and opportunities for cure. Int J Radiat Oncol Biol Phys 24: 223–227, 1992
8. Rose PG, Cha SD, Tak WK, Fitzgerald T, Reale F, Hunter RE: Radiation therapy for surgically proven para-aortic node metastasis in endometrial carcinoma. Int J Radiat Oncol Biol Phys 24:229–233, 1992
9. Feuer GA, Calanog A: Endometrial carcinoma: treatment of positive paraaortic nodes. Gynecol Oncol 27:104–109, 1987
10. Morrow CP, Bundy BN, Kurman RJ, Creasman WT, Heller P, Homesley HD, Graham JE: Relationship between surgical–pathological risk factors

and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol 40:55–65, 1991

11. Scully RE, Bonfiglio TA, Kurman RJ, Silverberg SG, Wilkinson EJ, in collaboration with pathologists in 10 countries: World Health Organization. International Histological Classification of Tumours: Histological Typing of Female Genital Tract Tumours. Second ed. Berlin, Springer-Verlag, 1994, pp 13–18
12. Broders AC: Grading of carcinoma. Minn Med 8:726–730, 1925
13. Pavy J-J, Denekamp J, Letschert J, Littbrand B, Mornex F, Bernier J, Gonzales-Gonzales D, Horiot J-C, Bolla M, Bartelink H: Late effects toxicity scoring: the SOMA scale. Radiother Oncol 35:11–15, 1995
14. Roos LL, Sharp SM, Cohen MM, Wajda A: Risk adjustment in claims-based research: the search for efficient approaches. J Clin Epidemiol 42:1193–1206, 1989
15. Mohan DS, Samuels MA, Selim MA, Shalodi AD, Ellis RJ, Samuels JR, Yun HJ: Long-term outcomes of therapeutic pelvic lymphadenectomy for stage I endometrial adenocarcinoma. Gynecol Oncol 70:165–171, 1998
16. Kilgore LC, Partridge EE, Alvarez RD, Austin JM, Shingleton HM, Noojin F III, Conner W: Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. Gynecol Oncol 56:29–33, 1995
17. Candiani GB, Belloni C, Maggi R, Colombo G, Frigoli A, Carinelli SG: Evaluation of different surgical approaches in the treatment of endometrial cancer at FIGO stage I. Gynecol Oncol 37:6–8, 1990
18. Anderson B, Connor JP, Andrews JI, Davis CS, Buller RE, Sorosky JI, Benda JA: Obesity and prognosis in endometrial cancer. Am J Obstet Gynecol 174:1171–1179, 1996
19. Girardi F, Petru E, Heydarfadai M, Haas J, Winter R: Pelvic lymphadenectomy in the surgical treatment of endometrial cancer. Gynecol Oncol 49:177–180, 1993
20. Izbicki JR, Hosch SB, Pichlmeier U, Rehders A, Busch C, Niendorf A, Passlick B, Broelsch CE, Pantel K: Prognostic value of immunohistochemically identifiable tumor cells in lymph nodes of patients with completely resected esophageal cancer. N Engl J Med 337:1188–1194, 1997
21. Orr JW Jr, Orr PF, Taylor PT: Surgical staging endometrial cancer. Clin Obstet Gynecol 39:656–668, 1996
22. Santin AD, Parham GP: Routine lymph node dissection in the treatment of early stage cancer: are we doing the right thing? (editorial) Gynecol Oncol 68:1–3, 1998