International Journal of Gynecological Pathology
30:218–230, Lippincott Williams & Wilkins, Baltimore

Original Article

Mucinous Tumor of Low Malignant Potential ("Borderline" or "Atypical Proliferative" Tumor) of the Ovary: A Study of 171 Cases With the Assessment of Intraepithelial Carcinoma and Microinvasion

Surapan Khunamornpong, M.D., Jongkolnee Settakorn, M.D., Kornkanok Sukpan, M.D., Prapaporn Suprasert, M.D., and Sumalee Siriaunkgul, M.D.

Summary: Mucinous tumors of the ovary are a continuing source of controversy in the field of gynecologic pathology. We examined a series of 171 intestinal-type mucinous tumors of low malignant potential ("borderline" or "atypical proliferative" tumors) to clarify the clinical significance of intraepithelial carcinoma (IECA) and microinvasion (area $\leq 10\,mm^2$). The diagnosis of IECA was based on the presence of marked nuclear atypia (grade 3). Stromal microinvasion was classified as low grade and high grade (with nuclear grade 3). IECA was observed in 67 of 171 cases (39.2%). Microinvasion was identified in 31 (18.1%) cases, low grade in 22 (12.9%) cases, and high grade in 9 (5.3%) cases. Follow-up status was known in 144 cases and tumor recurrence was observed in 6 patients (4.2%). The risk factors for recurrence included International Federation of Gynecology and Obstetrics stage $\geq$IC ($P = 0.002$), microinvasion ($P = 0.013$), age less than 45 years ($P = 0.032$), and IECA ($P = 0.042$). The amount of IECA $\geq 10\%$ was also associated with the risk of recurrence ($P = 0.007$). Among tumors with microinvasion, there was no significant association between the clinicopathologic variables and recurrence. When considering tumors with stage $\geq$IC, tumor recurrence was significantly associated with IECA $\geq 10\%$ ($P = 0.031$) and age less than 45 years ($P = 0.047$). It is important that mucinous tumors of low malignant potential should be staged and be optimally sampled for pathologic examination to document the status of the external surface or peritoneal involvement and to identify the worst degree of epithelial proliferation. Tumor stage $\geq$IC, IECA $\geq 10\%$, microinvasion, and age less than 45 years were the features that were associated with tumor recurrence. The study results also support the use of nuclear grade 3 as the sole criterion of IECA. **Key Words:** Ovary—Mucinous tumor—Tumor of low malignant potential—Borderline tumor—Atypical proliferative tumor—Intraepithelial carcinoma—Microinvasion.

Mucinous tumors of the ovary have been a continuing source of controversy in the field of gynecologic pathology (1). The dividing line between mucinous tumors of low malignant potential (LMP or "borderline" or "atypical proliferative" tumors) and invasive mucinous carcinoma is an important subject, and the spectrum of lesions around this area has received maximum interest. The upper end of LMP tumors without stromal invasion is classified as intraepithelial carcinoma (IECA) or, by some investigators, as intraglandular carcinoma (1,2). Microinvasion in LMP tumors has been regarded as the transition from LMP tumors to invasive carcinoma (3).

From the Department of Pathology (S.K., J.S., K.S., S.S.); and Department of Obstetrics and Gynecology (P.S.), Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

Address correspondence to Surapan Khunamornpong, MD, Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. E-mail: skhunamo@med.cmu.ac.th.

DOI: 10.1097/PGP.0b013e3181fcf01a

Definitions of IECA in earlier studies are not uniform (4–6). The diagnosis of IECA was based on either nuclear atypia and/or architectural complexity. Some studies have also classified tumors with grade 2 nuclei as IECA (4,6). In the recent workshop on ovarian serous and mucinous LMP tumors, there was a suggestion supporting the use of only marked nuclear atypia (grade 3) as the defining criterion for IECA, regardless of architectural complexity (1). However, the use of marked nuclear atypia alone as the diagnostic criterion for IECA has not been well evaluated.

There are still uncertainties regarding microinvasion in mucinous LMP tumors, which are as follows: the definition of microinvasion and the distinction from mucin granuloma containing epithelial cells, the significance of microinvasion in usual LMP tumors versus microinvasion in tumors with IECA, and the clinical significance of the extent, the number, and the cytologic features of microinvasive foci (''low-grade'' vs. ''high-grade'') (1). There is also a controversy about dividing mucinous tumors with microinvasion into 2 categories: ''microinvasive LMP tumor'' and ''microinvasive carcinoma'' (1,2). The presence of microinvasion in tumors containing IECA has been regarded by some investigators as microinvasive carcinoma (2). However, it has not been uniformly defined whether the term ''microinvasive carcinoma'' should be based on the coexistence of IECA or on the morphology of the focus of stromal invasion (''high-grade'' appearance) (1).

In this study, we examined a large series of mucinous LMP tumors to clarify the significance of morphologic characteristics of IECA and microinvasion, in correlation with other possible prognostic features of mucinous LMP tumors.

MATERIALS AND METHODS

The surgical pathology files of the Department of Pathology, Faculty of Medicine, Chiang Mai University (CMU) between January 1992 and December 2004 were searched for ovarian mucinous LMP tumors and mucinous adenocarcinomas. The study was approved by Research Ethics Committee of the Faculty. The histologic slides were reviewed and the diagnoses were classified according to the 2003 WHO classification (7). Exclusion criteria for LMP tumors were as follows: (a) benign mucinous tumors with focal atypical epithelial proliferation less than 10% of the histologic materials, (b) invasive mucinous carcinomas with expansile or infiltrative stromal invasion exceeding $10\,mm^2$ in area, (c) mucinous tumors associated with appendicial mucinous lesions or those associated with mucinous ascites/pseudomyxoma peritonei and without adequate exclusion of nonovarian neoplastic lesions, (d) mucinous tumors with other carcinomatous or malignant components, (e) mucinous tumors with features consistent with metastatic tumors based on clinicopathologic review (4,5,8) including mucinous tumors associated with endocervical adenocarcinomas, which might represent metastases from the cervical origin (9,10), and (f) mucinous tumors associated with mature cystic teratomas as these tumors may now be considered to be of germ cell origin (11). The gross specimens of the cases, which were resected within CMU Hospital, were evaluated by 1 or 2 pathologists (S.K./S.S.).

The mucinous LMP tumors were reevaluated for histopathologic characteristics, including architectural complexity, nuclear grade, presence of stromal microinvasion, and stromal mucin deposits. The International Federation of Gynecology and Obstetrics staging for ovarian cancer was applied (7). The number of sections represented the total count of tumor tissue sections as multiple sections of the cyst wall may be included in a single tissue block. High-grade architecture was defined by the presence of cribriform pattern, or complex papillary structures with stromal-free papillary pattern, or nuclear stratification of at least 4 layers (4). The epithelial nuclear atypia was classified into 3 grades based on recent description (12,13) (Fig. 1) and the worst nuclear grade in each tumor was recorded. Nuclear grade 3 was characterized by marked nuclear pleomorphism with a variation in size greater than 3 times, coarse chromatin granules, and prominent nucleoli (Fig. 1C). The determination of grade 3 nuclear atypia was based on a consensus agreement by 2 pathologists (S.K. and S.S.). The diagnosis of IECA was defined by the presence of marked nuclear atypia (grade 3) and the quantity of IECA was estimated as the percentage of the entire epithelial component of tumor.

A diagnosis of stromal invasion was based on the presence of single cells or clusters or cords/nests or irregular tubular infiltrative glands of atypical epithelial cells within the stroma, which may or may not show desmoplasia. Stromal microinvasion was divided into 2 grades (low grade vs. high grade) (Figs. 2, 3) based on the degree of nuclear atypia in the invasive cells with nuclear grade 3 being diagnostic of high-grade lesions. The number and

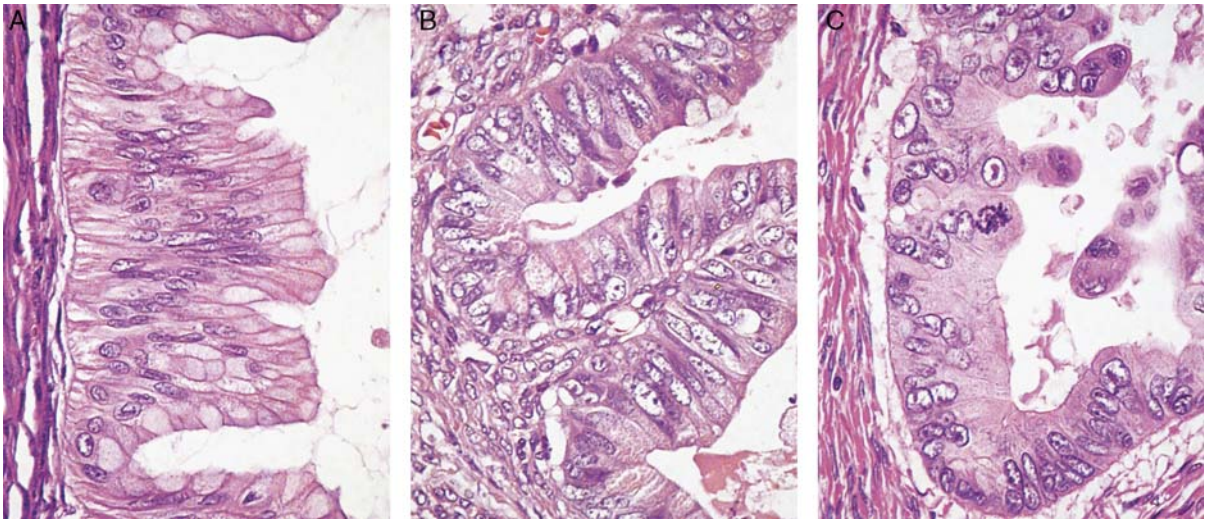

FIG. 1. Grading of nuclear atypia in mucinous LMP tumors. (A) Grade 1 with mild nuclear pleomorphism. (B) Grade 2 with moderate nuclear pleomorphism, increased chromatin clumping, and small nucleoli. (C) Grade 3 characterized by marked nuclear pleomorphism with coarse chromatins and prominent nucleoli.

the extent of microinvasive foci were recorded. The area size of stromal invasion was calculated by multiplying the length and the width of the largest focus of invasion.

Stromal mucin deposits including mucin granuloma and pseudomyxoma ovarii were recorded. Pseudomyxoma ovarii was defined by collection of mucin or mucin pool within the stroma, usually with small

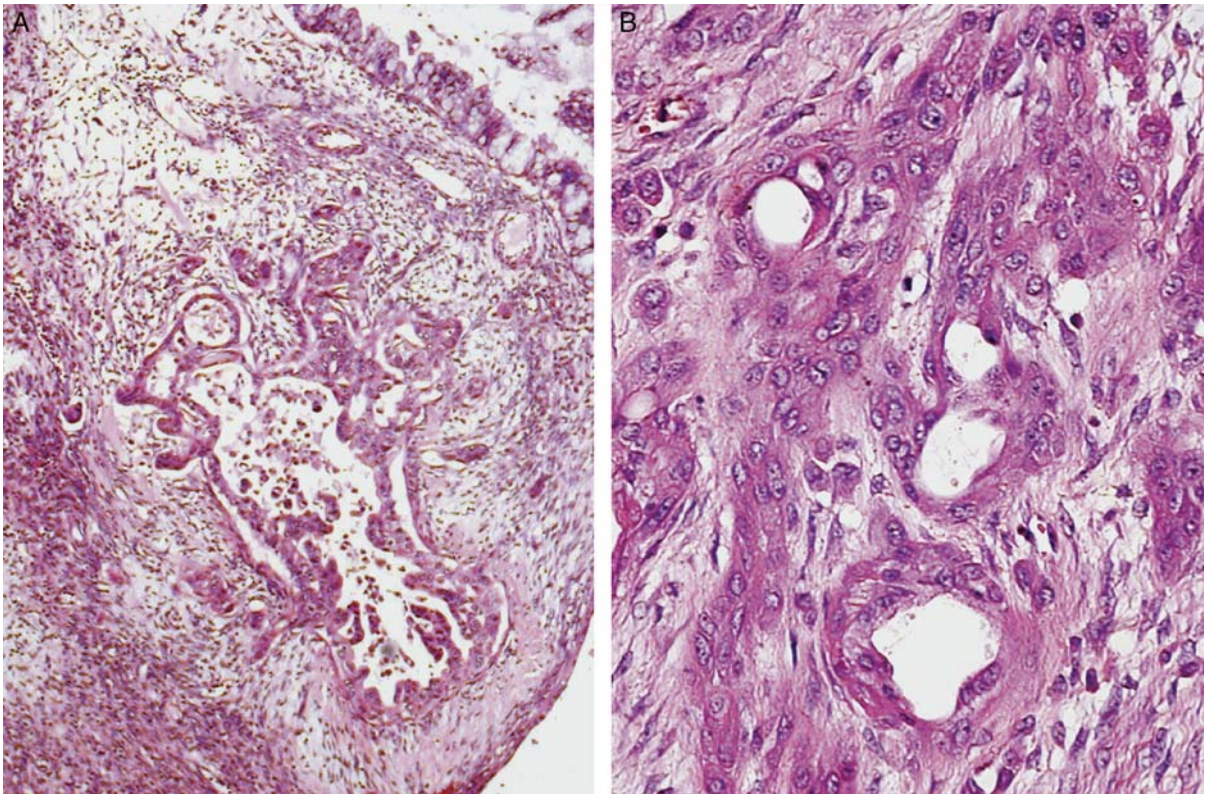

FIG. 2. Low-grade stromal microinvasion. (A) Infiltrative glands and small epithelial clusters are seen around an irregular cystic space beneath the mucinous epithelium with low-grade nuclear atypia. (B) Infiltrative glandular structures with mild-to-moderate nuclear atypia.

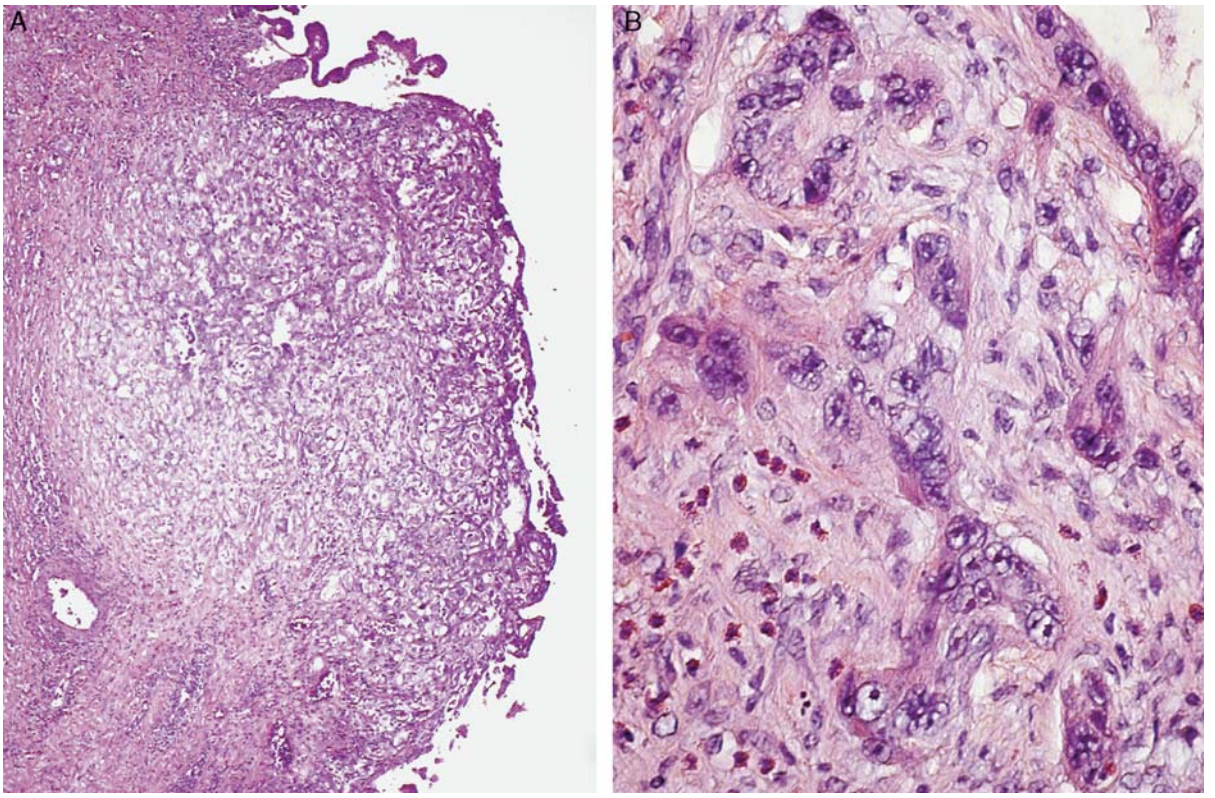

FIG. 3. High-grade stromal microinvasion. (A) Small nodule-like stromal invasion of malignant epithelial cells. (B) Clusters and cord-like groups of epithelial cells with grade 3 nuclear atypia are seen within the stroma beneath intraepithelial carcinoma lining.

number of macrophages. Mucin granuloma was defined by a collection of macrophages within the stroma accompanied by a scant amount of mucin. Foci of mucin granulomas or pseudomyxoma ovarii may contain neoplastic epithelial cells and were classified as those with epithelial cells. Stromal mucin deposits with epithelial cells were distinguished from stromal microinvasion by the circumscribed round or nodular contour of mucin collection or histiocytic aggregation surrounding the epithelial cells (Fig. 4). Identification of the epithelial cells within either pseudomyxoma ovarii or mucin granuloma was based on hematoxylin and eosin-stained slides. Mucin granuloma and pseudomyxoma ovarii may be identified adjacent to the typical foci of stromal microinvasion (Fig. 5).

Follow-up data were obtained from the medical records or by either letter or telephone contact to the patients or their family members. In cases with probable tumor recurrence or another neoplasm, the clinical data and the available radiologic or histologic materials were reviewed. Tumor recurrence of ovarian mucinous tumor was considered only when the possibility of other cancers had been excluded.

The clinicopathologic data were summarized and analyzed using SPSS for Windows program (Version 17.0). The association between the clinicopathologic variables was tested by χ^2 test or the Fisher exact test, as appropriate. A result was considered to be statistically significant when the P value was less than 0.05. Survival analysis was estimated by the Kaplan-Meier Method.

RESULTS

There were 171 cases of mucinous LMP tumors: 114 of these (66.7%) had the ovarian masses resected in CMU Hospital whereas the other 57 cases (33.3%) were referred from other hospitals. All the tumors were of intestinal type. The tumors were unilateral in all patients (right in 83 and left in 88). Patients' age ranged from 13 to 85 years (mean 42.4 ± 14.6 yr, median 42 yr).

Two patients had another cancer diagnosed simultaneously with ovarian tumors, including tubal serous adenocarcinoma in 1 case and pulmonary nonmucinous adenocarcinoma in 1 case. Postoperatively, 1 patient had pulmonary adenocarcinoma with

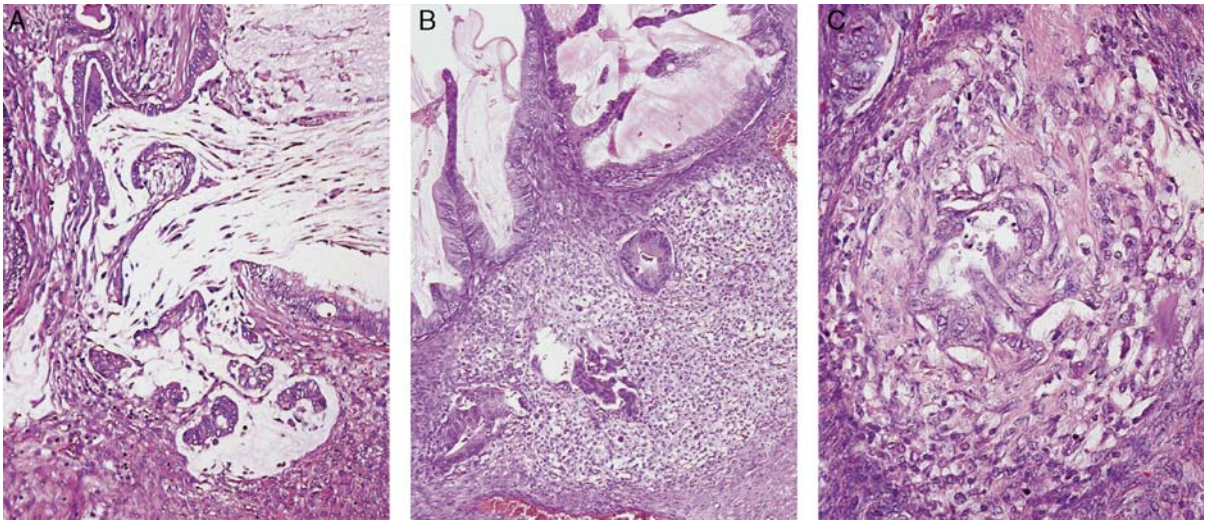

FIG. 4. Stromal mucin deposits containing epithelial cells. (A) Pseudomyxoma ovarii adjacent to a ruptured cystic space. Groups of epithelial cells are floated within circumscribed mucin collection. (B and C) Mucin granuloma containing small groups and individual forms of degenerated epithelial cells. Note the round-contoured histiocytic aggregation.

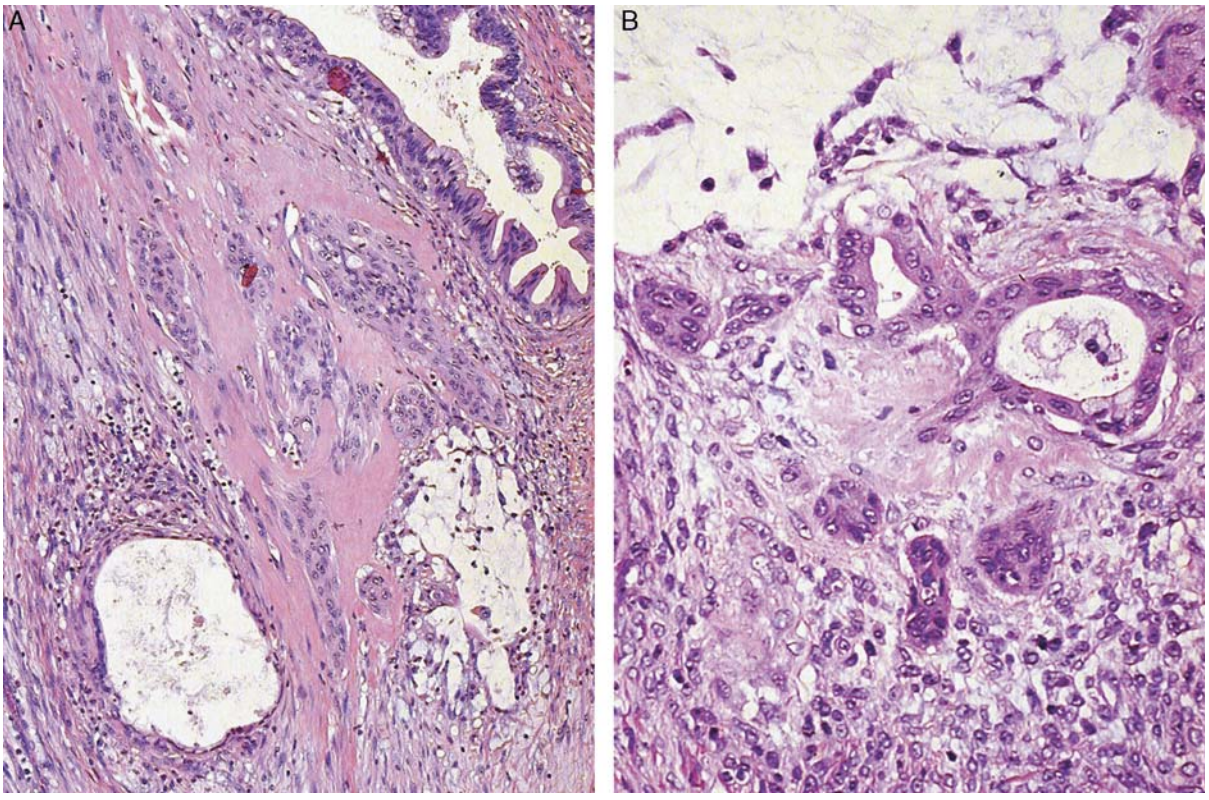

FIG. 5. Low-grade stromal microinvasion and adjacent stromal mucin deposits. (A) Small collection of mucin (bottom right) is seen adjacent to infiltrating groups of atypical cells within hyalinized stroma. (B) Small clusters of epithelial cells projecting from the periphery of mucin collection into the stroma.

TABLE 1. *Overview of characteristics of 171 cases of ovarian mucinous LMP tumors, stratified by type of stromal microinvasion*

	Tumors without microinvasion (n = 140)	Tumors with low-grade microinvasion (n = 22)	Tumors with high-grade microinvasion (n = 9)
Mean age (yr)	41.9 (16-79)	43.7 (13-85)	48.6 (29-71)
Mean tumor size (cm)	16.4 (3.5-32.0)	18.4 (8.0-30.0)	16.2 (10.0-30.0)
Mean no. tumor sections	15.8 (1-53)	25.0 (6-58)	24.6 (3-78)
Mean follow-up duration (mo)	78.8 (7-187)	82.1 (14-146)	69.4 (5-151)
Unknown follow-up status	23 (16.4%)	2 (9.1%)	1 (11.1%)

LMP indicates low malignant potential.

brain metastasis after 108 months of uneventful follow-up (cytologically confirmed pulmonary lesion with radiologic review, tissue biopsy not available).

Staging

The operations on the ovarian tumors included cystectomy in 1 patient (0.6%), unilateral salpingo-oophorectomy in 59 (34.5%) patients, and bilateral salpingo-oophorectomy in 111 (64.9%) patients. The uterus was also resected in 116 patients (67.8%). Staging procedures including omental or peritoneal biopsy and/or peritoneal cytology were performed in 120 of 171 patients (70.2%). The remaining 51 patients (29.8%) were incompletely staged intra-operatively but were considered to be of stage I by subsequent clinical and/or radiologic investigations. The tumors were of stage I in 169 patients (98.8%), whereas 2 patients (1.2%) had neoplastic involvement outside the ovaries (stages II and III). Of 169 patients with stage I tumors, 125 patients were of stage IA, 39 patients were of stage IC, and 5 patients were of unspecified stage I because of the uncertainty of the external surface status. Of 39 stage IC patients, 27 patients had earlier perforation and/or neoplastic cell growth on the surface, 8 patients had positive peritoneal cytology alone, and 4 patients had only intraoperative rupture of tumors.

Pathologic Findings

Tumor size ranged from 3.5 to 32.0 cm (mean 16.7 ± 6.2 cm, median 16.0 cm). Other additional components of ovarian lesions included the Brenner tumor in 5 cases, trabecular carcinoid in 1 case, and endometriosis in 1 case. The slides of simultaneously removed appendix were available in 109 cases (63.7%); none showed epithelial lesion.

The presence of nuclear grade 3 (IECA) was observed in 67 of 171 cases (39.2%). Microinvasion was observed in 31 cases (18.1%): 22 (12.9%) were low grade and 9 (5.3%) were high grade. All cases with stromal microinvasion had at least grade 2 nuclear atypia of the epithelial lining.

Overview features of cases as stratified by the type of microinvasion are shown in Table 1 and the clinicopathologic variables of each group are listed in Table 2. Nuclear grade 3 (IECA) was present in 30.0% of tumors without invasion, 72.7% of those with low-grade microinvasion, and 100% of those with high-grade microinvasion (Table 2). The presence of IECA $\geq 10\%$ was more common in tumors with high-grade microinvasion (77.8%) than in those with low-grade microinvasion (50.0%) or those without invasion (18.6%). Tumors with microinvasion were significantly associated with high architectural grade, compared with those without microinvasion, but there was no difference in the architectural grade between tumors with low-grade and high-grade microinvasion (Table 2).

In tumors with low-grade microinvasion, the presence of single cells or small cellular clusters was the predominant pattern (72.7%). The stroma was mostly loose, edematous, and occasionally hyalinized. The inflammatory response mainly included mild lymphocytic or histiocytic infiltration or, in few foci, neutrophilic infiltration. The number of microinvasion ranged from 1 to 11 (median 3). The size of microinvasive area ranged from less than 1 mm^2 (15 cases, 68.2%) to 5.25 mm^2. There was IECA in close vicinity to microinvasion in 8 cases (36.4%).

In tumors with high-grade microinvasion, the predominant invasion pattern was infiltrative glands. The number of microinvasion ranged from 1 to 16 (median 2). The area size ranged from less than 1 mm^2 (1 case, 11.1%) to 9.9 mm^2. Adjacent IECA was observed in all cases.

With regard to the pattern and size of microinvasion, 18 cases (58.1%) had single cell or small cluster pattern. The extent of this type of invasion was less than 1 mm^2 in 13 cases and was ≥ 1 mm^2 in 5 cases. Thirteen tumors (41.9%) had infiltrative pattern; 10 of these were ≥ 1 mm^2 in size. Tumors with high-grade microinvasion more commonly had infiltrative

TABLE 2. *Clinicopathologic features of 171 cases of mucinous LMP tumors, stratified by type of stromal microinvasion*

	Total cases (n = 171)	Without microinvasion (n = 140)	Low-grade microinvasion (n = 22)	High-grade microinvasion (n = 9)	*P** (without vs. with microinvasion)	*P*† (low-grade vs. high-grade microinvasion)
Age						
< 45 yr	96	76 (54.3%)	16 (72.7%)	4 (44.4%)	0.299	0.217
≥ 45 yr	75	64 (45.7%)	6 (27.3%)	5 (55.5%)		
Stage‡						
IA	125	108 (77.1%)	12 (57.1%)	5 (71.4%)	0.050	0.668
IC or more	41	30 (22.9%)	9 (42.9%)	2 (28.6%)		
Highest nuclear grade						
1-2	104	98 (70.0%)	6 (27.3%)	0	< 0.001	0.145
3	67	42 (30.0%)	16 (72.7%)	9 (100%)		
Amount of IECA						
Absent or < 10%	127	114 (81.4%)	11 (50.0%)	2 (22.2%)	< 0.001	0.237
≥ 10%	44	26 (18.6%)	11 (50.0%)	7 (77.8%)		
Architectural grade						
Low	104	95 (67.9%)	7 (31.8%)	2 (22.2%)	< 0.001	0.689
High	67	45 (32.1%)	15 (68.2%)	7 (77.8%)		
Stromal mucinous deposits						
Absent	69	59 (42.1%)	3 (13.6%)	7 (77.8%)	0.310	0.001
Present	102	81 (57.9%)	19 (86.4%)	2 (22.2%)		

‡Including only the cases with staging detail.
*χ^2 test.
†The Fisher exact test.

pattern and an extent $\geq 1\,mm^2$ compared with low-grade microinvasion group (77.8% vs. 27.3%, and 88.9% vs. 31.8%, respectively, $P = 0.017$ and 0.006).

The presence of stromal mucin deposits (with or without epithelial cells) was most frequently seen in tumors with low-grade microinvasion (86.4%) (Table 2), compared with those with high-grade microinvasion (22.2%, $P = 0.001$) and those without invasion (57.9%, $P = 0.011$). Stromal mucin deposits with epithelial cells were more frequently observed in tumors with low-grade microinvasion (10 of 22, 45.5%) than in those with high-grade microinvasion (2 of 9, 22.2%, $P = 0.418$) and those without invasion (26 of 140, 18.6%, $P = 0.010$). In tumors with low-grade microinvasion, stromal mucin deposits were observed in areas adjacent or close to microinvasion in 13 cases (59.1%).

Of 2 patients with extraovarian involvement, there were microscopic foci of noninvasive neoplastic mucinous epithelium of nuclear grade 2 involving the uterine serosa (stage IIA) in 1 patient, and the omentum (stage IIIA) in the other patient.

Follow-up Information

Chemotherapy was given postoperatively in 22 patients (12.9%). Eighteen of 39 stage IC patients received chemotherapy. Follow-up was available in 145 patients (84.8%), ranging from 5 to 187 months (median 68). One patient died of uncertain cancer and was excluded from the analysis of tumor recurrence. Of 144 patients, 134 were alive and well. Three patients died of medical conditions unrelated to tumors. One patient died of pulmonary cancer. The remaining 6 patients (4.2%) had tumor recurrence (Table 3). Of 6 recurrent cases, 3 were dead from disease, 2 were alive with disease, and 1 was alive and well 38 months after the treatment of recurrent tumor. Five of these 6 patients received complete initial surgical staging of the ovarian tumors.

The 6 cases with tumor recurrence included 1 LMP tumor and 5 tumors with IECA (Table 3). Microinvasion was also present in 4 of 5 cases with IECA: 2 were low grade and 2 were high grade. The tumors were of stage I in all the 6 cases (stage IC in 5, and unspecified stage I in 1 case). The rate of recurrence was 13.2% (5 of 38 cases) for stage IC tumors, whereas both cases of stages II to III did not recur. The rate of recurrence was 1.7% (2 of 116 cases) in the group without microinvasion and 14.3% (4 of 28 cases) in the group with microinvasion. Recurrence was observed 4 to 48 months postoperatively (median 36 mo). Histologic examination of recurrent lesions was available in 5 patients, all of which showed at least some evidence of stromal invasion with a range from microinvasion to invasive adenocarcinomas with expansile and/or infiltrative pattern.

Significant risk factors for tumor recurrence included age less than 45 years, stage ≥ IC, IECA, and microinvasion (Table 4). The proportion of cases

TABLE 3. *Clinicopathologic features of 6 recurrent cases of mucinous LMP tumors*

Age	Stage	External surface status or peritoneal cytology	Histology of extraovarian lesion at diagnosis	Microinvasion (number)	IECA	Sampling ratio (no. sections/cm size)	Postoperative chemotherapy	Follow-up (postoperative duration)	Histology of recurrent lesion
44	I	Uncertain	None	High-grade (1 focus)	70%	0.17	No	Contralateral ovarian involvement (17 mo) Pelvic recurrence and lymph node metastasis (21 mo) Alive and well (59 mo)	IECA-like with MIC Nodal CA
13	IC	Surface growth with positive cytology	None	Low-grade (1 focus)	60%	1.46	No	Contralateral ovarian and lymph node metastasis (36 mo) DOD (49 mo)	Ovarian IECA-like with MIC Nodal CA
30	IC	Surface growth	None	High-grade (4 foci)	80%	2.00	Yes	Pulmonary and brain metastasis (36 mo) Alive with disease (42 mo)	CA in brain
31	IC	Positive cytology	None	None	10%	0.43	No	Peritoneal and hepatic metastasis before lost (48 mo)	Not available
38	IC	Surface growth with positive cytology	None	Low-grade (1 focus)	50%	1.38	Yes	Pelvic recurrence (4 mo) Pelvic recurrence and DOD (14 mo)	Mucinous LMP with IECA and MIC
30	IC	Earlier rupture	None	None	None	1.53	No	Contralateral ovarian and peritoneal metastasis (36 mo) DOD (46 mo)	Ovarian and peritoneal CA

CA indicates invasive carcinoma; DOD, dead of disease; IECA, intraepithelial carcinoma; MIC, microinvasion.

with stage $\geq$IC having recurrence was 6.9% for tumors without invasion (2 of 29 cases), 22.2% with low-grade microinvasion (2 of 9 cases), and 50.0% with high-grade microinvasion (1 of 2 cases), compared with none in stage IA (including 86 cases without invasion, 11 with low-grade microinvasion, and 4 with high-grade microinvasion). IECA $\geq$10% was also a significant risk of recurrence (Table 4). The 10% cutoff value for the amount of IECA was probably the most appropriate as the recurrent risk was only slightly changed when the threshold was raised to 20%, 30%, 40%, 50%, 60%, 70%, or 80% (risks being 14.3%, 16.0%, 19.0%, 21.1%, 18.8%, 15.4%, and 12.5%, respectively).

Among tumors with microinvasion, there was a trend toward recurrence for stage $\geq$IC, IECA $\geq$10%, age less than 45 years, and high architectural grade (Table 5). However, there was no statistically significant association between these variables and tumor recurrence. The characteristic of microinvasion (grade, number, extent, and pattern) also did not significantly affect the risk of recurrence.

When only tumors with stage $\geq$IC were considered, recurrence was significantly associated with the presence of IECA $\geq$10% ($P = 0.031$) and age less than 45 years ($P = 0.047$) (Table 6). There was a trend toward recurrence in cases with microinvasion (27.3% vs. 6.9%) but the difference was not statistically significant. The architectural grade showed no association with risk of recurrence.

To evaluate whether the possible prognostic value of age less than 45 years was dependent on other features, comparison between the age group less than 45 years and the age group $\geq$45 years was made. Tumors with IECA $\geq$10% was more common in the age group less than 45 years than in the older age group (31.2% vs. 18.7%) but the difference was not statistically significant ($P = 0.062$). There was no significant association between age less than 45 years with tumor stage $\geq$IC ($P = 0.421$), microinvasion ($P = 0.299$), or high architectural grade ($P = 0.285$) (data not shown).

In stage I tumors, the rate of recurrence was 1.3% in LMP tumors without IECA or microinvasion (1 of

TABLE 4. *Association between the clinicopathologic features of mucinous LMP tumors and tumor recurrence*

Feature	Total cases with follow-up (n = 144)	No. cases with recurrence (n = 6)	P*
Age			
<45 yr	79	6 (7.6%)	0.032
≥45 yr	65	0	
Ovarian surgery			
Unilateral resection or cystectomy	50	4 (8.0%)	0.183
Bilateral resection	94	2 (2.1%)	
Stage†			
IA	101	0	0.002
IC or more	40	5 (12.5%)	
Chemotherapy			
No	122	4 (3.3%)	0.228
Yes	22	2 (9.1%)	
Most severe nuclear grade			
1-2	85	1 (1.2%)	0.042
3	59	5 (8.5%)	
Architectural grade			
Low	83	2 (2.4%)	0.401
High	61	4 (6.6%)	
Intraepithelial carcinoma			
Absent or <10%	103	1 (1.0%)	0.007
≥10%	41	5 (12.2%)	
Microinvasion			
Absent	116	2 (1.7%)	0.013
Present	28	4 (14.3%)	
Stromal mucin deposits			
Absent	59	4 (6.8%)	0.227
Present	85	2 (2.4%)	

LMP indicates low malignant potential.
†Including the cases with staging detail.
*The Fisher exact test.

TABLE 5. *Association between clinicopathologic features of mucinous LMP tumors with stromal microinvasion and tumor recurrence*

Feature	Total cases with follow-up (n = 28)	No. cases with recurrence (n = 4)	P*
Age			
<45 yr	18	4 (22.2%)	0.265
≥45 yr	10	0	
Stage†			
IA	15	0	0.063
IC or more	11	3 (27.3%)	
Intraepithelial carcinoma			
Absent or <10%	11	0	0.132
≥10%	17	4 (23.5%)	
Architectural grade			
Low	8	0	0.295
High	20	4 (20.0%)	
No. microinvasive foci			
1	11	3 (27.3%)	0.269
>1	17	1 (5.9%)	
Nuclear grade of microinvasion			
Low	20	2 (10.0%)	0.555
High	8	2 (25.0%)	
Extent of microinvasion			
<1 mm^2	15	2 (13.3%)	1.000
≥1 mm^2	13	2 (15.4%)	
Pattern of microinvasion			
Single cells/clusters	16	3 (18.8%)	0.613
Infiltrative	12	1 (8.3%)	

LMP indicates low malignant potential.
†Including only cases with staging detail.
*The Fisher exact test.

79), 2.9% in tumors with IECA and without microinvasion (1 of 35), and 14.3% in tumors with microinvasion (4 of 28). For stage IC tumors, the rate of recurrence was 5.6% in LMP tumors without IECA or microinvasion (1 of 18), 11.1% in tumors with IECA only (1 of 9), and 27.3% in tumors with microinvasion (3 of 11), whereas no stage IA tumors recurred (60 LMP, 26 IECA, and 15 microinvasion).

The Kaplan-Meier analysis for survival showed a 10-year disease-free survival rate of 95.4% (Fig. 6). The disease-specific survival rate and the overall survival rate at 10 years were 97.4% and 92.4%, respectively.

DISCUSSION

Mucinous tumor of the ovary is a common neoplasm in Thailand. Among 239 epithelial LMP tumors identified in our institution during the studied period, mucinous tumors accounted for 71.5% and were much more common than serous LMP tumors with a ratio of 4.2:1 (171:41 cases). All cases of mucinous LMP tumors observed during this period were of intestinal type, whereas only a few cases of the endocervical-like (mullerian) counterpart have been recently identified in our institution. These findings were rather similar to those of a study from Korea in which endocervical-like tumors accounted for only 3.7% (3 of 81 cases) of mucinous LMP tumors (14), in contrast with a 10% to 15% proportion in Western studies (15). These observations suggest that endocervical-like mucinous LMP tumors are uncommon in the Far East. We postulate that the incidence of endocervical-like mucinous LMP tumors might parallel with that of serous or mixed mullerian LMP tumors, which are rather uncommon in our region.

Cumulative data regarding the recurrence or progression rate of intestinal-type mucinous LMP tumors from the recent series since 1998 are summarized in Table 7, along with the results of our study (2,4–6,14,16–18). We chose only the recent series with detailed histopathologic review in this analysis as these studies are likely to approach the

TABLE 6. *Association between clinicopathologic features of mucinous LMP tumors with stage ≥IC and tumor recurrence*

Feature	Total cases with follow-up (n = 40)	No. cases with recurrence (n = 5)	*P**
Age			
<45 yr	20	5 (25.0%)	0.047
≥45 yr	20	0	
Intraepithelial carcinoma			
Absent or <10%	27	1 (3.7%)	0.031
≥10%	13	4 (30.8%)	
Architectural grade			
Low	20	2 (10.0%)	1.000
High	20	3 (15.0%)	
Microinvasion			
Absent	29	2 (6.9%)	0.117
Present	11	3 (27.3%)	

LMP indicates low malignant potential.
*The Fisher exact test.

spectrum of mucinous tumors in a rather uniform pattern based on the current diagnostic criteria, particularly the exclusion of metastatic tumors (4,5,8), compared with earlier reports.

Mucinous LMP tumors without IECA (nuclear grade 1 to 2) generally had an excellent prognosis. Tumors with nuclear grade 2 had been classified as IECA in some studies (4,6) and probably in other studies in which the architectural criteria for IECA were included (14,16). The recent suggestions from the workshop on borderline tumors supported the use of only marked atypia (grade 3) for the diagnosis of IECA (1). Classification of tumors with nuclear grade 3 as IECA seems appropriate as the risk of recurrence in this group was significantly higher than the tumors without IECA in our study (8.5% vs. 1.2%, $P = 0.042$), whereas there was no significant risk difference between low-grade and high-grade architecture. Although tumors with grade 2 nuclei generally had a very low risk of disease progression, recurrence may rarely occur in the presence of tumor perforation, as seen in 1 of our cases, which recurred as an invasive carcinoma (Table 3).

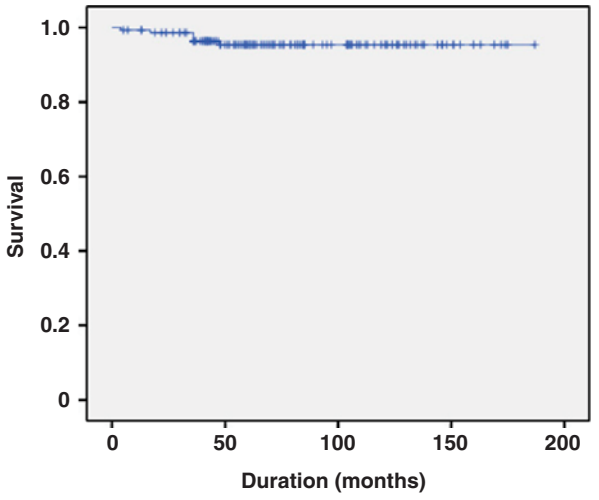

FIG. 6. Kaplan-Meier plot of disease-free survival.

The patients' age less than 45 years was a probable risk factor for recurrence in this study. To our knowledge, 6 cases of mucinous LMP tumors, which were reported earlier, which recurred and had available age information, ranged from 16 to 89 years (4,18,19). In combination with the 6 cases in our study, a total of 12 cases with recurrent disease had a mean age of 35.3 years (median 30.5) with 10 of these (83%) being younger than 45 years. The association between the patients' age and the risk of disease recurrence has not been emphasized earlier and deserves further study.

Microinvasion was observed in 18.1% of mucinous LMP tumors in this study, which is slightly more common than that of serous counterparts reported in the literature (10%) (20). The presence of microinvasion did not seem to be associated with an adverse outcome in most early studies of ovarian LMP tumors. However, microinvasion in serous LMP tumors has recently been reported as a possible adverse prognostic feature (20). It is of note that all cases of mucinous tumors with microinvasion, which were reported, earlier had stage I tumors and that the presence or the absence of stage IC tumors was mostly not mentioned (4–6,14,16). The results of our study suggest that microinvasion in mucinous LMP tumors might be an adverse feature in cases with stage ≥IC, although this may be at least partly explained by the association between microinvasion and IECA.

In a recent study, Kim et al. showed that microinvasion was present in 29.8% (39 of 131) of mucinous LMP tumors, which is a much higher proportion than those of our study (18.1%) and others (13.6%) (3). In that study, microinvasion was defined by the presence of epithelial cells within the stroma regardless of the presence of surrounding mucin granuloma or pseudomyxoma ovarii. The epithelial cells in such foci sometimes lacked nuclear atypia and were not easily recognized without the aid of cytokeratin immunohistochemistry (14). This may differ from our definition of microinvasion, which requires the presence of nuclear atypia of the epithelial cells and excludes typical mucin granuloma or pseudomyxoma ovarii that contains epithelial

TABLE 7. *Summary of the rate of recurrence and mortality rate in stage I ovarian mucinous LMP tumors in the recent series since 1998 (2,4–6,14,16–18)*

	Tumor recurrence			Tumor-related death		
Mucinous tumor stage I	Previous series	Present study	Recurrence rate	Previous series	Present study	Mortality rate
LMP without IECA	3*/256	1/79	1.2% (4/335)	0/256	1/79	0.3% (1/335)
Stage IA	0/43	0/60	0% (0/103)	0/43	0/60	0% (0/103)
Stage IC	0/6	1/18	4.2% (1/24)	0/6	1/18	4.2% (1/24)
LMP with IECA	2/125†	1/35	1.9% (3/160)	2/125†	0/35	1.3% (2/160)
Stage IA	0/62	0/26	0% (0/88)	0/62	0/26	0% (0/88)
Stage IC	2/9	1/9	16.7% (3/18)	2/9	0/9	11.1% (2/18)
Tumor with microinvasion	1/70	4/28	5.1% (5/98)	1/70	2/28	3.1% (3/98)
Stage IA	NA	0/15	0% (0/15)	NA	0/15	0% (0/15)
Stage IC	0/1	3/11	25.0% (3/12)	0/1	2/11	16.7% (2/12)

IECA indicates intraepithelial carcinoma; LMP, low malignant potential; NA, the number is not specified.
*Recurrent tumors in the ipsilateral ovary after cystectomy in 2 cases (17,18) and after incomplete removal in 1 case (18).
†IECA diagnosed by nuclear grade 3 alone in 20 cases (2,5) and combined nuclear grade 2 to 3 and/or complex architecture in 105 cases (4,6,14,16,17).

cells. It is possible that some microinvasions in their study might be classified as mucin granulomas containing epithelial cells in our study. In their study, there was no recurrence or death in the cases with microinvasion (14).

As there were some overlapping morphologic spectra between microinvasion and stromal mucin deposits with epithelial cells and sometimes the close vicinity between one and the other, we postulate that some low-grade microinvasions might arise from stromal mucin deposits. Although the neoplastic cells that enter into the stroma through the leakage and dissection of mucin may mostly become degenerated, some might gain benefit from this microenvironment, which commonly consists of infiltrating macrophages or reparative stroma. Release of growth factors and cytokines from macrophages, fibroblasts, and extracellular matrix may have a promoting effect on neoplastic progression as stimulation by these growth factors can lead to altered genetic expressions that affect cell adhesion system, cell cycle control, and survival of neoplastic cells (21). Furthermore, release of proteolytic enzymes from macrophages or fibroblasts may contribute to stromal invasion, without the need for protease production by neoplastic cells (22).

In this study, we divide stromal microinvasion into low-grade and high-grade, based on the nuclear grade of neoplastic cells within the microinvasion. Some clinicopathologic differences between tumors with low-grade and high-grade microinvasions were observed. Low-grade microinvasion was associated with stromal mucin deposits and tended to be associated with younger age and a lower proportion of IECA. However, the rate of recurrence in both groups (low-grade vs. high-grade microinvasion) was not significantly different. Among tumors with microinvasion, there was no significant association between the clinicopathologic variables and recurrence. The small number of cases in this group might be a limitation in the assessment for statistical significance.

A semiquantitative stratification of IECA by a 10% cutoff value might also be useful to indicate the risk of recurrence, which was 12.2% in this study. Although quantification of IECA is a subjective method and could be a source of interobserver variation, 22 of 23 cases with IECA less than 10% in this study had an amount of IECA of only 5% or less. Among cases with a significant proportion of IECA ($\geq$10%), there was only slight variation in the risk of recurrence (12.5–21.1%) with the other percentage threshold of IECA ranging from 20% to 80%. These findings support the use of the 10% threshold of IECA quantification for prognostic consideration. Among tumors with microinvasion, cases showing IECA $\geq$10% had a higher risk of recurrence than those with IECA less than 10% or without IECA, although the difference was not statistically significant. As the grading or classification of microinvasion has not been uniformly defined, we suggest that the presence of microinvasion and IECA $\geq$10% should be reported separately to indicate the sequentially increasing risk. Comments on the appearance or nuclear grade of microinvasion may be added for an academic interest and future study.

The presence of IECA and earlier perforation or surface involvement of tumor are the important features shared by almost all cases of mucinous LMP tumors with recurrence or disease progression in this study. It is important that mucinous LMP tumor should be staged and sampled for pathologic

examination to identify the worst degree of epithelial proliferation and to document the status of the external surface or extraovarian/peritoneal involvement. Nevertheless, the recent report by Ludwick et al. (19) described a progressive case of stage IA mucinous tumors with IECA and microinvasion. The finding emphasizes that progression of stage IA mucinous LMP tumors may occur although this should be uncommon in general practice. The possibility that there might be some occult invasive areas that were not sampled has been considered as an explanation for such occurrence (19). However, in a prospective view, it would not be possible to predict if there is any unsampled invasive focus left after a careful gross examination and sampling of each ovarian mass. The current suggestion for adequate sampling of ovarian epithelial LMP tumors has replaced the general guideline of 1 section per 1 cm size with 2 sections per 1 cm of tumor $\geq$10 cm (23), which is the level of sampling that may not have been reached in most studies (19). We agree with earlier suggestions by Ludwick et al. (19) to sample 1 section per 1 cm of tumor and to submit additional sampling to reach 2 sections per 1 cm in cases showing adverse features such as IECA, microinvasion, or tumor perforation.

Recurrent lesions of mucinous LMP tumors in this study frequently had morphologic features of invasive carcinoma at the extraovarian sites, whereas contralateral ovarian involvement at the time of recurrence may show only IECA-like features with microinvasion. It has been proposed that such discordance may be related to some factors associated with ovarian stromal cells or ovarian microenvironment (24). This might be comparable with the "maturation phenomenon" in metastatic adenocarcinoma to the ovary (25).

The use of the term "low malignant potential" or "borderline" or "atypical proliferative" tumors should be continued as the staging procedure is still an important part in the prognostic evaluation of these tumors and the prediction of cases with disease recurrence has not always been possible based on routine morphologic examination. Application of molecular biomarkers to predict the aggressive behavior is interesting and merits further studies, although the rather small proportion of patients with poor clinical outcome could be a limitation in recruiting the cases.

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