



Original contribution

Risk factor analysis of recurrence in low-grade endometrial adenocarcinoma[☆]



Andres A. Roma MD^{a,*}, Lisa A. Rybicki MS^b, Denise Barbuto MD^c,
Elizabeth Euscher MD^d, Bojana Djordjevic MD^e, Elizabeth Frauenhoffer MD^f,
Insun Kim MD^g, Sung Ran Hong MD^h, Delia Montiel MDⁱ, Rouba Ali-Fehmi MD^j,
Anais Malpica MD^d, Elvio G. Silva MD^{c,d}

^aRobert J. Tomsich Pathology and Laboratory Medicine Institute, Department of Pathology, Cleveland Clinic, Cleveland, OH, 44195

^bDepartment of Quantitative Health Sciences, Lerner Research Institute, Cleveland, Ohio, 44195

^cDepartment of Pathology, The University of Texas, MD Anderson Cancer Center, Houston, TX, 77030

^dDepartment of Pathology, Cedars-Sinai Medical Center, Los Angeles, CA, 90048

^eDepartment of Pathology, University of Ottawa, Ottawa, Ontario, K1H 8M5, Canada

^fDepartment of Pathology and Laboratory Medicine, Pennsylvania State University, Hershey, PA, 17033

^gDepartment of Pathology, Korea University Anam Hospital, Seoul, 136-705, Republic of Korea

^hDepartment of Pathology, Cheil General Hospital, Dankook University, Seoul, 100-450, Republic of Korea

ⁱInstituto Nacional de Cancerologia, C.P. 14080, Mexico, DF, Mexico

^jDepartment of Pathology, Wayne State University, Detroit, MI, 48201

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Summary Prognosis of endometrial adenocarcinoma is favorable; however, the risk of recurrence ranges from 7% to 13%. Recurrence has been related to age, tumor type, International Federation of Gynecology and Obstetrics grade, depth of invasion, and lymphovascular invasion (LVI); however, morphologic features that would predict the site of recurrence have not been established. In this multi-institutional study, we reviewed 589 patients with International Federation of Gynecology and Obstetrics grades 1 or 2 endometrial adenocarcinoma, endometrioid type. Cox proportional hazard analysis was used to identify univariate and multivariate risk factors for recurrence and survival. Univariate analysis revealed features of tumors that recurred only in the vagina: low nuclear grade; superficial myoinvasion; minimal to no LVI; and minimal myoinvasion with microcystic, elongated, and fragmented (MELF) pattern; low nuclear grade and superficial myoinvasion persisted on multivariate analysis. Features of tumors that recurred at other sites included large size, deep myoinvasion, tumor necrosis, 1 or more LVI foci, LVI foci distant/deeper than invasive tumor front, MELF myoinvasion pattern, lower uterine segment and cervical stromal involvement, pelvic and/or paraaortic lymph node metastases at presentation, and higher grade of tumor in the metastatic foci, whereas increased percentage of solid component and lower percentage of mucinous features were marginally associated. Tumors with recurrences only in vagina had different features than tumors that

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* Corresponding author at: 9500 Euclid Ave, L2, Cleveland, OH 44122.

E-mail address: romaa@ccf.org (A. A. Roma).

recurred at other sites. The presence of tumor necrosis, MELF foci at the invasive tumor front, and the percentage of solid component and mucinous features could be helpful in grading endometrioid adenocarcinomas, if a 2-tier rather than a 3-tier grading system is accepted in the future.

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1. Introduction

Prognosis of endometrial adenocarcinoma is favorable with recently reported overall 5-year all-stage survival rate of 89%, ranging from 59% for the International Federation of Gynecology and Obstetrics (FIGO) stage IV tumors to 94% in stage I tumors [1,2]. Overall 5-year survival rate improves for endometrioid-type adenocarcinoma, with all stages reaching 90%; 5-year survival rate in FIGO grades 1 and 2 is 93% and 94%, respectively. Survival for all stages of nonendometrioid endometrial adenocarcinoma was reported at 80% [2]. Recurrence risk of endometrioid carcinoma has been reported at 13% in a systematic review [3] but as low as 7% for only patients with low-grade endometrioid adenocarcinoma [4].

Advanced stage at presentation and/or recurrence in endometrial carcinoma has been related to age, tumor type, FIGO grade, depth of invasion, and the presence of lymphovascular invasion (LVI) [5-14]; however, morphologic tumor features predictive of the site of recurrence or metastatic disease have not been well established.

We recently published 2 studies evaluating morphologic features of low-grade endometrial carcinomas, one associated with vaginal recurrence [15] and the other associated with metastases in regional lymph nodes (LNs) [16]. The objective of this study was to identify morphologic features that could predict the recurrence of low-grade endometrioid adenocarcinoma at different sites.

2. Materials and methods

Institutional review board approval was obtained before initiation of the study. This multi-institutional study included cases from 9 tertiary care centers from 4 countries, Korea, Mexico, Canada, and the United States, from 1991 to 2007. Selection criteria included FIGO grades 1 or 2 endometrioid, endometrial adenocarcinoma (according to the current FIGO grading system) with histologic material available for review, metastases to pelvic or paraaortic LNs at presentation, and recurrence or metastatic spread to extrauterine sites at presentation or during follow-up [17] (Fig. 1). In addition, 1 to 2 endometrial endometrioid adenocarcinoma FIGO grade 1 or 2 cases with negative resected LNs, per case with extrauterine disease, were included in the analysis as a control set. The latter patients had no evidence of advanced disease beyond the uterus at any time during follow-up. Clinical and pathologic data were obtained from the patients' charts and/or pathology reports.

Members of the participating institutions convened in 1 consensus meeting at Cedars-Sinai Medical Center in Los Angeles, California. Selected cases from each author were reviewed by the group using a multiheaded microscope to define and unify features to be studied. Each participant then reviewed their cases and tabulated those features. All cases were restaged using the 2009 FIGO staging system [18]. The variables analyzed are described in the "Statistical analysis" section. Morphologic features reviewed included FIGO grade; amount of solid and mucinous components; nuclear grade; necrosis within tumor aggregates or glands; depth of myometrial invasion in millimeters and percentage of myometrial thickness; presence of microcystic, elongated, and fragmented (MELF) pattern of myoinvasion; amount of MELF pattern calculated as a percentage of the total invasive tumor at the advancing front; number of MELF pattern foci; predominant tumor pattern at the invasive tumor front (as defined below); LVI; tumor pattern of invasion adjacent to LVI; location of LVI foci (adjacent to tumor or deeper than invasive tumor front); stromal reaction surrounding tumor cells (desmoplasia); and tumor grade and largest dimension of metastatic tumor deposits in pelvic and paraaortic LNs.

Solid component was defined as nests or sheets of tumor cells that resemble the cells lining the glandular spaces, excluding any squamous component. It was calculated as a percentage of the tumor. *Mucinous component* was defined as glandular, solid, or papillary areas containing cells with intracytoplasmic mucin; mucin in the gland lumen alone was not counted. *Nuclear grade* was defined as follows: grade 1, nuclei are oval or round, without pleomorphism or size variation, and basal orientation of the nuclei is maintained; grade 2, features are between grades 1 and 3; and grade 3, there is greater than 3 times size difference between nuclei with loss of nuclear polarity and marked variation in the nuclear shape, plus or minus prominent nucleoli, and coarse chromatin. *MELF* was defined as tumor foci characterized by the presence of any of these 3 elements: (1) microcysts lined by cells with eosinophilic cytoplasm that may be flattened or form intraluminal tufts; (2) elongated structures with a compressed, sometimes slit-like luminal space, lined by eosinophilic or amphophilic cells; and (3) clusters of detached eosinophilic cells or individual eosinophilic cells lying in an edematous or myxoid background [19]. The predominant pattern of tumor invasive front was classified as single glands (isolated glands with rounded or ragged contours), multiple glands (groups of glands with rounded or ragged contours), MELF, or single-cell clusters (SCIs). SCI pattern was previously recognized as single cells or

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