Lymphovascular Invasion Is a Significant Predictor for Distant Recurrence in Patients With Early-Stage Endometrial Endometrioid Adenocarcinoma

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Abstract

To evaluate the value of lymphovascular invasion (LVI) in endometrial endometrioid adenocarcinoma (EEA) as a predictor for distant recurrence, we analyzed the histopathologic features of 513 consecutive cases of nonsurgically staged EEA limited to the uterus. Grade, myoinvasion, cervical involvement, and LVI were evaluated. With a median follow-up of 28 months (range, 2-144 months), 67 cases (13.1%) recurred, 37 (7.2%) had locoregional recurrence, and 30 (5.8%) developed distant recurrence. LVI was identified in 116 cases (22.6%) cases and was the only adverse histopathologic finding in 23 cases; 5 (22%) of the 23 recurred. Multivariate analysis demonstrated a significant association between any type of recurrence and cervical involvement (hazard ratio [HR], 2.760; 95% confidence interval [CI], 1.621-4.698) and LVI (HR, 2.717; CI, 1.568-4.707). Multivariate analysis revealed LVI as the only independent predictor for distant recurrence (HR, 2.841; CI, 1.282-6.297). Studies to examine the role of adjuvant systemic therapy in patients with early-stage disease should be considered.

Endometrial endometrioid adenocarcinoma (EEA), the most common type of uterine cancer, is confined to the uterine corpus at the time of diagnosis in the majority of patients. In general, endometrial carcinoma has a favorable prognosis, with an 80% 5-year survival. Numerous studies have demonstrated that cell type, histologic grade, depth of myometrial invasion, cervical involvement, and lymphovascular involvement (LVI) can predict recurrence and survival in patients with endometrial cancer.[1,2] Based on these histopathologic findings, patients are classified into 3 risk groups and adjuvant therapy is recommended based on the presence of these adverse histologic features.[3,4] Data from randomized clinical trials showed that in early stage, pelvic radiotherapy reduced locoregional recurrence but did not improve survival of patients with distant recurrences.[5]

The findings of previous studies have been contradictory with respect to the significance of LVI as an independent prognostic factor. The present study focused on patients with early-stage EEA as defined by the pathologic findings of disease confined to the uterus in the hysterectomy specimen combined with respective clinicoradiologic assessment. Our aim was to identify a subset of patients with a higher risk for recurrence, with an emphasis on extrapelvic sites.

Materials and Methods

Samples and Patients

A total of 827 hysterectomy specimens with pure EEA were accessioned in the Department of Anatomic Pathology, Sunnybrook Health Sciences Center, Toronto, Canada,

between July 1999 and June 2004. Because our hospital is a tertiary care facility, the referral patients more often have advanced disease and higher tumor grade. The majority of the referred cases did not have full surgical staging. The entire database was described in detail elsewhere.[6]

Our study population consisted of patients treated primarily by hysterectomy and without pathologic, clinical, or imaging evidence of serosal or extrauterine spread. Clinical information and follow-up data were retrieved from the electronic medical charts. In cases in which subsequent medical care was offered at another institution, the outside gynecologist or primary care practitioner was contacted and the given follow-up data were recorded. For much of this time, adjuvant radiotherapy was prescribed for patients with deep myometrial invasion of any grade, a high-grade tumor with any myometrial invasion, or cervical stromal involvement. Adjuvant therapy was omitted for patients who declined and whenever substantial comorbidity that contraindicates therapy was identified.

The patterns of first failure were classified as locoregional or distant failure according to the sites of failure following the PORTEC (Post Operative Radiation Therapy in Endometrial Cancer) study protocol.[5] Locoregional failures were defined as vaginal and/or pelvic recurrences. If distant *and* locoregional recurrences were detected, the failure type was recorded as distant metastases.

Pathology

A group of gynecologic pathologists assessed the histopathologic features of all in-house and consultation cases. The diagnosis of endometrioid type was assigned when at least 95% of the tumor displayed morphologic features of endometrioid adenocarcinoma. The tumor grade was reported in a 2-tiered system, with high grade defined as having more than 50% solid areas.[7] LVI was defined by the presence of malignant cells within endothelial-lined spaces on H&E-stained sections. Controversial cases were reviewed by more than 1 pathologist, and consensus was reached at a multiheaded microscope.

Analyses

Because the information on mortality and cause of death was limited, we used 2 end points for the analysis. One was the development of any recurrence, whether it was locoregional or distant, and the second was the development of distant recurrence. The disease-free interval was defined as the time from date of surgery to the date of recurrence detected clinically or radiologically or to the date when the patient was last seen. Cox proportional hazards models were fitted with potential factors associated with recurrence, including age, adjuvant radiotherapy, tumor grade, depth of myometrial invasion, presence of cervical involvement, and LVI. Effects were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). An HR greater than 1.0 represented a higher risk of recurrence compared with the reference category for each variable. The Kaplan-Meier method was used to create time-to-event graphs with time to any recurrence and, more specifically, time to distant recurrence. Possible interaction between LVI and the traditional prognosticators were studied by using the χ^2 test. Statistical analysis was performed using SAS 8.2 software (SAS Institute, Cary, NC).

Ethics approval for this study was obtained from the Research Ethics Board of the Toronto Academic Health Sciences Council.

Results

Of 827 patients, 513 met our inclusion criteria. Of 513 patients, 204 were treated surgically at this center and 309 were referred from community hospitals for consultation following surgery. The median age at diagnosis was 63 years (range, 28-94 years). Surgical staging was performed in 44 (21.6%) of 204 in-house cases and in 6 (1.9%) of 309 referral cases. Adjuvant radiotherapy was used in 218 cases (42.5%). In a median follow-up of 28 months (range, 2-144 months), 67 cases (13.1%) recurred; 37 (7.2%) had locoregional recurrence, and 30 (5.8%) developed distant disease. In 2 of the 30 cases with distant recurrence, the primary failure site was the vaginal vault while the tumor continued to progress systemically. The median time to recurrence was 14 months (range, 3-57 months) for locoregional recurrence and 18 months (range, 2-58 months) for distant recurrence. Distant failure occurred most commonly in extrapelvic lymph nodes (n = 11), followed by liver (n = 6) and lung (n = 5). The distal recurrence sites are listed in **Table 1**.

Histopathologic evaluation revealed that 449 (87.5%) of the tumors were classified as low grade and 64 (12.5%) as high grade. The tumor was confined to the endometrium in 82 cases (16.0%) and invaded the inner half of the myometrium in

Table 1
Sites of Distant Recurrence in 30 Cases of Endometrial Endometrioid Adenocarcinoma

Site	No. of Cases
Lymph nodes*	11
Liver	6
Lung/pleural effusion	5
Colon	3
Bone	3
Brain	1
Skin	1

* The involved lymph nodes were as follows: para-aortic and retroperitoneal, 8; inguinal, 1; supraclavicular, 1; and neck, 1.

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248 (48.3%) and the outer half in 183 cases (35.7%). Cervical involvement was identified in 123 cases (24.0%). In 54 cases (10.5%), the tumor was limited to the endocervical glands, and in 69 cases (13.4%), cervical stromal invasion was also present. LVI was identified in 116 cases (22.6%). In 23 cases, LVI was the only adverse histopathologic finding when the tumor was low grade, myometrial invasion was limited to the inner half, and cervical involvement was absent. Of these 23 cases, 5 (22%) recurred, 2 locally and 3 at distant sites. In LVI-negative cases with no additional adverse histopathologic findings, only 26 (8.7%) of 298 cases recurred. LVI was significantly associated with the following: age older than 60 years ($P = .0298$), high tumor grade ($P < .001$), deep myometrial invasion ($P < .001$), and cervical involvement ($P < .001$).

Lymph node sampling was performed at the time of hysterectomy in only 50 cases (9.7%). **Table 2** outlines the distribution of clinicopathologic features for the study population.

Univariate analysis demonstrated significant association between any recurrence and the following prognostic factors: adjuvant radiotherapy ($P = .0452$), cervical involvement ($P < .0001$), and LVI ($P < .0001$). The factors that were predictive for distant recurrence were adjuvant radiotherapy ($P = .0105$), cervical involvement ($P = .0107$), LVI ($P = .0002$), and deep myometrial invasion ($P = .0213$). Multivariate analysis demonstrated a significant association between any type of recurrence and cervical involvement (HR, 2.760; CI, 1.621-4.698) and LVI (HR, 2.717; CI, 1.568-4.707). Adjuvant radiotherapy only approached significance **Table 3** and **Figure 1**. In multivariate analysis using only distant recurrence as an end point, LVI was the only significant prognostic factor (HR, 2.841; CI, 1.282-6.297) **Table 4** and **Figure 2**.

Discussion

We retrospectively studied the prognostic significance of histopathologic characteristics in 513 consecutive cases of pure EEA, analyzing their association with any type of recurrence

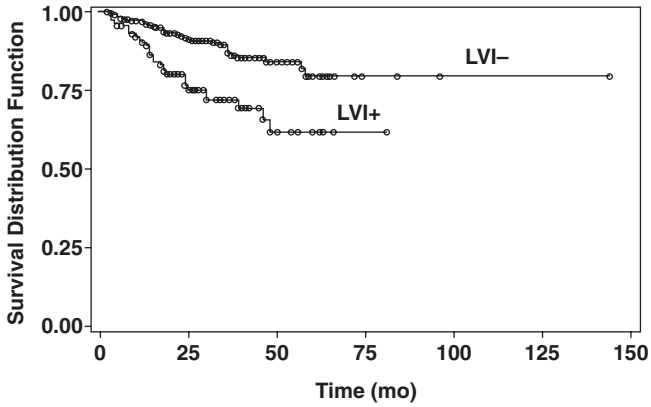

Figure 1 Any recurrence-free survival rates with and without lymphovascular invasion (LVI).

Table 2
Clinicopathologic Characteristics in 513 Cases of Endometrial Endometrioid Adenocarcinoma

Characteristic	No Recurrence (n = 446)	Locoregional Recurrence (n = 37)	Distant Recurrence (n = 30)
Age >60 y	245	29	17
Adjuvant radiotherapy	182	16	20
High grade	53	6	5
Deep myometrial invasion	152	13	18
Cervical involvement	51	9	9
Lymphovascular involvement	85	15	16
Lymph node sampling	44	3	3

Table 3
Independent Predictors of Any Recurrence* Among 513 Patients With Early Endometrial Endometrioid Adenocarcinoma

Predictor	Relative Risk†	95% Confidence Interval	*P*
Age	1.009	0.988-1.031	.4081
Adjuvant radiotherapy	0.554	0.306-1.004	.0517
High grade	0.985	0.493-1.969	.9665
Deep myometrial invasion	0.942	0.535-1.659	.8366
Cervical involvement	2.760	1.621-4.698	.0002
Lymphovascular involvement	2.717	1.568-4.707	.0004

* Locoregional and distant recurrence included.
† Relative risks approximated with hazard ratios from a proportional hazards model.

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Table 4
Independent Predictors of Distant Recurrence Among 513 Patients With Early Endometrial Endometrioid Adenocarcinoma

Predictor	Relative Risk*	95% Confidence Interval	*P*
Age	0.987	0.957-1.018	.3966
Adjuvant radiotherapy	0.857	0.344-2.133	.7395
High grade	0.719	0.246-2.101	.5469
Deep myometrial invasion	1.376	0.588-3.217	.4615
Cervical involvement	1.693	0.776-3.696	.1862
Lymphovascular involvement	2.841	1.282-6.297	.0101

* Relative risks approximated with hazard ratios from a proportional hazards model.

and, specifically, with distant recurrence. Our findings are based on central pathology review by a group of pathologists with special expertise in gynecologic pathology, ensuring a high level of consistency. Prospective reviews (before sign-out) are uniformly carried out, and a consensus diagnosis is reached in controversial cases at a multiheaded microscope. The diagnostic accuracy, consistency, and completeness of pathology reports of referred cases to our institution were described earlier.[8] About 60% of cases were reviewed by a pathologist from the group on a rotation basis as part of our weekly tumor board presentations, and no disagreement regarding LVI was documented within the study period (data not shown).

By univariate analysis, we found that LVI and cervical involvement were significant predictors for any recurrence and, along with deep myometrial invasion, predicted distant recurrence. However, owing to the strong interaction among the histopathologic parameters, the relative importance of these factors as independent prognosticators was further assessed. Multivariate analysis that accounts for these interrelationships demonstrated that only cervical involvement and LVI were significant independent predictors of recurrence. In our study, LVI, as identified on routine H&E-stained sections, was the only significant predictor of distant recurrence on multivariate analysis, which suggests that it may be an important indicator for reduced survival. Because patients with locoregional recurrence can be salvaged with radiotherapy, survival is compromised mainly in patients with distant recurrence.[9,10] Although to date there is no evidence that radiotherapy improves overall survival in endometrial cancer, it is possible that its effect on survival could be demonstrated with longer follow-up. By analogy, a study on the effect of radiotherapy in early breast cancer that reviewed data from 42,000 patients demonstrated significant 15-year survival benefit in patients who underwent radiotherapy.[11]

The recurrence rate in our study was 13.1%, compared with an 11.2% recurrence rate reported by Keys et al[3] for surgically staged, node-negative, intermediate-risk EEA. The slightly higher rate of recurrence in our study within a shorter follow-up interval may be attributed to the inclusion of cases

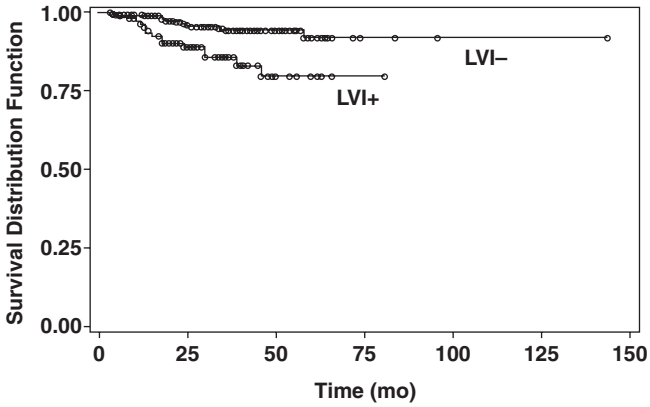

Figure 2 Distant recurrence-free survival rates with and without lymphovascular invasion (LVI).

with more advanced stages owing to the inherent underestimation of the extent of disease in understaged cases referred from community hospitals. In addition, although we included patients with any type of cervical involvement, only occult stage II cases were included in the Gynecologic Oncology Group study. Data from several Gynecologic Oncology Group studies suggest that most recurrences occur within 18 months of initial therapy.[3] In our study, the median follow-up was 29 months, and the median time to recurrence was 17 months.

We found that 22.6% of the cases had LVI. Previous studies reported that the rate of LVI was 12% to 34% in EEA.[3,12,13] LVI is an obligatory step in tumor progression toward metastasizing and, therefore, may be a surrogate marker for metastatic potential. Vascular invasion by tumor cells has been shown to be a significant prognostic factor in several malignancies, including cervical,[14] rectal,[15] and breast[16] cancer. Previous studies demonstrated the significance of LVI as a predictor of nodal disease. Based on this observation, it has been suggested that in unstaged or understaged cases, the presence of LVI may indicate the presence of extrauterine disease and the need for adjuvant therapy.[17,18]

A number of studies have underlined LVI as a predictor of survival in endometrial carcinoma in patients with and without surgical staging.[2,5,12,19-22] In some studies, only cases treated

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after 1988 received surgical staging.[12,23] However, some of these investigators included cases with nonendometrioid histologic features, such as serous and clear cell carcinoma, that are known to have a more aggressive course. Data from studies on nonsurgically staged cases suggested an important role for LVI as a prognostic factor. Briët et al[20] studied prognostic factors in 609 patients with endometrial carcinoma of any cell type and showed that LVI was an independent significant prognosticator for relapse. They found that the presence of LVI in low- and high-risk stage I endometrial cancer conferred a 2.6-times increased risk of relapse compared with cases without LVI. The analysis of stage IC grade 3 cases in the PORTEC study found that the presence of vascular space invasion was associated with a significantly increased risk of relapse and a particularly interesting increased risk for distant relapse (32% in LVI+ compared with 8% in LVI–) but no difference in the rate of locoregional relapse (0% in LVI+ and 3.5% in LVI–). In that study, survival rates at 5 years with and without vascular space invasion were 57% and 82%, respectively. However, in multivariate analysis, LVI did not reach statistical significance.[24]

Likewise, the role of LVI has also been demonstrated in surgically staged cases. Mariani et al[23] found that LVI was a strong predictor of extra-abdominal failure and survival in patients with positive peritoneal cytologic findings identifying the only site of extrauterine disease (stage IIIA1). In a different study on predictors of distant failure in surgically staged, stage I endometrial cancers of all cell types, Mariani et al[25] found that deep myometrial invasion was the only independent predictor of distant recurrence. In the later study,[25] lymph node dissection was defined as removal of at least 1 node.

It is interesting that a study comparing H&E-detected LVI with immunohistochemically detected LVI found that only the former was an important predictive factor of disease recurrence.[26] Two studies of patients with surgically staged, stage IB disease found that LVI was not an independent prognostic factor.[13,27] Alektiar et al[13] suggested that LVI was directly related to the depth of myometrial invasion and showed significant increase in the frequency of the presence of LVI between carcinoma that involves the inner and middle thirds, even when limited to the inner half.

In our study, we did not find an association between any of the other traditional prognosticators and risk of distant recurrence, namely age, tumor grade, depth of myometrial invasion, and cervical involvement. Although age was not a significant prognosticator in our study, previous reports have suggested otherwise. Older age was associated with a worse prognosis in several series, including 2 prospective studies.[5,28,29] However, age is associated with an increased risk for recurrence in patients with more aggressive histologic findings, such as uterine serous carcinoma, high-grade endometrioid carcinoma, deep myometrial invasion, and higher stage at diagnosis. This is probably a reflection of the more aggressive biologic behavior of hormone-independent cancers that occur at an older median age. A previous study that examined endometrial cancers with similar pathologic features in 455 cases did not find differences in survival rates by age. In patients younger than 60 years, the survival rate was 74%; at 60 to 69 years, it was 70%; and at 70 years or older, it was 60%.[30]

The results of our study are important because the majority of patients with endometrial carcinoma have no evidence of extrauterine disease at diagnosis. In clinical practice outside the setting of clinical trials and tertiary care centers in North America, not all patients with EEA undergo formal staging,[6] and in these patients, adjuvant treatment decisions are based on the combination of pathologic findings and clinicoradiologic assessment. The presence of LVI is an important predictor for distant recurrence, and studies to examine the role of adjuvant systemic therapy in this subset of patients with stage I disease should be considered.

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