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Staging Laparotomy for Endometrial Carcinoma: Assessment of Retroperitoneal Lymph Nodes

LINUS CHUANG, M.D., M.P.H., M.S.,* THOMAS W. BURKE, M.D.,*,[1] CARMEN TORNOS, M.D.,†
BARBARA D. MARINO, M.D.,* MICHELE F. MITCHELL, M.D.,* GUILLERMO TORTOLERO-LUNA, M.D., PH.D.,*
CHARLES LEVENBACK, M.D.,* MITCHELL MORRIS, M.D.,* AND DAVID M. GERSHENSON, M.D.*

*Departments of *Gynecologic Oncology and †Pathology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030*

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The surgical staging scheme for uterine corpus cancer adopted in 1988 by the International Federation of Gynecology and Obstetrics assigns patients with tumor spread to retroperitoneal lymph nodes to stage IIIC. However, a recommended approach to the detection of lymph node metastasis is not delineated. As part of an ongoing project to assess the value of surgical staging procedures, we reviewed the techniques of lymph node evaluation in 295 at-risk patients. Cases included clinical stage I patients whose preoperative biopsies demonstrated grade 2 or 3 adenocarcinoma or papillary serous, clear cell, or mixed carcinoma. We arbitrarily divided the retroperitoneal space into 10 lymphatic zones: left and right para-aortic, common iliac, external iliac, hypogastric, and obturator. Eighty-two percent of patients had some type of node sampling that involved a mean of three zones. Thirty-three of 244 sampled cases (13.5%) had nodal metastases: 20 had gross involvement and 13 had microscopic. We stratified patients into three groups: (1) those who had no node sampling (n = 51), (2) those with some nodes biopsied (n = 193), and (3) those whose node sampling included a minimum of one para-aortic plus at least one right and left pelvic specimen (n = 51). Retroperitoneal recurrences thought to originate from lymph node sites were identified for the "node-negative" patients in each group: Group 1, 4/51 (8%); Group 2, 9/173 (5%); and Group 3, 0/38 (0%). Lymphatic site failures were seen in 8 of 33 (24%) patients with biopsy-proven metastases. We found that failure to systematically sample pelvic and para-aortic nodes results in a small, but real, risk of undetected extrauterine metastasis. A selective approach to sampling that includes biopsy from both para-aortic and bilateral pelvic lymphatic zones appears to provide an accurate estimate of true node negativity. Further evaluation of this approach is warranted.

INTRODUCTION

Based upon surgical staging data compiled during the 1970s and 1980s that suggested frequent errors in the clinical staging of uterine corpus cancers [1–3], the International Federation of Gynecology and Obstetrics (FIGO) adopted a surgical staging system in 1988 [4]. In this system, women with biopsy-confirmed metastases to the retroperitoneal nodes are assigned to substage IIIC. The presence of retroperitoneal nodal metastasis clearly conveys a poor prognosis. Unfortunately, the staging rules fail to provide precisely defined recommendations regarding the type of nodal assessment required to properly assign a surgical stage. While some advocate biopsy of palpable abnormalities only [5], others perform complete lymphadenectomy [6–9], and still others have suggested that a selective approach to nodal sampling provides adequate risk assessment [10].

This study was undertaken as a part of an ongoing project to assess the value of surgical staging procedures in women with endometrial carcinoma. An evaluation of our approach to intraperitoneal assessment has been described separately [11]. In brief, we review the techniques for retroperitoneal lymph node evaluation in a large group of patients and focus on the predictability of sampling approaches that involve less than full dissection. In this study, our purpose was to better define the operative sampling procedures that were most informative in identifying lymph node metastasis. Once identified, this approach could be incorporated into a broader concept used for the routine staging of all at-risk patients.

METHODS

Between January 1985 and March 1993, 612 women underwent surgical exploration and hysterectomy for treatment of malignant uterine corpus tumors at The University of Texas M. D. Anderson Cancer Center. Only patients felt to be at risk for extrauterine metastasis were evaluated in this study. Risk factors were determined from endometrial biopsy and intraoperative frozen section specimens and included grade 1 adenocarcinoma with >50% myometrial invasion, any grade 2 or 3 adenocarcinoma, and any variant of papillary serous or clear cell carcinoma. Two hundred ninety-five

[1] To whom correspondence and reprint requests should be addressed at Gynecologic Oncology, Box 67, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. Fax: (713) 792-7586.

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patients demonstrated these risk features and form the basis of this study. The remaining 317 cases had superficially invasive grade 1 carcinoma or uterine sarcoma and were not studied. Retrospective review of medical records was used to abstract data for cases from 1985 to 1988 (n = 170). Beginning in 1989 with the development of a conceptual approach to surgical staging, all subsequent patients (n = 125) were prospectively monitored with relevant data entered into the department's Society of Gynecologic Oncologists Database.

Patients underwent a standard preoperative workup to evaluate the clinical extent of tumor. This included history and physical examination, review of endometrial biopsy specimen, laboratory tests, chest radiograph, and electrocardiogram. Additional studies and consultations were obtained based upon individualized assessment of the patient's preoperative risk.

All patients underwent exploratory laparotomy with total abdominal hysterectomy and bilateral salpingo-oophorectomy. The extent of retroperitoneal lymph node sampling was determined by the individual attending staff physician and ranged from exploration only to selective dissection of pelvic and para-aortic nodes. After September 1988, a systematic sampling approach was recommended for those patients who were not felt to present excessive risk for additional staging procedures because of obesity, comorbid medical disease, or unstable intraoperative course. The pelvic and para-aortic areas were arbitrarily divided into 10 lymphatic zones based upon their anatomic association with the arterial blood supply: right and left para-aortic, common iliac, external iliac, hypogastric, and obturator. Selective node biopsies from as many sites as possible were recommended. Operative reports and narrative summaries were scanned to identify operative complications related to lymph node biopsy. For this analysis, the number, location, clinical impression, and pathologic evaluation for all node specimens were abstracted in detail.

Recommendations for postoperative adjuvant therapy were made at a multidisciplinary planning conference and were based upon the cytologic and pathologic findings from the exploratory operation. Many high-risk patients were treated on our adjuvant chemotherapy protocol with cisplatin, doxorubicin, and cyclophosphamide; others received external beam irradiation. Patients were followed on a regular basis every 3–4 months for 2 years, biannually for 3 additional years, and then annually. Patient follow-up status and duration were recorded for all cases. For women who developed recurrent disease, careful attention was paid to evaluating the site of recurrence.

Demographic and staging data were abstracted and presented descriptively. Descriptive statistical comparisons were accomplished with SPSS software. Univariate and multivariate analyses of prognostic factors were performed using a Cox proportional hazards model.

TABLE 1
Surgical Stage, Grade, and Histology for 295 Cases

	Endometrial			Variant histology			
Surgical stage	G1	G2	G3	UPSC	CC	AS	Mixed
Ia	0	12	3	7	0	0	1
Ib	0	57	20	4	1	2	1
Ic	4	10	6	2	1	2	2
IIa	1	4	0	0	0	0	0
IIb	2	6	1	1	0	0	1
IIIa	2	11	4	4	1	1	2
IIIb	0	0	1	1	1	2	0
IIIc	3	6	11	7	1	1	2
IV	0	6	5	11	2	2	0
Unstaged	2	43	6	4	1	1	0
Total	14	155	57	41	8	11	9

Note. Abbreviations used: G1, grade 1; G2, grade 2; G3, grade 3; UPSC, uterine papillary serous carcinoma; CC, clear cell; AS, adenosquamous.

RESULTS

The 295 study patients had a mean age of 63 years (range 32–88). Their racial distribution was 77% white, 11% black, 11% Hispanic, and 1% Asian. Virtually all patients were postmenopausal (95%) and had a median parity of 2. Twenty-two percent of patients exceeded their ideal body weight by 20% or more. Preoperative risk assignment to American Society of Anesthesiologists category III or IV was made in 68% of patients.

All women had a total abdominal hysterectomy and bilateral salpingo-oophorectomy. The extent of retroperitoneal dissection and lymph node sampling varied: 51 patients (17%) had exploration and palpation of the retroperitoneal areas without biopsy, 193 (65%) had biopsy of at least one lymph node (but less than bilateral pelvic and para-aortic biopsies), and the remaining 51 (17%) had a selective sampling that included a minimum of one para-aortic plus bilateral pelvic node specimens. Patients in this latter group had biopsies from a mean of 6.2 sites (range 3–10) yielding an average of nine lymph nodes (range 3–22).

The median duration of the hysterectomy and staging procedure was 145 min with a median blood loss of 300 ml. Two intraoperative injuries (1%)—one ureteral transection and one major venous laceration—were directly attributable to lymph node sampling. Two women developed postoperative bowel dysfunction (one ileus and one partial small bowel obstruction) that may have been indirectly related to sampling procedures. Both dysfunctions resolved with conservative management.

All 295 patients were thought to have clinical stage I disease preoperatively. However, 103 of 244 patients (42%) who had staging biopsies taken were upstaged on the basis of surgical findings. Surgical stage, histologic grade, and cell type for all cases are outlined in Table 1.

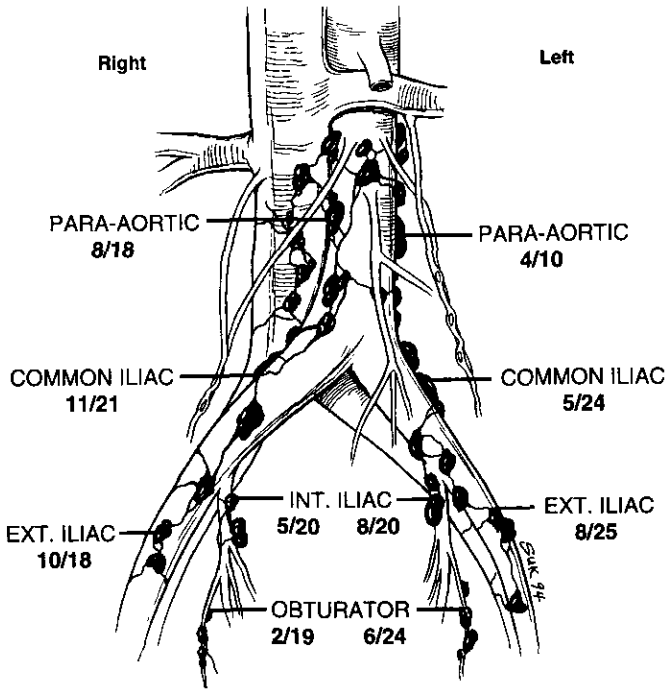

FIG. 1. Locations and numbers of positive retroperitoneal nodes identified in 33 patients as part of an operative staging procedure for endometrial carcinoma. Sixty-seven of 199 resected lymph nodes contained metastatic cancer. Tumor metastases were observed at all sites. Values represent the number of positive nodes/total nodes resected at each anatomic site.

Lymph node metastases were detected in 33 of 244 cases (14%), with at least one nodal specimen being pathologic. After careful review of the operative reports, it was evident that 20 of these women had clinically suspicious nodes at the time of laparotomy while the remaining 13 had microscopic metastases not detected intraoperatively. In these cases, a mean of 8 nodes (range 3–13) were sampled and yielded an average of 1.4 positive nodes (range 1–3). All patients with microscopic metastases had typical endometrial adenocarcinomas, and none had other evidence of extrauterine disease. Sites of detected gross and microscopic nodal metastases are graphically depicted in Fig. 1.

Median follow-up is 39 months. Sixty-one patients (21%) have developed clinical recurrences, 21 of these originating in retroperitoneal lymph node areas. These cases were examined in particular detail because they represent potential staging failures. Eight retroperitoneal recurrences were observed in women with previously identified nodal metastases. The remaining 13 women developed a retroperitoneal recurrence following a "negative" nodal assessment. These were analyzed by the technique used for nodal evaluation: 4 of 51 patients (8%) with no nodes sampled had retroperitoneal recurrence, 9 of 173 patients (5%) with some nodes sampled recurred, and none of 38 patients with negative biopsies from both para-aortic and bilateral pelvic areas had nodal recurrence. Clinical details regarding the 13 unexpected retroperitoneal failures are summarized in Table 2.

Cox proportional hazards univariate analysis was employed to analyze several possible prognostic features including age at diagnosis, race, tumor histology, presence of lymph–vascular space invasion, lymph node status, and FIGO stage. Endpoints for analysis were time to recurrence and survival. Histology, presence of lymph–vascular space invasion, presence of lymph node metastasis, and FIGO stage were found to be significant predictors of both recurrence and survival (Table 3). A stepwise model for multivariate analysis was developed to evaluate age at diagnosis, histology, depth of myometrial invasion, presence of lymph–vascular space invasion, and presence of lymph node metastasis on both time to recurrence and survival. Only presence of retroperitoneal nodal metastasis was significant in the multivariate survival analysis (Table 4).

DISCUSSION

All large reviews of women with endometrial carcinoma have identified lymph node spread as a major prognostic factor for recurrence and survival [1–3]. Unfortunately, there is considerable controversy regarding the most appropriate method of obtaining information about nodal metastases. Options for retroperitoneal evaluation include palpation with biopsy of clinically enlarged nodes only, selective sampling from multiple sites, and complete lymphadenectomy.

Staging issues are further complicated by the complex lymphatic drainage routes of the uterine fundus. Lymphatic vessels parallel the vascular supply to reach the pelvic, para-aortic, and, occasionally, the inguinal lymph nodes. Although women with para-aortic metastases frequently have pelvic metastases, predictable stepwise nodal spread is not universal. For example, in the Gynecologic Oncology Group's staging study, 18 patients had positive para-aortic nodes with negative pelvic nodes [3]. In his autopsy series, Henriksen found aortic node metastases without pelvic node involvement in 20 of 114 women with stage I–II endometrial cancer who died of their disease [12]. Consequently, selecting the locations of node biopsy sites may be as important as determining the extent of the sampling technique.

Detection of nodal metastasis, particularly microscopic involvement, is also dependent upon the precision of the pathologic assessment of biopsy specimens. Girardi and colleagues noted that 37% of lymph node metastases were less than 2 mm in greatest dimension [9]. This is similar to our observation that 39% of nodal metastases were microscopic. Complete processing of all submitted material with step sectioning will yield an increased number of nodes and metastatic sites compared with selected processing with limited sections [9]. Because step sectioning is cumbersome, time-consuming, and relatively expensive, it is not widely employed or recommended. Nevertheless, the protocol for the

TABLE 2
Clinical Summary of 13 Women with "Negative" Nodal Assessment Who Developed Retroperitoneal Failure

Patient	Stage	Histology	Retroperitoneal nodes		Time to recur (months)	Status
			No bx	Limited bx (No. of sites)		
1	Ib	endometrial	x		21	AWD
2	Ib	endometrial	x		55	NED
3	IIb	clear cell	x		20	AWD
4	Ib	endometrial	x		20	AWD
5	Ib	endometrial		1	18	AWD
6	IIIa	endometrial		1	45	DOD
7	Ib	endometrial		1	35	DOD
8	IIb	endometrial		2	10	DOD
9	Ic	endometrial		3	17	AWD
10	Ib	endometrial		2	12	NED
11	Ib	endometrial		1	31	DOD
12	Ib	endometrial		1	39	DOD
13	Ia	endometrial		1	25	DOC

Note. Abbreviations used: bx, biopsy; AWD, alive with disease; NED, no evidence of disease; DOD, died of disease; DOC, died of intercurrent disease.

handling of tissue samples assumes significance equal to that of the surgical techniques used to obtain them.

Perceived patient risk and physical factors sometimes limit the application of retroperitoneal node sampling. Both total and selective lymphadenectomy are associated with a small risk of major vascular or ureteral injuries: the incidence of such complications is probably 1–4% [6, 13–15]. We have approached this problem by performing retroperitoneal dissection only in patients believed to be at risk for metastasis based upon histologic grade, cell type, or myometrial invasion [16]. An additional proportion of patients are not suitable candidates for retroperitoneal staging because of poor medical condition or marked obesity. About 25% of our patients presented technical problems that hindered staging efforts. Vardi and co-workers noted similar conditions in 35% of their cases [7].

We detected nodal metastases in 14% of patients, 13 of whom had no clinically suspicious nodes. Although we had a preselected study group, multivariate analysis confirmed that metastasis to retroperitoneal nodes was the single significant prognostic factor in predicting recurrence and survival. Our review of 21 women with retroperitoneal recurrences identified 13 in whom operative assessment of the retroperitoneal space was felt to be negative. None of these cases had a selective sampling of both pelvic and para-aortic areas, and all but one had biopsies of only 0–2 nodes. When we calculated the incidence of unexpected retroperitoneal failure by the extent of sampling, no patient with a negative selective lymphadenectomy that included para-aortic and bilateral pelvic sites recurred. These data suggest that such a selective approach provides clinically reliable information regarding the true absence of nodal metastasis. Interestingly, Kilgore and others recently presented information that dem-

TABLE 3
Cox Proportional Hazards Univariate Analysis of Possible Prognostic Factors for Recurrence and Decreased Survival

Factor	*P* value	
	Recurrence	Survival
Age at diagnosis, years (≤50 vs >50)	0.945	0.556
Race (white vs other)	0.891	0.470
Histology (endometrial vs variant)[a]	0.013	0.001
LVSI (positive vs negative)	0.004	0.003
Node status (positive vs negative)	<0.001	<0.001
Nodes sampled (yes vs no)	0.907	0.627
FIGO stage	<0.001	<0.001

Note. Abbreviation used: LVSI, lymph–vascular space invasion.
[a] Variant indicates uterine papillary serous, clear cell, and mixed types.

TABLE 4
Cox Proportional Hazards Multivariate Analysis of Possible Prognostic Factors for Recurrence and Decreased Survival

Factor	*P* value	
	Recurrence	Survival
Age at diagnosis, years (≤50 vs >50)	0.164	0.724
Histology (endometrial vs variant)[a]	0.333	0.085
Depth of myometrial invasion (≤50% vs >50%)	0.080	0.425
LVSI (positive vs negative)	0.239	0.422
Retroperitoneal nodes (positive vs negative)	0.201	0.028

Note. Abbreviation used: LVSI, lymph–vascular space invasion.
[a] Variant indicates uterine papillary serous, clear cell, and mixed types.

onstrated a survival advantage for patients whose staging procedure included selective lymphadenectomy compared with those with either limited or no nodal biopsies [17]. However, at present selective lymphadenectomy is best considered a staging, rather than a therapeutic procedure.

We believe that selective lymphadenectomy is an effective clinical method for detecting microscopic metastases in women with endometrial carcinoma. Our data suggest that complete lymphadenectomy would not have improved the rate of detection. If this observation holds true in a larger prospectively evaluated population, the additional operative time of and blood loss from complete lymphadenectomy could be avoided. The value of a staging para-aortic dissection has recently been questioned because relatively few patients with clinically limited tumors have metastases to these nodes and because most women with positive para-aortic nodes do not obtain long-term survival [10, 18]. Nevertheless, accurate assessment of retroperitoneal spread, if obtained with minimal morbidity in at-risk subpopulations, provides important prognostic information for the patient and permits testing of treatment strategies designed to deal with advanced primary disease.

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