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Original Article

Mesothelin expression in gynecologic carcinosarcoma: clinicopathological significance and correlation with HER2 expression

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ABSTRACT

Objective: This study aimed to evaluate mesothelin (MSLN) expression and determine its clinical significance and correlation with human epidermal growth factor receptor 2 (HER2) expression in gynecological carcinosarcoma.
Methods: We retrospectively evaluated patients with uterine carcinosarcoma (UCS) and ovarian carcinosarcoma (OCS) who underwent surgery between 1997 and 2019. Immunohistochemical staining of formalin-fixed, paraffin-embedded specimens for MSLN (clone SP74) and HER2 (clone 4A5) was also performed. MSLN was scored using the H-score and 4-tired scoring system (0–3+). MSLN positivity was defined as any positive cell at any intensity, while high MSLN expression was defined as an intensity of ≥2+ in ≥30% of tumor cells. HER2 expression was scored according to modified 2018 American Society of Clinical Oncology/College of American Pathologists criteria.
Results: A total of 128 patients were recruited, including 119 with UCS and 9 with OCS. All cases in UCS exhibited MSLN positivity, and 33.9% showed high-MSLN expression. Clinicopathological characteristics were not significantly associated with high or low-MSLN expression. However, the high-MSLN group showed more prolonged overall survival (OS) than the low-MSLN group (not assessed vs. 36.8 months; hazard ratio=0.48, 95% confidence interval=0.26–0.89, p=0.016). HER2-high patients had higher MSLN expression than HER2-negative patients. In high-MSLN and low-MSLN expression groups, HER2 status did not affect OS. OCS showed 100% MSLN positivity, with 66.6% high-MSLN.
Conclusion: MSLN expression is widely observed in gynecological carcinosarcomas. Moreover, high-MSLN expression is a favorable prognostic factor for UCS. MSLN could be a promising therapeutic target for UCS, even in the era of anti-HER2 therapy.

Keywords: Uterine Carcinosarcoma; Ovarian Carcinosarcoma; Mesothelin; Human Epidermal Growth Factor Receptor 2; Immunohistochemistry; Prognosis

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Conflict of Interest
Kan Yonemori reports receiving grants or contracts from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. (Rahway, NJ, USA), Daiichi-Sankyo, AstraZeneca, Taiho, Pfizer, Novartis, Takeda, Chugai, Ono, Seattle Genetics, Eisai, Eli Lilly, Genmab, Boehringer Ingelheim, Kyowa Hakko Kirin, Nihon Kayaku, Sanofi and Haihe. He also reports receiving honoraria for lectures, presentations, and speakers' bureaus for Pfizer, Eisai, AstraZeneca, Eli lilly, Takeda, Chugai, MSD, FujiFilm Pharma, Bayer, Asteras, Boehringer Ingelheim, Daiichi-Sankyo, PDR Pharma and Sanofi.

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Synopsis
High mesothelin (MSLN) expression correlated with longer overall survival. Despite clinicopathological differences, MSLN expression was observed in all uterine carcinosarcoma (UCS). Patients with high human epidermal growth factor receptor 2 (HER2) expression had higher MSLN expression. MSLN could be a therapeutic target even for HER2-negative UCS.

INTRODUCTION

Gynecologic carcinosarcoma (GCS) is a rare and aggressive malignant neoplasm of the uterus and ovary. Uterine carcinosarcoma (UCS) and ovarian carcinosarcoma (OCS) are biphasic cancers comprising both malignant epithelial and mesenchymal components that account for approximately 5% of all uterine malignancies [1] and 1%–3% of all ovarian malignancies [2]. At the time of diagnosis, myometrial invasion in UCS and lymphovascular invasion in GCS are common, and 60% of clinical stage I tumors reportedly exhibit lymph node metastasis [2]. Although surgical debulking with or without adjuvant chemotherapy is the mainstay therapy for both UCS and OCS [3], it has a high recurrence rate, with an extremely low 5-year overall survival (OS) rate of less than 30% [2,4]. In a phase III trial, a non-inferiority study, in UCS and OCS [5], paclitaxel and carboplatin regimens were not inferior to paclitaxel and ifosfamide regimens, with a median OS of 37 vs. 29 months. However, treatment options remain limited, and developing additional systemic treatments are required.

Mesothelin (MSLN) is a membrane glycoprotein with limited expression in normal mesothelial cells, but is highly expressed in many cancers, such as malignant mesothelioma, pancreatic cancer, and ovarian cancer [6]. It has also been identified in lung and uterine malignancies [7,8]. MSLN promotes cancer cell invasion, proliferation, and migration [9], implying it could be a therapeutic target. MSLN-targeting therapies have been developed in recent years, including monoclonal antibodies, antibody-drug conjugates (ADCs), immunotoxin therapy, vaccine-directed therapy, chimeric antigen receptor T cells, chimeric antigen receptor natural killer cells, T cell receptor-like agents, and alpha-particle therapies [10]. Only one study evaluated MSLN expression in patients with GCS and reported that 50% of UCS and 65% of OCS are MSLN-positive when immunohistochemistry (IHC) using an anti-MSLN antibody (MSVA-235M) was performed [11]. However, the antibody used in the study was not the same as that used (clone SP74) in clinical trials of MSLN-targeted therapy [12]. Furthermore, the prognostic impact of MSLN expression in patients with GCS remains unknown.

Recently, human epidermal growth factor receptor 2 (HER2)-targeted therapy, including ADC, has demonstrated promising efficacy in various solid tumors, including UCS. The ADCs, trastuzumab deruxtecan and trastuzumab duocarmazine, are effective in HER2-overexpressed GCS [13,14]. Because HER2-targeted therapy is a promising treatment strategy for patients with GCS, it is necessary to assess the relationship between the target molecule and HER2 expression.

In this study, we evaluated MSLN expression in UCS and OCS. Furthermore, we investigated the association between MSLN expression, clinicopathological characteristics, and prognosis of patients with UCS. In addition, we examined the relationship between MSLN and HER2 expression and prognosis based on HER2 status in patients with UCS.

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MATERIALS AND METHODS

1. Study population

This retrospective study evaluated patients with UCS and OCS who underwent primary surgery between 1997 and 2019 at the National Cancer Center Hospital, Tokyo, Japan. The patients had histologically proven UCS and OCS. Pathological diagnoses were confirmed by an expert gynecological pathologist (H.Y.) according to the 2020 World Health Organization classification of Female Genital Tumors [15]. Clinicopathological data regarding age, histology, stage defined by the International Federation of Gynecology and Obstetrics (FIGO) in 2008 (OCS) and 2014 (UCS), Eastern Cooperative Oncology Group performance status (PS), adjuvant treatment, and survival time after surgery were collected. The patients were followed up until June 2022. This study was approved by the Institutional Review Board (IRB) of the Institutional Review Board of the National Cancer Center (Tokyo, Japan) (No. 2014-393). This study was conducted following the principles of the Declaration of Helsinki. The IRB waived the requirement for informed consent because of the retrospective nature of the study.

2. Pathological diagnoses, immunohistochemical staining, and evaluation

The hematoxylin and eosin-stained slides for each case were reviewed to obtain representative sections. New 4-μm-thick sections were prepared from 10% neutral-buffered formalin-fixed paraffin-embedded surgical specimens and were immunohistochemically stained. We evaluated MSLN expression using the VENTANA MSLN (SP74) IHC assay (clone SP74, rabbit monoclonal antibody, ready to use, ethylenediaminetetraacetic acid buffer; Roche Diagnostics, Basel, Switzerland) on the Ventana BenchMark XT automated immunostainer (Roche Diagnostics), according to the manufacturer's protocols. The H-score of MSLN expression was calculated using the following formula: 3X+2Y+Z, where X, Y, and Z are the proportions of tumor cells showing strong (X), moderate (Y), and weak (Z) staining intensities, respectively. The maximum H-score was 300 (intense staining of all tumor cells) and the minimum was 0 (no staining of any tumor cells). We defined MSLN positivity if MSLN was expressed at any intensity based on previous reports [16]. High MSLN expression was defined as ≥2+ intensity in ≥30% of tumor cells, according to a previous study [16]. Regarding HER2 expression, we previously performed IHC on 118 cases in this study cohort [17]. For HER2 evaluation, the IHC score was evaluated according to the latest American Society of Clinical Oncology/College of American Pathologists (2016) criteria for gastric cancer modified for UCS [17-19]. IHC was performed using a standard Food and Drug Administration-approved IVD kit, Pathway HER2 (clone 4B5), on the BenchMark XT automated system (Ventana Medical Systems Inc., Tucson, AZ, USA), according to the manufacturer's recommended protocol. HER2 IHC score of 0 was defined as HER2-negative, score 1+ were defined as HER2-low and score 2+ or 3+ were defined as HER2-high [13].

3. Statistical analysis

Continuous variables were compared using the t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. In contrast, categorical variables were compared using Fisher's exact test. The Kruskal-Wallis test and Bonferroni correction were used to determine the statistical significance of the medians of the 3 independent groups. OS was defined as the time from surgery until death due to any cause or the date of the last follow-up, whereas progression-free survival (PFS) was defined as the time from surgery to recurrence or death from any cause. The Kaplan-Meier method was used to estimate OS and PFS, and survival curves were compared using the log-rank test. The Cox proportional hazard models were used to evaluate several risk factors. All p-values were based on 2-sided tests, with $p<0.05$

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considered statistically significant. Statistical analyses were conducted using SPSS software (released 2021, IBM SPSS Statistics for Windows, version 28.0; IBM Corp., Armonk, NY, USA).

RESULTS

1. Patient and clinical characteristics

A total of 128 patients with GCS underwent primary surgery between 1997 and 2019, 119 of whom had UCS and 9 had OCS. The baseline characteristics of the UCS are shown in **Table 1**. The median age of the patients was 63 years (range, 34–87 years). FIGO stage I disease was found in 49 patients (41.2%), stage II in 7 (5.9%), stage III in 38 (31.9%), and stage IV in 25 (21.0%). One hundred and eight patients (90.8%) had a PS of 0, and 11 (9.2%) had a PS of 1. The predominant carcinoma component was endometrioid in 54 patients (45.0%), serous in 34 patients (28.3%), and others in 32 patients (26.7%). The sarcomas were homologous in 70 patients (58.8%) and heterogeneous in 49 patients (41.2%). Among the 119 UCS patients, HER2 expression was evaluated in 118 UCS patients. Thirty-two patients (26.9%) were HER2-negative (IHC 0), 40 (33.6%) were HER2-low (IHC 1+), and 46 (38.7%) were HER2-high (IHC 2+ or IHC 3+). Fifty-three patients (44.5%) underwent chemotherapy. Regardless of clinicopathological differences, MSLN expression was observed in all UCS. Seventy-nine patients (66.4%) showed low MSLN expression and 40 (33.9%) showed high MSLN expression. There were no statistically significant differences, including HER2

Table 1. Clinicopathological characteristics and MSLN expression in uterine carcinosarcoma patients

Characteristics	Total (n=119)	Low-MSLN (n=79)	High-MSLN (n=40)	p-value
Median age (range; yr)	63 (34–87)	63 (37–87)	62.5 (34–79)	0.383
Age (yr)				0.744
	62 (52.1)	42 (53.2)	20 (50.0)	
	57 (47.9)	37 (46.8)	20 (50.0)	
FIGO stage (2008)				0.107
I	49 (41.2)	38 (48.1)	11 (27.5)	
II	7 (5.9)	5 (6.3)	2 (5.0)	
III	38 (31.9)	20 (25.3)	18 (45.0)	
IV	25 (21.0)	16 (20.3)	9 (22.5)	
ECOG PS				0.383
0	108 (90.8)	73 (92.4)	35 (87.5)	
1	11 (9.2)	6 (7.6)	5 (12.5)	
Carcinoma component				0.418
Endometrioid	54 (45.4)	39 (49.4)	15 (37.5)	
Serous	34 (28.6)	20 (25.3)	14 (35.0)	
Others	31 (26.1)	20 (25.3)	11 (27.5)	
Sarcoma component				0.330
Homologous	70 (58.8)	44 (55.7)	26 (65.0)	
Heterologous	49 (41.2)	35 (44.3)	14 (35.0)	
HER2 IHC				0.207
Score 0	32 (26.9)	22 (27.8)	10 (25.0)	
Score 1+	40 (33.6)	31 (39.3)	9 (22.5)	
Score 2+	36 (30.3)	21 (26.6)	15 (37.5)	
Score 3+	10 (8.4)	5 (6.3)	5 (12.5)	
NA	1 (0.8)	0 (0.0)	1 (2.5)	
Chemotherapy				0.942
No	53 (44.5)	35 (44.3)	18 (45.0)	
Yes	66 (55.5)	44 (55.7)	22 (55.0)	

Values are presented as number (%).
ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MSLN, mesothelin; NA, not available.

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status, in clinicopathological characteristics based on MSLN expression status. MSLN IHC in the UCS is shown in **Fig. 1.** Although MSLN expression was detected in both carcinoma

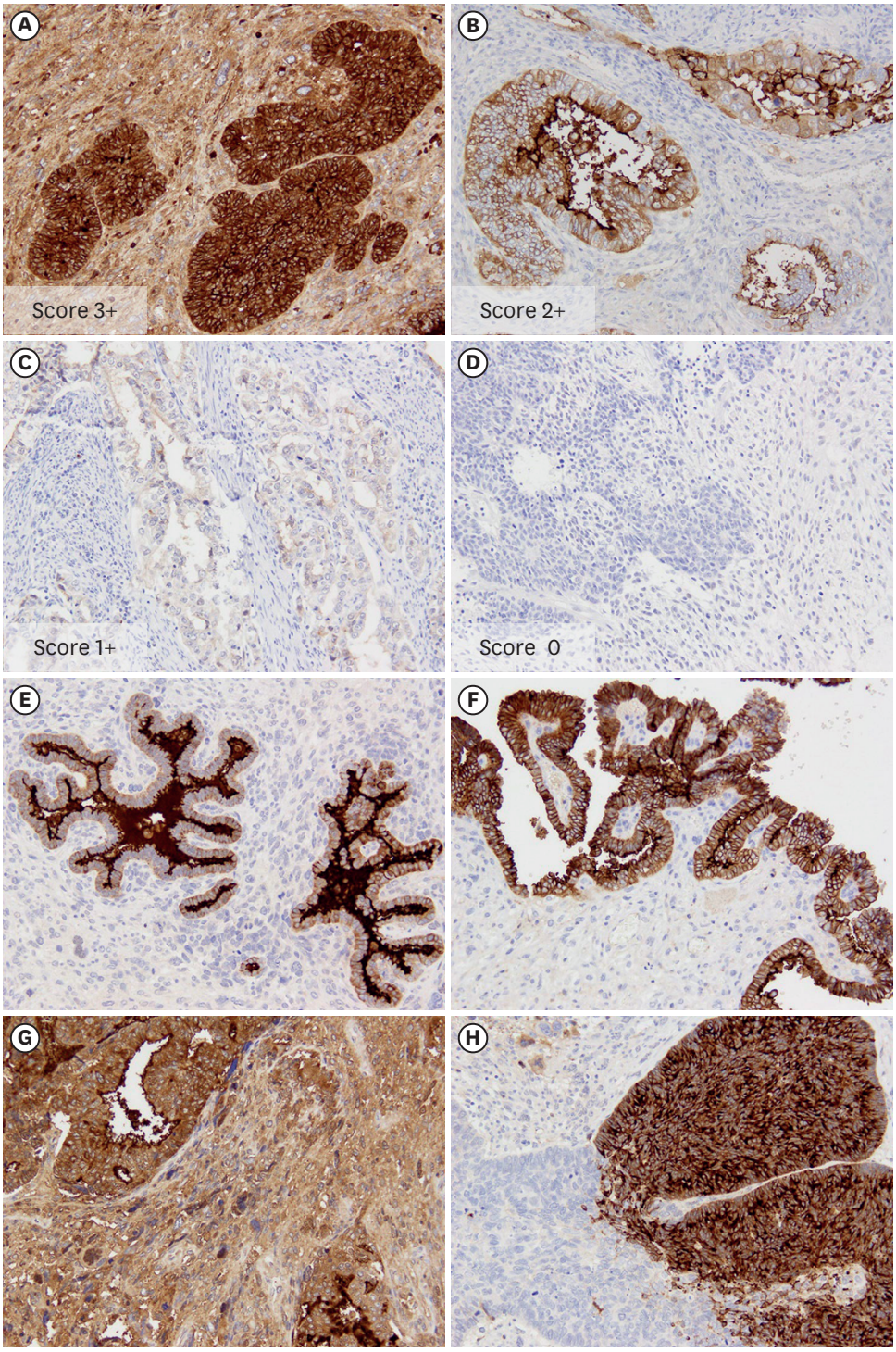

Fig. 1. Mesothelin immunohistochemistry in uterine carcinosarcoma. Images depict strong/score 3+ (A), moderate/score 2+ (B), weak/score 1+ (C) positivity, and negative/score 0 (D) expression of mesothelin. Usually, expression is restricted to carcinomatous components (E, F). Periodically, mesothelin expression is detected in both carcinoma and sarcomatous components (G). Intratumoral heterogeneity in mesothelin expression is commonly observed (H) (A-H, ×200).

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and sarcomatous components in some cases, most showed MSLN expression restricted to carcinomatous components, revealing intratumoral heterogeneity.

The characteristics of the 9 patients with OCS are shown in **Table S1**. The median patient age was 64 (range, 55–81) years. Of the 9 patients, 7 had stage III disease and 1 had stage IV disease. The predominant carcinoma component was endometrioid in 2 patients, high-grade serous in 2, clear cell in 1, and others in 4. All OCS cases had MSLN positivity, and 6 (66.7%) cases showed high expression. Only 2 patients underwent HER2 evaluation; one was HER2-negative and the other HER2-low.

2. Association between MSLN expression and survival outcomes among patients with UCS

Among UCS patients, the median OS was 47.2 (95% confidence interval [CI]=21.0–73.4) months and the median PFS was 31.1 (95% CI=14.0–48.3) months (**Fig. 2A and B**). Patients with high-MSLN showed longer OS (hazard ratio=0.48; 95% CI=0.26–0.89) than patients with low-MSLN (NA vs. 36.8 months; p=0.016; **Fig. 2C**). There was no significant difference in PFS between the high-MSLN and low-MSLN groups (36.0 vs. 29.1 months; p=0.55; **Fig. 2D**). Median PFS after chemotherapy conducted at the recurrence time was longer in patients with high MSLN expression (11.1 vs. 13.9 months). Univariate analysis revealed that prolonged OS was significantly associated to high-MSLN and early stage (FIGO stage I/II), whereas multivariate analysis revealed that prolonged OS was independently related to high-MSLN (p<0.001), younger age (p=0.017), and early FIGO stage (p<0.001) (**Table 2**).

Table 2. Univariate and multivariate analyses of overall survival among patients with uterine sarcoma

Characteristics	No. of patients	Univariate		Multivariate	
		HR (95% CI)	p-value	HR (95% CI)	p-value
MSLN expression					
Low	79	1.00			
High	40	0.48 (0.26–0.89)	0.016	0.29 (0.15–0.57)	<0.001
Age (yr)					
<63	62	1.00			
≥63	57	1.53 (0.91–2.57)	0.111	1.94 (1.13–3.35)	0.017
Stage					
I/II	56	1.00			
III/IV	63	2.22 (1.29–3.82)	0.003	3.51 (1.97–6.25)	<0.001
ECOG PS					
0	108	1.00			
1	11	1.52 (0.69–3.35)	0.328	1.88 (0.80–4.41)	0.146
Carcinoma component					
Endometrioid	54	1.00			
Serous	34	1.36 (0.72–2.57)	0.341		
Others	31	1.66 (0.90–3.08)	0.104		
Sarcoma component					
Homologous	70	1.00			
Heterologous	49	1.49 (0.89–2.50)	0.133		
HER2 status					
Negative	32	1.00			
Low	40	0.87 (0.46–1.62)	0.655		
High	46	0.61 (0.32–1.16)	0.129		
Chemotherapy					
No	53	1.00			
Yes	66	1.17 (0.70–1.99)	0.559		

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Groups performance status; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; MSLN, mesothelin.

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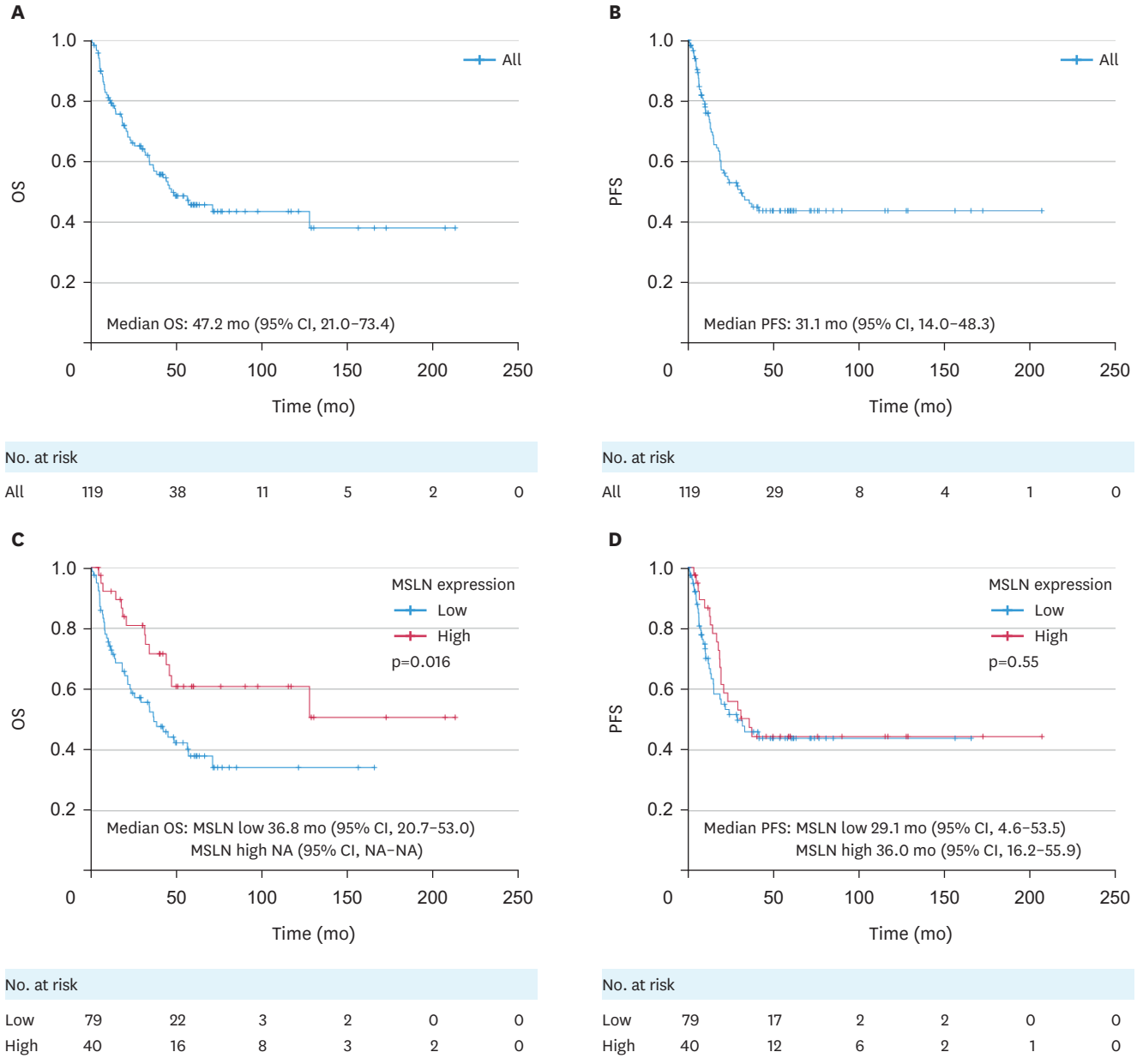

Fig. 2. Kaplan-Meier curves for OS and PFS among all patients (A, B) and patients according to MSLN expression status (C, D).
CI, confidence interval; MSLN, mesothelin; NA, not available; OS, overall survival; PFS, progression-free survival.

3. Association between MSLN expression and HER2 expression

The MSLN H-scores according to the HER2 status are shown in **Fig. 3**. The median H-scores of the HER2-negative (score of 0), HER2-low (score of 1+), and HER2-high (score of 2+/3+) groups were 44, 52, and 88, respectively. There was a significant association between HER2 expression and the MSLN H-score (p=0.017). Among the 3 groups, the HER2-high group had a higher H-score than the HER2-negative group (p=0.038). There was no significant difference in OS between patients with high-MSLN and low-MSLN expression groups in HER2-negative (127.8 vs. 21.6 months; p=0.10; **Fig. 4A**), HER2-low (NA vs. 36.8 months; p=0.44; **Fig. 4B**), and HER2-high (NA vs. 42.3; p=0.17; **Fig. 4C**) groups.

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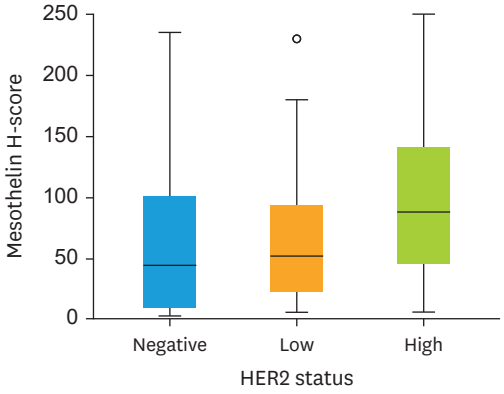

Fig. 3. Mesothelin expression and HER2 expression of uterine carcinosarcoma. The median H-score of each group was 44 (HER2-negative), 52 (HER2-low). and 88 (HER2-high).
HER2, human epidermal growth factor receptor 2.

DISCUSSION

According to our knowledge, this is the first study to report a link between MSLN expression and clinicopathological features, survival outcomes, and HER2 expression in patients with UCS. MSLN expression was generally observed regardless of age, FIGO stage, or pathological features. We also demonstrated favorable OS in UCS patients with high MSLN expression and MSLN expression, even in patients with HER2-negativity. These findings may be helpful for the development of anti-MSLN therapy for GCS.

Despite clinicopathological features, high MSLN expression was observed in 33.9% of UCS patients. One study on MSLN expression evaluated using the MSVA-235 antibody in UCS revealed that 50% of patients had high MSLN expression [11]. However, the anti-MSLN antibody and criteria for positivity used in their study differed from those used in ours. For therapeutic development, we used the VENTANA MSLN (SP74) IHC assay for MSLN evaluation and positive criteria based on a Phase II trial of anetumab ravtansine for MSLN-positive malignant pleural mesothelioma [12]. In a study conducted using the same IHC assay (SP74) and positive criteria in the present study, high MSLN expression was observed in 85% to 87% of patients with mesothelioma and ovarian cancer [20], which was higher than that of UCS in our study cohort. MSLN expression is more prevalent in the carcinoma component than sarcomatous component, which may explain why carcinomas have a higher proportion of high MSLN expression than carcinosarcomas. From the drug development standpoint, this intratumoral heterogeneity of MSLN expression may result in false-negative MSLN expression in patient-derived xenografts (PDX), necessitating caution when using PDX to evaluate the efficacy of anti-MSLN therapies. This study did not find a significant association between MSLN expression and clinicopathological features. Similar results have been observed in gastric, mesothelioma, and ovarian cancers [21]. In OCS, 65% are reported MSLN-positive in the study applying the MSVA-235 antibody [11]. From reports on ovarian cancer, 50%–85% are reported to be high-MSLN or overexpressed [22,23]. Although, we could not compare these results due to differences in the primary antibody and the criteria for positivity in each study, we observed 66.7% of OCS with high MSLN expression, which suggests that most OCS show frequent MSLN positivity.

The results of this study indicated that high MSLN expression might be a favorable prognostic factor. The median OS for UCS patients in our cohort was 47.2 months, which was

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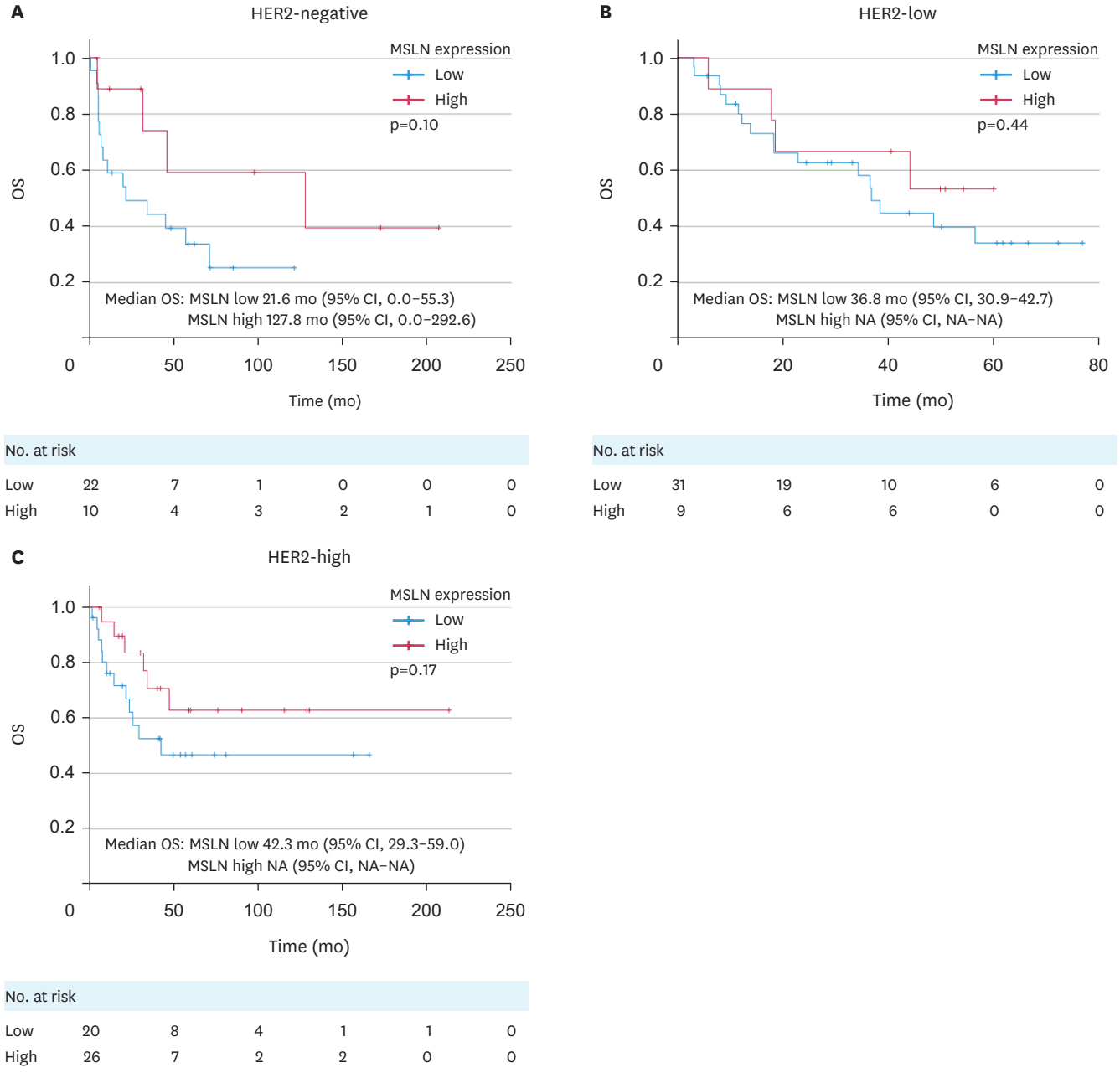

Fig. 4. Kaplan-Meier curves for OS among patients with HER2-negative (A), HER2-low (B), and HER2-high (C) according to MSLN expression status.
CI, confidence interval; HER2, human epidermal growth factor receptor 2; MSLN, mesothelin; NA, not available; OS, overall survival.

longer than that of a phase 3 trial for UCS patients treated with paclitaxel and carboplatin, which was 37 months [5]. However, because our study included patients who did not require chemotherapy, our results seem reasonable. Patients with high MSLN expression showed a longer median OS than those with low MSLN expression. The mechanisms underlying the improved prognosis of the high-MSLN group remain unclear; however, one plausible reason could be the immune response to MSLN-expressing tumor cells. A humoral immune response to MSLN has been observed in patients with ovarian cancer and mesothelioma [20]. Another study reported that MSLN-specific cellular immune responses to IL-2 and IL-7 correlate with prolonged survival in patients with brain metastases. Further studies are

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required to reveal the association between immune response and MSLN expression [24]. In contrast, the present study showed no significant difference in PFS between high-MSLN and low-MSLN patients. The reason for this might be the differences in the efficacy of chemotherapy conducted at the recurrence time between the 2 groups, where median PFS after chemotherapy was longer in patients with high MSLN expression. There are no reports on the association between MSLN expression and survival outcomes in patients with UCS. Some malignancies, including endometrial cancer [25], pancreatic cancer [26], non-small cell lung cancer [27], and triple-negative breast cancer [28] with high MSLN expression, reportedly have poorer survival than those with low-MSLN expression, whereas this association is conflicting in ovarian [22,29], mesothelioma [30], and gastric cancers [21,31].

Revealing the association between MSLN and HER2 expression has become important, since anti-HER2 therapy for UCS has been drastically developed. Notably, a novel ADC for HER2 reportedly showed clinical efficacy even in patients with low HER2 expression (IHC score 1+) [13]. A study on invasive breast cancer reported no correlation between MSLN and HER2 expression [32]; however, there have been no reports on UCS. In this study, patients with HER2-high expression had higher MSLN expression levels than those with HER2-negative expression. However, high MSLN expression was observed in HER2-negative and -low patients as well as in HER2-high patients with UCS. The basis of the relationship between MSLN and HER2 remains unknown since the intracellular signal crosstalk between MSLN and HER2 has not been elucidated. In addition, there was no association between MSLN expression and prognosis among the groups with different HER2 statuses.

This study had some limitations. First, it was a retrospective study performed at a single institution. Second, because UCS is a rare malignancy, the sample size not was small to analyze the prognostic outcomes according to HER2 or MSLN status. However, the present study included the largest number of UCS cases ever reported. To the best of our knowledge, this is the first report of MSLN expression in UCS indicating its significance.

We discovered frequent MSLN expression in both UCS and OCS. All UCS exhibited MSLN expression; high MSLN expression was a significant favorable prognostic factor. MSLN expression could be observed in patients with HER2-negativity as well, although patients with HER2-high showed higher MSLN expression than those with HER2-low/negative. MSLN could be a potential therapeutic target for HER2-positive and -negative UCS patients.

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SUPPLEMENTARY MATERIAL

Table S1

Patient characteristics and mesothelin expression in ovarian carcinosarcoma patients

REFERENCES

1. Cantrell LA, Blank SV, Duska LR. Uterine carcinosarcoma: a review of the literature. Gynecol Oncol 2015;137:581-8. PUBMED | CROSSREF
2. Berton-Rigaud D, Devouassoux-Shisheboran M, Ledermann JA, Leitao MM, Powell MA, Poveda A, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for uterine and ovarian carcinosarcoma. Int J Gynecol Cancer 2014;24:S55-60. PUBMED | CROSSREF
3. Tanner EJ, Leitao MM Jr, Garg K, Chi DS, Sonoda Y, Gardner GJ, et al. The role of cytoreductive surgery for newly diagnosed advanced-stage uterine carcinosarcoma. Gynecol Oncol 2011;123:548-52. PUBMED | CROSSREF
4. Rauh-Hain JA, Diver EJ, Clemmer JT, Bradford LS, Clark RM, Growdon WB, et al. Carcinosarcoma of the ovary compared to papillary serous ovarian carcinoma: a SEER analysis. Gynecol Oncol 2013;131:46-51. PUBMED | CROSSREF
5. Powell MA, Filiaci VL, Hensley ML, Huang HQ, Moore KN, Tewari KS, et al. Randomized phase III trial of paclitaxel and carboplatin versus paclitaxel and ifosfamide in patients with carcinosarcoma of the uterus or ovary: an NRG oncology trial. J Clin Oncol 2022;40:968-77. PUBMED | CROSSREF
6. Hassan R, Thomas A, Alewine C, Le DT, Jaffee EM, Pastan I. Mesothelin immunotherapy for cancer: ready for prime time? J Clin Oncol 2016;34:4171-9. PUBMED | CROSSREF
7. Dainty LA, Risinger JI, Morrison C, Chandramouli GV, Bidus MA, Zahn C, et al. Overexpression of folate binding protein and mesothelin are associated with uterine serous carcinoma. Gynecol Oncol 2007;105:563-70. PUBMED | CROSSREF
8. Ho M, Bera TK, Willingham MC, Onda M, Hassan R, FitzGerald D, et al. Mesothelin expression in human lung cancer. Clin Cancer Res 2007;13:1571-5. PUBMED | CROSSREF
9. Faust JR, Hamill D, Kolb EA, Gopalakrishnapillai A, Barwe SP. Mesothelin: an immunotherapeutic target beyond solid tumors. Cancers (Basel) 2022;14:1550. PUBMED | CROSSREF
10. Kelly RJ, Sharon E, Pastan I, Hassan R. Mesothelin-targeted agents in clinical trials and in preclinical development. Mol Cancer Ther 2012;11:517-25. PUBMED | CROSSREF
11. Weidemann S, Gagelmann P, Gorbokon N, Lennartz M, Menz A, Luebke AM, et al. Mesothelin expression in human tumors: a tissue microarray study on 12,679 tumors. Biomedicines 2021;9:397. PUBMED | CROSSREF
12. Kindler HL, Novello S, Bearz A, Ceresoli GL, Aerts JG, Spicer J, et al. Anetumab ravtansine versus vinorelbine in patients with relapsed, mesothelin-positive malignant pleural mesothelioma (ARCS-M): a randomised, open-label phase 2 trial. Lancet Oncol 2022;23:540-52. PUBMED | CROSSREF
13. Nishikawa T, Hasegawa K, Matsumoto K, Mori M, Hirashima Y, Takehara K, et al. Trastuzumab deruxtecan for human epidermal growth factor receptor 2-expressing advanced or recurrent uterine carcinosarcoma (NCCH1615): the STATICE trial. J Clin Oncol 2023;41:2789-99. PUBMED | CROSSREF
14. Menderes G, Bonazzoli E, Bellone S, Black J, Predolini F, Pettinella F, et al. SYD985, a novel duocarmycin-based HER2-targeting antibody-drug conjugate, shows antitumor activity in uterine and ovarian carcinosarcoma with HER2/Neu expression. Clin Cancer Res 2017;23:5836-45. PUBMED | CROSSREF
15. World Health Organization (WHO) Classification of Tumours Editorial Board. Female genital tumours. WHO classification of tumours. 5th ed. Geneva: WHO; 2020.
16. Hassan R, Blumenschein GR Jr, Moore KN, Santin AD, Kindler HL, Nemunaitis JJ, et al. First-in-human, multicenter, phase I dose-escalation and expansion study of anti-mesothelin antibody-drug conjugate anetumab ravtansine in advanced or metastatic solid tumors. J Clin Oncol 2020;38:1824-35. PUBMED | CROSSREF
17. Mizoguchi C, Nishikawa T, Yoshida H, Yamamoto K, Kitadai R, Sudo K, et al. HER2-negative or low expression as an unfavorable prognostic factor in patients with stage I/II uterine carcinosarcoma. Research Square 2022 Dec 20. Available from: https://www.researchsquare.com/article/rs-2369378/v1. CROSSREF
18. Yoshida H, Nishikawa T, Matsumoto K, Mori M, Hirashima Y, Takehara K, et al. Histopathological features of HER2 overexpression in uterine carcinosarcoma: proposal for requirements in HER2 testing for targeted therapy. Virchows Arch 2021;478:1161-71. PUBMED | CROSSREF
19. Bartley AN, Washington MK, Colasacco C, Ventura CB, Ismaila N, Benson AB, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. J Clin Oncol 2017;35:446-64. PUBMED | CROSSREF

20. Ho M, Hassan R, Zhang J, Wang QC, Onda M, Bera T, et al. Humoral immune response to mesothelin in mesothelioma and ovarian cancer patients. Clin Cancer Res 2005;11:3814-20. PUBMED | CROSSREF
21. Baba K, Ishigami S, Arigami T, Uenosono Y, Okumura H, Matsumoto M, et al. Mesothelin expression correlates with prolonged patient survival in gastric cancer. J Surg Oncol 2012;105:195-9. PUBMED | CROSSREF
22. Yen MJ, Hsu CY, Mao TL, Wu TC, Roden R, Wang TL, et al. Diffuse mesothelin expression correlates with prolonged patient survival in ovarian serous carcinoma. Clin Cancer Res 2006;12:827-31. PUBMED | CROSSREF
23. Scales SJ, Gupta N, Pacheco G, Firestein R, French DM, Koeppen H, et al. An antimesothelin-monomethyl auristatin e conjugate with potent antitumor activity in ovarian, pancreatic, and mesothelioma models. Mol Cancer Ther 2014;13:2630-40. PUBMED | CROSSREF
24. Zhenjiang L, Rao M, Luo X, Sandberg E, Bartek J Jr, Schoutrop E, et al. Mesothelin-specific immune responses predict survival of patients with brain metastasis. EBioMedicine 2017;23:20-4. PUBMED | CROSSREF
25. Kakimoto S, Miyamoto M, Einama T, Takihata Y, Matsuura H, Iwahashi H, et al. Significance of mesothelin and CA125 expression in endometrial carcinoma: a retrospective analysis. Diagn Pathol 2021;16:28. PUBMED | CROSSREF
26. Shimizu A, Hirono S, Tani M, Kawai M, Okada K, Miyazawa M, et al. Coexpression of MUC16 and mesothelin is related to the invasion process in pancreatic ductal adenocarcinoma. Cancer Sci 2012;103:739-46. PUBMED | CROSSREF
27. Kachala SS, Bograd AJ, Villena-Vargas J, Suzuki K, Servais EL, Kadota K, et al. Mesothelin overexpression is a marker of tumor aggressiveness and is associated with reduced recurrence-free and overall survival in early-stage lung adenocarcinoma. Clin Cancer Res 2014;20:1020-8. PUBMED | CROSSREF
28. Li YR, Xian RR, Ziober A, Conejo-Garcia J, Perales-Puchalt A, June CH, et al. Mesothelin expression is associated with poor outcomes in breast cancer. Breast Cancer Res Treat 2014;147:675-84. PUBMED | CROSSREF
29. Cheng WF, Huang CY, Chang MC, Hu YH, Chiang YC, Chen YL, et al. High mesothelin correlates with chemoresistance and poor survival in epithelial ovarian carcinoma. Br J Cancer 2009;100:1144-53. PUBMED | CROSSREF
30. Vizcaya D, Farahmand B, Walter AO, Kneip C, Jöhrens K, Tukiainen M, et al. Prognosis of patients with malignant mesothelioma by expression of programmed cell death 1 ligand 1 and mesothelin in a contemporary cohort in Finland. Cancer Treat Res Commun 2020;25:100260. PUBMED | CROSSREF
31. Einama T, Homma S, Kamachi H, Kawamata F, Takahashi K, Takahashi N, et al. Luminal membrane expression of mesothelin is a prominent poor prognostic factor for gastric cancer. Br J Cancer 2012;107:137-42. PUBMED | CROSSREF
32. Wang L, Niu Z, Zhang L, Liu X, Wang X, Li F, et al. Clinicopathological significance of mesothelin expression in invasive breast cancer. J Int Med Res 2012;40:909-16. PUBMED | CROSSREF