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New Pattern-Based Personalized Risk Stratification for Endocervical Adenocarcinoma with Important Clinical Implications and Surgical Outcome

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Abstract

We present a recently introduced three tier pattern-based histopathologic system to stratify endocervical adenocarcinoma (EAC) that better correlates with lymph node (LN) metastases than FIGO staging alone, and has the advantage of safely predicting node-negative disease in a large proportion of EAC patients. The system consists of stratifying EAC into one of three patterns: pattern A tumors characterized by well-demarcated glands frequently forming clusters or groups with relative lobular architecture and lacking destructive stromal invasion or lymphvascular invasion (LVI), pattern B tumors demonstrating localized destructive invasion (small clusters or individual tumor cells within desmoplastic stroma often arising from pattern A glands), and pattern C tumors with diffusely infiltrative glands and associated desmoplastic response. Three hundred and fifty-two cases were included; mean follow-up 52.8 months. Seventy-three patients (21%) had pattern A tumors; all were stage I and there were no LN metastases or recurrences. Pattern B was seen in 90 tumors (26%); all were stage I and LVI was seen in 24 cases (26.6%). Nodal disease was found in only 4 (4.4%) pattern B tumors (one IA2, two IB1, one IB not further specified (NOS)), each of which showed LVI. Pattern C was found in 189 cases (54%), 117 had LVI (61.9%) and 17% were stage II or greater. Forty-five (23.8%) patients showed LN metastases (one IA1, 14 IB1, 5 IB2, 5 IB NOS, 11 II, 5 III and 4 IV) and recurrences were recorded in 41 (21.7%) patients. This new risk stratification system identifies a subset of stage I patients with essentially no risk of nodal disease, suggesting that patients with pattern A tumors can be spared

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lymphadenectomy. Patients with pattern B tumors rarely present with LN metastases, and sentinel LN examination could potentially identify these patients. Surgical treatment with nodal resection is justified in patients with pattern C tumors.

Key words of phrases

endocervical adenocarcinoma; invasive carcinoma; pattern-based; risk stratification; classification system; lymph node metastasis

Introduction

We recently reported on a new classification system that stratifies endocervical adenocarcinoma (EAC) by the morphologic pattern of invasion into three categories. This new system better predicts compared to FIGO stage, for the presence of lymph node (LN) metastasis as well as clinical behavior in patients with EAC [1, 2]. A subsequent study from an independent group indicated the system's good reproducibility [3].

Staging cervical cancer is based on a combination of clinical and pathologic evaluation when using the International Federation of Gynecology and Obstetrics (FIGO) staging system [4]. Same criteria apply to both squamous and glandular lesions; however, these represent different tumor types; cervical cancer is not just one disease [5]. When an organ confined tumor is visible or palpable on examination, it is staged IB. When a tumor is not clinically visible, pathologists use the depth of invasion (DOI) of the tumor to determine its stage [4, 6]. The accurate pathologic measurement of DOI in some tumors can be quite challenging [7,8]. By definition, DOI is calculated from the basement membrane of the epithelium from which the invasive tumor arose [6]. This is easier for squamous carcinomas, since the overlying squamous epithelium is flat but endocervical glands normally extend into the superficial cervical stroma, vary in size and shape as well as normal extension and location in the underlying stroma [7,8]. The lack of a specific point of reference could determine a difference of several mm when calculating the depth of invasion; polypoid or ulcerated tumors could also affect DOI. Given the architectural complexity of the endocervical glands that are formed by a deeply invaginated epithelium with secondary branching and tunnel formation, the accurate measurement of depth of invasion is often problematic in early EAC [7,8].

While pathologists may struggle to determine an accurate DOI, this measurement has significant implications since it is the basis to stage and treat non-visible lesions; according to current NCCN guidelines only patients with EAC Stage IA1 (DOI 3 mm or less), without LVI can be spared pelvic LN dissection [9]. In addition, recently established NCCN guidelines following the Society of Gynecologic Oncology guidelines, recommend that tumors with less than 3 mm DOI but with LVI should undergo the same procedures as higher stage tumors including radical hysterectomy (radical trachelectomy in fertility sparing procedures) in addition to pelvic LN dissection and possible paraaortic LN sampling [9–12]. However, the literature reports few patients with early stage tumors and evidence of LN metastasis; less than 1% of patients with stage IA1 tumors had LN metastasis; while stage

IA2 tumors revealed LN metastasis in about 2% of the cases [13–23]. This low yield is troubling since there can be significant morbidity after LN dissection [23–25].

Our objective is to present this recently introduced histopathologic pattern-based risk stratification system, highlighting that it better predicts nodal status and outcome than FIGO staging, and would allow for personalized selection of patients who can safely undergo conservative treatment.

Materials and methods

After Institutional Review Board approvals were obtained, cases diagnosed and treated as invasive endocervical adenocarcinoma of usual type were retrieved and studied from 12 national and international institutions.

Selection criteria included: 1) tumors diagnosed as invasive endocervical adenocarcinoma, usual type (as defined by most recent World Health Organization classification [26]); 2) tumor resected by cone/LEEP procedure, trachelectomy and/or hysterectomy with tumor slides available for microscopic examination; and 3) lymphadenectomy with more than one lymph node or clinical/radiological evidence of metastatic nodal disease.

Members of the participating institutions convened in three consensus meetings at Cedar-Sinai Medical center in Los Angeles, California. A presentation of the histopathologic pattern-based risk stratification system started the initial meeting and available slides were then reviewed by the group utilizing a multiheaded microscope. Cases were classified by consensus according to the newly developed system (Silva system of endocervical adenocarcinoma) based on “pattern of invasion” as A, B, or C (Table 1; Figure 1).

EAC with pattern A is characterized by well-demarcated glands with rounded contours, frequently forming clusters or groups and sometimes showing relatively well preserved lobular architecture. Tumor glands demonstrate a pushing or expansile pattern of invasion. Most pattern A cases extend below the level of benign endocervical glands, with the neoplastic glands often adjacent to thick walled blood vessels, an established criteria for invasion [27]. Complex intraglandular pattern including cribriform morphology or papillary intraglandular growth can also be seen in gland profiles exceeding the size of normal glands. The presence of LVI excludes a tumor from pattern A.

Pattern B tumors show early or limited, localized destructive invasion, defined as individual or small clusters of tumor cells or fragments of glands set in a desmoplastic, edematous, or inflamed stroma adjacent to an intact gland. The typical appearance is that of limited destructive invasion arising from glands with a pattern A appearance. LVI may be seen in pattern B tumors.

Pattern C tumors have diffusely infiltrative glands, with associated extensive, diffuse desmoplastic response; the glands show a destructive (or tentacular) pattern with angulated and often incomplete glands open to the stroma. Additional criteria for pattern C tumors include confluent growth of cribriform or papillary structures within stroma, filling a low power microscopic field (4x field; 5 mm), and/or extensive mucin lakes with tumor cells.

Solid and/or poorly differentiated component (architecturally high grade) is also included in pattern C. Cases with mixed patterns are classified based on the worst tumor pattern areas.

Data analyzed included: tumor size, horizontal spread, DOI, LVI, and LN metastasis. Data collected were summarized using descriptive statistics with Microsoft Excel (e.g., averages, frequencies, percentages). Data is normally distributed. All statistical analyses performed in IBM -SPSS 22.0 using Levene statistics of homogeneity of variance and Q-Q plots of each variable. Normality rechecked with Kurtosis measurement in IBM-SPSS 23.0.

Results

Clinical data previously reported is summarized in Tables 2 [1, 2]. Overall, 352 patients diagnosed with invasive EAC were included in this study.

Seventy-three cases (20.7%) contained morphologic features that corresponded to pattern A. All tumors were stage I, including 14 IA1, 8 IA2, 46 IB1, 1 IB2 and 4 IB not further specified. Tumor size ranged from 1.8 mm to 42 mm (mean 13.4 mm). DOI ranged from 0.1 mm to 10 mm (mean 3.8 mm). None of the cases had LVI. LNs were resected in all cases (total 1333 LNs; range 2 to 78 resected LNs per patient; mean 20.5 LNs); all were negative for metastatic carcinoma. Follow-up was available in 71 patients (range 6 to 252 months; mean 50.1 months; median 44 months). Recurrences were not observed and all patients were alive and well at last follow-up.

Ninety patients (25.6%) had tumors with morphologic features that corresponded to pattern B. All patients had FIGO stage I tumors, including 7 IA1, 8 IA2, 51 IB1, 4 IB2 and 20 IB not further specified. Tumor size ranged from 2 mm to 65 mm (mean 17 mm). DOI ranged from 0.2 to 27 mm (mean 9.1 mm). Twenty-four cases (26.6%) demonstrated LVI. LNs resected totaled 1750 (range 4 to 60 resected LNs per patient, mean 22.1). Only 4 (4.4%) patients demonstrated metastatic adenocarcinoma in pelvic LNs, and all 4 of the primary tumors had LVI. There were 5 metastatic LNs in total. Follow-up was available in 83 patients and ranged from 6 month to 392.5 months (mean, 56.3; median 42 months). All four patients with positive LNs had no recurrence at last follow-up; two patients received chemotherapy and radiation treatment and had no evidence of disease (NED) 22 and 54 months after surgery, respectively. The other two patients did not receive adjuvant therapy, but also were NED at 56 and 60 months, respectively. Only 1 (1.2%) patient suffered recurrence in the vagina, 8 months after hysterectomy; this patient had 60 resected negative LNs, no evidence of LVI in the tumor, and was alive and well 49 months after resection of the recurrence. No patient with pattern B tumors died of disease (DOD).

The remaining 189 patients (53.7%) had tumors with morphologic features of pattern C. Most of these patients, 157 (83%), had stage I tumor (4 IA1, 10 IA2, 107 IB1, 12 IB2 and 24 IB not further specified), while 32 (16.9%) had stage II or higher stage tumors (21 II, 6 III and 5 IV). Tumor size ranged from 1.5 mm to 70 mm (mean 26.7 mm). DOI ranged from 0.3 to 20 mm (mean 9.1 mm). LVI was present in 117 (61.9%) cases. LN metastases were recorded in 45 (23.8%) patients; 43 with metastatic carcinoma documented in surgically resected LNs, and 2 patients with clinically positive LNs. At least 73 LNs had metastatic

carcinoma out of 3423 resected LNs, with only a single positive node in 21 patients. Follow-up was available in 179 patients and ranged from 3 to 258 months (mean 56 months, median 39 months). Recurrences were recorded in 41 (21.5%) patients; 10 (5.2%) with vaginal or vulvar recurrence and 31 (16.4%) with pelvic or distant recurrence. At last follow-up, 18 patients were DOD at 9 to 107 months (mean 45.1 months, medium 39 months). Table 3 summarizes data on pattern C tumors in patients with metastatic lymph nodes at presentation and status at last follow-up including tumors with recurrence; while Table 4 shows recurrences by stage and pattern and Table 5 shows patients with metastatic LN by stage and pattern.

Statistical analysis revealed that pattern B tumors had statistically more extensive horizontal spread ($p<0.002$) than pattern A tumors. Pattern C tumors 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 pattern A tumors. Pattern C tumors 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

This new histopathologic pattern-based risk stratification system separates EAC into pattern A tumors with no risk of LN metastasis; therefore, avoiding LN dissection should be considered. In addition, there were no recurrences seen in pattern A tumors, and this may indicate that adjuvant therapy following surgery would not be indicated even for bulky tumors, using Sedlis criteria [28]. Patients with pattern B tumors rarely show nodal metastasis, and only if there is LVI; recurrences are very rare and all these patients had stage I tumors. In addition to conservative surgery, limited LN dissection or sentinel LN sampling in these patents might be beneficial and should be investigated. Patients with pattern C tumors require radical treatment with nodal resection, since nearly one-quarter of these tumors showed LN metastases and over 20% suffered recurrences.

It is important to note that all study cases were diagnosed as invasive EAC, including all pattern A tumors. A small minority of pattern A tumors may be interpreted by some pathologists as endocervical adenocarcinoma in situ (AIS); however, many of the cases in this study classified as pattern A had large grossly visible and deep tumors that could not have been considered as in situ lesions. While studies indicate that a clear distinction of invasive EAC from adenocarcinoma in situ is not possible in up to 20% of cases [29–30], this new system makes that distinction in difficult cases irrelevant as nodal dissection is unnecessary in both AIS and pattern A tumors, as patients would have an excellent prognosis.

Current NCCN guidelines determine how patients with EAC at different stages should be treated, with radical surgery and nodal resection in most patients [9]. However, morbidity for radical surgery and lymph node resection are significant including voiding difficulty, urinary tract infection, hemorrhage, port-site hematoma, pain, pyrexia, and nerve injury as early complications. Late complications include lymphedema, lymphocyst, urinary incontinence,

voiding difficulty, venous thrombosis and rectocele, in addition to the loss of childbearing capability for these often young patients [24, 25, 31].

Although several studies reported on the potential safety of conservative management of early-stage glandular lesions, there remains controversy regarding the use of less radical treatments [13–23, 32–51]. In the last few years, there have been attempts to better determine patients that can be safely treated with conservative surgery. Reynolds et al, found only one case of nodal metastasis, a micrometastasis, in a set of 66 Stage IA EAC cases [17]. There was no parametrial involvement nor recurrences in their patients. Similar data was confirmed by other studies, supporting consideration for less radical surgery performed in conjunction with pelvic lymphadenectomy for patients with tumor size no greater than 2 cm, no LVI, negative pelvic lymph nodes and DOI less than 10 mm [33–37]. However, most these studies included both squamous carcinoma and adenocarcinomas, with a predominance of the former; pelvic lymph nodes were still resected, but in some series, sentinel lymph node mapping plus or minus completion of pelvic node resection depending on sentinel lymph node status was performed. There is an attempt to predict tumor behavior but it is independent of the morphologic features of the tumor (aside from lymphovascular invasion) and in particular not recognizing EAC as a specific tumor.

We are proposing a different, and we believe more specific, risk stratification system for EAC that better discriminates patients' LN status and recurrence rate; it decreases the significance of measuring DOI with all its difficulties, instead focusing on tumor morphologic features. Analysis of morphologic tumor pattern enabled stratification of EAC into three distinct groups identified by histologic examination. Table 4 illustrates that when pattern A and B tumors are excluded, recurrence rate increases with stage: 13% in stage IB1, 33.3% in stage IB2, 43% in stage II, 50% in stage III and 100% in stage IV; this risk stratification system improves on the current FIGO staging system. Table 5 shows that early stage tumors can have LN metastasis, which are rare and hard to predict with the current staging system and better predicted with the new risk stratification system.

We are completing a reproducibility study and the preliminary data confirms that pathologists who have not been included in the original reviews of the cases were able to classify most EAC agreeing with our interpretation.

We are also currently moving into the next stage which is working with a group of gynecologic oncologists to explore the possibility of modifying the staging and treatment of this tumor. In our opinion, if these findings are confirmed in additional, prospective studies, consideration may be given to staging based on the tumor pattern with a new three tier stage I: IA for pure pattern A tumors, IB for pattern B tumors with or without pattern A, and IC for pattern C tumors, pure or combined with any of the other patterns. If new studies are successful in stratifying either pattern B or pattern C tumors, substaging could be incorporated to better predict tumor behavior and treatment. Alternatively, the transition from the current system to the new system could require adding tumor pattern (A, B or C) and still assessing DOI, albeit redefining it to measure depth of destructive invasion (DODI) (i.e. measuring destructive invasion from pattern A type glands). The refinement of the definition of DOI would determine that pattern A tumors have no DODI, most Pattern B

have DODI < 3 mm and < 7 mm horizontal extent, and most but not all Pattern C have DODI > 3 mm. This change would allow pathologists and clinicians to determine the FIGO stage as it currently stands, but clinicians will have more data to evaluate the need for radical vs. conservative surgery, lymphadenectomy vs. sentinel lymph node or close follow-up with no additional treatment.

Further validation and study of additional cases is necessary; however, this new system has significant clinical implications. We propose the following algorithm to help gynecologic oncologists and other treating physicians better determine patient treatment, along with other criteria. Tumor pattern in the diagnostic cervical biopsy would be reported which might consist of a pure pattern or combination thereof; the worst or highest pattern should be reported. If any pattern C is present in the biopsy, then based on published observations, current treatment modalities would be appropriate. Radical surgery (e.g. radical hysterectomy or trachelectomy) plus pelvic lymph node resection would be the recommended treatment. However, the treating physician could include other known variables or criteria that might modify treatment accordingly (i.e. cervical conization or simple trachelectomy and LN evaluation seems to be an acceptable treatment strategy for selected patients with small-volume (2 cm or less) stage I cervical cancer [40–50].

Conservative management similar to management for AIS would be the recommended treatment approach when pure pattern A tumor is seen in the biopsy. Treatment would proceed with a cervical cone, entirely submitted for microscopic examination. If pattern A tumor persists in the cone and the margins are negative, the patient might be managed with observation. If the tumor involves the surgical margins of the cone, a second cervical conization or wider excision, could be necessary; the tumor should be entirely resected with negative margins but radical surgery or lymph node resection is not necessary. If the subsequent cervical cone reveals pattern C tumor, a hysterectomy or trachelectomy plus pelvic lymph node resection would be appropriate treatment (as we have presented, these are aggressive tumors); the role of pelvic radiation therapy, in particular, in patients with Sedlis criteria might need to be investigated and could decrease recurrence rate [28]. If tumor in the initial biopsy or subsequent cervical conization specimen revealed pattern B, then the treatment would include conservative surgery plus sentinel lymph node sampling. Future studies might determine that only patients with LVI need sentinel lymph node sampling since very few patients had lymph node metastasis (only 4.4% of patients with pattern B tumors). If frozen section evaluation of the sentinel lymph nodes is performed, metastatic EAC should trigger completion of the lymphadenectomy. We recommend conservative surgery to resect pattern B tumors since all were stage I and parametrial involvement was not reported [2].

In pattern A tumors, it is important that pathologists examine the tumor very carefully to exclude LVI. Deeper sections might be necessary to exclude any areas worrisome for pattern B or LVI.

One of the limitations of the study is that we only included EAC, usual type and did not include special types: clear cell or serous carcinoma, mucinous adenocarcinoma (minimal deviation, intestinal, signet-ring cell or the newly described gastric-type adenocarcinoma) or

mesonephric carcinoma; however, we believe most of these special types would represent examples of pattern C tumors [26, 52, 53].

This new risk stratification system combined with modification of the current FIGO stage I and treatment algorithm of patients with EAC better predict patient prognosis and avoids unnecessary lymphadenectomy and its complications in a significant subset of patients. This new personalized approach allows for many of these patients to be treated with conservative modalities, rather than radical hysterectomy and LN dissection for most, hence avoiding morbidity without risking an increase in the rate of recurrence or lymph node metastasis. This is a step in the right direction of personalized medicine that analyzes all features of the tumor, not just size or DOI.

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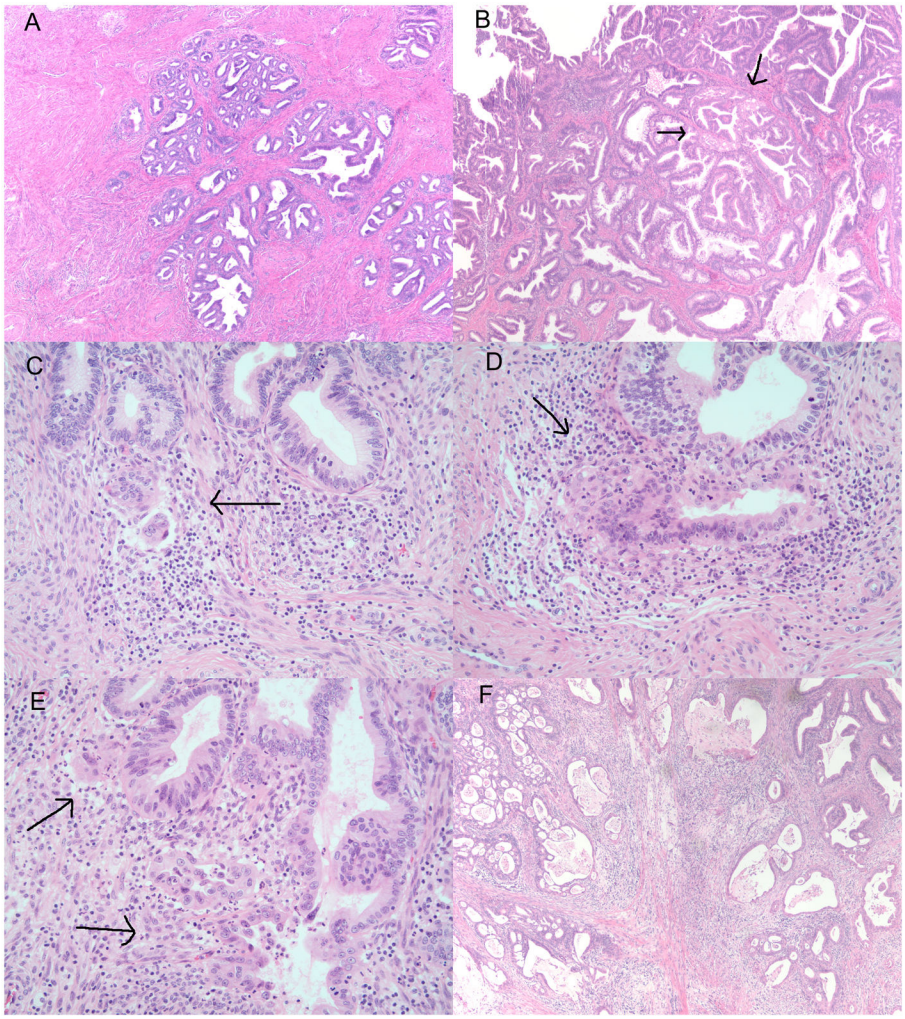

Figure 1.

Figure 1A: Deeply invasive well differentiated endocervical adenocarcinoma corresponding to pattern A tumor. H&E 40X. B: Low power examination of exophytic and invasive endocervical adenocarcinoma also corresponding to pattern A tumor. Higher examination is recommended to rule out questionable pattern B areas (arrows). H&E 40X. C–E: High power examination of invasive endocervical adenocarcinoma composed of glands with irregular contours (arrows) in a focally desmoplastic stroma arising from pattern A type glands. H&E 200X. F: Pattern C composed of diffuse destructive invasion, irregular and incomplete glands, some with cribriform architecture in a diffuse desmoplastic stroma. H&E40X.

Table 1

New risk stratification system for invasive endocervical adenocarcinomas based on pattern of invasion (Silva system).

	Silva system
Pattern A	• Well-demarcated glands with rounded contours, usually forming groups • No destructive stromal invasion • No single cells or cell detachment • No lymphovascular invasion • Complex intraglandular growth acceptable (cribriform, papillae) • Lack of solid growth (well-moderately differentiated) • Irrelevant depth of the tumor or relationship to large cervical vessels
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 pattern A-type glands, frequently in desmoplastic or inflamed stroma • Single, multiple, or linear foci at base of tumor • Lymphovascular invasion (present/absent) • Lack of solid growth (well-moderately differentiated)
Pattern C	• Diffuse destructive stromal invasion, characterized by: Diffusely infiltrative glands, with associated extensive desmoplastic response Glands often angulated or with canalicular pattern, with interspersed open glands • Confluent growth filling a 4x field (5 mm): glands, papillae (stroma only within papillae), or mucin lakes • Solid, poorly differentiated component (architecturally high grade); nuclear grade is disregarded • Lymphovascular invasion (present/absent)

Adapted from Roma AA, et al. Am J Surg Pathol. 2015 May;39(5):667–72.

Table 2

Outcome data comparing the standard method of tumor evaluation (depth of invasion) versus the newly proposed pattern-based system.

	Patients	Patients with metastatic LN	# metastatic LNs	Stage I	Stage II–IV
Standard	352	49 (14%)	83 (1%)	320 (91%)	32 (9%)
Pattern A	73 (20.7%)	0	0	73 (100%)	0
Pattern B	90 (25.6%)	4 (4.4%)	5 (0.2%)	90 (100%)	0
Pattern C	189 (53.7%)	45 (24%)	76 (1.7%)	157 (83%)	32 (17%)

LNs: lymph nodes

Table 3

Follow-up and adjuvant treatment modalities in patients with pattern C tumors and initial metastatic lymph nodes

	Adjuvant treatment in patients with recurrence			
	Chemotherapy (4 cases)	**Radiation (2 cases)**	**Both (8 cases)**	**None (3 cases)**
Site of recurrence; stage; status at last follow-up	Abdomen; stage IIB; NED	Ovary; stage IIIB; AWD	Lung; stage IIA1; AWD	Vagina; stage IB1, lost follow-up
	Para-aortic LN; stage IIB; DOD	Para-aortic LN; stage IB1; DOD	Lung and pelvis; stage IV; AWD	Ovary, pelvis; stage IV; DOD
	Lung; IB1; AWD		Pleural fluid; stage IIB; DOD	Ovary, bladder wall; stage IIIB; AWD
	Lung and liver; stage IB1; DOD		Pelvis; stage IV; AWD	
			Abdominal wall; stage IB1; DOD	
			Retroperitoneum; stage IB2; AWD	
			Ovary, liver, retroperitoneum; stage IV; AWD	
			Vagina; stage IIA1; AWD	
	Adjuvant treatment in patients with no recurrence at last follow-up			
	Chemotherapy (4 cases)	Radiation (7 cases)	Both (13 cases)	None (6 cases)
Stage	IB1	IB1 (5 cases)	IB1 (8 cases)	IA1
	IIA	IB2	IB2 (2 cases)	IA2
	IIIB (2 cases)	IIA	IIA (2 cases)	IB1
			IIIB	IB2
				IIA
				IIB

NED: no evidence of disease; AWD: alive with disease; DOD: died of disease

Table 4

Comparison of FIGO stage vs. tumor pattern and recurrence.

Stage	IA1	IA2	IB1	IB2	IB NOS	II	III	IV	Total
Recurrence/Pattern A	0/14	0/8	0/46	0/1	0/4	0/0	0/0	0/0	0/73
Recurrence/Pattern B	0/7	0/8	1/51 (2%)	0/4	0/20	0/0	0/0	0/0	1/90 (1.1%)
Recurrence/Pattern C	0/4	0/10	14/107 (13%)	4/12 (33.3%)	6/24 (25%)	9/21 (43%)	3/6 (50%)	5/5 (100%)	41/189 (21.7%)

FIGO: International Federation of Gynecology and Obstetrics; NOS: not otherwise specified

Table 5

Comparison of FIGO stage vs. tumor pattern and lymph node metastasis.

Stage	IA1	IA2	IB1	IB2	IB NOS	II	III	IV	Total
LN mets/Pattern A	0/14	0/8	0/46	0/1	0/4	0/0	0/0	0/0	0/73
LN mets/Pattern B	0/7	1/8 (12.5%)	2/51 (3.9%)	0/4	1/20 (5%)	0/0	0/0	0/0	4/90 (4.4%)
LN mets/Pattern C	1/4 (25%)	0/10	14/107 (13%)	5/12 (41.7%)	5/24 (20.8%)	11/21 (52.4%)	5/6 (83.3%)	4/5 (80%)	45/189 (23.8%)
LN mets by stage	1/25 (4%)	1/26 (3.8%)	16/204 (7.8%)	5/17 (29.4%)	6/48 (12.5%)	11/21 (52.4%)	5/6 (83.3%)	4/5 (80%)	49/352 (13.9%)

FIGO: International Federation of Gynecology and Obstetrics; NOS: not otherwise specified