Invasive Endocervical Adenocarcinoma

A New Pattern-based Classification System With Important Clinical Significance

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Abstract: A new 3-tier pattern-based system to classify endocervical adenocarcinoma was recently presented. In short, pattern A tumors were characterized by well-demarcated glands frequently forming clusters or groups with relative lobular architecture. Pattern B tumors demonstrated localized destructive invasion defined as desmoplastic stroma surrounding glands with irregular and/or ill-defined borders or incomplete glands and associated tumor cells (individual or small clusters) within the stroma. Tumors with pattern C showed diffusely infiltrative glands with associated extensive desmoplastic response. In total, 352 cases (all FIGO stages) from 12 institutions were identified. Mean patient age was 45 years (range, 20 to 83 y). Forty-nine (13.9%) cases demonstrated lymph nodes (LNs) with metastatic endocervical carcinoma. Using this new system, 73 patients (20.7%) were identified with pattern A tumors (all stage I); none had LN metastases and/or recurrences. Ninety patients (25.6%) were identified with pattern B tumors (all stage I); only 4 (4.4%) had LN metastases; 1 had vaginal recurrence. The 189 (53.7%) remaining patients had pattern C tumors; 45 (23.8%) of them had LN metastases. This new classification system demonstrated 20.7% of patients (pattern A) with negative LNs, and patients with pattern A tumors can be spared of lymphadenectomy. Patients with pattern B tumors rarely presented with metastatic LNs, and sentinel LN examination could potentially identify these patients. Aggressive treatment is justified in patients with pattern C tumors.

Key Words: invasive endocervical adenocarcinoma, new pattern-based classification system, lymph node metastasis

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Currently, the parameters that determine stage and prognosis of the patients with endocervical adenocarcinoma include the size and depth of invasion (DOI) of the tumor, irrespective of the pathologic features of the tumor itself.[1,2] The same criteria apply to both squamous and glandular lesions; however, these represent different tumor types. Accurately assessing DOI in some tumors can be quite challenging. In addition, tumors with >3 mm invasion undergo lymph node (LN) dissection. However, most patients do not show evidence of LN metastasis.[3–11] Moreover, these patients, who are often young, can experience significant morbidity with LN dissection.[12,13]

With the objective to identify better predictor factors of endocervical adenocarcinoma, recently, we studied and presented a new pattern-based system to classify endocervical adenocarcinoma.[14] This new classification stratifies patients into 3 distinct groups on the basis of the morphologic features of the invasive carcinoma and is predictive of the risk for LN metastasis (Table 1).

Patients with pattern A endocervical adenocarcinoma do not develop LN metastasis, and therefore avoiding LN dissection in these patients should be considered. Patients with pattern B rarely show metastasis to LNs—that is, only if there is lymphovascular invasion (LVI) and/or recurrence—whereas those with pattern C require aggressive treatment, as 23.3% of patients with this pattern have LN metastasis.

In this paper, we describe in more detail the morphology of patterns B and C and how to accurately classify tumors with destructive invasion. In addition, we updated follow-up of the patients as well as clinicopathologic data.

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TABLE 1. New Classification System for Invasive Endocervical Adenocarcinomas Based on Pattern of Invasion (Silva System)

	Silva System
Pattern A	Well-demarcated glands with rounded contours, frequently forming groups
	No destructive stromal invasion
	No single cells or cell detachment
	No LVI
	Complex intraglandular growth acceptable, ie, cribriform, papillae
	Lack of solid growth, ie, architecture well-moderately differentiated
	Depth of the tumor or relationship to large cervical vessels not relevant
Pattern B	Localized (limited, early) destructive stromal invasion arising from pattern A glands (well-demarcated glands)
	Individual or small groups of tumor cells, separated from the rounded gland, often in a focally desmoplastic or inflamed stroma
	Foci may be single, multiple, or linear at base of tumor
	LVI ±
	Lack of solid growth, ie, architecturally well-moderately differentiated
Pattern C	Diffuse destructive stromal invasion, characterized by: Diffusely infiltrative glands, with associated extensive desmoplastic response
	Glands often angulated or with a canalicular pattern, with interspersed open glands
	Confluent growth filling a ×4 field (5 mm): glands, papillae (stroma only within papillae), or mucin lakes
	Solid, poorly differentiated component (architecturally high grade); nuclear grade is disregarded
	LVI ±

MATERIALS AND METHODS

Data on case selection and analysis have been previously published.[14] Briefly, after IRB approvals were obtained, cases diagnosed and treated as invasive endocervical adenocarcinoma of usual type from 12 national and international institutions from the above-mentioned authors were retrieved and studied.

Selection criteria included: (1) diagnosis of invasive endocervical adenocarcinoma, usual type (defined as the most common form of endocervical adenocarcinoma, with relative mucin depletion by the most recent World Health Organization classification[15]); (2) complete tumor resection by cone/loop electrosurgical excision procedure, trachelectomy, and/or hysterectomy and tumor entirely submitted for microscopic examination; (3) lymphadenectomy with >1 LN available for evaluation or clinical/radiologic evidence of metastatic LNs. Patients with other nonusual tumor types of endocervical adenocarcinoma (adenosquamous, mucinous gastric/intestinal, adenoma malignum, serous, clear cell, and endometrioid), patients with biopsies only, and/or patients with <2 resected LNs were excluded.

Members of the participating institutions convened in 3 consensus meetings at Cedar-Sinai Medical Center in Los Angeles, CA. All available slides were reviewed by the group utilizing a multiheaded microscope, and cases were further classified by consensus according to the newly developed system (Silva system of endocervical adenocarcinoma) on the basis of "pattern of invasion" as A, B, or C (Table 1; Fig. 1).

Pattern A cases were characterized by well-demarcated glands frequently forming clusters or groups and sometimes showing relatively well-preserved lobular architecture. The neoplastic glands demonstrated a pushing, rather than a destructive (or tentacular), pattern of invasion. Most pattern A cases extended below the level of benign endocervical glands. Complex neoplastic glands with cribriform morphology or papillary intraglandular growth were also seen. LVI is not present in pattern A tumors. Pattern B tumors contain localized destructive invasion, defined as desmoplastic stroma, frequently including inflammatory infiltrate surrounding glands with irregular and/or ill-defined borders or incomplete glands and associated tumor cells in the stroma, as individual or small clusters of tumor cells separated from the pattern A gland. Tumors with pattern C include 3 different architectural features: (1) Diffusely infiltrative glands, with associated extensive desmoplastic response, glands often with angulated contours, and interspersed incomplete glands or glands open to the stroma; (2) Confluent growth filling a ×4 field (5 mm) composed of glands with intraglandular papillary structures (exophytic papillary features are not included in this pattern); extensive mucin lakes with tumor cells were also included in this pattern; (3) Solid and/or poorly differentiated component (architecturally high grade). Cases with mixed patterns were classified on the basis of the worst areas (eg, cases with pattern B and focal pattern C, classified as pattern C). In the second meeting, emphasis was placed on better defining, describing, and recognizing endocervical adenocarcinomas with pattern B or C with LN metastasis.

Data collected and analyzed included: patient age, tumor size, horizontal spread, DOI, tumor thickness, LVI, and LN metastases. The data were summarized using descriptive statistics with Microsoft Excel (eg, averages, frequencies, percentages). Multiple comparison procedures using the post hoc Tukey-Kramer method (Tukey HSD) and the Bonferroni-Dunn test after analysis of variance were performed on IBM SPSS 22.0.

RESULTS

Clinical data were previously reported and are summarized in Table 2.[14] The study included 352 patients with the diagnosis of invasive endocervical adenocarcinoma who met the selection criteria. Cases were classified into 3 patterns.

Pattern A

Approximately, 1 in 5 patients with invasive adenocarcinoma contained exclusively pattern A features (73 cases; 20.7%). In some of these cases, there was deep stromal invasion with involvement of up to a depth of 10 mm; however, destructive-type invasion was absent. All tumors were stage I. Pattern A cases were characterized by well-demarcated glands, single but more frequently forming clusters as previously described in the

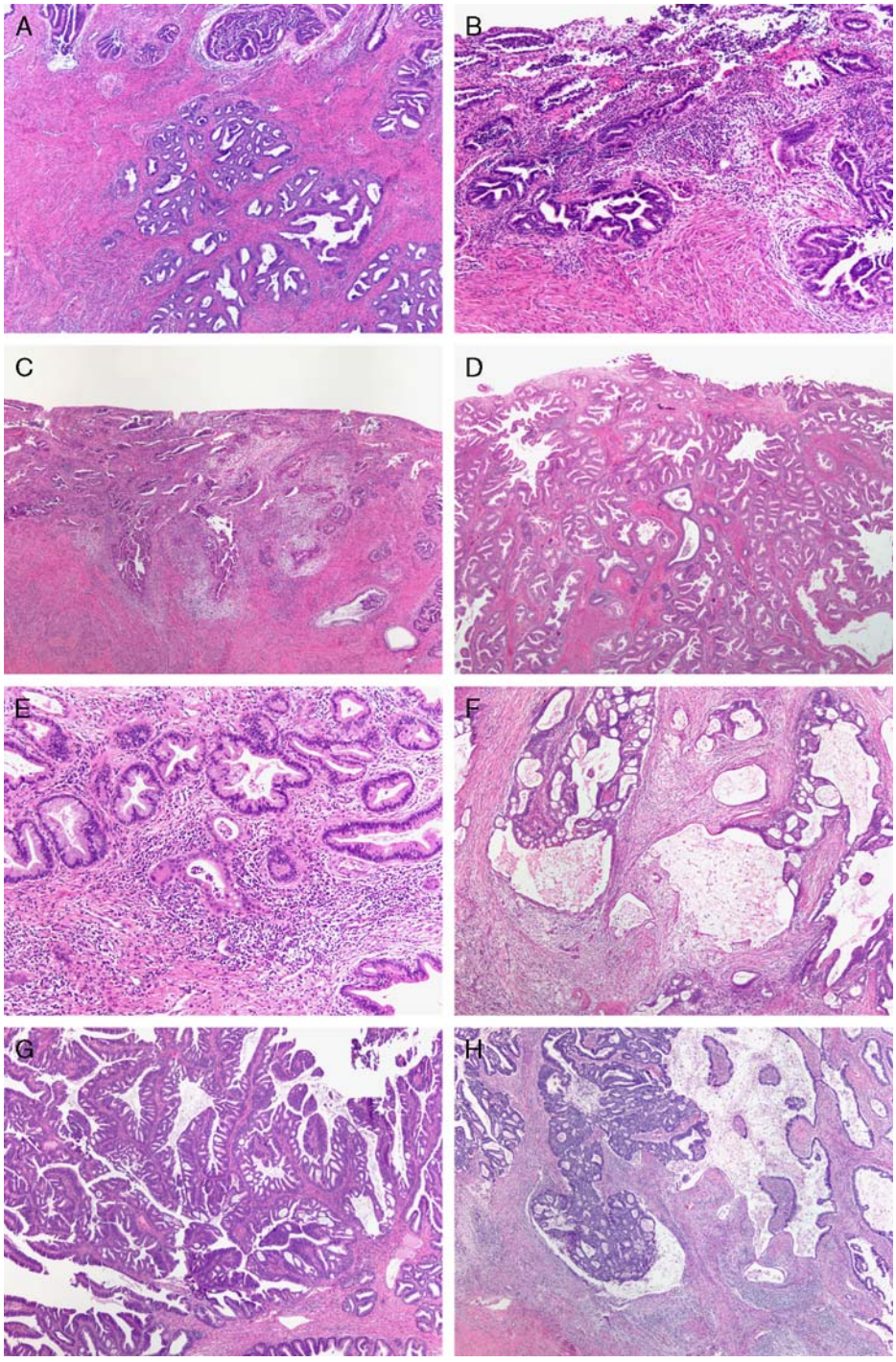

FIGURE 1. A, Invasive well-differentiated endocervical adenocarcinoma, predominantly pattern A with questionable desmoplasia in the superficial aspect of the tumor (pattern B), whereas the deep most invasive component (>5 mm DOI) elicits no desmoplasia. B, Superficial well-differentiated endocervical adenocarcinoma with desmoplasia, glands with irregular contours and LVI (pattern B) associated with well-demarcated glands (pattern A). C, Superficially invasive endocervical adenocarcinoma (1 mm DOI) with widespread desmoplasia and irregular gland contours corresponding to pattern C. D, Invasive well-differentiated endocervical adenocarcinoma corresponding to pattern A. E, Irregular contoured gland with desmoplasia (pattern B) associated with well-delimitated glands (pattern A). F, Pattern C with diffuse destructive invasion. G, Cribriform and exophytic component in well-differentiated adenocarcinoma with well-demarcated tumor/stromal interface corresponding to pattern A. H, Invasive carcinoma with cribriform pattern but diffuse desmoplastic stroma as well as irregular and angulated glands, corresponding to pattern C. A–H, hematoxylin and eosin.

TABLE 2. Outcome Data Comparing the Standard Method of Tumor Evaluation (DOI) Versus the Newly Proposed Pattern-based System

	Patients (n [%])	Patients With Pos LNs (n [%])	Total LNs	#Pos LNs (%)	Stage I (n [%])	Stage II-IV (n [%])
Standard	352	49 (14)	6506	83 (1)	320 (91)	32 (9)
Pattern A	73 (20.7)	0	1333	0	73 (100)	0
Pattern B	90 (25.6)	4 (4.4)	1750	5 (0.2)	90 (100)	0
Pattern C	189 (53.7)	45 (24)	3423	76 (1.7)	157 (83)	32 (17)

Pos indicates positive.

Materials and Methods section. Destructive stromal invasion composed of glands with irregular and/or ill-defined borders, incomplete glands, or desmoplastic stroma with associated tumor cells was not seen in these cases. None of the cases had LVI. Over 1300 LNs were resected in patients with pattern A invasive adenocarcinoma, and every LN was negative for metastatic adenocarcinoma (range, 2 to 78 resected LNs per patient; mean 20.5; total 1333). Follow-up in 71 patients yielded no recurrences, and all patients were alive and well at last follow-up (range, 6 to 252 mo; mean 50.1 mo; median 44 mo).

The remaining cases included in the study (pattern B and C tumors) revealed a pattern of invasion that did not fulfill criteria for pattern A. These 279 patients showed a pattern of destructive stromal involvement. Depth of stroma invasion varied from minimal (0.2 mm) to very extensive (27 mm). One hundred and forty-one (50.5%) of these cases showed LVI, and 49 (17.6%) patients had LN metastasis. However, if cases were separated into those with minimal destructive invasion arising from well-demarcated glands (pattern B) and those with obvious and extensive destructive invasion (pattern C), most cases with LN metastasis corresponded to pattern C.

Pattern B

Ninety patients (25.6%) presented with localized destructive invasion arising from well-demarcated neoplastic glands as described in the Materials and Methods section. Tumors demonstrated localized destructive invasion associated with pattern A–type glands. Cases with destructive stromal invasion without association with or not emanating from a gland were classified as pattern C tumors. Cases with any poorly differentiated carcinoma or solid component, or confluent architecture with intraglandular papillary features or abundant extracellular mucin comprising an area larger than one $\times 4$ field, were also classified as pattern C.

Using these rules, all patients had clinical stage I pattern B endocervical carcinoma. Classically determined DOI ranged from minimal to very extensive (0.2 to 27 mm; mean 9.1 mm). Twenty-four cases (26.6%) demonstrated LVI. Only 4 (4.4%) patients had evidence of metastatic adenocarcinoma in pelvic LNs, and all 4 patients had LVI. Three patients had only a single positive LN, and 1 patient had 2 positive LNs. A total of 1750 LNs were resected (range, 4 to 60 resected LNs per patient, mean 22.1), with only 5 positive LNs overall. Follow-up information in this group was available in 83 patients and ranged from 6 to 392.5 months (mean, 56.3 mo; median 42 mo). Only 1 (1.2%) patient recurred, and none died of disease. The only recurrence was in the vagina, 8 months after hysterectomy, in a patient with 60 resected negative LNs and no evidence of LVI. The patient was alive with no evidence of disease (NED) 49 months after surgery. All 4 patients with metastatic LNs had no recurrence at last follow-up. Two received chemotherapy and radiation treatment and had NED 22 and 54 months after surgery, respectively; however, the remaining 2 did not undergo treatment and also had NED at 56 and 60 months, respectively.

Pattern C

Diffuse destructive invasive endocervical adenocarcinoma was diagnosed in the remaining 189 patients (53.7%) corresponding to pattern C. The majority of these patients, 157 (83%), had stage I tumor, whereas the remainder 32 (17%) had stage II or higher stage tumors. DOI ranged from minimal to very extensive (0.3 to 20 mm; mean 9.1 mm). LVI was present in 117 (61.9%) cases. Forty-five patients (23.8%) showed metastasis to LNs: 21 patients with 1 positive LN, 13 with 2, 4 with 3, 2 with 4, 1 with 5, 1 with matted (nonenumerated) LNs, 1 with an LN as a periaortic mass, and 2 clinically positive LNs. There were 73 pathology-proven positive LNs of a total of 3423. Follow-up time (available in 179 women) ranged from 3 to 258 months (mean 56 mo; median 39 mo).

Recurrences were seen in 41 (21.7%) patients; 10 (5.2%) patients had vaginal or vulvar recurrence, and 31 (16.4%) patients had local pelvic or distant recurrence.

Twenty-eight patients had positive LNs but did not experience recurrence. Only 1 died of disease 27 months after advanced-stage endocervical adenocarcinoma, whereas the remaining had NED after an average follow-up of 52 months (range, 3 to 121 mo). Twenty-three of them received additional chemotherapy, radiation, or in many cases a combination treatment.

Patients with negative LNs had NED at last follow-up, including patients with or without evidence of LVI.

Statistical analysis revealed no difference in patient age between the 3 groups. Tumors in the pattern B group had statistically more extensive horizontal spread ($P < 0.002$) than pattern A tumors. Tumors in the pattern C group were larger ($P < 0.0001$), had deeper invasion (tumor thickness $P < 0.0001$), and demonstrated a higher frequency of LN metastasis ($P < 0.0001$) than tumors

classified as pattern A. Tumors in the pattern C group were larger ($P < 0.0001$), had more extensive horizontal spread ($P < 0.0001$), had deeper invasion (tumor thickness $P < 0.0001$ or DOI $P < 0.0001$), and demonstrated LVI ($P < 0.0001$) and LN metastases ($P < 0.001$) more frequently than tumors with pattern B.

DISCUSSION

Additional analysis of endocervical adenocarcinoma cases stratified by the architectural pattern rather than DOI supports separation into 3 distinct groups: one group of tumors that do not have LN metastasis and do not recur (pattern A), another group that includes the most aggressive cases, evidenced by LN metastasis (always accompanied by LVI), recurrence, and spread to local and distant sites (pattern C), and a third intermediate group (pattern B) with rare instances of LN metastasis, which was always accompanied by LVI, and exceedingly rare recurrence but with clinical stage I disease. These patients can also benefit from different treatment modalities on the basis of this pattern stratification. Patients with tumors exhibiting pattern A could be observed without additional treatment, and LN dissection could be avoided. Patients with pattern B tumors could undergo selected LN dissection, in particular sentinel LN sampling, as patients had 1 or at most 2 LNs with metastasis (all patients with metastatic disease had also LVI). The necessity of additional treatment including chemotherapy or radiation needs to be investigated but might not be indicated in patients with negative LNs and lacking evidence of LVI. In contrast, patients with pattern C tumors need extensive LN dissection, and additional treatment might be justified on the basis of stage or if clinically indicated.

As mentioned, current criteria for staging endocervical adenocarcinoma are based on DOI, with a DOI of 3 mm being the cutoff to avoid LN dissection. Most patients do not show evidence of LN metastasis[3–11] but can experience significant morbidity after LN dissection.[12,13] Studies have reported cases with < 3 mm invasion that had LN metastasis, and, although rare, it provides additional evidence that the current staging system applied to endocervical adenocarcinoma is imperfect. In our study, 2 of 4 pattern B cases and 2 of 45 pattern C cases with LN metastasis had < 3 mm invasion; however, all 4 cases had LVI, suggesting that the latter is probably a better predictor of LN status than DOI alone.

The current staging system for cervical carcinoma does not take into consideration the presence of LVI, a parameter known to be associated with LN metastasis not only in the gynecologic tract but throughout other organ systems.[2] Tumor architecture or pattern is not included in the staging, in a belief that all tumors, irrespective of their morphologic features, will behave similarly according to stage. With these inadequacies of the staging system and unnecessary LN dissection in many cases of endocervical adenocarcinoma, a new concept for stratifying tumors on the basis of pattern, rather than depth, of invasion began to be forged. LVI should also be included, and perhaps, in the future, DOI will help further stratify pattern C cases into the most aggressive ones versus tumors with less potential for metastatic spread or recurrence.

This new method stratifies tumors into 3 different patterns of invasion. Tumors with pattern A are characterized by well-demarcated neoplastic glands frequently forming groups and sometimes showing relatively well-preserved lobular architecture. The neoplastic glands demonstrate a pushing, rather than a destructive, pattern of invasion; however, they can extend deep into the cervical wall. Complex glands with cribriform morphology or papillary intraglandular growth can be seen and do not influence behavior. Pattern A should not be diagnosed in the presence of any desmoplastic reaction, isolated invasive cells, high-grade cytologic features, solid architecture, or confluent papillary pattern (more than one $\times 4$ field) that involves the cervical wall. After determination of the low-power pattern of invasion, careful examination of the glands at medium to high magnification should be performed to exclude small groups of cells with destructive stromal invasion arising from well-demarcated (pattern A) glands. At first review of the cases with pattern A, none had LVI, and the absence of LVI was incorporated in the definition of pattern A. Tumors with pushing invasion, but with evidence of LVI, may have unsampled areas of destructive stromal invasion, and deeper sections might help to demonstrate them. A caveat is that the entire tumor needs to be submitted to rule out a more aggressive pattern. Applying these criteria, pattern A cases represented 20% of the overall cases, had no evidence of LVI, LN metastasis, or recurrence, and all patients were alive and had NED at last follow-up.

It is important to note that all cases included had a diagnosis of invasive adenocarcinoma at its original institution, and all patients underwent LN dissection with sampling of at least 2 LNs. We recognized that some of these cases might be classified as adenocarcinoma in situ by others; however, unfortunately, a clear distinction of invasive from adenocarcinoma in situ is not possible in up to 20% of cases.[16,17] Moreover, some of the cases in this study classified as pattern A had large grossly visible and deep tumors that would not have been considered as in situ lesions. This new system makes that distinction in difficult cases irrelevant, as patients would not be unnecessarily treated, would not experience added morbidity, and will have an excellent prognosis. Another benefit of the system is that if patients had cone/loop electrosurgical excision procedure with pure pattern A and if the tumor was entirely submitted with negative margins, the patient might also be spared a hysterectomy.

Destructive-type invasion was not identified in any case with pattern A and, if present, should prompt classification of the tumor as pattern B or C (Table 3). Significant inflammation was also not a predominant feature; however, any focus with inflammation or loose stroma, a few angulated or open glands, or glands with more abundant eosinophilic cytoplasm needs to be examined at high power to determine whether there are small groups of individual tumor cells within the stroma, separated from the type A glandular pattern.

TABLE 3. Comparison of Histologic Features Between Patterns A and C

	Pattern A	Pattern C
Diffuse desmoplasia	No	Yes
Gland contours	Round	Angulated
Interspersed open glands*	No	Yes
Cluster or groups of glands	Yes	No
Canalicular pattern†	No	Yes

*Open glands (incomplete glandular structures) describe glands with a discontinuous contour showing a break opening to the stroma, often associated with loosened stroma and/or inflammatory cells.

†Canalicular pattern means labyrinthine, interconnected glands.

Pattern B is characterized by localized destructive stromal invasion mostly arising from neoplastic glands with pattern A–like configuration with or without LVI. Only 4 of 90 pattern B cases, < 5%, had LN metastasis, and all 4 also had LVI. All patients had clinical stage I tumors, and only 1 patient experienced a vaginal recurrence that might be contamination related, similar to what has been proposed as the mechanism for vaginal recurrence in endometrial adenocarcinoma.[18]

Pattern C endocervical adenocarcinomas are by far the most aggressive and are defined by extensive desmoplastic reaction and destructive invasion. Over 15% of patients presented with advanced stage. Sixty percent had evidence of LVI, and almost 1 in 4 had metastatic LNs. Recurrences were demonstrated in > 21% of patients. Aggressive treatment is warranted for these patients.

In conclusion, the new system better stratifies one fifth of invasive endocervical adenocarcinomas into pattern A tumors, which do not require additional treatment. Another 25% of patients, who present with clinical stage I disease, will rarely have LN metastasis (only if there is LVI) and will rarely recur. Sentinel LN dissection might be beneficial in avoiding unnecessary morbidity of extensive LN dissection in these patients. The remaining patients need early and aggressive LN dissection and staging; however, a subset with no LVI appears to behave less aggressively. Additional studies with new cases, evaluating the reproducibility of the system among other pathologists, a new staging system, and treatment proposal are in progress.

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