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New pattern-based personalized risk stratification system for endocervical adenocarcinoma with important clinical implications and surgical outcome☆,☆☆

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HIGHLIGHTS

• Histopathologic pattern-based system to better stratify endocervical adenocarcinoma
• Stratification better correlates with lymph node metastasis than FIGO staging alone
• Safely predicts node-negative disease in proportion of adenocarcinoma patients

ARTICLE INFO

ABSTRACT

We present a recently introduced three tier pattern-based histopathologic system to stratify endocervical adeno-carcinoma (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 lymphovascular 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 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.

1. 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 <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; <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.

2. 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; Fig. 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

Table 1
New risk stratification system for invasive endocervical adenocarcinomas based on pattern of invasion (Silva system).
Adapted from Roma AA et al. Am. J. Surg. Pathol. 2015 May;39(5):667–72. Copyright: Wolters Kluwer Health, Inc.

	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 and glands often angulated or with 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
	– Lymphovascular invasion (present/absent)