

Original Article



Prognosis in primary mucinous ovarian carcinoma: focusing on the five pathological findings indicating metastatic mucinous carcinoma to the ovary

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ABSTRACT

Objective: Pathological features indicating metastatic mucinous carcinoma to the ovary (MMCO) have been rarely reported in primary mucinous ovarian carcinoma (PMOC). However, little is known about how often they are observed in PMOC and how they relate to patient prognosis. In this study, we investigated the pathological features indicating MMCO in a large cohort of PMOCs and analyzed their association with patient prognosis.

Methods: We reviewed surgically treated PMOC patients diagnosed at the Seoul National University Hospital from 1995 to 2019, according to the updated WHO classification, and investigated the presence of pathological features indicating MMCO.

Results: A total of 144 patients with PMOCs were included. The 5 pathological findings indicating MMCO, including an infiltrative invasive pattern, the absence of benign or borderline components, a smaller tumor size, the presence of signet ring cells and the presence of extracellular mucin were observed in PMOC (21.6%, 43.1%, 20.8%, 4.3% and 12.9%, respectively), and were significantly correlated with poor overall and progression-free survival rates in PMOC. The patient's prognosis worsened as the extent of the infiltrative invasive pattern increased ($p < 0.001$). In addition, the prognostic power was stronger when the 5 pathological factors were analyzed together (new grouping system) than when analyzed individually ($p < 0.001$) and the new grouping system was identified as an independent prognostic factor regardless of FIGO stage.

Conclusion: Five pathological findings indicating MMCO in PMOC were significantly associated with poor prognosis in PMOC patients. Also, the new grouping system combining these findings was identified as an independent prognostic factor.

Keywords: Carcinoma, Ovarian Epithelial; Cystadenocarcinoma, Mucinous; Histology; Pathology; Prognosis

Synopsis

Pathologic features indicating metastatic mucinous carcinoma to the ovary (MMCO) have been rarely reported in primary mucinous ovarian carcinomas (PMOCs). We found the 5 pathological findings indicating MMCO in PMOC were significantly associated with poor prognosis in PMOC patients.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: L.C.; Data curation: L.S.W.; Formal analysis: L.S.W.; Investigation: L.S.W., L.C.; Methodology: L.S.W., L.C.; Project administration: L.C.; Supervision: L.C., K.H.; Validation: L.S.W., L.C.; Writing - original draft: L.S.W.; Writing - review & editing: L.S.W., L.C., J.M., S.J.A., K.H.

INTRODUCTION

Primary mucinous ovarian carcinoma (PMOC) is a rare subtype of epithelial ovarian cancer (EOC), and although its proportion varies from study to study, PMOC is known to account for approximately 3% of EOCs [1-3]. Most PMOC is diagnosed at stage I and has a favorable prognosis, but in the advanced stage, the prognosis is worse than that of high-grade serous carcinoma at the same stage [4-6]. Although it is necessary to evaluate the histopathological findings associated with poor prognosis to improve patient treatment options, there are only a few reports about the histopathological features of PMOC and their association with prognosis. Moreover, most studies included a significant number of borderline tumors; thus, only a small number of PMOC cases have been analyzed.

Differentiation between PMOC and metastatic mucinous carcinoma to the ovary (MMCO) is important because the prognosis of MMCO is usually extremely poor and an accurate diagnosis is necessary for the determination of treatment and for the prediction of prognosis [7]. However, there is a report stating that 50-70% of tumors that were initially diagnosed as PMOC were later revised to MMCO after clinicopathologic review, indicating that the differentiation between these 2 conditions is not simple [3,8]. There are some features that are indicating MMCO instead of PMOC. These features include unilateral tumors smaller than 10 cm, bilateral tumors, ovarian surface involvement, infiltrative stromal invasion, nodular growth patterns, the absence of benign or borderline components, vascular involvement, extracellular mucin production in more than 50% of the specimen, extensive signet ring cells, hilar involvement and extensive necrosis [3,9-14]. PMOC has been found to progress from benign and borderline tumors through genetic analysis; therefore, the presence of benign or borderline components has been reported to be indicative of PMOC [15,16]. However, these findings do not always allow for the differentiation between PMOC and MMCO. For example, the infiltrative invasive pattern was originally believed to be highly related to MMCO, but it can also be seen in PMOC and is now known to be one of the invasive patterns indicative of PMOC [7,11,17,18].

In this study, we analyzed the clinicopathologic findings of PMOCs and their association with patient prognosis in a larger set of tumors over longer follow-up periods. As mentioned earlier, the findings indicating MMCO are also observed in PMOC, but it is not well reported how often they are observed and how they are related to patient prognosis. Therefore, we investigated whether pathological findings indicating MMCO were observed in PMOC and, if observed, whether they were associated with prognosis. Prior to our analysis, in a clinicopathologic review of patients previously diagnosed with PMOC, differentiation from MMCO and reclassification in accordance with the changes in the WHO classification system were performed.

MATERIALS AND METHODS

This retrospective cohort study was conducted after an approval from the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. H-2001-017-1091).

From the institution's ovarian cancer cohort database, we selected patients diagnosed with PMOC after cystectomy or oophorectomy at Seoul National University Hospital between January 1995 and December 2019. At our institution, all patients with PMOC are subjected

to primary surgical treatment followed by adjuvant chemotherapy according to the NCCN guidelines [19].

All cases underwent independent pathological review by 2 pathologists (SWL and CL). All available hematoxylin and eosin-stained slides were used to review the diagnosis. Clinical and pathological information was collected from the electronic medical records and pathological reports. Immunohistochemical (IHC) staining of ER (Leica, 1:50), PR (Leica, 1:100), PAX8 (Cell Marque, 1:100), CK7 (Dako, 1:300), CK20 (Dako, 1:50), CDX2 (Ventana, RTU), SATB2 (Abcam, 1:100), p16 (Ventana, RTU) and WT1 (Abcam, 1:300) was performed for all tumors using a tissue microarray including 2 representative tumor areas (2 mm in diameter) (SuperBioChips Laboratories, Seoul, Korea) to differentiate PMOCs from MMCO and other EOCs. IHC was performed using the Ventana Benchmark XT automated system (Ventana Medical Systems, Tucson, AZ, USA) (2 mm in diameter).

To differentiate PMOC from MMCO, it is necessary to clinically confirm that there are no other possible primary tumors because some tumors are difficult to differentiate histologically due to similar histological and IHC findings [20,21]. Therefore, we performed a thorough review of the electronic medical records to look for any documentation of a primary tumor outside the ovary.

In addition, we also collected clinicopathologic characteristics of patients with PMOC, including age at initial diagnosis, size of tumor, bilaterality, salpingeal involvement, uterine involvement, lymph node (LN) metastasis, adjuvant chemotherapy status, 2014 International Federation of Gynecology and Obstetrics (FIGO) stage [22], serum CA-125 levels, invasive pattern, capsular involvement, presence of benign or borderline component, presence of extracellular mucin, presence of signet ring cells, and the presence of a coexisting teratoma.

1. Statistical analysis

We investigated the clinicopathologic findings of PMOC and their association with patient prognosis. Progression-free survival (PFS) was defined as the time interval between the initial date of the primary treatment and disease progression based on the computed tomography scans per Response Evaluation Criteria in Solid Tumors version 1.1 [22] or based on the serum CA-125 levels per Gynecologic Cancer InterGroup criteria [23]. Overall survival (OS) was defined as the time interval between the date of diagnosis and date of cancer-related death or the end of the study. The Pearson's correlation analysis was used to analyze the relationship between clinicopathological characteristics. For survival analysis, we used Kaplan-Meier methods with the log-rank test. In multivariate analysis, Cox proportional hazard models were used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CI).

All statistical analyses were performed using SPSS ver. 25.0 (IBM Co., Armonk, NY, USA). The values of *p* less than 0.05 were considered statistically significant.

RESULTS

1. Clinicopathologic characteristics

The number of mucinous ovarian carcinoma patients selected was 181 during the 25-year study period. After the clinicopathologic review and additional IHC staining of these

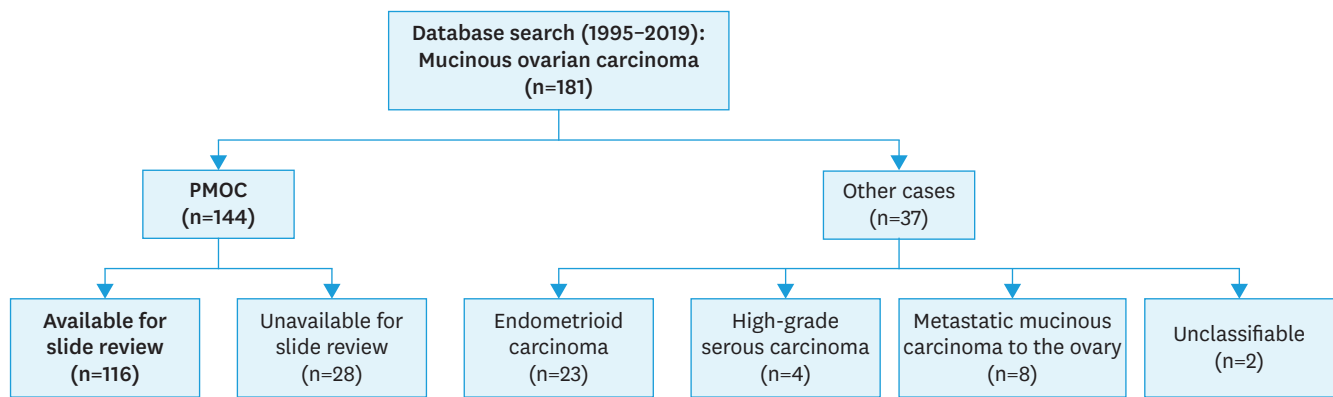


Fig. 1. Flow chart of patients included in the study. The number of mucinous ovarian carcinoma patients selected was 181. After the clinicopathologic review and additional immunohistochemical staining, 144 PMOCs remained and 37 cases were excluded. Among 144 PMOCs, 116 cases were reviewed with available slides. PMOC, primary mucinous ovarian carcinoma.

tumors were conducted by 2 pathologists (SWL and CL), 144 PMOCs remained and 37 cases were excluded. Among these excluded cases, 23 tumors were reclassified as endometrioid carcinomas, due to morphological findings and ER, PR, and PAX8 staining results, and 4 WT1-positive tumors were reclassified as high-grade serous carcinomas. Eight tumors were reclassified MMCO due to clinical features, morphological findings and CK7, CK20, CDX2, SATB2, p16 staining results (primary sites: appendix [n=4], uterine cervix [n=2], lower gastrointestinal tract [n=2]). Two tumors that were still difficult to classify on the basis of clinical and pathological findings were excluded. Finally, 144 cases of PMOC remained, among which 116 cases had slides available for review (**Fig. 1**).

The clinicopathological characteristics are summarized in **Table 1** and **Table S1** presents treatment details of PMOC patients. For the 144 patients, the mean age at diagnosis was 49 years (range: 14–90 years). Of them, 50.0% (72/144) received bilateral salpingo-oophorectomy and total hysterectomy. Surgical staging per the NCCN guidelines was performed in 95.1% (137/144). Overall, complete cytoreduction was achieved in 86.8% (125/144).

On pathologic examination, bilaterality was observed in 20 patients (13.9%), while salpingeal and uterine involvement were found in 16 (11.1%) and 18 (12.5%) patients, respectively. LN dissection was conducted in 41.7% (60/144), and 7 patients were identified to have pathologic LN metastasis. The gross tumor size ranged from 2.8 to 40.5 cm, and the mean size was 15.9 cm. As a tumor size of less than 10 cm has been more frequently reported in MMCO, we divided PMOCs into 2 groups based on size: less than 10 cm (30 cases, 20.8%) or greater than 10 cm (114 cases, 79.2%) [3,10]. Out of all the patients, 111 (77.1%) had FIGO stage I tumors, 7 (4.9%) had FIGO stage II tumors, 17 (11.8%) had FIGO stage III tumors and 9 (6.2%) had FIGO stage IV tumors [24]. Adjuvant chemotherapy was administered to 74 patients (51.4%). The most common chemotherapy regimen was paclitaxel plus carboplatin combination (57/74, 77.0%).

Among the 116 cases with available slides, expansile invasive patterns were observed in 91 (78.4%) cases, and infiltrative invasive patterns were observed in 25 (21.6%) cases (**Fig. 2**). Infiltrative invasive patterns were further classified into the following 2 groups as previously reported [25]: locally (<5 mm) infiltrative invasive patterns or widely (≥5 mm) infiltrative invasive patterns. Nine tumors (7.8%) showed locally infiltrative invasive patterns, and 16 tumors (13.8%) showed widely infiltrative invasive patterns. Twenty-six tumors (22.4%)

Pathology of primary mucinous ovarian carcinoma
Table 1. Clinicopathologic characteristics of primary mucinous ovarian carcinoma

Characteristics	No. of cases (%)	No. of cases (%), adjusted cases for pathological review	Group*		p-value
			1 (n=101, 87.1%)	2 (n=15, 22.9%)	
Age (yr)					0.086
<49	69/144 (47.9%)	55/116 (47.4%)	51	4	
≥49	75/144 (52.1%)	61/116 (52.6%)	50	11	
Site					<0.001
Unilateral	124/144 (86.1%)	100/116 (86.2%)	96	4	
Bilateral	20/144 (13.9%)	16/116 (13.8%)	5	11	
Salpinx involvement					<0.001
No	128/144 (88.9%)	103/116 (88.8%)	95	8	
Yes	16/144 (11.1%)	13/116 (11.2%)	6	7	
Uterus involvement					<0.001
No	126/144 (87.5%)	101/116 (87.1%)	95	6	
Yes	18/144 (12.5%)	15/116 (12.9%)	6	9	
Lymph node metastasis					<0.001
No	137/144 (95.1%)	109/116 (93.7%)	99	10	
Yes	7/144 (4.9%)	7/116 (6.3%)	2	5	
Adjuvant chemotherapy					0.003
No	70/144 (48.6%)	64/116 (55.2%)	61	3	
Yes	74/144 (51.4%)	52/116 (44.8%)	40	12	
Capsule involvement					<0.001
No	90/116 (77.6%)	90/116 (77.6%)	89	1	
Yes	26/116 (22.4%)	26/116 (22.4%)	12	14	
Invasive pattern					<0.001
Expansile	91/116 (78.4%)	91/116 (78.4%)	91	0	
Locally infiltrative	9/116 (7.8%)	9/116 (7.8%)	7	2	
Widely infiltrative	16/116 (13.8%)	16/116 (13.8%)	3	13	
Benign or borderline component					<0.001
Present	66/116 (56.9%)	66/116 (56.9%)	64	2	
Absent	50/116 (43.1%)	50/116 (43.1%)	37	13	
Size of tumor (cm)					<0.001
≥10	114/144 (79.2%)	90/116 (77.6%)	87	3	
<10	30/144 (20.8%)	26/116 (22.4%)	14	12	
Signet ring cells					<0.001
Absent	111/116 (95.7%)	111/116 (95.7%)	111	0	
Present	5/116 (4.3%)	5/116 (4.3%)	0	5	
Extracellular mucin					<0.001
Absent	101/116 (87.1%)	101/116 (87.1%)	96	5	
Present	15/116 (12.9%)	15/116 (12.9%)	5	10	
Background teratoma					0.634
Absent	111/116 (95.7%)	111/116 (95.7%)	97	14	
Present	5/116 (4.3%)	5/116 (4.3%)	4	1	
FIGO stage					<0.001
I	111/144 (77.1%)	89/116 (76.7%)	87	2	
II–IV	33/144 (22.9%)	27/116 (23.3%)	14	13	

*Based on how many of the 5 pathological findings indicating metastatic mucinous carcinoma to the ovary were observed, we classified the patients into 2 groups: 2 or fewer features (group 1) or three or more features (group 2).

demonstrated capsular involvement. Benign components (mucinous cystadenoma) and borderline components were seen in 42 (36.2%) and 65 (56.0%) cases, respectively. Signet ring cells were observed in 5 tumors (4.3%), and extracellular mucin was seen in 15 tumors (12.9%) (**Fig. 2**). The presence of signet ring cells or extracellular mucin was focal in all cases. Coexisting teratomas were found in 5 patients (4.3%).

2. Survival analysis

The infiltrative invasive patterns were significantly associated with shorter OS and PFS ($p < 0.001$ for OS and PFS) (**Fig. 3**). Patients with the widely infiltrative invasive patterns showed particularly worse prognosis, compared to those with the locally infiltrative invasive

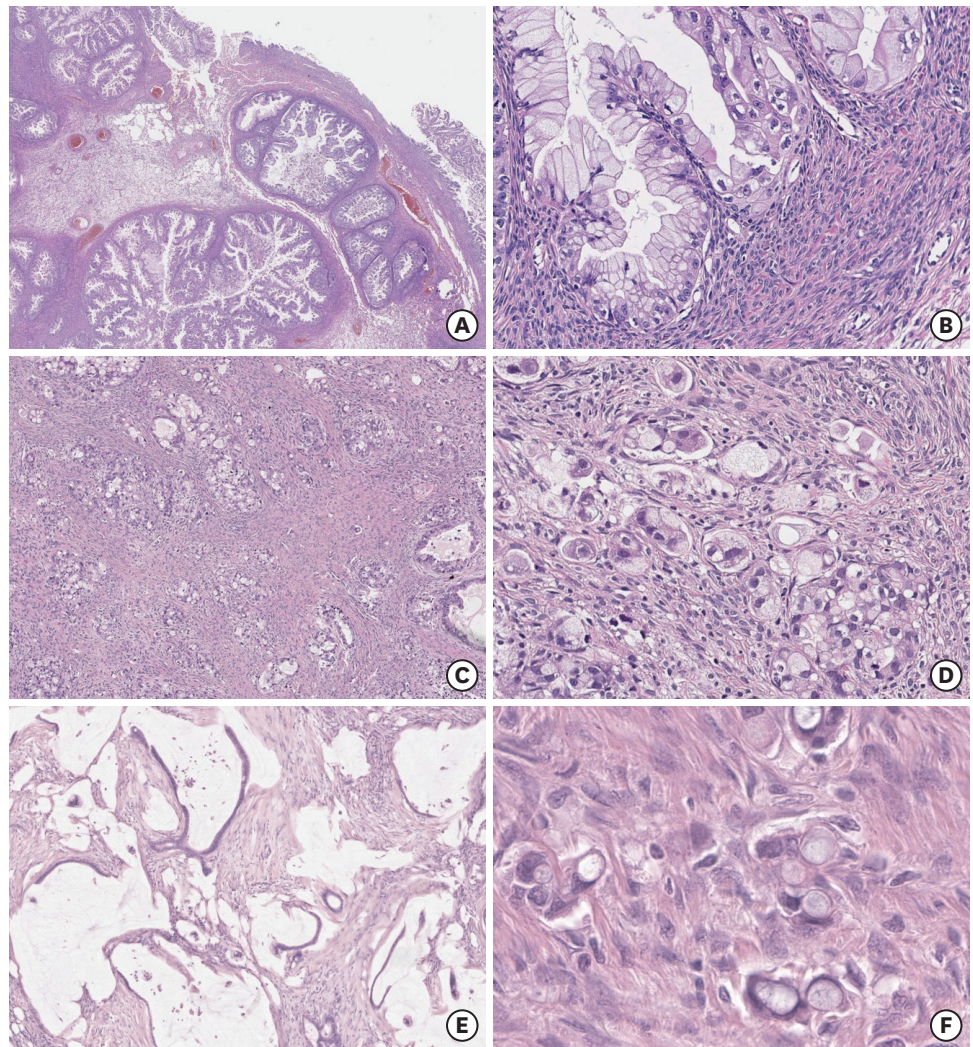


Fig. 2. Invasive pattern and unusual pathologic characteristics of PMOC. Invasive pattern includes expansile invasive pattern (A, H&E, $\times 10$ and B, H&E, $\times 200$) and infiltrative invasive pattern (C, H&E, $\times 50$ and D, H&E, $\times 200$). Unusual pathologic characteristics of PMOC, signet ring cells (E, H&E, $\times 400$) and extracellular mucin production (F, H&E, $\times 40$) were focally observed in PMOCs.

patterns and those with the expansile invasive patterns. Most of the other clinicopathologic findings were significantly associated with worse OS ($p=0.002$ for age, $p=0.001$ for the absence of benign or borderline components and the size of tumor less than 10 cm, and $p<0.001$ for others) and worse PFS ($p=0.016$ for age, $p=0.001$ for the absence of a benign or borderline component, $p=0.002$ for the size of tumor less than 10 cm, and $p<0.001$ for the others). However, the presence of a coexisting teratoma did not influence survival (OS: $p=0.936$, PFS: $p=0.375$) (data not shown).

In the multivariate Cox regression analysis adjusted for age, invasive pattern, the absence of benign or borderline components, tumor size, the presence of signet ring cells, the presence of extracellular mucin and FIGO stage, only the infiltrative invasive pattern was significantly associated with worse OS outcomes (HR=2.120; 95% CI=1.206–3.726; $p=0.009$) (Table S2).

Pathology of primary mucinous ovarian carcinoma

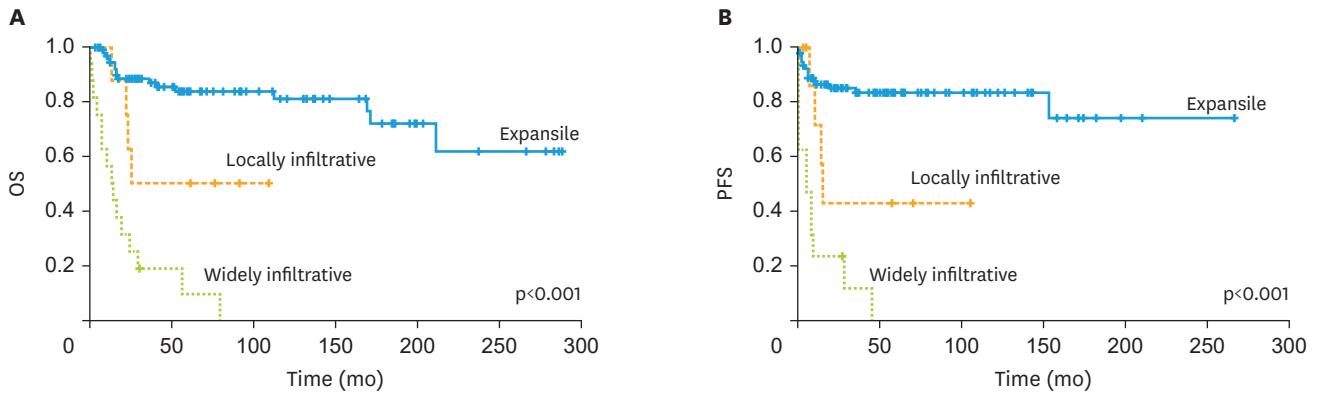


Fig. 3. Kaplan-Meier curves and difference in survival outcome compared using the log-rank test. OS time (A) and PFS time (B) according to invasive patterns (expansive, locally infiltrative and widely infiltrative). OS, overall survival; PFS, progression-free survival.

3. New prognostic grouping of PMOC patients based on pathological findings

To better predict patient prognosis with pathological findings other than FIGO stage, patients were grouped according to how many of the following 5 pathological findings indicating MMCO were observed: infiltrative invasive pattern, absence of benign or borderline components, tumor size <10 cm, presence of signet ring cells and presence of extracellular mucin. We classified the patients into 2 groups: 2 or fewer features (group 1) or three or more features (group 2) (Fig. 4).

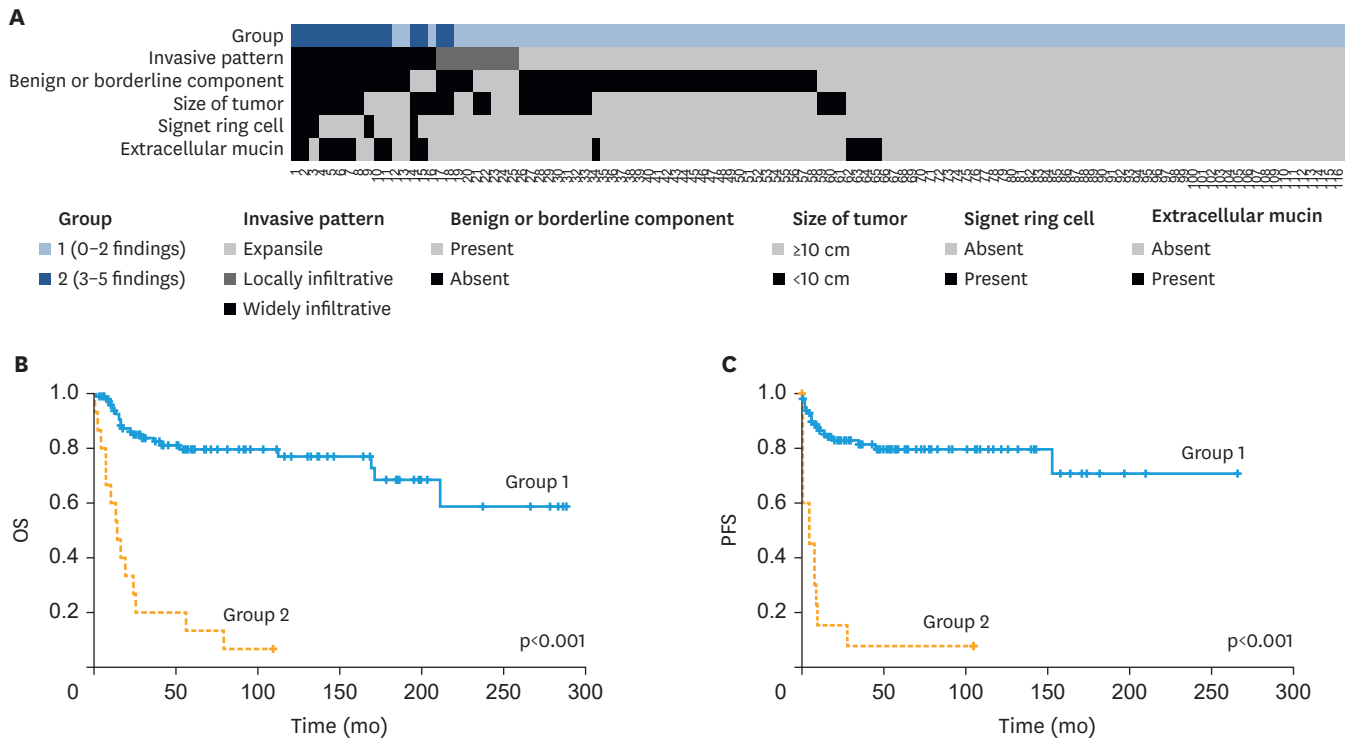


Fig. 4. Grouping according to 5 pathological findings indicating metastatic mucinous carcinoma to the ovary in primary mucinous ovarian carcinoma (A) and Kaplan-Meier curves and difference in survival outcomes compared using the log-rank test. OS time (B) and PFS time (C) according to new prognostic grouping (group 1 and group 2). OS, overall survival; PFS, progression-free survival.

Of the 116 patients, 101 (87.1%) were classified as group 1, and 15 (12.9%) were classified as group 2. The tumors in group 2 were significantly associated with bilaterality, salpingeal involvement, uterine involvement, capsular involvement and more advanced FIGO stage ($p < 0.001$, all) but were not associated with age ($p = 0.086$) or the presence of coexisting teratomas ($p = 0.634$) (**Table 1**).

In the multivariate Cox regression analysis adjusted for age, group and FIGO stage, the new prognostic group was a FIGO stage-independent prognostic factor (HR=2.629; 95% CI=1.167–6.213; $p = 0.02$ for OS; HR=2.480; 95% CI=1.104–6.064; $p = 0.047$ for PFS) (**Table 2**).

DISCUSSION

In this study, we investigated the clinicopathologic characteristics of PMOC, and association between prognosis using a large number of PMOCs. We confirmed that the widely infiltrative invasion pattern was associated with a poor prognosis, as in previous studies. Moreover, we newly found that patients with a locally (<5 mm) infiltrative invasion pattern had a moderately worse prognosis, in contrast to a previous study that showed a similar prognosis to that of patients with an expansile invasion pattern. We also found that other pathologic findings such as the absence of benign or borderline components, a tumor smaller than 10 cm, the presence of signet ring cells and the presence of extracellular mucin, indicating MMCO, were associated with poor prognosis in PMOC patients, as in the infiltrative invasion pattern. We confirmed that the prognostic predictive power of each pathological factor representing MMCO in PMOC was higher when analyzed together than when analyzed individually. Based on these results, our proposed new grouping system was shown to function as a prognostic predictor independent of the FIGO stage.

In literature, approximately 80% of PMOC is diagnosed at an early stage, while most high-grade serous carcinoma, another histologic subtype of EOC, is diagnosed at an advanced stage [5]. In addition, patients diagnosed with PMOC are generally younger than patients diagnosed with other EOCs [26,27]. In our study, 77.1% of PMOCs were FIGO stage I, which is similar to the findings of a previous study and the median age of PMOC diagnosis was 49 years, and the mean age was 48.1 years; thus, the patients were younger than those diagnosed with other EOCs [26].

Most PMOCs are diagnosed at stage I and the prognosis is favorable; however, when diagnosed at an advanced stage, the prognosis is worse than that of patients with advanced high-grade serous carcinoma [4-6]. In a previous study comparing the outcomes of advanced-stage PMOC with other EOCs, the median OS time was shorter in PMOC patients than in those with other EOCs [28-30]. The reason for the prognosis divergence is the worse response of PMOC to standard platinum-based therapy than that observed for other EOCs [31,32]. Therefore, it is important to classify PMOC properly by differentiating it from other ovarian carcinomas and MMCO to evaluate the prognosis accurately and to select the proper treatment for PMOC patients.

There are some features that suggest MMCO rather than PMOC, and these include unilateral tumors smaller than 10 cm, bilateral tumors, ovarian surface involvement, infiltrative stromal invasion, nodular growth patterns, an absence of benign and borderline components, vascular involvement, extracellular mucin production in more than 50% of the sample,

Table 2. Univariate and multivariate Cox regression analysis of overall and progression-free survival outcomes

Parameters	Overall survival				Progression-free survival							
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis					
	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI			
Age (>49 yr vs <49 yr)	0.003	2.560	1.372-4.777	0.292	1.481	0.713-3.077	0.020	2.159	1.131-4.120	0.473	1.327	0.612-2.878
Site (bilateral vs. unilateral)	<0.001	7.720	4.224-14.108				<0.001	9.444	4.933-18.081			
Salpinx involvement	<0.001	7.470	3.955-14.106				<0.001	9.34	4.747-18.376			
Uterus involvement	<0.001	6.895	3.700-12.849				<0.001	7.506	3.906-14.423			
Lymph node metastasis	<0.001	7.934	3.286-19.157				<0.001	5.772	2.210-15.077			
Adjuvant chemotherapy	<0.001	4.158	2.001-8.639				<0.001	7.597	2.974-19.404			
Capsule involvement	<0.001	12.961	6.273-26.781				<0.001	15.667	7.148-34.338			
Invasive pattern (widely infiltrative vs. locally infiltrative vs. expansile)	<0.001	3.648	2.494-5.337				<0.001	3.384	2.287-5.006			
Absence of benign or borderline component	0.002	3.079	1.535-6.176				0.002	3.344	1.582-7.071			
Size of tumor (<10 cm vs. ≥10 cm)	0.002	2.613	1.418-4.815				0.004	2.614	1.361-5.022			
Presence of signet ring cells	<0.001	6.145	2.342-16.125				<0.001	6.866	2.592-18.186			
Presence of extracellular mucin	<0.001	5.987	2.927-12.245				<0.001	7.319	3.430-15.619			
Group (2 vs.1)	<0.001	9.157	4.510-18.595	0.020	2.692	1.167-6.213	<0.001	10.217	4.845-21.543	0.047	2.480	1.014-6.064
FIGO stage (II-IV vs. I)	<0.001	12.122	6.393-22.984	<0.001	7.548	3.313-17.199	<0.001	15.898	7.916-31.928	<0.001	10.269	4.262-24.742

CI, confidence interval; HR, hazard ratio.

*Based on how many of the 5 pathological findings indicating metastatic mucinous carcinoma to the ovary were observed, we classified the patients into 2 groups: 2 or fewer features (group 1) or three or more features (group 2).

extensive signet ring cells, hilar involvement, and extensive necrosis [3,9-14]. However, these features do not always exclude PMOCs and can be seen in some PMOCs.

PMOC has 2 different patterns of invasion: the expansile invasive pattern and the infiltrative invasive pattern. The expansile invasive pattern is characterized by marked glandular crowding that forms a labyrinthine appearance with sparse intervening stroma. The infiltrative invasive pattern is characterized by irregular glands, nests, and single cells with atypical cytologic features, often in a desmoplastic stroma. Expansile invasive patterns are more common and can coexist with infiltrative invasive patterns [7]. Some studies have revealed an association between the invasive pattern of PMOC and patient prognosis, and the infiltrative invasive pattern was associated with relapse and LN metastasis, resulting in a worse prognosis [17,32-36]. In a recent study, the prognosis of PMOC patients was shown to be poor when the infiltrative invasive pattern comprised more than 10% of the total tumor volume; in another study, patients with the locally (<5 mm) infiltrative invasive pattern had a similar prognosis to those with the expansile invasive pattern [25,37]. In our study, the invasive patterns were significantly associated with patient prognosis, and even locally infiltrative invasive patterns were associated with moderately worse prognosis in PMOC patients compared to the expansile invasive patterns and widely infiltrative invasive patterns in our analysis of a large number of PMOC cases. We newly found that patient prognosis worsened as the extent of the infiltrative invasive pattern increased, which was not previously reported, and the infiltrative invasive pattern was an important prognostic factor for PMOC patients independent of the FIGO stage. Whereas previous studies analyzed 50 and 46 PMOC samples, respectively [25,37], in our study, 144 carcinoma samples were analyzed to find previously unreported findings.

As the coexistence of benign or borderline mucinous components in carcinoma was indicated to be a precursor to invasive mucinous components in mucinous ovarian carcinoma in a genetic study, the presence of benign or borderline components is suggested to be associated with PMOC [11,14-16]. In our study, we confirmed for the first time that the absence of benign or borderline components was associated with a poor prognosis, although it was not an independent prognostic factor.

A tumor size less than 10 cm is another pathological finding that suggests MMCO in mucinous ovarian carcinoma [3,10], although Lee et al. [11] reported that the size of the tumor alone is unreliable for the distinction between PMOC and MMCO. In one study, a method based on gross findings was proposed to differentiate between PMOCs and MMCO, and a tumor size of 13 cm was suggested as the most reliable criterion [38]. No studies have been conducted to determine whether a smaller tumor size is associated with patient prognosis in PMOC. In our study, a larger tumor size was associated with better patient prognosis regardless of the criterion (data not shown). A tumor size smaller than 10 cm was significantly associated with poor prognosis, although it was not an independent prognostic factor

PMOC usually shows little extracellular mucin but large levels of intracellular mucin [9]. Extensive extracellular mucin production indicates MMCO; however, the presence of focal mucin production may indicate PMOC [9]. Similarly, the presence of signet ring cells in mucinous ovarian carcinoma is generally highly indicating MMCO, usually from the gastrointestinal tract [39]. However, these findings have been observed focally in rare PMOC cases [13,39]. In previous studies, the focal appearance of both features has been reported very rarely in PMOC, and their frequency is unknown. In our study, signet ring cells were seen

in 5 tumors (4.3%) and extracellular mucin components were seen in 15 tumors (12.9%), and this proportion is worth further consideration. In our study, we found for the first time that these 2 features were significantly associated with poor prognosis, although they were not independent prognostic factors.

Histological grading systems, such as the FIGO and Silverberg grading systems, have been studied in relation to the ovarian cancer patient prognosis, including PMOC [36,37]. As yet, histological grading systems alone are not reliable for predicting the clinical course of PMOC, unlike their use for other ovarian carcinoma subtypes [7]. In the previously mentioned study, a new growth-based grading system was proposed, dividing patients into 2 groups; expansile invasion only or infiltrative invasion comprising $\leq 10\%$ of the tumor volume versus infiltrative invasion comprising $>10\%$. This new grading system also showed a correlation with patient prognosis, but it was not a prognostic factor independent of the FIGO stage [37]. In our study, we analyzed a larger number of PMOC cases and confirmed that patient prognosis worsened as the extent of the infiltrative invasive pattern increased. Additionally, a new grouping system based on overall pathological findings indicating MMCO rather than using the invasion pattern alone was found to function as a prognostic predictor independent of the FIGO stage.

This study has several limitations. As it is a retrospective study, there may be selection bias in the use of only preserved samples, and there were differences in the sampling methods. Additionally, MMCO cannot be clearly distinguished only by clinical and pathological findings. However, in this study, we reviewed PMOC cases from previously diagnosed ovarian mucinous carcinoma and analyzed the clinical and pathological findings associated with patient prognosis. We reclassified all cases for an accurate diagnosis and followed them for a long period of time. Other studies included a significant number of borderline tumors, but we only included carcinoma cases on a large scale. By selecting 5 features in setting up a new grouping system, selection bias may occur and may result in another limitation. There are several features indicating MMCO which are mentioned in the introduction of this article. Among them, the final 5 findings were selected, excluding findings not observed in our cohort, findings that could not be confirmed on the medical records or slides, and findings related to the FIGO stage.

We found that the clinicopathologic findings indicating MMCO, including an infiltrative invasive pattern, the absence of benign or borderline components, a tumor smaller than 10 cm, the presence of signet ring cells and the presence of extracellular mucin, were significantly associated with poor patient prognosis in PMOC. We also found that patient prognosis worsened as the extent of the infiltrative invasive pattern increased. In addition, it was confirmed that the prognostic predictive power was higher when each pathological factor was analyzed together than when analyzed individually. Suppose these findings are observed in mucinous ovarian carcinoma specimens. In that case, it is necessary first to differentiate PMOC from MMCO. If the tumor is primary, the prognosis may be poor; therefore, additional treatment, for example, administration of adjuvant chemotherapy after surgery without exception in stage I disease, or intensive surveillance for early detection of disease recurrence may be required. If our findings are supported by the analysis of more cases in the future, additional treatment plans and more accurate prognosis predictions for PMOC patients will be possible.

SUPPLEMENTARY MATERIALS

Table S1

Treatment details of primary mucinous ovarian carcinoma patients

[Click here to view](#)

Table S2

Univariate and multivariate Cox regression analysis of overall and progression-free survival outcomes without new prognostic grouping

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