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Original Article

Factors Predicting Pelvic Lymph Node Metastasis, Relapse, and Disease Outcome in Pattern C Endocervical Adenocarcinomas

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Summary: A pattern-based classification system has recently been proposed for invasive endocervical adenocarcinoma (EAC), which is predictive of the risk for lymph node metastases (LNM). The main utility of the system lies in separating cases with very low risk for LNM (pattern A) from those with higher risk (pattern B and C). Different growth patterns (GPs) are found in pattern C cases. The aim of the study was to evaluate the effect of GP on the behavior of pattern C EAC. By reevaluating 189 pattern C EACs, we documented 6 architectural GPs: diffuse destructive (DD), confluent (CON), extensive linear destructive (ELD), band-like lymphocytic infiltrate (BLL), solid (SOL), and micropapillary (MP). When an EAC had an appreciable second component ($\leq$50%) the designation of a mixed EAC was used. We found 32 (17%) tumors to be DD, 23 (12%) CON, 27 (14%) ELD, 9 (5%) SOL, 7 (4%) BLL, and 7 (4%) micropapillary. A total of 84 (44%) EACs were mixed (DD + CON). All micropapillary EACs had LNM versus none of the patients with EAC with an ELD GP ($P = 0.002$). Recurrent disease was seen in 44% of EACs with a DD GP, whereas 0% of EACs with BLL GP developed recurrent disease. Mixed (DD + CON) tumors had a significantly worse 6-year overall survival. This study demonstrated that not all pattern C EACs have an aggressive behavior. These patients should be treated with radical hysterectomy and sentinel lymph node biopsy. **Key Words:** Endocervical adenocarcinoma—Pattern C—Growth pattern—Behavior.

The pattern-based classification system for evaluating endocervical adenocarcinoma (EAC) (1,2) has been created because it is impossible for pathologists to separate in situ adenocarcinoma from some invasive adenocarcinomas (3,4). We realized that there is a group of EACs that do not have destructive invasion and never have lymph node metastases (LNM) or recurrences. These are the pattern A tumors, and some could be in situ adenocarcinomas and some probably represent invasive tumors with glands having pushing borders. As we cannot determine which ones are in situ or invasive, and because this distinction becomes inconsequential, all are included in pattern A.

Pattern B tumors are adenocarcinomas with predominant pattern A characteristics but with focal, minimal destructive invasion. Pattern C includes tumors with diffuse destructive invasion (5). Different

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patterns of invasion are found in pattern C cases, and we have noted that tumors with some patterns are more aggressive than tumors with other patterns. Therefore, we decided to investigate this issue.

MATERIALS AND METHODS

This study involves a multi-institutional IRB for patient sample exchange. Collated data on invasive adenocarcinoma (EAC) of the usual type from 12 international institutions were reviewed (1,2).

A total of 189 cases of EAC originally diagnosed with a pattern C of invasion were rereviewed to assess the following architectural patterns of growth (PG):

Diffuse Destructive (DD)

This pattern is defined by diffusely infiltrative glands with associated extensive desmoplastic response. The glands have a haphazard distribution and are angulated and open (Figs. 1A, B).

Confluent (CON)

This pattern is defined by growth filling a 4 × field (5 mm), downward proliferation of closely packed glands or papillae, separated by scant intervening stroma or mucin lakes to create a tightly packed glandular growth (Fig. 1C).

Solid (SOL)

This pattern is defined by a poorly differentiated component (architecturally high grade) with SOL sheets of large malignant cells. Nuclear grade is disregarded (Figs. 1D, E).

Extensive Linear Destructive (ELD)

This pattern comprises diffuse laminar EACs $\geq$5 mm. The invasion is seen only at the base of the tumor and extends parallel to the surface. Tumor cells or individual glands are present in a desmoplastic stroma with a mild inflammatory infiltrate (Figs. 2A, B).

Band-like Lymphocytic Infiltrate (BLL)

This pattern is composed of superficial dense band-like infiltrate that obscures the neoplastic aggregates (indistinct blending of neoplastic glandular elements with a prominent lymphoid infiltrate) (Figs. 2C, D).

Micropapillary (MP)

This pattern was identified by numerous small clusters of tumor cells; the neoplastic cells are polygonal in shape with abundant eosinophilic cytoplasm (Figs. 2E, F).

Mixed

When an invasive EAC had an appreciable second component ($\leq$50%), the designation of a mixed EAC was given.

Clinical and gross pathologic data were obtained from the patients' charts and pathology reports. Tumor size was determined from the clinical record or the pathologic slides. The tumor grade was determined on the basis of the architectural pattern. Lymphatic vascular space invasion (LVSI) was considered to be present only if viable tumor cells were present inside an endothelial-lined space within an area of stroma of the uterine cervix.

The extent of LVSI was classified as negative, low (0–4 LVSI), moderate (5–19 LVSI), and extensive ($\geq$20 LVSI).

The pattern of tumor invasion, depth of stromal invasion, lower uterine segment (LUS) involvement, parametrial invasion (PI), polypoid configuration, and LVSI were analyzed for their association with pelvic LNM.

Statistical Analysis

A Mann-Whitney U test was used to compare medians between groups. A χ^2 test or Fisher exact test was used to compare variables. A P-value <0.05 was considered statistically significant. Univariate analyses were performed with log-rank tests. The Cox proportional hazards model was used to construct a multivariate model to predict survival. Statistical analyses were performed with SPSS software (SPSS Inc., Chicago, IL).

RESULTS

There were 189 patients eligible for the study. The mean age was 49.4 years (range, 23–82 y). A total of 80% (151) were stage I, with 0.7% IA1, 1.4% IA2, and 78% (148) IB, whereas 20% were stages II and III. Polypoid tumors were found in 38 (20%) cases; the mean tumor size was 3.56 cm (2–5 cm). Coexistent CIN occurred in up to 52% of cases.

Depth of invasion (DOI) ranged from 0.3 to 31 mm (mean: 10.2 mm). In addition, PI was found in 13 patients (6.8%). Grade 1 was found in 14 (7%)

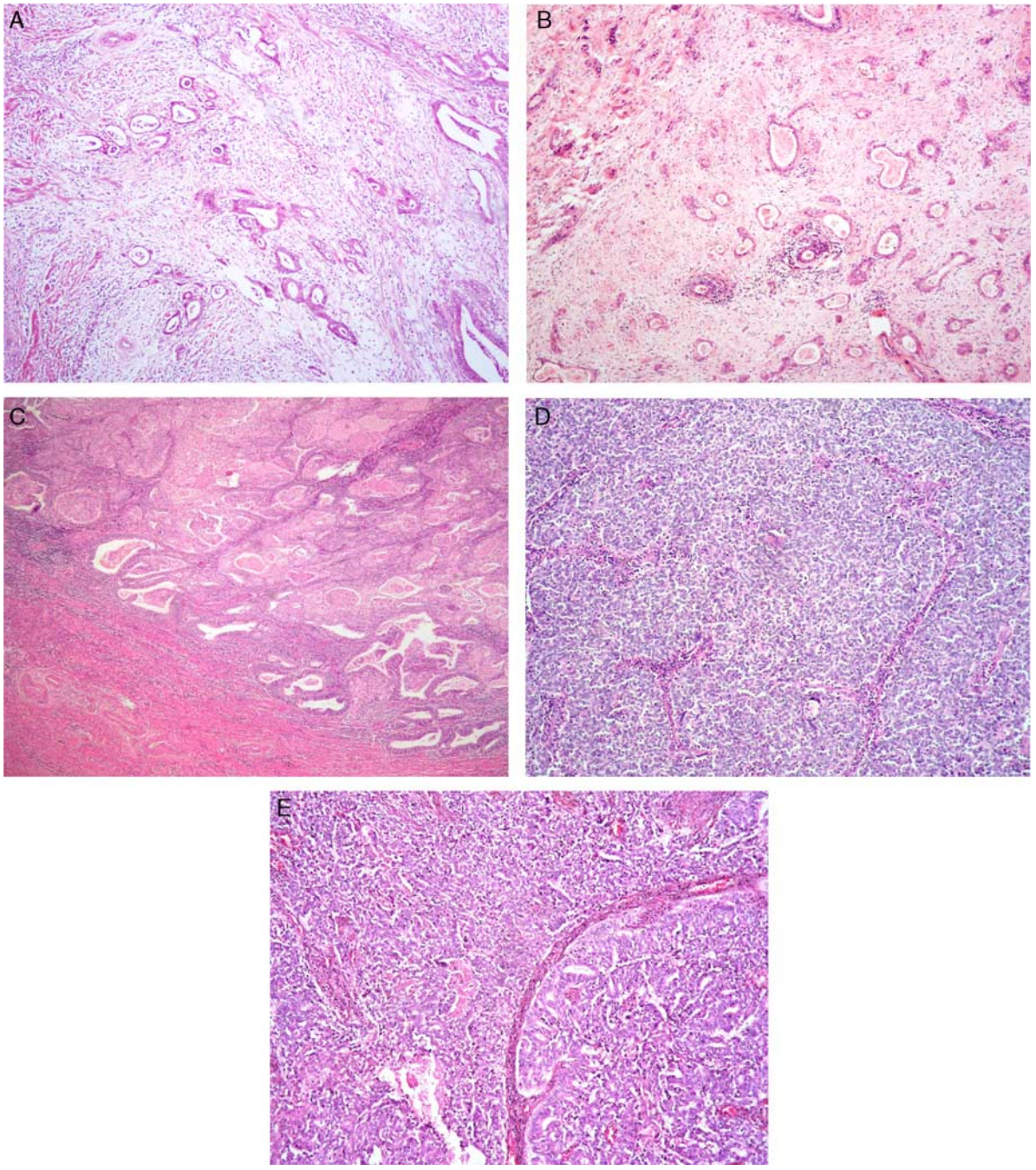

FIG. 1. Growth patterns of invasion in pattern C endocervical adenocarcinoma: diffuse destructive (A and B), confluent (C), and solid (D and E).

tumors; grades 2 and 3 were found in 119 (63%) and 56 (30%) cases, respectively.

The architectural PG were assessed as DD in 32 (17%) patients, CON in 23 (12%), ELD in 27 (14%), SOL in 9 (5%), BLL in 7 (4%), and MP in 7 (4%) patients. A total of 84 (44%) invasive EACs exhibited both DD and CON PG (mixed PG). Mixed tumors were characterized by a varying combination of pure areas of EAC with a DD PG areas and pure areas of EAC with a CON PG and areas in which both morphologic features were mixed, with a gradual or abrupt transition from one tumor type to the other.

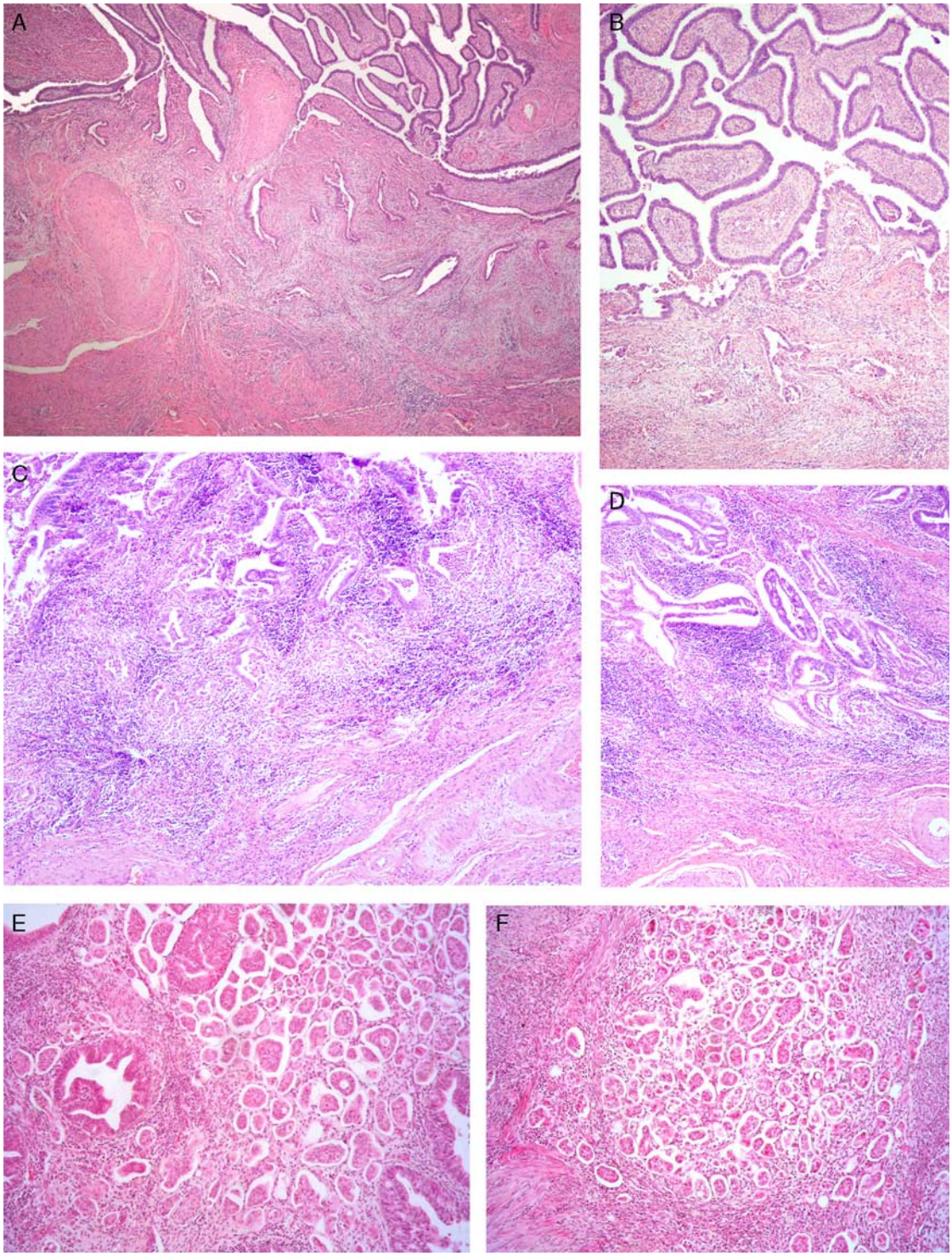

FIG. 2. Growth patterns of invasion in pattern C endocervical adenocarcinoma: extensive linear destructive (A and B), band-like lymphocytic infiltrate (C and D), and micropapillary (E and F).

LVSI was identified in 132 (69.8%) patients. The LVSI was considered low in 21 patients (15.9%), moderate in 72 (54.5%), and high in 39 (29.5 %). Tumor involvement in the LUS was present in 44 (23.2%) cases.

A total of 45 women (23.8%) showed metastatic disease to lymph nodes (LNs): 21 patients with 1 positive LN, 13 with 2, 4 with 3, 2 with 4, 1 with 5, 1 matted, 1 as a retroperitoneal mass, and 2 clinically positive. The size of the metastatic deposits ranged from 1 to 12 mm (mean: 3.5 mm). The follow-up time for surviving patients ranged from 5 to 72 months (median: 49 mo).

Correlation of LNM With Other Clinicopathologic Prognostic Factors

The clinicopathologic factors that associated significantly with LNM are shown in Table 1.

Patients were segregated into 2 groups: those 45 years or younger and those older than 45 years. Patients with LNM were 10 years older than patients without LNM (median ages, 49.8 and 39.6 y, respectively; $P<0.001$). However, we found that tumor grade did not significantly differ between these groups on the basis of age.

The incidence of positive node involvement correlated with the stage of the disease. Therefore, patients with stage IA, IB, II, and III disease showed positive LNs of 11%, 26%, 29%, and 34%, respectively (data not shown).

Tumor Size

There was a significant increase in the presence of LNM as tumor size increased over 3.5 cm ($P<0.001$). Tumor grade was also a significant prognostic factor when positive LNs were found ($P<0.001$).

A higher incidence of nodal metastases (60%, $P<0.001$) was found among those patients with tumor involvement in the LUS. The topographic distribution of the LN with metastases was similar among tumors that involved the LUS when compared with tumors that were located in the upper cervix or only in the bottom cervix. The risk of LNM was significantly correlated with the quantity of LVSI. Among patients with $\geq$20 LVSI, 55.6% had LNM versus 2.2% of patients with 0 to 4 LVSI ($P<0.001$).

Neither depth of stromal invasion nor PI was an independent factor for LNM (data not shown). Within the 38 (20%) polypoid EACs, only 5 (3%) had LNM ($P = 0.032$).

Correlation of Clinicopathologic Factors With Endocervical Carcinomas' Architectural PG

We did not find a statistically significant relationship between the PG invasion and the age of patients (data not shown).

Thirteen of our 189 cases had parametrial involvement. Of these, 5 (38%) had a DD PG, 4 (31%) a mixed (DD + CON) PG, and 4 (31%) a CON PG.

LNM were present among all patients with EACs with a MP PG ($P<0.001$), compared with zero patients with EACs with an ELD PG ($P = 0.002$).

Thirty-nine (29.5%) tumors showed $\geq$20 lymphatic vascular spaces with invasion. Of these, 100% were EACs with MP PG, 39% were EAC with mixed PG, and 34% were EAC with DD PG. The opposite was true for the EAC with an ELD PG, which was enriched in tumors with low LVSI (0–4).

Larger tumor size was found more often in EACs with a mixed (DD and CON) PG ($P<0.001$). Forty-four of the 189 cases (23.2%) were located in the higher portion of the cervical canal or involved the entire cervix as well as the LUS. Those tumors with a mixed (DD and CON) and DD PG were dominant in 20 (45%) and 13 (29.5%) patients, respectively ($P<0.001$).

Tumors with a DD PG had deeper stromal invasion than tumors with a BLL PG (data not shown). Twenty-five of the 27 EACs with an ELD PG and all 7 cases of EACs with a BLL PG were located in the lower cervical canal. The difference in location in the 2 groups was significant ($P<0.001$) (data not shown).

Within the 38 (20%) polypoid EACs, we found 14 (36.8%) tumors to have CON PG, 12 (31.5%) to have mixed (DD + CON), 9 (23.6%) to have DD, and 3 (7.8%) cases to have SOL PG. Of these tumors, only 5 (13%) had LNM ($P = 0.032$). When comparing nonpolypoid with polypoid tumors, no statistical difference in either survival rate or recurrence rate was found.

Finally, comparison between EACs with a SOL PG versus EACs with a BLL PG revealed a statistically significant difference in histologic grade; specifically, 100% of the EACs with a SOL PG were grade 3, whereas 0% of the EACs with a BLL PG ($P<0.001$) were grade 3.

Recurrences

Recurrences were seen in 41 (21.6%) patients (Table 2). Ten patients (24.3%) had vaginal or vulvar recurrence, 14 (34%) had local pelvic recurrence, 7

TABLE 1. *Tumor characteristics in patients with and without lymph node metastases*

	n (%)		
	Patients With LNM (N = 45)	Patients Without LNM (N = 144)	*P*
Tumor size [mean (SD)] (mm)	39.5 (4.6)	31.8 (11.5)	<0.001*
Grade			
G1	0	13 (9)	<0.001†
G2	23 (51.1)	96 (66.7)	
G3	22 (48.9)	35 (24.3)	
LVSI			
0-4	1 (2.2)	76 (53.1)	<0.001†
5-19	19 (42.2)	53 (37.1)	
≥20	25 (55.6)	14 (9.7)	
LUSI			
Yes	27 (60)	17 (11.8)	<0.001‡
No	18 (40)	127 (88.2)	
Polypoid configuration			
Yes	5 (11.1)	33 (22.9)	0.032‡
No	40 (88.9)	111 (77.1)	
Growth patterns of invasion			
Band-like lymphocytic infiltrate			
Yes	1 (2.2)	7 (4.2)	0.54‡
No	44 (97.8)	138 (95.8)	
Extensive linear destructive			
Yes	0	27 (18.8)	0.002‡
No	45 (100)	117 (81.2)	
Confluent			
Yes	8 (17.8)	15 (10.4)	0.18‡
No	37 (82.2)	129 (89.6)	
Solid			
Yes	3 (6.7)	6 (4.2)	0.49‡
No	42 (93.3)	138 (95.8)	
Mixed§			
Yes	16 (35.6)	68 (46.5)	0.19‡
No	29 (64.4)	77 (53.5)	
Diffuse destructive			
Yes	10 (22.2)	22 (15.3)	0.28‡
No	35 (77.8)	122 (84.7)	
Micropapillary pattern			
Yes	7 (15.6)	0	<0.001‡
No	38 (84.4)	144 (100)	

*2-tailed Student *t* test.
‡The χ^2 test.
†The χ^2 lineal by lineal.
§Mixed: diffuse destructive + confluent.
LNM indicates lymph node metastasis; LUSI, lower uterine segment involvement; LVSI, lymphatic vascular space invasion.

(17%) had retroperitoneal recurrence, 5 (12%) had liver recurrence, and 5 (12%) had recurrence in the lungs. Recurrence was not observed in any patient with EAC with either ELD ($P = 0.002$) or BLL PG ($P = 0.004$), whereas 44% of those with EAC with a DD PG and 29% of tumors with a mixed (DD + CON) PG developed recurrent disease.

Patients with LNM at the time of the diagnosis, an LVSI ≥ 20, high-grade tumors, and LUS involvement developed recurrences more often than did patients without those features (Table 2).

There was also an association between tumor FIGO stage and the patient having a recurrence: women with stage II or III disease were more likely to have a recurrence compared with patients with stage I disease ($P = 0.001$). Neither parametrium involvement nor size of metastatic deposits in LNs was an independent prognostic parameter for recurrence ($P = 0.62$).

Overall Survival (OS)

The overall 6-year survival for stage I patients was 92.5%, for stage II patients it was 79.4%, and for stage III patients it was 38.9% ($P < 0.001$) (Fig. 3). The majority of patients with mixed (DD + CON) and DD PG adenocarcinomas presented at advanced stages, II to III (64% and 59%, respectively). In

TABLE 2. *Variables associated with recurrence*

	n (%)		
	Patients With Recurrence (N = 41)	Patients Without Recurrence (N = 148)	*P*
Grade			
G1	0	13 (8.8)	<0.001*
G2	17 (41.5)	102 (68.9)	
G3	24 (58.5)	33 (22.3)	
LVSI			
0-4	11 (26.8)	60 (44.9)	0.029*
5-19	16 (39.0)	56 (38.1)	
≥20	14 (34.1)	25 (17.0)	
LUSI			
Yes	15 (36.6)	29 (19.6)	0.035†
No	26 (63.4)	119 (80.4)	
Growth patterns of invasion			
Band-like lymphocytic infiltrate			
Yes	0	7 (4.7)	0.004†
No	41 (100)	141 (95.3)	
Extensive linear destructive invasion			
Yes	0	27 (18.2)	0.002†
No	41 (100)	121 (81.8)	
Confluent			
Yes	7 (17.1)	16 (10.8)	0.28†
No	34 (82.9)	132 (89.2)	
Solid			
Yes	3 (7.3)	6 (4.1)	0.41†
No	38 (92.7)	142 (95.9)	
Mixed‡			
Yes	18 (43.9)	65 (43.9)	1.00†
No	23 (56.1)	83 (56.1)	
Diffuse destructive			
Yes	11 (26.8)	21 (14.2)	0.063†
No	30 (73.2)	127 (85.8)	
Micropapillary			
Yes	2 (4.9)	6 (3.4)	0.64†
No	39 (96)	172 (96.6)	
LNM			
Yes	18 (43.9)	27 (18.2)	0.001†
No	23 (56.1)	121 (81.8)	

*The χ^2 test.
†The Fisher exact test.
‡Mixed: diffuse destructive + confluent.
LNM indicates lymph node metastasis; LUSI, lower uterine segment involvement; LVSI, lymphatic vascular space invasion.

comparison, the EACs with a band-like lymphocytic PG mostly presented at stage I (81%).

A Cox proportional hazards model with covariates added in the regression was also used to conduct an analysis of EAC by PG. Once again, the mixed (DD + CON) EAC was revealed to be a significant prognostic factor. None of the other EACs studied showed predictive value (Table 3).

Depth of stromal invasion and LUS involvement had a significant influence on outcome; each millimeter raised the risk of dying from disease by 11%. The tumor characteristics associated significantly with OS were LVSI and LUS involvement.

The 6-year OS rate of LN-positive patients with EAC was much lower than those without LNM (60% vs. 97.8%) ($P < 0.001$) (Fig. 4). The OS rates were lower in patients with PI and pelvic LN metastases ($P = 0.003$). However, there was no association between patients without LN metastases and PI (data not shown).

DISCUSSION

A newly proposed pattern-based method (1) has shown that classifying EAC by growth pattern correlates better with LNM than by using DOI. Additional analyses of EAC (2,5,6) stratified by the architectural growth pattern rather than DOI supports separation into 3 distinct groups: patients with pattern A EAC who do not have LNM and/or recurrence; patients with pattern B who rarely present with LNM and/or recurrence; and those patients with

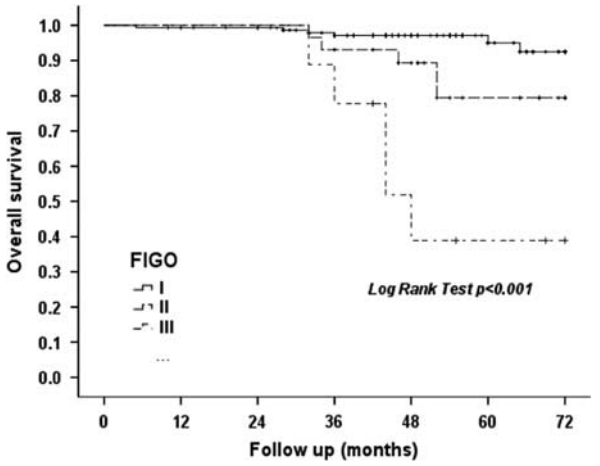

FIG. 3. Six-year overall survival for 189 patients with endocervical adenocarcinoma according to stage of disease.

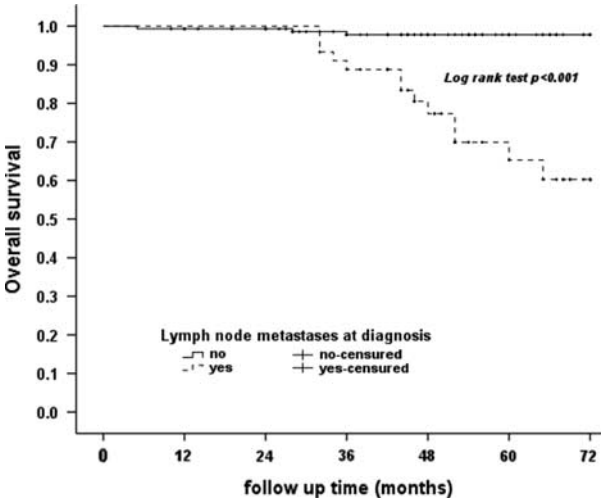

FIG. 4. Overall survival for patients with and without lymph node metastases.

pattern C who are more likely to have pathologic features at the time of radical hysterectomy that might require adjuvant therapy.

Unlike patterns A and B EAC, pattern C EAC can exhibit a variety of PG. On the basis of this study, we found and categorized 6 distinct tumor growth patterns: DD, 32 (17%); CON, 23 (12%); ELD, 27 (14%); SOL, 9 (5%); BLL, 7 (4%); and MP, 7 (4%).

TABLE 3. *Overall survival according to tumor characteristics*

	Overall Survival	
Tumor Characteristics	HR	95% CI
LVSI		
0-4	1	
5-19	2.8	0.57-14
≥20	7.5	1.6-35
Grade		
G1	1	
G2	0.5	0.6-4.3
G3	1.5	0.2-12
LUSI	6	2.2-16
Growth patterns of invasion		
Mixed*	3.5	1.2-10
Diffuse destructive	1.2	0.3-4.3
Solid	0.7	0.08-6.2
Confluent	0.9	0.2-4.3
	0.7	
Band-like lymphocytic infiltrate	0.04	0-2320
Micropapillary pattern	0.04	0-922
Extensive linear destructive	0.03	0-5.8
Polypoid configuration	0.7	0.15-2.9
Depth of invasion per each mm	1.11	1.02-1.2
Horizontal spread per each mm	1.11	1.05-1.17

*Mixed: diffuse destructive + confluent; bivariate analysis by Cox regression.

CI indicates confidence interval; HR, hazard ratio; LUSI, lower uterine segment involvement; LVSI, lymphatic vascular space invasion.

In 44% of cases, a mixed PG (DD + CON) was present.

According to some reports, carcinomas of the cervix have the same prognoses in younger and older patients, whereas other studies have observed decreased survival in women younger than 35 or 40 years of age who have a greater frequency of poorly differentiated tumors (7,8). In this study, patients with LNM were 1 decade older than those without LNM. Most of the patients without LNM were between 20 and 70 years of age (mean: 45), whereas patients with LNM ranged between 40 and 82 years of age (mean: 58). There is no statistically significant relationship between the PG invasion and age of patients.

In patients with stages I-IIA (n = 200) disease, Baalbergen et al (9) found a 5-year survival rate of 91% for patients with negative LNs versus 74.4% for patients with positive LNs. Delgado et al (10) found a disease-free survival of 85.6% at 3 years for patients with negative pelvic LNs versus 74.4% for patients with ≥1 positive LNs. In this study, the 6-year OS rate of LN-positive patients with EAC was much lower than that for patients without LNM (60% vs. 97.8%). In the present study, LNM were present among all patients with EAC with a MP PG ($P < 0.001$) versus none of the patients with EAC with an ELD PG ($P = 0.002$).

The clinical significance of LVSI in cervical adenocarcinoma is not well known, despite the large number of reported studies that deal with this subject (11,12). Chandacham et al (13) reported that

the extent of LVSI to a minimal or extensive degree significantly influenced pelvic node metastases. They found that among 397 patients, 146 (36.8%) had tumors containing LVSI: 82 (20.7%) and 64 (16.1%) had minimal and extensive LVSI, respectively. A study by Roman et al (14) also evaluated the influence of quantity of LVSI on the risk for nodal metastases in women with stage I-IIA disease and found that the risk of pelvic LNM was 54% when >45% of sections with tumor contained LVSI. In the present study, LVSI was found to be predictive of LNM. If LVSI was present, 23.8% of patients had LNM. When LVSI was not present, the chance of LNM was only 3%.

Moreover, in this study, the extent of lymphatic vascular invasion ≥20 (extensive) was noted to be an independent predictor of LNM ($P<0.001$). The highest number of LVSI was found in tumors with MP, mixed (diffused destructive + CON), and DD PG (100%, 39%, and 34%, respectively).

Horn et al (15) evaluated 366 pathologically staged patients with cervical cancer confined to the uterine cervix (pT1B). Those with small tumors (<2.0 cm) showed a significantly lower frequency of pelvic LN involvement when they were compared with patients with a tumor size ranging between 2.1 and 4.0 cm (13.3% vs. 23.4%; $P<0.001$). In our study, there was a significant increase in the presence of LNM as tumor size increased over 3.5 cm ($P<0.001$). Larger tumor size was found more often in EACs with a mixed (DD + CON) PG ($P<0.001$).

Within the 38 (20%) polypoid EACs, we found 14 (36.8%) tumors to have a CON PG, 12 (31.5%) to have mixed (DD + CON), 9 (23.6%) to have DD, and 3 (7.8%) cases to have SOL PG. Of these tumors, only 5 (13%) had LNM ($P = 0.032$). When we compared nonpolypoid with polypoid tumors, we found no statistical difference in survival or recurrence rates.

The extension of EACs into the LUS is rarely encountered (16). In contrast, it is difficult to collect data on this feature as it is not consistently reported. In this study, the risk for LNM was statistically higher for those patients with EAC involvement of the LUS ($P<0.001$). The tumors with mixed (DD + CON) and DD PG demonstrated a strong predilection for LUS involvement ($P<0.001$).

The impact of PI on the survival of patients with stage IB-IIB cervical cancer remains controversial. Ho et al (17) reported that the incidence of PI was 11.2% and that it was not a significant predictor of disease-free survival ($P = 0.110$) or OS ($P = 0.115$). However, Liu et al (18) reported that PI was an independent indicator for disease-free survival ($P = 0.001$) and OS rates ($P = 0.0121$).

In our study, the incidence of PI was 6.8%, and it was not a significant prognostic factor for LNM or recurrence. The OS rates were lower in patients with PI and pelvic LNM ($P = 0.003$). However, there was no association between patients without LN metastases and PI. The tumors that more often involved the parametrium were those with a DD, mixed (DD + CON), and CON PG.

Several publications found the assessment of the depth of stromal invasion (DOI) by EAC to be valuable. In fact, current criteria for staging EAC are based on DOI (4,19). Studies have reported that prognosis worsens when cervical tumor invasion exceeds 7 mm in depth, and this trend worsens at an even faster rate when invasion exceeds 10 mm (20).

In our study, depth of stromal invasion was not an independent factor for LNM. However, it had a significant influence on outcome; each millimeter raised the risk of dying from disease by 11%. Tumors with a DD PG had deeper stromal invasion than did tumors with a BLL PG.

In this study of 189 resected invasive EACs of usual type, we systematically investigated the presence of different PG and demonstrated that these tumors, grouped by PG, show a striking correlation with recurrent disease and OS.

Disease recurrence was not observed in any patient with EAC with ELD PG ($P = 0.002$) or BLL PG ($P = 0.004$), whereas 44% of patients with tumors with a DD PG and 29% of those with tumors with a mixed (DD + CON) PG developed recurrent disease.

In our present study, patients with EAC with a mixed (DD + CON) PG had a significantly worse 6-year OS when compared with patients with EAC with an ELD and BLL PG.

CONCLUSIONS

- Reviewing the pattern C cases, we realized that many of them did not have an aggressive behavior.
- By focusing specifically on LNM, the current study provides evidence that LNM were present in all MP carcinomas.
- The tumors with an aggressive behavior had more extensive destructive invasion with lymphatic vascular invasion than did tumors with less aggressive behavior.
- Tumors with less aggressive behavior should be treated with radical hysterectomy and sentinel LN biopsy.

- This and previous studies (1,2) prove that the current staging system and treatment recommendations need to be reevaluated.

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