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Clinicopathologic and Molecular Characteristics of Mesonephric Adenocarcinoma Arising From the Uterine Body

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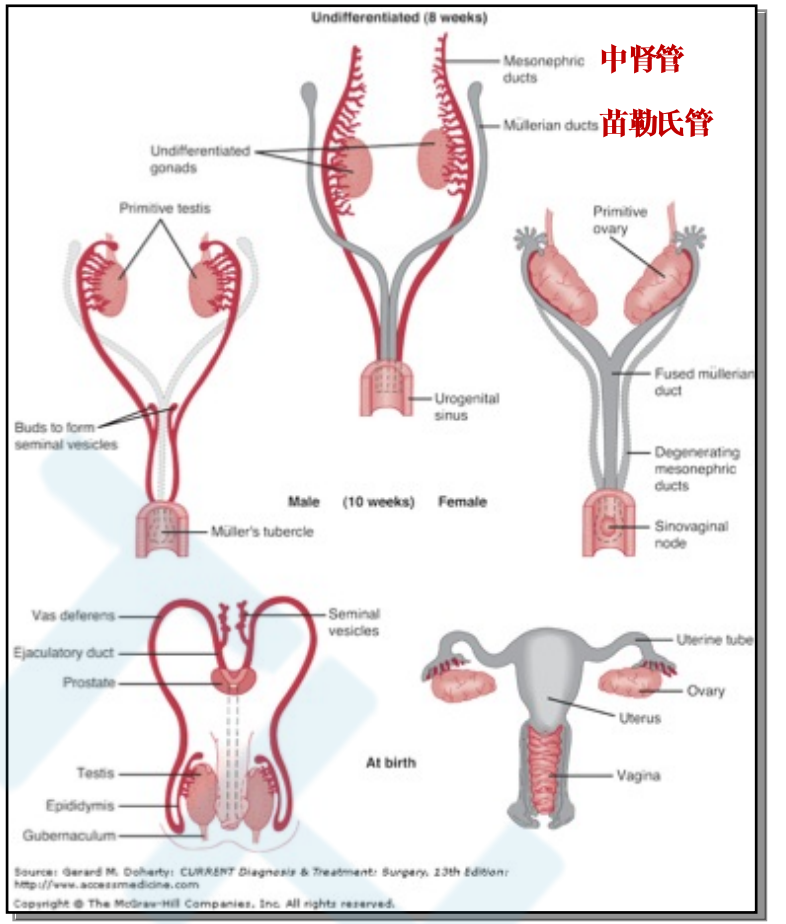
BACKGROUND

Mesonephric Carcinoma

- **Definition：** An adenocarcinoma arising from mesonephric remnants.
- These tumous are not associated with high-risk HPV.
- **Macroscopy**
  - These tumors commonly arise in the lateral to posterior cervical wall and may be deeply invasive and bulky or exophytic.
  - They more commonly involve the lower uterine segment than do other cervical adenocarcinomas.

Mesonephric duct

- 哺乳动物在胚胎早期，雌、雄两性都发生两套原始生殖管道——一对中肾管(mesonephric duct)和一对苗勒氏管(Mullerian duct，又称中肾旁管（paramesonephrie duct）。
- 在雄性，中肾管后来演变为雄性生殖管道，苗勒氏管退化；
- 在雌性，中肾管退化，苗勒氏管演变为雌性生殖管道(输卵管、子宫及阴道上端)。



Mesonephric remnants

- The remnants are sometimes found within the lateral wall of the cervix, mesoovaries, or broad ligaments. Although much more rare, the remnants can also be found in the lateral wall of the vagina or uterine corpus.

Ando *et al. Diagnostic Pathology* (2017) 12:63
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Diagnostic Pathology

CASE REPORT Open Access

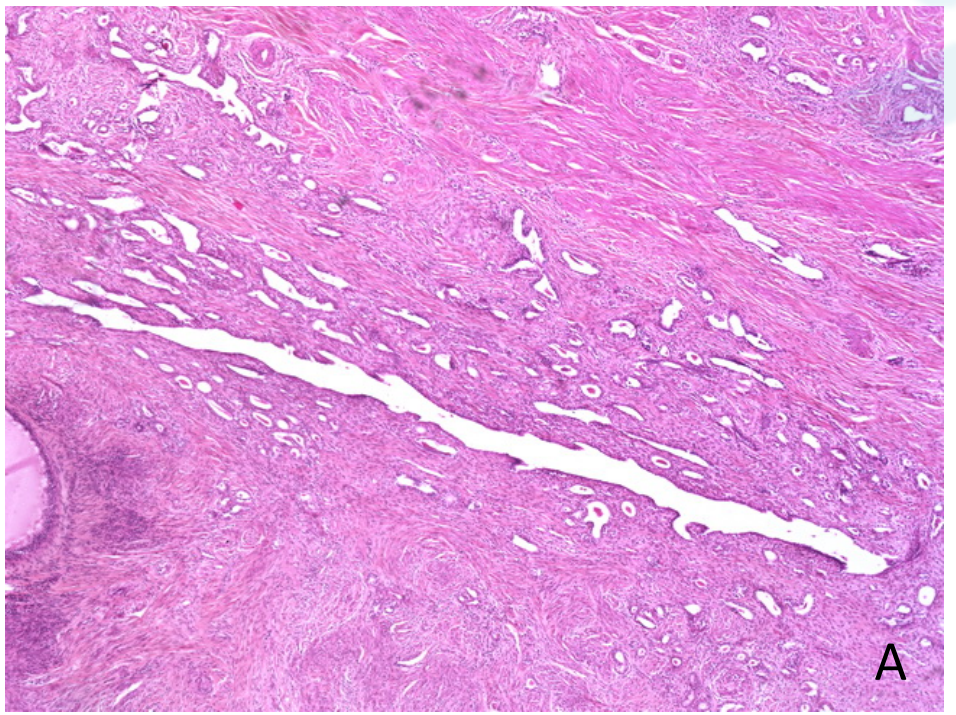
Mesonephric adenocarcinoma of the uterine corpus with intracystic growth completely confined to the myometrium: a case report and literature review

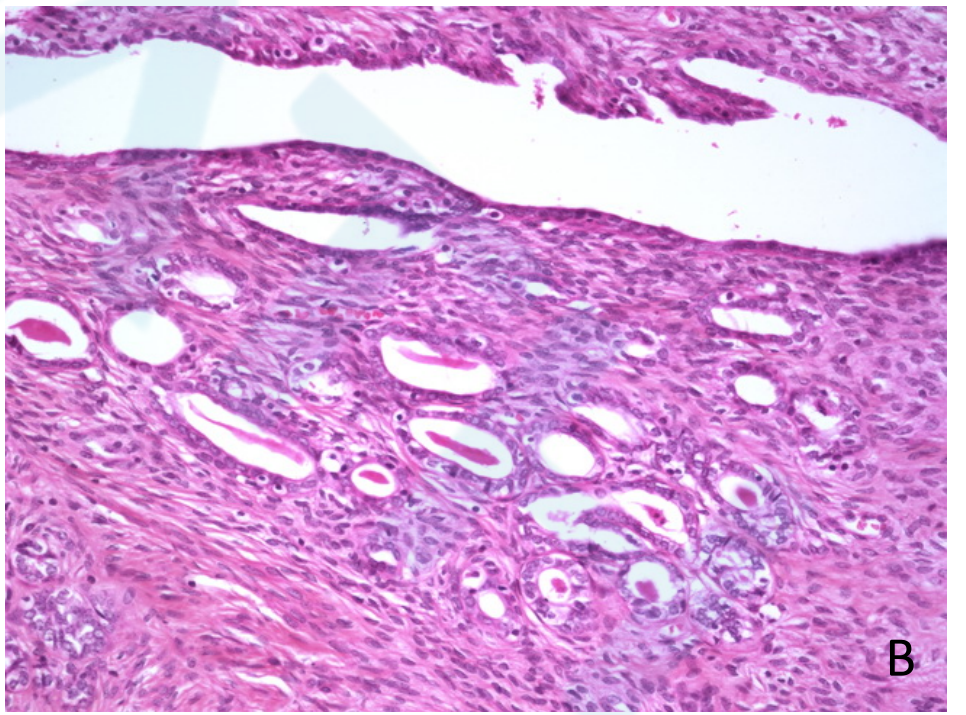
Hiroka Ando[1*], Yuko Watanabe[2], Minori Ogawa[2], Hiromi Tamura[1], Tomomi Deguchi[2], Kayo Ikeda[2], Mayumi Fujitani[2], Mitsunori Shioji[2], Tomoko Tsujie[2], Reiko Doi[1], Akinori Wakimoto[2] and Shiro Adachi[1]

Mesonephric remnants

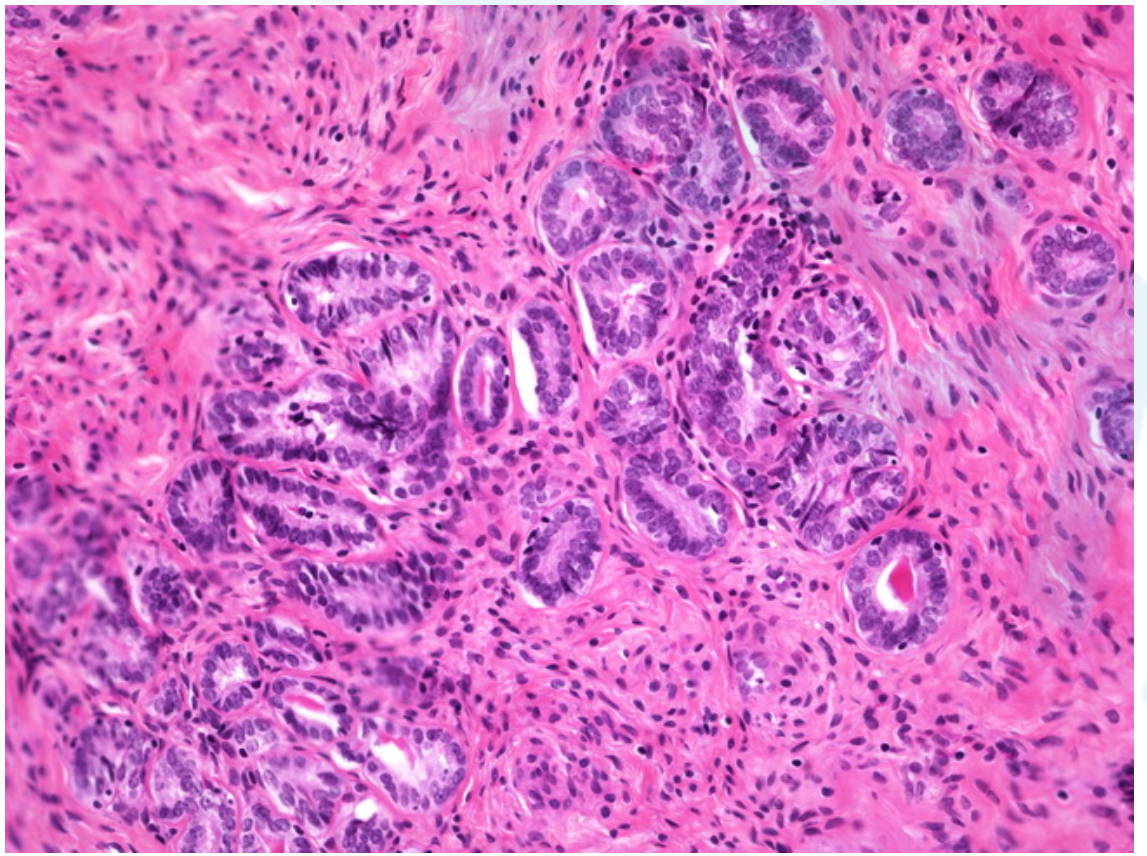
Mesonephric duct remnants are found deep in the **lateral endocervical wall** of about **20% adult cervices**. Usual appearance consists of **small glands or tubules** that may be arranged around a **mother duct(A).**

The lining epithelium consists of a **single layer of cuboidal or columnar epithelium** with scant cytoplasm. Nuclei are bland and mitotic activity is not increased. Many of the tubules contain dense **eosinophilic material(B)**.





Mesonephric Duct Hyperplasia (MDH)



Three types of MDH have beendescribed : **lobular** (shown here), **diffuse**, and **ductal** types.

Distinction of MDH from mesonephric adenocarcinoma is important.
Presence of a mass, clinical symptoms, nuclear atypia, high mitotic activity, vascular invasion and high Ki-67 reactivity support malignancy.

Mesonephric Carcinoma

- Histopathology ：a combination of diverse growth patterns, including tubular, glandular, papillary, retiform, glomeruloid and spindle cell patterns.
- IHC:
  - Uniformly reactive: CK , EMA
  - Often express: CR、Vimentin and CD10(apical and luminal)
  - May express: PAX8、TTF1、p16 focally
  - Negative : ER、PR、CEA

- Previous studies have documented that mesonephricm remnant in any location can be the origin of mesonephric adenocarcinoma(MNAC). Although most cases of MNAC are found in the uterine cervix (UC), several cases of MNAC arising from the ovaries, vagina, and uterine corpus have been reported.

- Most patients with MNAC of the UC(UC-MNAC) present at FIGO stage I.
- Distant metastases at initial diagnosis are detected in ~ 5% of UC-MNAC patients.
- Thirty-two percent of FIGO stage I UC-MNAC patients develop recurrence even after curative resection.
- This rate of recurrence is substantially higher than that of FIGO stage I cervical squamous cell carcinoma (11.0%) and usual-type endocervical adenocarcinoma (16.0%), suggesting that patients with UC-MNAC have a worse prognosis than those with more common types of cervical carcinoma.

- Because of the limited number of cases reported, less is known regarding the clinical outcomes of MNAC arising from the uterine body (UB-MNAC). Most publications on UB-MNAC are individual case reports.
- In this study, we analyzed the clinical characteristics, histopathologic features, and immunohistochemistry of UB-MNAC. Using NGS technology, we investigated the molecular genetic alterations associated with UB-MNAC.

MATERIALS AND METHODS

- Case Selection
  - Severance Hospital (Seoul, Republic of Korea) , 2012 and 2017
  - The inclusion criteria were:
    - (1) histopathologically confirmed MNAC;
    - (2) no involvement of the UC and low uterine segment;
    - (3) tumor epicenter within the myometrium of the UB.
  - 11 cases of UB-MNAC were included in this study.

MATERIALS AND METHODS

- Medical Record Review
  - pathology reports, and gross photographs.
  - Clinical details
  - pathologic characteristics
- Pathologic Examination
  - Two independent pathologists specialized in gynecologic oncology

MATERIALS AND METHODS

- Immunohistochemistry
  - calretinin, CD10, cytokeratin, ER, GATA3 ,p16, p53 ,PAX2, PR, and PTEN
  - p53
    - missense-mutation(diffuse and strong, >60% of tumor cell nuclei),
    - nonsense-mutation(absent , <5%),
    - wild-type pattern(focal and weakly positive)
  - p16
    - positive (diffuse) : continuous and strong, nuclear or nuclear plus cytoplasmic staining.
    - negative (patchy): focal nuclear staining or wispy, blob-like, puddled, or scattered cytoplasmic staining

MATERIALS AND METHODS

- Next-generation Sequencing
- Literature Review
- Statistical Analysis
  - χ^2 test or Fisher exact test
  - Multivariate logistic regression with a backward stepwise
  - Statistical analyses were carried out using PASW Statistics for Windows (version 18.0; IBM, Armonk, NY).
  - Statistical significance was defined as a *P*-value <0.05.

RESULTS

EC 5例
MANC 2例
CS 1例
NA 3例

IA/1B 7例

III\IV 4例

TABLE 1. Clinical Characteristics of UB-MNAC

Case	Year Reported	Age (y)	Presenting Symptom/Sign	CA-125 (U/mL)	Preoperative Diagnosis Through EM Curettage	Surgical Treatment	FIGO Stage	Postoperative Clinical Course	PFS (mo)	OS (mo)	Current Status
12	2017	58	Vaginal bleeding	65.0	EC	TH+BSO+PLND +PALND	IIIB	RTx+CTx (carboplatin+paclitaxel, 3 cycles) Lung metastasis CTx (carboplatin+paclitaxel, 3 cycles) Stable disease	50	56	AWD
13	2017	55	Vaginal bleeding	WNL	NA	TH+BSO	IVB	RTx+CTx (carboplatin+paclitaxel, 6 cycles) Partial response CTx (carboplatin+paclitaxel, 6 cycles) Increased size of lung metastasis and elevated CA-125 CTx (carboplatin+paclitaxel, 9 cycles) Stable disease	14	21	AWD
14	2017	54	Vaginal bleeding	WNL	NA	TH+BSO	IIIB	RTx+CTx (carboplatin+paclitaxel, 6 cycles) Lung metastasis CTx (doxorubicin+cisplatin +cyclophosphamide, 3 cycles) Stable disease	9	20	AWD
15	2017	60	Vaginal bleeding	WNL	CS	TH+BSO+PLND +PALND	IA	CTx (carboplatin+paclitaxel, 6 cycles) Lung metastasis CTx (carboplatin+paclitaxel, 3 cycles) Stable disease	10	14	AWD
16	2017	53	Vaginal bleeding	WNL	EC	TH+BSO+PLND +PALND	IA	No postoperative treatment No specific event	NA	12	NED
17	2017	57	Vaginal bleeding	WNL	EC	TH+BSO+PLND +PALND	IIIC	CTx (carboplatin+paclitaxel, 6 cycles) Lung metastasis CTx (carboplatin+paclitaxel, 3 cycles) Stable disease	8	13	AWD
18	2017	70	Vaginal bleeding	WNL	EC	TH+BSO+PLND +PALND	IB	RTx No specific event	NA	10	NED
19	2017	61	Vaginal bleeding	WNL	MNAC	TH+BSO+PLND +PALND	IB	CTx (carboplatin+paclitaxel, 3 cycles) No specific event	NA	7	NED
20	2017	65	Vaginal bleeding	WNL	MNAC	TH+BSO+PLND +PALND	IB	No postoperative treatment No specific event	NA	6	NED
21	2017	52	LAP	101.0	NA	TH+BSO+PLND +PALND	IIIC	RTx+CTx (carboplatin+paclitaxel, 2 cycles) No specific event	NA	3	NED
22	2017	59	Vaginal bleeding	WNL	EC	TH+BSO+PLND +PALND	IA	No postoperative treatment No specific event	NA	11	NED

AC indicates adenocarcinoma; AWD, alive with disease; BSO, bilateral salpingo-oophorectomy; CA-125, cancer antigen 125; CS, carcinosarcoma; CTx, chemotherapy; DOD, died of disease; EC, endometrioid carcinoma; EM, endometrium; LAP, low abdominal pain; NA, not applicable; NED, no evidence of disease; OS, overall survival; PALND, para-aortic lymph node dissection; PFS, progression-free survival; PLND, pelvic lymph node dissection; RTx, radiation therapy; TH, total hysterectomy; WNL, within normal limit.

RESULTS

TABLE 1. Clinical Characteristics of UB-MNAC

Case	Year Reported	Age (y)	Presenting Symptom/Sign	CA-125 (U/mL)	Preoperative Diagnosis Through EM Curettage	Surgical Treatment	FIGO Stage	Postoperative Clinical Course	PFS (mo)	OS (mo)	Current Status
1	1995[10]	58	Polyuria	WNL	EC 1例 MANC 4例 AC 1例 NA 5例	TH+BSO	IA/1B 9例 III\IV 2例	No postoperative treatment Paraaortic and mediastinal LN metastasis CTx (cisplatin+cyclophosphamide)	4	8	DOD
2	2001[11]	33	LAP	47.0		TH+BSO+P		RTx No specific event	NA	8	NED
3	2003[12]	33	LAP	41.0		TH+BSO+PLND +PALND	IB	RTx Lung, abdomen, and perihepatic LN metastasis and elevated CA-125 CTx (carboplatin+paclitaxel, 12 cycles) Partial response	10	22	AWD
4	2004[13]	37	Vaginal bleeding	NA	NA	TH+BSO	IB	No postoperative treatment No specific event	NA	45	NED
5	2006[14]	81	Vaginal bleeding	55.0	MNAC	TH+BSO+PLND +PALND	IB	No postoperative treatment No specific event	NA	9	NED
6	2008[15]	73	Multiple pulmonary nodules	WNL	NA	TH+BSO	IVB	CTx (carboplatin+paclitaxel) Increased size of lung metastasis and abdominal recurrence CTx (carboplatin+paclitaxel) Stable disease	6	28	AWD
7	2014[16]	55	Vaginal bleeding	NA	MNAC	TH+BSO+PLND	IB	No postoperative treatment No specific event	NA	7	NED
8	2014[16]	62	Vaginal bleeding	NA	MNAC	TH+BSO+PLND	IB	No postoperative treatment No specific event	NA	1	NED
9	2016[17]	66	Vaginal bleeding	WNL	EC	TH+BSO+PLND	IB	No postoperative treatment No specific event	NA	2	NED
10	2016[18]	55	Vaginal bleeding	163.8	AC with sarcomatous feature	TH+BSO+PLND	II	CTx (cisplatin+paclitaxel, 4 cycles) Mediastinal LN metastasis, abdominal recurrence, and elevated CA-125 CTx (pirarubicin+cisplatin+ifosfamide)	8	12	DOD
11	2016[18]	62	Vaginal bleeding	WNL	MNAC	TH+BSO+PLND	IIIC	RTx+CTx (cisplatin+docetaxel) No specific event	NA	16	NED

RESULTS

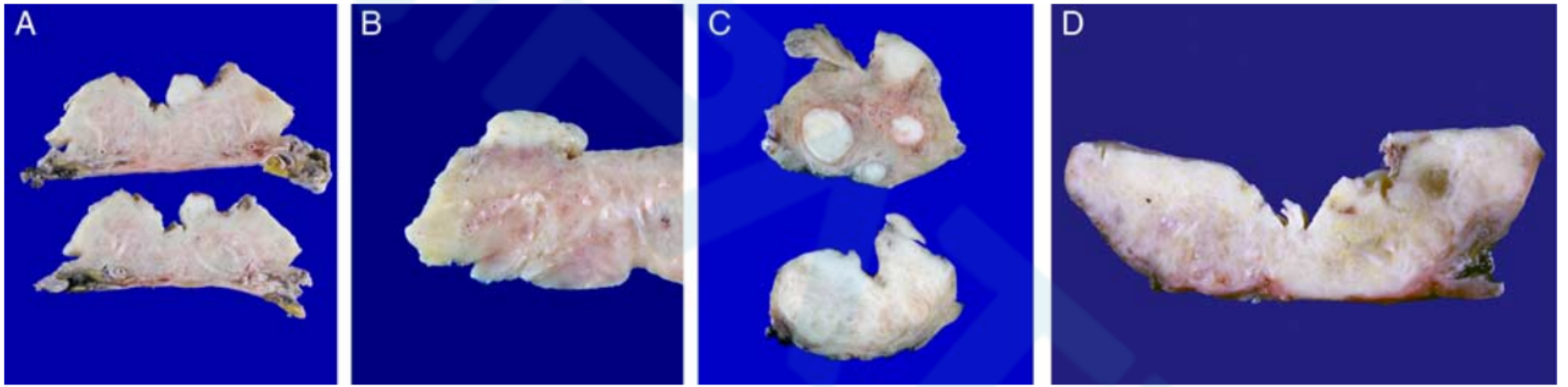


FIGURE 1. Gross findings of UB-MNAC. A and B, The tumor protrudes into the endometrial cavity, without grossly definite myometrial invasion. C, The tumor deeply infiltrates into the myometrium (lower panel). The cut surface of the tumor closely resembles that of intramural leiomyoma (upper panel). D, The tumor infiltrates the entire uterine wall.

RESULTS

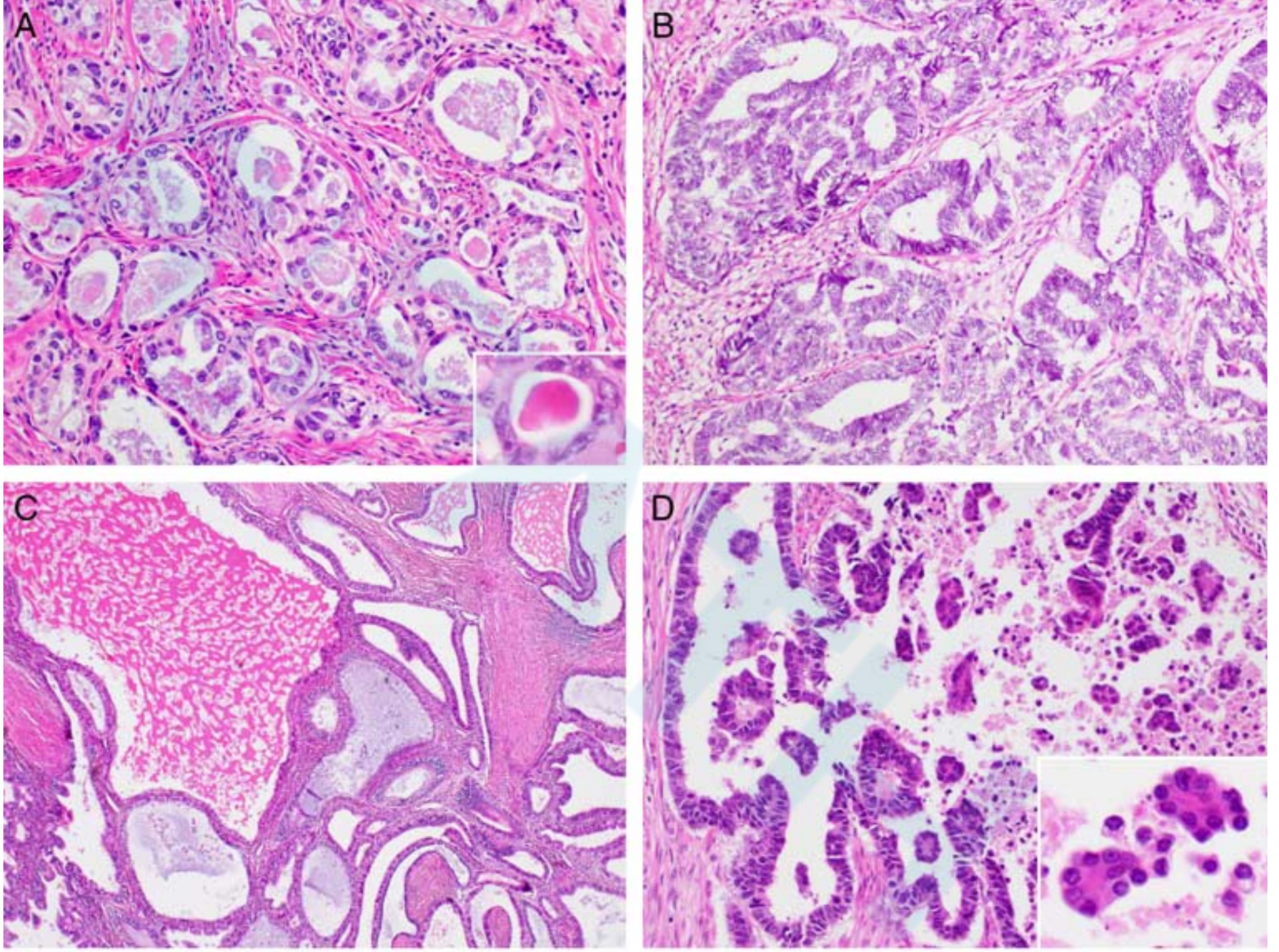
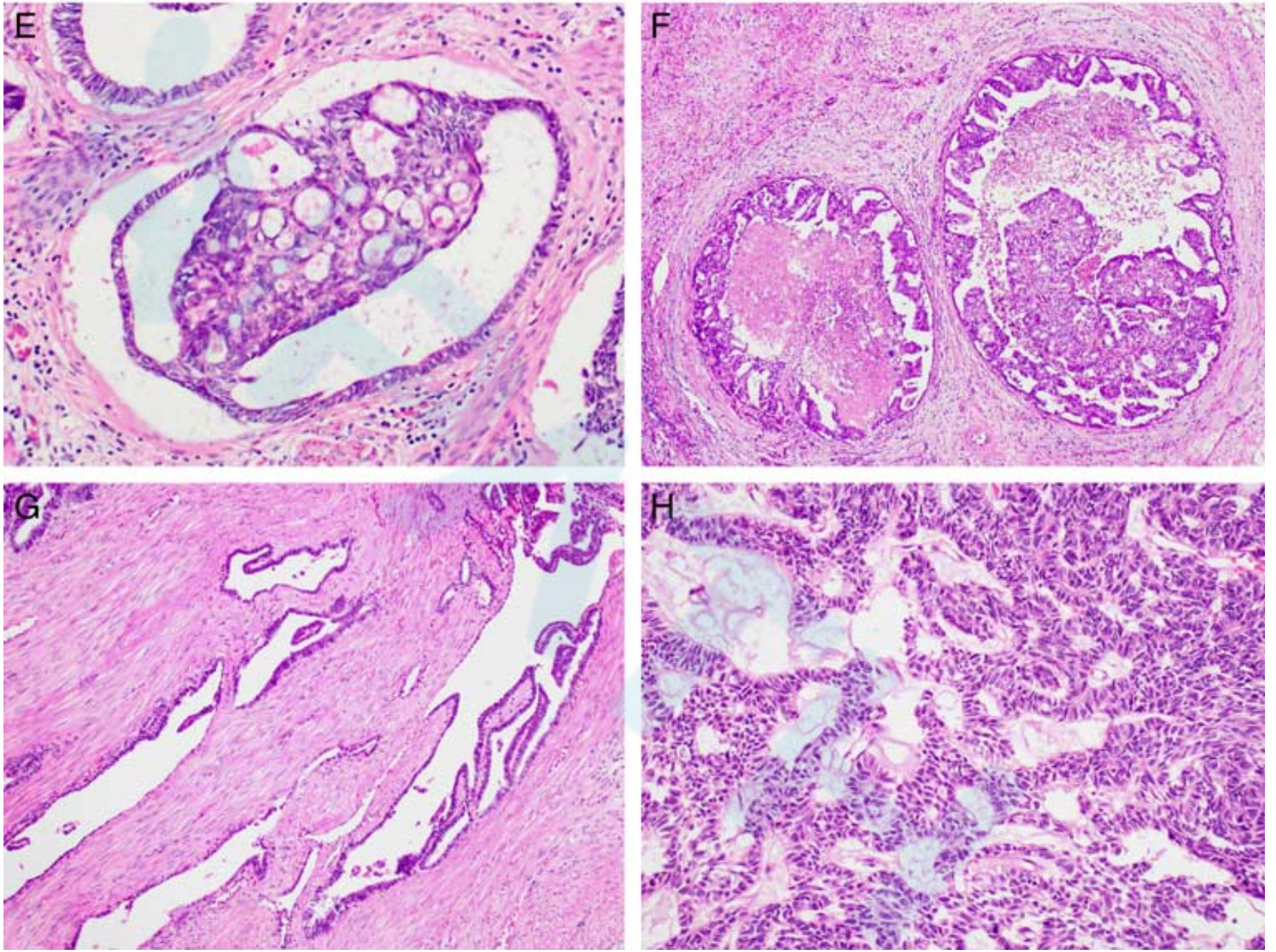


FIGURE 2. Histopathologic findings of UB-MNAC: architectural patterns.
A, Tubular pattern. The tubules are lined by a single layer of cuboidal cells and possess intraluminal eosinophilic material (inset).
B, Glandular pattern. The endometrioid-like glands are lined by several layers of columnar epithelium.
C, Glandular pattern. Some glands are cystically dilated and irregular in shape.
D, Papillary pattern. Note the intraluminal papillary projections and floating micropapillary tufts (inset).

RESULTS

FIGURE 2. Histopathologic findings of UB-MNAC: architectural patterns.
E, Glomeruloid pattern. Dilated glands contain intraluminal cribriform structures with 2 points of attachment, resembling a renal glomerulus.
F, Comedonecrosis-like pattern showing necrotic debris centrally located in the dilated glandular lumina and surrounded by tumor cells arranged in a papillary, cribriform, or solid pattern.
G, Retiform pattern showing elongated, slit-like branching tubules.
H, Sex cord-like pattern showing anastomosing trabeculae and cords of tumor cells with background of edematous or myxoid stroma.



RESULTS

1. Size:1.5 to 7.4cm (median, 3.7cm)

2. border: 5 ill-defined, 6 well-defined

3. Mitotic counts : from 4 to 23/10 high-power fields (median, 15/10 high-power fields)

4. Parametrial extension: 4/11

5. LVI: 7/11

In all cases, neither mesonephric remnant nor mesonephric hyperplasia was identified in the adjacent myometrium.

TABLE 2. Pathologic Features of UB-MNAC

	Gross Finding		Histopathologic Finding													
			Architecture													
Case	Tumor Size (cm)	Tumor Border	Tubular	Glandular	Papillary	Retiform	Glomeruloid	Sex Cord-like	Comedonecrosis-like	Sarcomatous Component	Invasion Depth	FIGO Stage	Nuclear Atypia	CTCN	Mitosis	LVI
1	14.0	Ill-defined	Present	Present	Present	Absent	Absent	Present	NA	Present (spindle cell)	SM to DM	IB	Severe	Present	Frequent	Present
2	8.0	Well-defined	Present	Present	Absent	Present	Absent	Absent	NA	Present (spindle cell)	SM to DM	IB	Moderate	Present	Up to 3/ HPF	NA
3	8.0	Ill-defined	Present	Present	Absent	Present	Absent	Absent	NA	Present	SM to DM	IB	NA	NA	NA	NA
4	3.5	Well-defined	Present	Present	Absent	Present	Absent	Absent	NA	Present (ESS-like)	EM to DM	IB	Mild to moderate	NA	2/10 HPFs	Absent
5	3.7	Well-defined	Present	Present	Present	Absent	Absent	Absent	NA	Absent	EM to DM	IB	NA	NA	NA	NA
6	8.0	Well-defined	Present	Present	Present	Present	Present	Absent	NA	Absent	EM to DM	IVB	Mild	Present	27/10 HPFs	Present
7	3.5	Well-defined	Present	Present	Absent	Present	Present	Present	NA	Present (spindle cell)	SM to DM	IB	NA	NA	NA	NA
8	8.0	Well-defined	Present	Present	Absent	Present	Present	Present	NA	Present (spindle cell)	EM to DM	IB	NA	NA	NA	NA
9	2.7	Well-defined	Present	Present	Present	Present	Present	Absent	NA	Absent	EM to DM	IB	Mild to moderate	Absent	10/10 HPFs	NA
10	3.5	NA	NA	NA	NA	NA	NA	NA	NA	Present	SM to DM	II	NA	NA	NA	Absent
11	5.8	NA	NA	NA	NA	NA	NA	NA	NA	Present	EM to DM	IIIC	NA	NA	NA	Absent
12	2.3	Ill-defined	Present	Present	Present	Present	Absent	Absent	Absent	Absent	EM to PM	IIIB	Mild to moderate	Present	15/10 HPFs	Present
13	7.4	Well-defined	Present	Present	Present	Present	Present	Absent	Absent	Absent	EM to DM	IVB	Mild to moderate	Present	23/10 HPFs	Present
14	4.3	Ill-defined	Present	Present	Present	Present	Present	Present	Present	Present (spindle cell)	EM to PM	IIIB	Severe	Present	19/10 HPFs	Present
15	4.1	Ill-defined	Present	Present	Present	Present	Present	Absent	Absent	Present (spindle cell)	EM to SM	IA	Severe	Present	21/10 HPFs	Present
16	2.3	Well-defined	Present	Present	Present	Present	Present	Present	Absent	Present (ESS-like)	EM to SM	IA	Mild to moderate	Absent	4/10 HPFs	Absent
17	5.7	Ill-defined	Present	Present	Present	Present	Present	Absent	Present	Absent	SM to PM	IIIC	Severe	Present	19/10 HPFs	Present
18	2.6	Well-defined	Present	Present	Present	Present	Present	Present	Absent	Absent	EM to DM	IB	Mild to moderate	Absent	8/10 HPFs	Absent
19	2.2	Well-defined	Present	Present	Present	Present	Present	Present	Absent	Absent	EM to DM	IB	Mild to moderate	Absent	7/10 HPFs	Present
20	3.7	Well-defined	Present	Present	Present	Present	Absent	Absent	Absent	Absent	EM to DM	IB	Severe	Present	5/10 HPFs	Absent
21	4.8	Ill-defined	Present	Present	Present	Present	Absent	Absent	Absent	Present (spindle cell)	EM to PM	IIIC	Mild to moderate	Present	17/10 HPFs	Present
22	1.5	Well-defined	Present	Present	Present	Present	Absent	Absent	Absent	Absent	EM to SM	IA	Mild to moderate	Absent	6/10 HPFs	Absent

CTCN indicates coagulative tumor cell necrosis; DM, deep myometrium; EM, endometrium; ESS, endometrial stromal sarcoma; HPFs, high-power fields; LVI, lymphovascular invasion; NA, not applicable; PM, parametrium; SM, superficial myometrium.

RESULTS

TABLE 3. Association Between Metastasis and Pathologic Characteristics of UB-MNAC

Characteristics	Univariate: Metastasis Present	Univariate: Metastasis Absent	Univariate P	Multivariate P
Tumor size				
>4 cm	5 (100.0)	0	0.015*	0.102
≤4 cm	1 (16.7)	5 (83.3)		
Tumor border				
Ill-defined	5 (100.0)	0	0.015*	0.102
Well-defined	1 (16.7)	5 (83.3)		
Architecture				
Tubular				
Present	6 (54.5)	5 (45.5)	—	—
Absent	0	0		
Glandular				
Present	6 (54.5)	5 (45.5)	—	—
Absent	0	0		
Papillary				
Present	6 (54.5)	5 (45.5)	—	—
Absent	0	0		
Retiform				
Present	6 (54.5)	5 (45.5)	—	—
Absent	0	0		
Glomeruloid				
Present	4 (57.1)	3 (42.9)	1.000	—
Absent	2 (50.0)	2 (50.0)		
Sex cord-like				
Present	1 (25.0)	3 (75.0)	0.242	—
Absent	5 (71.4)	2 (28.6)		
Comedonecrosis-like				
Present	2 (100.0)	0	0.455	—
Absent	4 (44.4)	5 (55.6)		
Sarcomatous component				
Present	3 (75.0)	1 (25.0)	0.545	—
Absent	3 (42.9)	4 (57.1)		
Extrauterine extension				
Present	4 (100.0)	0	0.061	—
Absent	2 (28.6)	5 (71.4)		
Invasion depth				
EM-SM	5 (62.5)	3 (37.5)	0.545	—
DM-PM	1 (33.3)	2 (66.7)		
FIGO stage				
III-IV	5 (100.0)	0	0.015*	0.046*
I-II	1 (16.7)	5 (83.3)		
Nuclear atypia				
Severe	3 (75.0)	1 (25.0)	0.545	—
Mild to moderate	3 (42.9)	4 (57.1)		
Coagulative tumor cell necrosis				
Present	6 (85.7)	1 (14.3)	0.015*	0.102
Absent	0	4 (100.0)		
Mitosis				
> 10/10 HPFs	6 (100.0)	0	0.002*	0.025*
< 10/10 HPFs	0	5 (100.0)		
Lymphovascular invasion				
Present	6 (85.7)	1 (14.3)	0.015*	0.046*
Absent	0	4 (100.0)		

HPFs indicates high-power fields.
*Statistically significant.

Six characteristics were significantly associated with the development of metastasis

1.including large tumor size (>4 cm),

2.ill-defined tumor border,

3.advanced FIGO stages (III to IV),

4.presence of coagulative tumor cell necrosis,

5.high mitotic activity (>10/10 high-power fields),

6.presence of lymphovascular invasion,

RESULTS

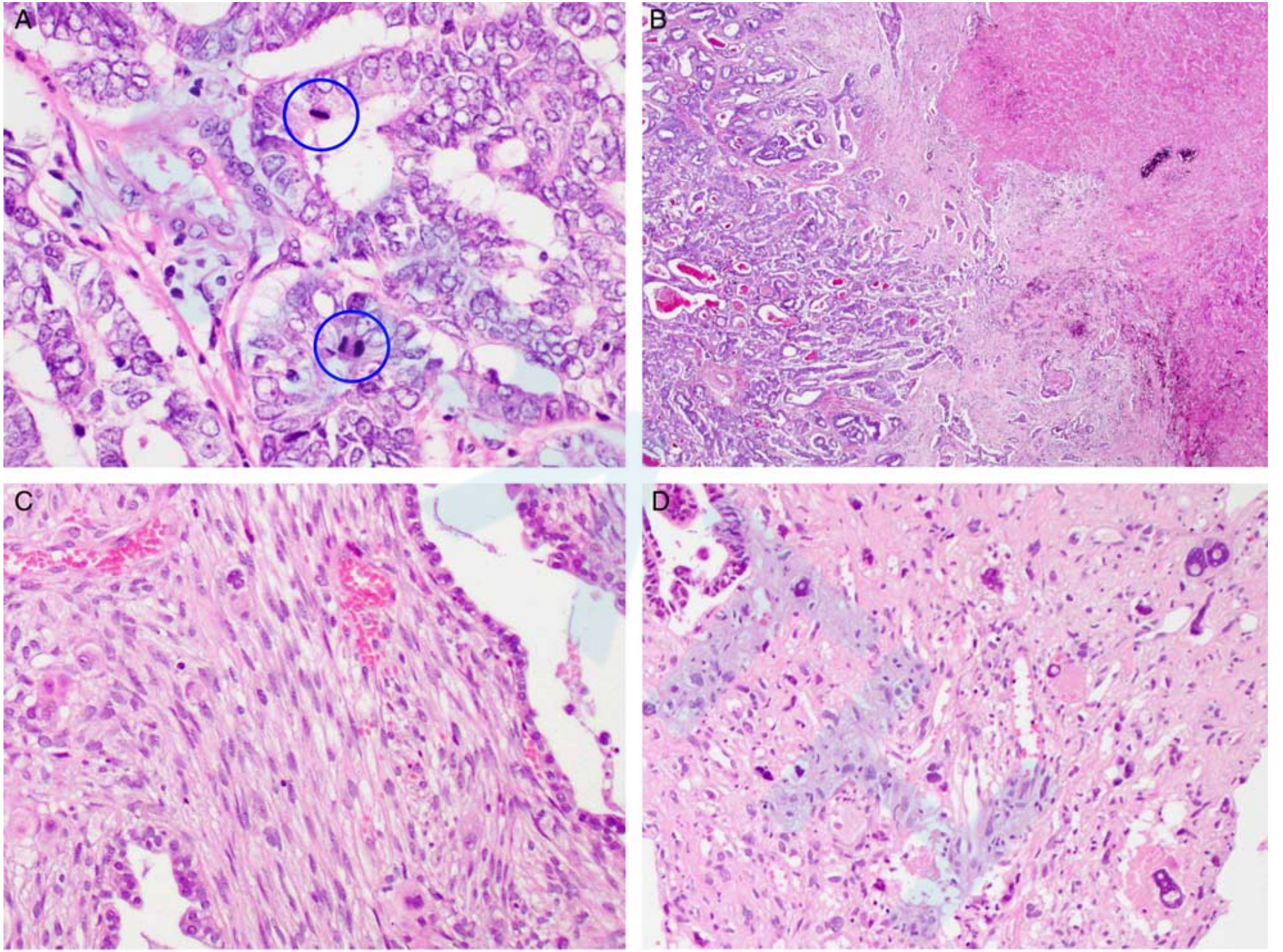


FIGURE 3. Histopathologic findings of UB-MNAC: adverse pathologic characteristics and metastasis.
A, High mitotic activity. Blue circles indicate mitotic figures.
B, Coagulative tumor cell necrosis.
C, Sarcomatous component resembling nonspecific spindle cell sarcoma.
D, Sarcomatous component showing severe nuclear pleomorphism. Note large, bizarre nuclei with intranuclear vacuoles (right upper and lower corners).

RESULTS

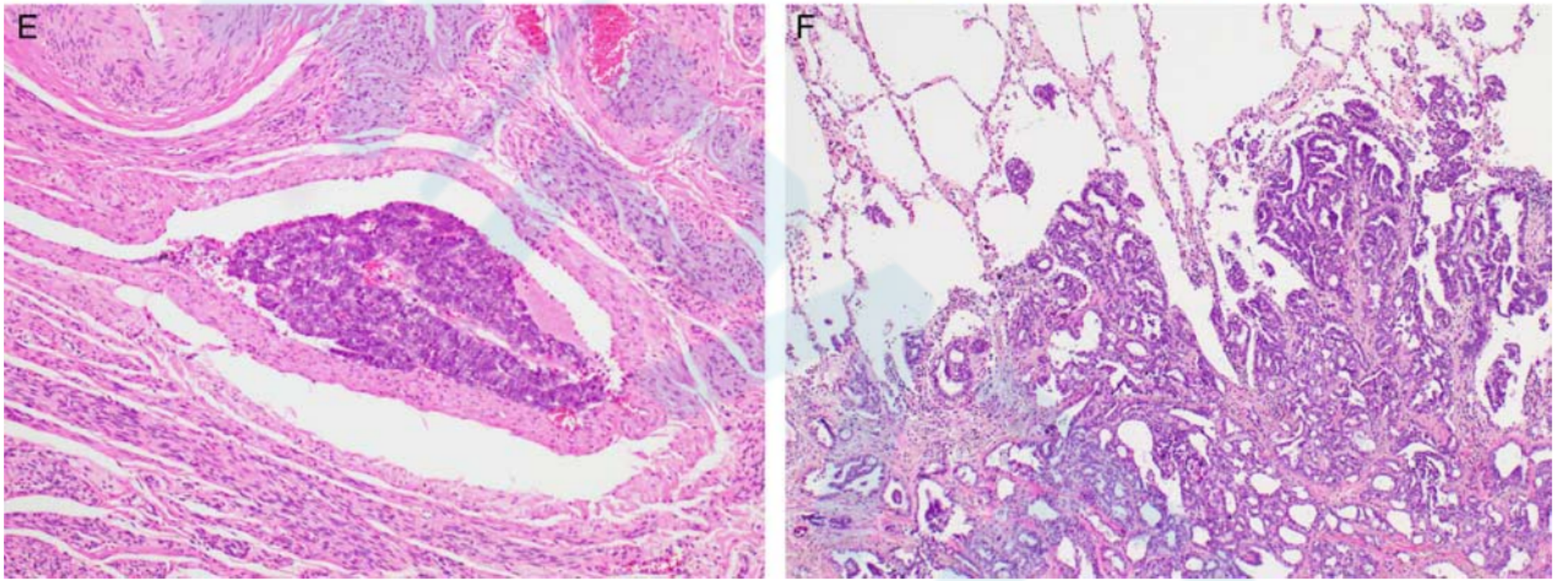


FIGURE 3. Histopathologic findings of UB-MNAC: adverse pathologic characteristics and metastasis. A, High mitotic activity. Blue circles indicate mitotic figures. B, Coagulative tumor cell necrosis. C, Sarcomatous component resembling nonspecific spindle cell sarcoma. D, Sarcomatous component showing severe nuclear pleomorphism. Note large, bizarre nuclei with intranuclear vacuoles (right upper and lower corners). E, Lymphovascular invasion. F, Histopathologic examination of pulmonary metastatic lesion reveals the carcinomatous component in the glandular pattern only.

RESULTS

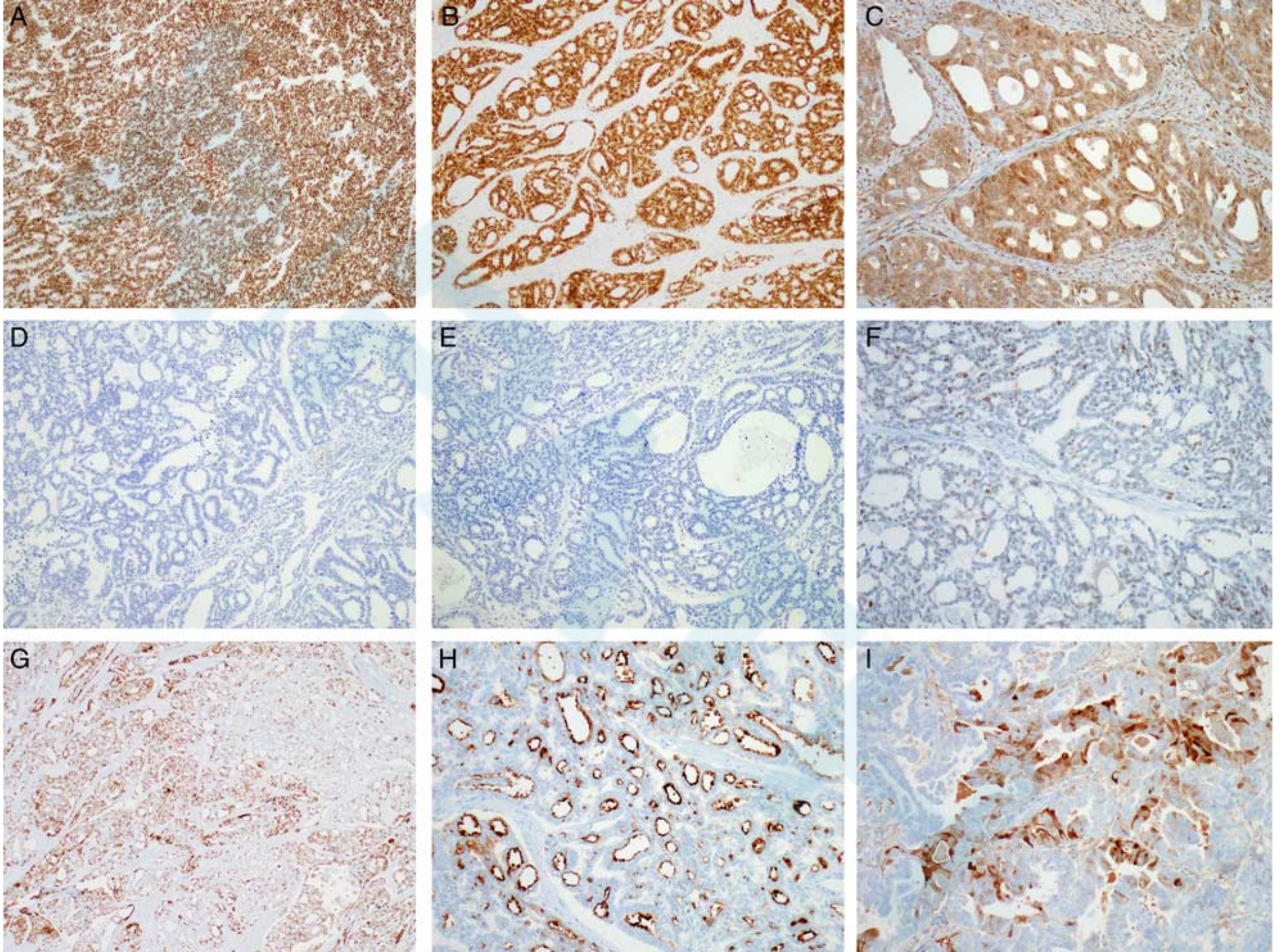


FIGURE 4. Immunostaining results of UB-MNAC.
A, Uniform nuclear GATA3 expression.
B, Diffuse and strong nuclear PAX2 immunoreactivity.
C, Preserved PTEN expression.
D, Lack of ER expression.
E, Lack of PR expression.
F, Wild-type p53 immunostaining pattern.
G, Focal p16 expression.
H, Uniform CD10 immunoreactivity along the luminal surface.
I, Focal calretinin expression.

RESULTS

TABLE 4. Immunophenotype of UB-MNAC

Case	GATA3	PAX2	PTEN	ER	PR	p53	p16	CD10	Calretinin	CK7
1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2	NA	NA	NA	Negative	Negative	Wild-type pattern	NA	Positive (luminal)	NA	Positive
3	NA	NA	NA	Negative	Negative	Wild-type pattern	NA	Positive	NA	Positive
4	NA	NA	NA	NA	NA	NA	NA	Positive	Positive (focal)	NA
5	NA	NA	NA	Negative	Negative	NA	NA	Negative	Positive	NA
6	NA	NA	NA	Negative	Negative	Wild-type pattern	NA	Positive (luminal)	Positive (focal)	NA
7	NA	NA	NA	Negative	Negative	NA	NA	Positive (luminal)	Positive	NA
8	NA	NA	NA	Negative	Negative	NA	NA	Positive (luminal)	Positive	NA
9	NA	Positive	NA	Negative	Negative	Wild-type pattern	NA	Positive (luminal)	Negative	Positive
10	NA	NA	NA	Negative	Negative	NA	NA	Positive	Positive	NA
11	NA	NA	NA	Negative	Negative	Wild-type pattern	NA	Positive	Negative	NA
12	Positive	Positive	Positive	Negative	Negative	Wild-type pattern	Negative (patchy)	Positive (luminal)	Negative	Positive
13	Positive	Positive	Positive	Negative	Negative	Wild-type pattern	Negative (patchy)	Positive (luminal)	Positive (focal)	Positive
14	Positive (focal)	Positive	Positive	Negative	Negative	Wild-type pattern	Negative (patchy)	Positive (luminal)	Positive (focal)	Positive
15	Positive (focal)	Positive	Positive	Negative	Negative	Wild-type pattern	Negative (patchy)	Positive (luminal)	Negative	Positive
16	Positive	Positive	Positive	Negative	Negative	Wild-type pattern	Negative (patchy)	Positive (luminal)	Negative	Positive
17	Positive	Positive	Positive	Negative	Negative	Wild-type pattern	Negative (patchy)	Positive (luminal)	Negative	Positive
18	Positive	Positive	Positive	Negative	Negative	Wild-type pattern	Negative (patchy)	Positive (luminal)	Negative	Positive
19	Positive	Positive	Positive	Negative	Negative	Wild-type pattern	Negative (patchy)	Positive (luminal)	Negative	Positive
20	Positive	Positive	Positive	Negative	Negative	Wild-type pattern	Negative (patchy)	Positive (luminal)	Negative	Positive
21	Positive (focal)	Positive	Positive	Negative	Negative	Wild-type pattern	Negative (patchy)	Positive (luminal)	Negative	Positive
22	Positive	Positive	Positive	Negative	Negative	Wild-type pattern	Negative (patchy)	Positive (luminal)	Positive (focal)	Positive

CK7 indicates cytokeratin 7; NA, not applicable.

RESULTS

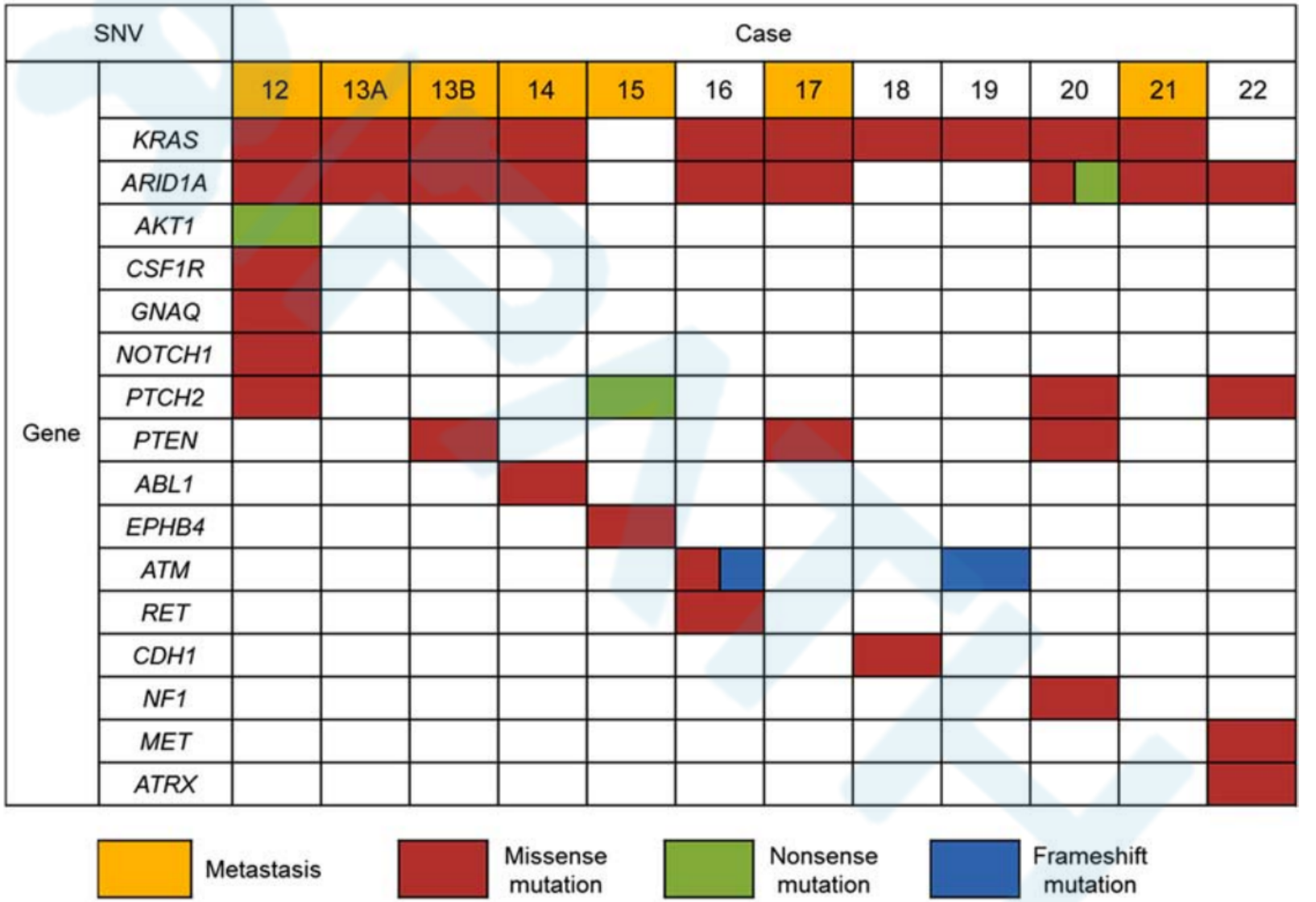


FIGURE 5. Summary of SNVs identified in 12 UB-MNACs by NGS. Each column represents a case, and each row represents a gene.

RESULTS

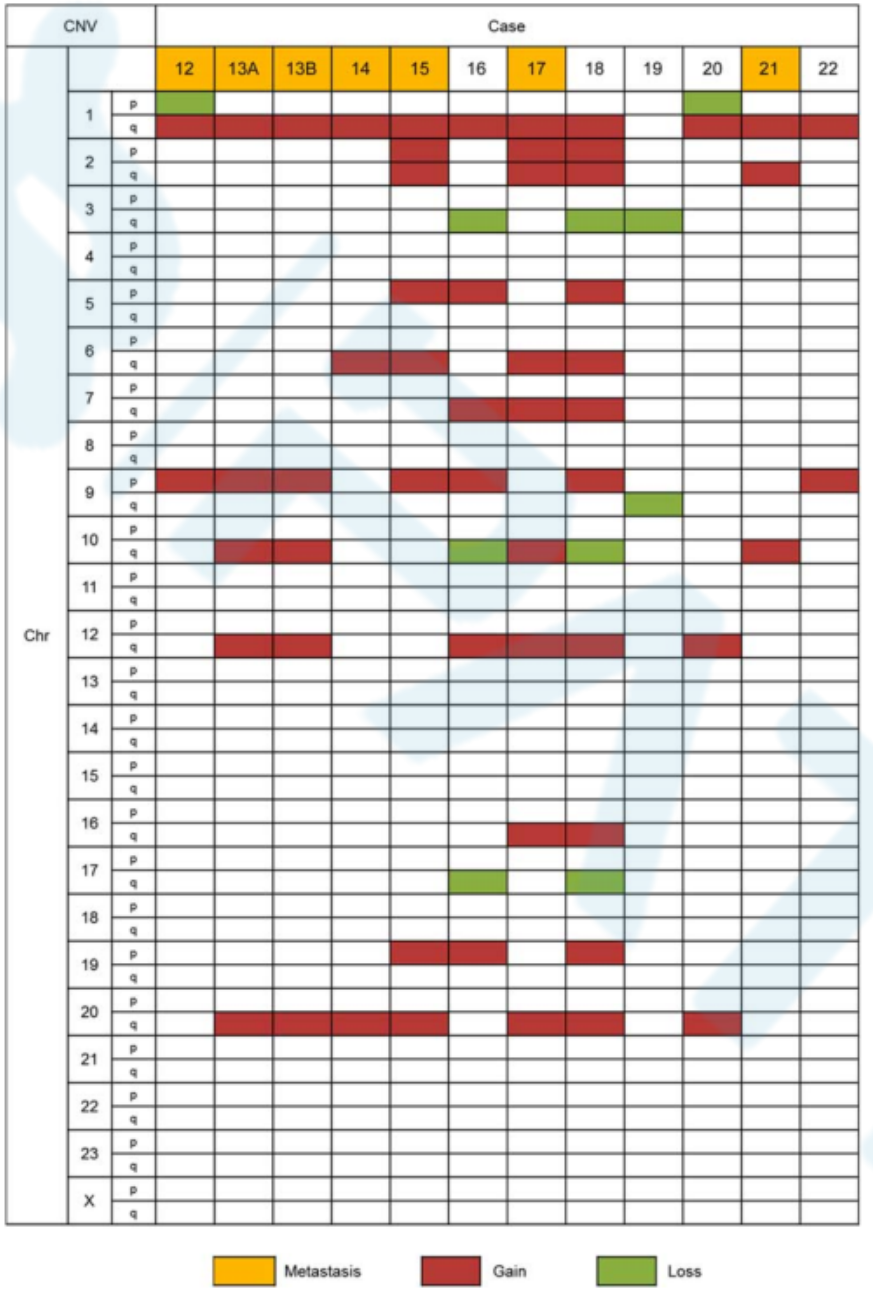


FIGURE 6. Summary of CNVs identified in 12 UB-MNACs by NGS. Each column represents a case, and each row represents a chromosome.

DISCUSSION

- This study aimed to comprehensively analyze the clinicopathologic characteristics of and molecular genetic alterations associated with UB-MNAC. Eleven cases of UB-MNAC have been reported to date.
- Among our 11 cases and the reported 11 cases of UB-MNAC, half (11/22) of the patients developed metastatic disease. We found that the metastatic rate of UB-MNAC (50.0%) was substantially higher than that reported for UC-MNAC, which shows metastatic disease in ~ 10% of the cases.

DISCUSSION : UB-MNAC and metastasis

- UB-MNAC presented with more advanced FIGO stages (III to IV) than does UC-MNAC (36.3% vs. 5%).
- Furthermore, disease progression in UB-MNAC patients mainly manifested as distant metastasis.
- Pulmonary metastasis is a very unusual event in endometrial carcinoma. However, in this study, UB-MNAC most commonly metastasized to the lungs.
- The reason for frequent pulmonary involvement of UB-MNAC is unclear, but our observation of vascular invasion in the peritumoral areas supports hematogenous spread as one of the possible mechanisms.
- Our findings warrant caution in the clinical surveillance and therapeutic strategies for UB-MNAC, considering its high metastatic potential and frequent pulmonary involvement.

DISCUSSION: Differential Diagnosis of UB-MNAC

- **endometrioid carcinoma**
- predominantly consists of tubular and glandular architectural patterns
- Features in favor of UB-MNAC include lack of endometrial hyperplasia or endometrioid intraepithelial neoplasia(EIN) in the background, absence of squamous differentiation and mucin, and identification of myometrial based lesions.
- Positive immunoreactivity for GATA3 and PAX2 and negativity for hormone receptors ER and PR support the diagnosis of UB-MNAC

DISCUSSION: Differential Diagnosis of UB-MNAC

- **endometrial serous carcinoma**
- papillary architectural pattern in association with high-grade nuclear atypia
- The presence of intraluminal eosinophilic colloid-like material, wild-type p53 immunostaining pattern, patchy p16 expression, and positive GATA3 expression are features supportive of UB-MNAC

DISCUSSION: Differential Diagnosis of UB-MNAC

- **clear cell carcinoma**
- admixtures of architectural patterns.
- wild-type p53 immunostaining pattern, patchy p16 expression, and negative staining for ER and PR.
- However, the absence of hobnail cells, a prominent clear cell change, and eosinophilic stromal hyalinization, in addition to positive immunoreactivity for GATA3 and PAX2, helps to exclude the possibility of clear cell carcinoma.

DISCUSSION: endometrial curettage and UB-MNAC

- **The diagnosis of UB-MNAC on the basis of endometrial curettage is complicated,** as these specimens may include only part of the tumor tissue, showing only a single growth pattern.
- Upon review of 8 curettage specimens from our cohort, 3 cases displayed >1 architectural pattern, whereas 5 specimens had only the glandular pattern.
- In these cases, it was almost impossible to differentiate UB-MNAC from endometrioid carcinoma without additional immunohistochemical staining data.
- However, we doubt that immunostaining should be performed in all curettage specimens exhibiting malignant tumors with glandular differentiation to exclude the possibility of UB-MNAC. This is a cost-effect issue, as UB-MNAC is extremely rare.

DISCUSSION: metastasis and 11 pathologic characteristics

- Large tumor size, ill-defined tumor border, advanced FIGO stage, presence of coagulative tumor cell necrosis, high mitotic activity, and presence of lymphovascular invasion were significantly associated with the development of metastasis.
- In addition, in multivariate regression, advanced FIGO stage, high mitotic activity, and lymphovascular invasion were identified as independent factors predicting the development of metastasis.

DISCUSSION: metastasis and 11 pathologic characteristics

- These findings suggest that pathologic characteristics conventionally used for the prognostication of patients with endometrial carcinoma are also valuable in classifying patients with UB-MNAC into high-risk and low-risk groups for metastasis.

DISCUSSION:FIGO grading system and UB-MNAC

- In this study, the degree of nuclear atypia determined based on the FIGO grading system for endometrioid carcinoma did not show a significant relationship with metastasis. It has been reported that MNAC nuclear features in most cases would be graded 2 to 3 by the FIGO grading system, but are not classic grade 3 nuclei.
- To our experience and that of other authors, **the FIGO grading system may not appropriately reflect the severity of UB-MNAC.**

DISCUSSION: molecular characteristics

- **The molecular pathogenesis and driver-mutation profile of MNAC remain largely unknown.**
  - 10/12 cases of UB-MNAC harbored activating *KRAS* mutation.
  - 9/12 cases harbored *ARID1A* mutation, The most common *ARID1 A*mutation in UB-MNAC was T294P, which has been also reported in endometrial endometrioid carcinoma, serous carcinoma, and carcinosarcoma.
  - Two *ARID1A* mutations (Q288P and Q287Pfs) identified in this study were novel missense mutations.

DISCUSSION: molecular characteristics

- Gain of 1q was the most common CNV (Copy number variation), detected in 11/12 UB-MNACs.
- In fact, 1q gain is the most common chromosomal alteration across all types of endometrial carcinoma.

SUMMARY

- we comprehensively analyzed clinicopathologic and molecular characteristics of UB-MNAC.
- Our observations indicate that UB-MNAC displays an aggressive biological behavior, with a tendency to metastasize to the lungs.
- Adverse pathologic characteristics, including large tumor size, ill-defined tumor border, presence of coagulative tumor cell necrosis, high mitotic activity, extrauterine extension, and presence of lymphovascular invasion, are likely to reflect the aggressive nature of UB-MNAC.
- NGS data revealed distinct molecular features of UB-MNAC, including frequent somatic mutations of *KRAS* and *ARID1A* and gain of 1q.

THANKS YOU