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Original Article

HER2-positive mucinous adenocarcinomas of the ovary have an expansile invasive pattern associated with a favorable prognosis

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Abstract: Ovarian primary mucinous adenocarcinomas (MACs) are refractory to conventional therapy. Biomarkers for ovarian MAC could facilitate prognosis and targeted therapy, but are not currently available. The expression of human epidermal growth factor 2 (HER-2) has been linked to enhanced survival of MAC patients and may hold potential as a biomarker, but this potential has not been sufficiently investigated. In this study, we examined the clinicopathological features of 46 cases of MAC and 36 cases of patients with mucinous borderline tumors (MBTs). The expression of estrogen receptors (ER), progesterone receptors (PR), and HER2 were measured by immunohistochemistry and fluorescent *in situ* hybridization (FISH). Next, we compared the clinicopathological characteristics according to the HER2 expression profile. MBTs of the endocervical type tended to have simultaneous ER and PR expression ($P = 0.0028$) while MACs rarely showed ER or PR expression. HER2 expression was observed in 14 out of the 46 MACs (37.84%) and in none of the MBTs ($P = 0.0002$). HER2-positive MACs occurred approximately 10 years earlier than HER2-negative MACs (35.21 ± 4.768 years compared to 46.78 ± 1.977 years; $P = 0.0105$). All HER2-positive MACs demonstrated an expansile invasive pattern, while all MACs with infiltrative invasion pattern were HER2-negative ($P = 0.0406$). Kaplan-Meier survival analysis demonstrated a tendency for improved overall survival in HER2-positive MACs compared to HER2-negative MACs ($P = 0.0389$). In conclusion, HER2 overexpression in ovarian MACs is associated with an expansile, but not an infiltrative, invasion pattern and a favorable prognosis. Therefore, we suggest that HER2 may be a practical marker for histopathological categorization and a prognostic marker in ovarian MACs.

Keywords: Mucinous adenocarcinoma, ovary, HER2, prognostic factor

Introduction

Approximately 30% of cancers of the female genital tract are ovarian, and in North America and Western Europe, 90% of these are surface epithelial-stromal tumors [1]. Mucinous neoplasm is the second most common subcategory of surface epithelial-stromal tumors. This subcategory consists of a spectrum of types: benign mucinous cystadenoma, mucinous borderline tumor (MBT) with low malignant potential, and mucinous adenocarcinoma (MAC). Although mucinous cystadenoma is the most common ovarian mucinous neoplasm comprising 14% of all ovarian neoplasms, ovarian MBT and MAC are less numerous than their serous counterparts comprising 1% of all ovarian neoplasms in each [2]. 80% of MBTs are confined to the ovaries and they have a favorable prognosis even in advanced stages showing over 90% survival rate [3-6]. On the contrary, ovarian MAC is known to be highly aggressive because most patients will already have extra-pelvic metastasis at diagnosis and it shows a high recurrent rate even after invasive treatment [7, 8].

Currently, few biomarkers of ovarian cancer are available. Although several studies have shown estrogen receptor (ER) and progesterone receptor (PR) expression in ovarian tumors, their clinical significance in terms on survival and/or prognosis remains controversial [9-13]. In studies of breast cancer, the expression of human epidermal growth factor 2 (HER2) is routinely assessed, as it is a well-known marker for

aggressive behavior of the tumor. It is also useful because it can be targeted by adjuvant immunotherapy [14-16]. A study adopting monoclonal humanized anti-HER2 antibody described HER2 over-expression in recurrent or refractory ovarian carcinomas [17]; however, this study was not focused on primary spontaneous MACs.

Recently, HER2 overexpression and/or amplification was described in some ovarian MACs, in which subset were nearly exclusive of *KRAS* mutations. This suggests that either HER2 amplification/overexpression and/or *KRAS* mutations were associated with decreased likelihood of disease recurrence or death [18, 19]. However, it is difficult to explain why HER2-positive MACs were associated with favorable outcomes considering the fact that HER2-positive breast cancers show aggressive behavior.

In this study, we examined the status of ER, PR, and HER2 in ovarian tissues of patients with MBT and MAC, according to their histological subtypes. The relevance of these markers to factors related to the prognosis of patients with primary MAC was also assessed.

Materials and methods

Case selection

This retrospective study was approved by the institutional review board of Yonsei University Medical Center (IRB no. 4-2014-0034). Our study population consisted of 36 patients with MBT and 46 patients with MAC; all consecutive patients who had undergone treatment at Yonsei University Medical Center from 2001 to 2012.

The patients' tissue samples were fixed in 10% buffered formalin and embedded in paraffin. Archival tissues stained with hematoxylin and eosin (H&E) were reviewed by two obstetrics and gynecology pathologists (SK Kim and NH Cho). Patients' clinical characteristics included age at initial diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage, adjuvant chemotherapy, and survival. All the patients who had received adjuvant chemotherapy had been treated with paclitaxel and platinum regimen.

Tissue microarray

A representative area was selected on an H&E-stained tissue slide, and the corresponding area was marked on the surface of the corresponding paraffin-embedded tissue block. We used 5-mm sized tissue core because mucinous neoplasms usually have variable amounts of mucin materials. The selected area was punctured using a biopsy needle, and a 5-mm tissue core was extracted and transferred onto a 5 × 4 recipient block. Each tissue core was assigned a unique tissue microarray location number that was linked to a database record containing other clinicopathological data.

Immunohistochemistry

Antibodies used were as follows. The antibody to ER was from Thermo Scientific, San Diego, CA, USA (clone SP1, dilution rate of 1:100). The antibody to PR was from DAKO, Glostrup, Denmark (clone PgR, dilution rate of 1:50). The antibody to HER2 was acquired from Ventana medical systems, Tucson, AZ, USA (monoclonal, antibody concentration of 6 μg/ml). Immunohistochemistry (IHC) was performed using formalin-fixed, paraffin-embedded (FFPE) tissue sections. Briefly, 5-μm-thick sections were cut using a microtome, transferred onto adhesive slides, and dried at 62°C for 30 minutes. After incubation with primary antibodies, IHC was performed using a Dako Envision Kit or BenchMark XT staining system (Ventana medical systems) following the manufacturers' instructions. Slides were counterstained with Harris hematoxylin.

Interpretation of immunohistochemical staining

A cut-off value of >1% of nuclei that were strongly stained was used to define expression of ER and PR [20]. HER2 staining was analyzed according to guidelines by the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP). These guidelines are as follows: a value of 0 represents no immunostaining; 1+, weak incomplete membranous staining of <10% of tumor cells; 2+, complete membranous staining, either uniform or weak, of ≥10% of tumor cells; and 3+, uniform intense membranous staining of ≥30% of tumor cells [21]. HER2 immunostaining was considered positive when strong (3+) membranous staining was observed, while values of 0 to 1+ were considered negative. Tissues that had staining values of 2+ were further examined by fluorescent *in situ* hybridization (FISH) for HER-2 amplification.

Table 1. Clinicopathologic features of MBT and MAC ovarian mucinous tumors

	MBT	MAC	*P*-value
Number of cases	36	46	
Age at diagnosis	44.36 ± 2.502	43.26 ± 2.122	0.7369
Follow-up (months)	55.08 ± 6.053	51.13 ± 5.184	0.6199
Stage at diagnosis			<0.0001
Localized (FIGO IA, IB)	34	22	
Regional (FIGO IC, II)	2	14	
Distant (FIGO III, IV)	0	10	
Histological type (%)			
Intestinal	30 (83.33)	NA	
Endocervical	6 (16.67)	NA	
Invasion pattern (%)			
Expansile	NA	37 (80.43)	
Infiltrative	NA	9 (19.57)	
ER positive (%)	6 (16.67)	1 (2.17)	0.0398
Intestinal	0 (0.00)	NA	0.0002
Endocervical	6 (100.00)	NA	
PR positive (%)	3 (8.33)	0 (0.00)	0.0806
Intestinal	0 (0.00)	NA	0.0028
Endocervical	3 (50%)	NA	
HER2 positive (%)	0/36 (0)	14/46 (37.84)	0.0002

NA, not applicable.

FISH

FISH was performed on tumor sections after examination by H&E microscopy. A PathVysion *HER-2* DNA Probe Kit (Vysis, Downers Grove, IL, USA) was used according to the manufacturer's instructions. The copy number of *HER-2* on the slides was evaluated using an epifluorescence microscope (Olympus, Tokyo, Japan). At least 60 tumor cell nuclei in three separate regions were investigated for *HER-2* and chromosome 17 signals. *HER-2* gene amplification was determined according to the ASCO/CAP guidelines [21].

Statistics

Statistical analyses were performed using GraphPad Prism 5 software, version 5.01 (GraphPad Software, Inc., La Jolla, CA, USA) and SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA). For the analysis of age at diagnosis, a significant difference between means was determined by t-test. FIGO stage; invasion pattern; and expression of ER, PR, and HER2 in ovarian mucinous neoplasms were compared by Chi-square and Fisher's exact. Kaplan-Meier survival curves and log-rank statistics were employed to evaluate overall survival. Univariate and multivariate regression analysis was performed using Cox proportional hazards model.

Results

Clinicopathological features of ovarian mucinous neoplasms

First, we examined the clinical characteristics of patients with ovarian mucinous neoplasms (**Table 1**). There was no significant difference in the median age at diagnosis of patients with MBT (n = 36, 44.36 ± 2.502 years) and MAC (n = 46, 43.26 ± 2.122 years, *P* = 0.7369). We grouped cases of mucinous neoplasms based on the stage of the tumor at diagnosis according to the following criteria. The localized stage encompassed the FIGO stages IA and IB, the regional stage corresponded to FIGO stages IC and II, and the distant stage corresponded to FIGO stages III and IV. Most of the cases with MBT were at the localized stage: 34 out of 36 cases (94.44%), while more of the cases with MAC were advanced. 22 cases of MAC out of 46 were in the localized stage (47.83%), while 14 cases were in the regional stage (30.43%), and 10 cases were in the distant stage (21.74%).

For further characterization of the pathologic features, we categorized MBTs and MACs into two groups according to their tumor cell types and invasion patterns. MBTs could be classified according to their mucinous cell types, which are MBT of intestinal type or endocervical type [1]. Among the 36 MBTs, 30 were intestinal type (83.33%) and 6 were endocervical type (16.67%) which profile was similar to a previous report which described intestinal type to account for 85-90% of MBTs [1]. MACs differ from MBTs in that they demonstrate stromal invasion. Features such as complex glandular proliferation (defined as expansile invasive pattern) or infiltrative glands/tubules (defined as infiltrative invasive pattern) are considered as evidence of invasion [1]. Among the 46 cases of MAC studied here, 37 had the expansile inva-

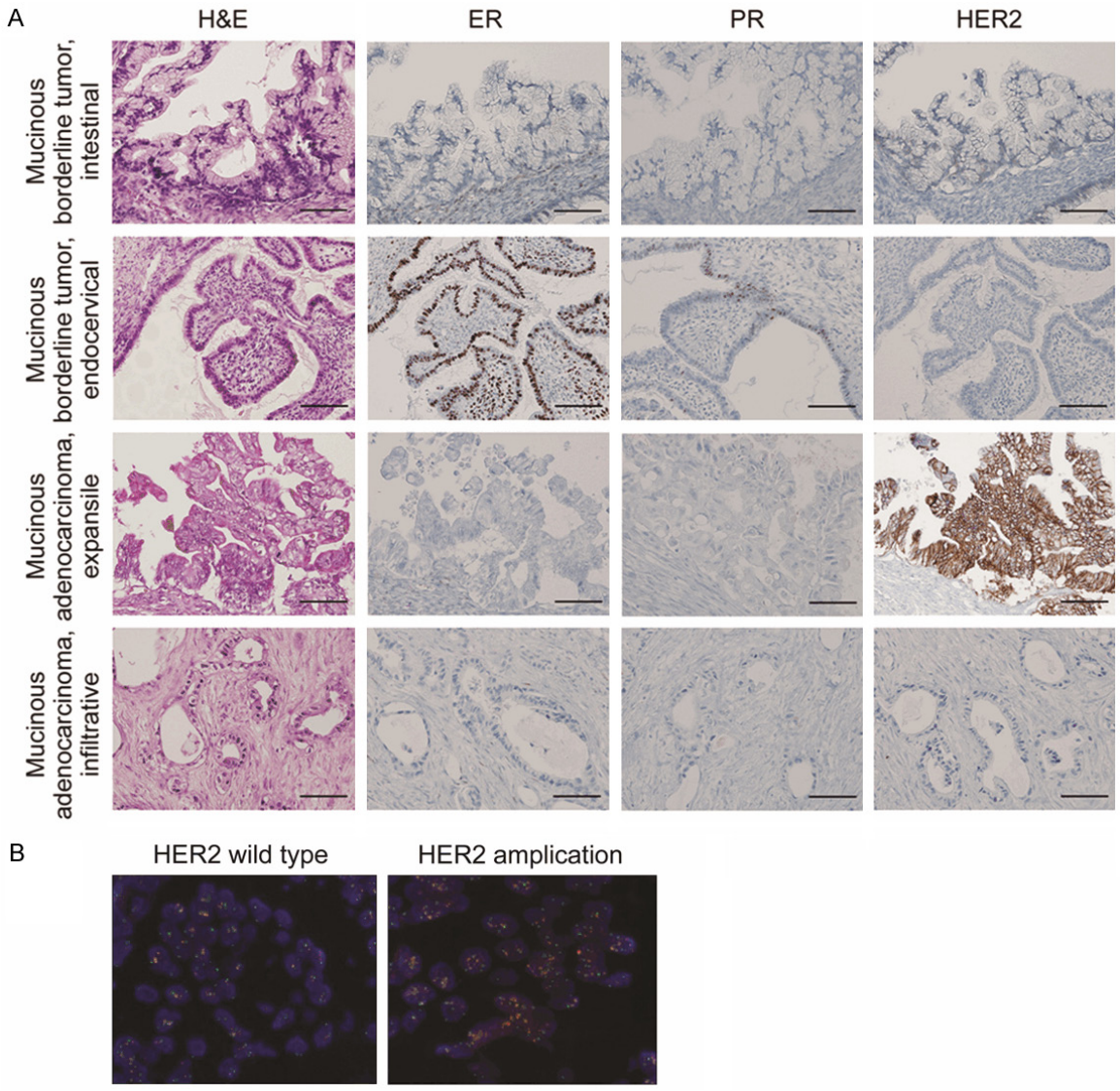

Figure 1. HER2 expression profiles of ovarian mucinous borderline tumors (MBTs) and mucinous adenocarcinomas (MACs). A. Representative histological pictures of MBTs of the intestinal type (top lane, first column) and the endocervical type (second lane, first column) and MACs with the expansile invasive pattern (third lane, first column) and the infiltrative invasive pattern (bottom lane, first column). Immunohistochemical staining results for ER (second column), PR (third column), and HER2 (fourth column) performed in MBTs and MACs. Scale bar = 100 μm. B. Representative pictures of FISH assay for HER2 amplification. Centromere of chromosome 17 represented by a green signal and HER-2 gene represented by an orange signal. (Magnification = 1,000 ×).

sive pattern (80.43%) and the remaining nine had the infiltrative invasive pattern (19.57%).

Next, we performed immunohistochemistry to determine the ER and PR status of each tumor (**Figure 1A** and **Table 1**). ER and PR were rarely or not expressed in the 46 ovarian MACs. Only one tumor (2.17 %) expressed ER, while none expressed PR. In contrast, in the 36 MBT tumors, six expressed ER (15.67%) and three expressed PR (8.33%); the differences were significant (P = 0.0398 and 0.0806 for the comparison of ER and PR expression in the two types of tumors, respectively). All six MBT tumors of the endocervical type expressed ER (P = 0.0002) as described in a previous study [22]. PR expression was confined to MBT tumors of endocervical type (3 tumors out of 36, 8.33%). Three tumors out of the six (50%) that expressed ER also expressed PR and it means that ER expression was significantly correlated with PR expression (P = 0.0028).

Table 2. Comparison of clinicopathological features of ovarian MAC according to HER2 expression

	HER2-negative	HER2-positive	*P*-value
Case number	32	14	
Age at diagnosis (years)	46.78 ± 1.977	35.21 ± 4.768	0.0105
Follow-up (months)	47.06 ± 5.769	60.43 ± 10.71	0.2397
Vital status			0.0389
Alive	17	10	
Died	8	0	
Follow-up loss	5	4	
Stage at diagnosis			0.3344
Localized (FIGO IA, IB)	13	9	
Regional (FIGO IC, II)	11	3	
Distant (FIGO III, IV)	8	2	
Adjuvant chemotherapy (%)	23 (71.88)	7 (50.00)	0.1886
Invasion pattern (%)			
Expansile	23	14	0.0406
Infiltrative	9	0	

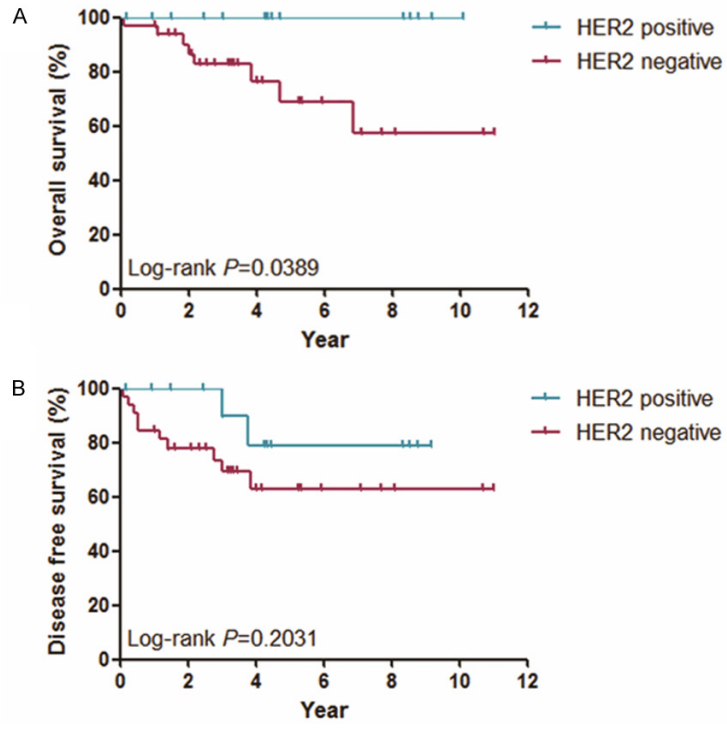

Figure 2. Survival analysis of patients with MAC according to their HER2 status. A. Overall survival of MAC patients according to their HER2 status. B. Disease-free survival relative to HER2 status.

Next, we assessed the HER2 status using immunohistochemical staining and FISH analysis in MBTs and MACs (**Figure 1A** and **1B**) [23]. HER2 overexpression or amplification was not apparent in any of the MBTs, but 14 of the 46 MACs (37.84%) had increased levels of HER2 expression ($P = 0.0002$). The number of MAC tumors exhibiting overexpression was higher than has been previously reported [18, 19, 24].

Clinicopathological characteristics of HER2-positive MACs compared to HER2-negative MACs

Next, we attempted to compare the clinical and histopathological features of MACs according to their HER2 expression (**Table 2**). Several clinicopathological parameters believed to be associated with the survival of the MAC patients were assessed. These included age, tumor stage, adjuvant chemotherapy, and the invasive pattern.

In our study population, HER2-positive MACs were diagnosed approximately 10 years earlier (35.21 ± 4.768 years) than HER2-negative MACs (46.78 ± 1.9777 years, $P = 0.0105$). There was no significant difference in the stage of the tumor at diagnosis between HER2-positive and HER2-negative patients ($P = 0.3344$). Adjuvant chemotherapy after oophorectomy had been performed at a similar rate in both groups of patients ($P = 0.1886$).

It is well known that the current grading system of mucinous carcinomas can predict neither the tumor behavior nor treatment response [1, 24, 25]. However, the occurrence of infiltrative stromal invasion has been proven to represent a more aggressive biological feature in comparison with expansile invasion [1]. Therefore, we examined the invasion patterns of MACs on the whole slide and categorized them according to their expression of HER2. All the HER2-positive MACs demonstrated an expansile invasive pattern (14 out of

Table 3. Univariate analysis of overall survival and disease-free survival in patients with ovarian MAC

Predictor variable	Overall survival			Disease-free survival		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Age at diagnosis	1.090	1.025-1.158	0.006	1.098	1.042-1.158	0.001
Invasive pattern						
Expansile versus Infiltrative	3.845	0.959-15.410	0.057	3.301	1.006-10.828	0.049
Stage at diagnosis			0.038			0.005
Localized versus regional	0.742	0.066-8.294	0.6809	1.459	0.205-10.363	0.706
Localized versus distant	5.839	1.131-30.138	0.035	9.292	1.924-44.880	0.006
HER2 status						
Negative versus positive	0.025	0.000-11.142	0.235	0.199	0.025-1.562	0.125
Adjuvant chemotherapy	3.054	0.375-24.873	0.297	5.369	0.387-41.953	0.109

Table 4. Multivariate analysis of overall survival and disease-free survival in patients with ovarian MAC

Predictor variable	Overall survival		
	Hazard ratio	95% CI	*P*-value
Age at diagnosis	1.090	1.025-1.158	0.006
Invasive pattern			
Expansile versus Infiltrative	4.818	1.147-20.242	0.032
Predictor variable	**Disease free survival**		
	Hazard ratio	95% CI	*P*-value
Age at diagnosis	1.098	1.042-1.158	0.001
Stage at diagnosis			0.009
Localized versus regional	0.912	0.123-6.749	0.928
Localized versus distant	7.104	1.328-38.005	0.022
HER2 status			
Negative versus positive	0.109	0.012-0.965	0.046

46) whereas all MACs showing infiltrative invasive pattern were HER2-negative (9 out of 46, *P* = 0.0406) (**Figure 1** and **Table 2**).

HER2-positive MACs with a favorable outcome

We speculated that HER2 overexpression in MACs might be associated with a favorable prognosis, as it seemed to be correlated with the less aggressive expansile invasive pattern. We collected follow-up data of MAC patients and performed Kaplan-Meier survival analysis to compare the HER2-positive to the HER2-negative groups (**Table 2** and **Figure 2**). Mean follow-up duration for MAC patients was 47.06 ± 5.769 months for HER2-negative patients and 60.43 ± 10.71 months for HER2-positive patients and the follow-up time between the two groups was not significantly different (*P* = 0.2397).

Patients with the HER2-positive MACs have had a relatively favorable outcome compared with that of HER2-negative MACs when overall survival is considered (**Figure 2A**, *P* = 0.0389). This result agrees with a previous report, in which it was concluded that HER2 amplification or overexpression was associated with a lower risk of disease recurrence and death [18].

Next, we conducted a statistical analysis to find the effect of predictor variables on the survival of ovarian MAC patients. In univariate analysis, age at diagnosis, invasive pattern, and the tumor stage at diagnosis were statistically significantly associated with overall survival and disease-free survival (**Table 3**). When we used multivariate analysis to adjust variables that might affect survival, advanced age at diagnosis (Hazard ratio: 1.090, 95% CI: 1.025-1.158, *P* = 0.006) and the infiltrative invasive pattern (Hazard ratio: 4.818, 95% CI: 1.147-20.242, *P* = 0.032) were associated with worse overall survival (**Table 4**). On the other hand, advanced age at diagnosis (Hazard ratio: 1.098, 95% CI: 1.042-1.158, *P* = 0.001) and a distant tumor stage (Hazard ratio: 7.104, 95% CI: 1.328-38.005, *P* = 0.022) decreased disease-free survival, however, HER2 positivity (Hazard ratio: 0.109, 95% CI: 0.012-0.965, *P* = 0.046) improved disease-free survival.

Discussion

Ovarian MAC is a highly aggressive tumor with a 5-year survival rate of only 10-30% even if the patients receive platinum-taxane based chemotherapy after aggressive surgery [8, 26-28].

Recent studies suggest that ER or PR can be used as biomarkers in some ovarian cancers to predict survival [9-13]. However, the validity of these markers in prognosis of ovarian MACs is unclear. Consistent with a previous report [22], we observed that MBTs of the endocervical type tend to have simultaneous expression of both ER and PR while MACs rarely expressed either of these receptors. Also, in this study, PR expression was confined to MBTs of the endocervical type while ER expression correlated with PR expression

HER2 overexpression or amplification was identified only in MACs in this study. This result agrees with previous in vitro experiments, which suggest that HER2 signaling regulated by the mucin 4 protein (MUC4) is involved in malignant transformation and invasion in ovarian cancers [29-32]. Recently, McAlpine *et al.* reported that amplification of HER2 was observed in 18.8% of MBTs and 18.2% of MACs [19]. In another study, Angleio *et al.* observed the occurrence of overexpression of HER2 in 6.2% of MBTs and 18.8% of MACs [18]. In our study, the frequency of HER2 positivity in MACs was much higher (37.84%). We believe that this discrepancy could reflect differences in the patient population, as a large cohort study of Asian patients similarly reported a higher frequency of HER2-positive MACs than that of Western patients [24]. We also noticed that the HER2-positive MACs occurred approximately 10 years earlier than HER2-negative MACs (P = 0.0105).

We hypothesize that the HER-2 status is related to prognosis. This hypothesis is supported by our comparison of invasion patterns of MAC and the HER2 expression profile. Infiltrative stromal invasion pattern of MAC is known to be biologically more aggressive than expansile invasion pattern [1]. We assessed the invasion patterns of MACs, and matched them with the HER-2 expression profile. Of note, all HER2-positive MACs demonstrated an expansile invasive pattern, and HER2-negative MACs more frequently showed an infiltrative invasive pattern (P = 0.0406). Therefore, we inferred that HER2 expression could be associated with a favorable prognosis in MAC patients.

When we performed Kaplan-Meier analysis according to the HER2 expression status, we observed statistically significant superior overall survival in patients with HER2-positive MAC compared to patients with HER2-negative MAC (P = 0.0389). When we adjusted variables that could affect disease-free survival using multivariate analysis, HER2 positivity was considered to be a valid marker for prediction of outcome (Hazard ratio: 0.109, 95% CI: 0.012-0.965, P = 0.046).

In conclusion, HER2-positive MACs tend to have early disease onset, an expansile invasive pattern, and a favorable prognosis. Therefore, we suggest that the HER2 protein could be utilized as a biomarker to predict the prognosis of MAC patients and could be useful in classifying the molecular subtype of ovarian mucinous neoplasm.

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Disclosure of conflict of interest

None.

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