J Gynecol Oncol. 2025 Jan;36(1):e14
https://doi.org/10.3802/jgo.2025.36.e14
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

HER2-negative or low expression as an unfavorable prognostic factor in patients with stage I/II uterine carcinosarcoma

Chiharu Mizoguchi [1], **Tadaaki Nishikawa** [1], **Hiroshi Yoshida** [2], **Masanori Yasuda** [3], **Tomoyasu Kato** [4], **Kosei Hasegawa** [5], **Kan Yonemori** [1]

[1]Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan
[2]Department of Diagnostic Pathology, National Cancer Center Hospital, Tokyo, Japan
[3]Department of Diagnostic Pathology, Saitama Medical University International Medical Center, Hidaka, Japan
[4]Department of Gynecology, National Cancer Center Hospital, Tokyo, Japan
[5]Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Hidaka, Japan

Received: Feb 28, 2024
Revised: May 3, 2024
Accepted: Jun 11, 2024
Published online: Jul 2, 2024

Correspondence to
Tadaaki Nishikawa
Department of Medical Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-Ku, Tokyo 104-0045, Japan.
Email: tnishika@ncc.go.jp

ORCID iDs
Chiharu Mizoguchi
https://orcid.org/0000-0002-2929-1396
Tadaaki Nishikawa
https://orcid.org/0000-0003-2606-4208
Hiroshi Yoshida
https://orcid.org/0000-0002-7569-7813
Masanori Yasuda
https://orcid.org/0000-0002-0769-360X
Tomoyasu Kato
https://orcid.org/0000-0001-9561-1522
Kosei Hasegawa
https://orcid.org/0000-0002-1903-7001

ABSTRACT

Objective: Uterine carcinosarcoma (UCS) is uncommon high-grade endometrial cancer with limited treatment options. We evaluated the prognostic significance of human epidermal growth factor receptor 2 (HER2) expression and HER2 gene amplification within large cohorts of UCS, and clarify clinicopathologic characteristics of HER2-low UCS.
Methods: We examined HER2 protein expression in 148 patients of UCS using in vivo diagnostic HER2 immunohistochemistry (IHC) kits and HER2 gene amplification using fluorescence in situ hybridization (FISH) in 72 patients.
Results: HER2 IHC score was evaluated according to the latest American Society of Clinical Oncology/College of American Pathologists criteria for gastric cancer, which was negative in 41 patients, low expression of 1+ was observed in 57 patients, and HER2 high expression was observed in 50 patients (2+ in 38 and 3+ in 12 patients). There was no significant statistical difference in clinicopathological characteristics based on HER2 protein expression status. HER2 negative and low expression compared to high expression revealed poor overall survival in stage I/ II. The concordance between IHC and FISH results were relatively low compared to other cancer types (HER2 IHC score 1+, 2+, and 3+ were 5%, 15%, and 50%), and combining these results was not efficient as a prognostic factor in UCS. In contrast, the HER2 IHC score alone was a prognostic factor in stage I/II UCS. HER2 low group did not show specific clinicopathologic features.
Conclusion: Since the HER2 IHC score low in advanced UCS is a predictive factor, stratification of UCS using HER2 IHC score for HER2 IHC score low group and developing adjuvant therapy may be proposed in the near future.

Keywords: Carcinosarcoma; ERBB2 Protein, Human; Immunohistochemistry; In Situ Hybridization; Prognosis

Synopsis

Human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) low and negative scores had poor prognosis in stage I/II uterine carcinosarcoma. Unlike HER2 testing in other cancer types, protein expression did not correlate with gene amplification. Stratification using HER2 IHC for low group and developing may be proposed in the future.

Kan Yonemori
https://orcid.org/0000-0002-7624-7611

Preprint
This manuscript was preprinted at https://doi.org/10.21203/rs.3.rs-2369378/v1.

Conflict of Interest
Chiharu Mizoguchi, Hiroshi Yoshida, Masanori Yasuda, and Tomoyasu Kato declare they have no financial interests. Tadaaki Nishikawa has received grants from AstraZeneca, Daiichi Sankyo, and speaker and consultant honoraria from Eisai, Chugai, Takeda, MSD, AstraZeneca, Roche, Sanofi, Kosei Hasegawa has received grants and honoraria from Daiichi-Sankyo, Kan Yonemori has received grants 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 Bayer, Jansen pharma and Haihe, consulting fees from Novartis, Eisai, AstraZeneca, Chugai Takeda, Genmab, Sanofi, OncXerna, speaker and consultant honoraria from Pfizer, Eisai, AstraZeneca, Eli Lilly, Takeda, Chugai, MSD, Fuji Film Pharma, Bayer, Astellas, Boeringer Ingelheim, Daiichi Sankyo, PDR pharma, Sanofi outside the submitted work.

Author Contributions
Conceptualization: M.C., N.T., Y.H., Y.K.; Data curation: M.C., N.T., Y.H.; Formal analysis: M.C., N.T., Y.H.; Investigation: M.C., N.T., Y.H., Y.M., Y.K.; Methodology: M.C., N.T., Y.H., H.K., Y.K.; Project administration: M.C., N.T., Y.K.; Resources: N.T., Y.H., Y.M., K.T., H.K.; Validation: N.T.; Writing - original draft: M.C., N.T., Y.H.; Writing - review & editing: M.C., N.T., Y.H., Y.M., K.T., H.K., Y.K.

INTRODUCTION

Uterine carcinosarcoma (UCS) is uncommon endometrial cancer that has a highly malignant potential [1]. It is treated as high-grade endometrial cancer and usually shows poor therapeutic efficacy with limited treatment options and a high recurrence rate of 40%–57% [2-4]. Despite these treatments, the overall 5-year survival rate in stage III and IV remains poor, range from 10% to 25% [5]. Thus, new therapeutic strategies are desirable for patients with UCS. Several reports showed that the prognostic factor is stage, performance status, CA-125 level, lymphovascular space invasion, and myometrial invasion within a limited patient population [3,6].

Human epidermal growth factor receptor 2 (HER2) is known as a therapeutic target in various types of cancers such as breast cancer, gastric cancer, and endometrial serous carcinoma [7-9]. Recently, HER2 targeted therapy including antibody-drug conjugates (ADCs) has been discussed in multiple solid tumors including UCS, and shown promising efficacy [7,10-17]. Although some previous studies discuss HER2 expression in patients with UCS [11,18-21], there are still unsolved issues. First, the significance of HER2 expression as a prognostic factor in patients with UCS is controversial due to conflicting reports [22]. These discordant results could be explained by the fact that each study used a different set of HER2 scoring criteria, different protocol and/or primary antibodies for HER2, and was small in size, less than 100 cases, because of the rarity of UCS. Second, unlike in breast cancer, *HER2* gene amplification detected fluorescence in situ hybridization (FISH) does not always correspond to HER2 protein overexpression assessed by immunohistochemistry (IHC) [23], but these studies were also small in size, and the prognostic significance of FISH positivity, *HER2* gene amplification, has not been established in UCS. Moreover, not only HER2 high status but HER2 low status has been recently suggested as a therapeutic target in breast cancer [24]. Finally, anti-HER2 therapy for UCS is being developed, and a type of HER2-ADC, trastuzumab deruxtecan has been demonstrated its promising antitumor activity in patients with UCS regardless of HER2 IHC score (1+, 2+, or 3+) [25]. In contrast to UCS with HER2 overexpression, the clinicopathological characteristics of patients with HER2-low expression UCS have not yet been well reported.

Herein, we aim to investigate the issues above, within large cohorts of patients with UCS using the in vivo diagnostic (IVD) kit for HER2 testing. Thus, we validate the prognostic significance of HER2 expression and/or *HER2* gene amplification in patients with UCS and clarify clinicopathologic characteristics of patients with HER2-low UCS.

MATERIALS AND METHODS

1. Study and patient characteristics

The study was conducted in accordance with the Declaration of Helsinki and the approval of the institutional ethics committee of the National Cancer Center Hospital (2014-393) and Saitama Medical University International Medical Center (17-233). The option of refusal of participation was ensured with opt-out consent. We retrospectively reviewed patients of UCS at the National Cancer Center Hospital and Saitama Medical University International Medical Center between 1997 and 2019. All cases were histopathologically diagnosed at each institution as primary UCS according to the 2014 WHO tumor classification of the female genital tracts [26]. The follow-up for most patients consisted of vaginal examinations, pap

smear, and computed tomography (CT) every 3–6 months for the first 2 years. During the third and fourth years of follow-up, patients underwent annual examinations, and those with suspected recurrence underwent CT and histological examination. The patients who were enrolled in the STATICE trial were excluded [25].

Patient data including staging, histological characters, previous treatment, recurrence date, and outcomes were retrieved from electronic medical records under appropriate anonymization circumstances.

2. HER2 testing

IHC was performed using a standard Food and Drug Administration-approved IVD kit, the Pathway HER2 (Clone 4B5), on the BenchMark XT automated staining system (Ventana Medical Systems Inc., Tucson, AZ, USA) according to the manufacturer's recommended protocol. The method used to evaluate IHC was identical to that used in our previous clinical trial [25], which was conducted as described below. Staining intensity was initially evaluated using the 0 to 3+ scale according to the 2016 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guideline for gastric/esophagogastric junction (EGJ) carcinoma [27]. Considering the resemblance of HER2 staining pattern, lateral/basolateral staining, between UCS and gastric adenocarcinoma, a scoring system of HER2 by the gastric cancer criteria that accepts lateral/basolateral staining patterns was applied [18]. In surgical specimens, a score of 0 was given if there was no reactivity or membranous reactivity in <10% of tumor cells. A score of 1+ was given if faint or barely perceptible membranous reactivity was seen in ≥10% of tumor cells, and the cells were reactive in part of their membrane only in **Fig. 1**. A score of 2+ was given if weak to moderate complete, basolateral, or lateral membranous reactivity was seen in ≥10% of tumor cells in **Fig. 1**. A score of 3+ was given when strong complete, basolateral, or lateral membranous reactivity was seen in ≥ 10% of tumor cells in **Fig. 1**. A gynecological pathologist (H.Y.) who had sufficient experience in HER2 scoring evaluated all stained slides [18,28]. FISH was conducted in 73 cases using the PathVysion HER2 DNA probe kit (Abbott Molecular, Des Plaines, IL, USA) according to the manufacturer's recommendations by SRL Co. Ltd. (Hamura, Japan). The total numbers of HER2 and CEP17, chromosome enumeration probe 17 (CEP17) signals were counted in 20 adjacent interphase tumor cell nuclei examined with fluorescent microscopes and appropriate filters. Without the knowledge of IHC status, the ratio of HER2 signal to CEP17 signal of ≥2.0 was considered positive, and a ratio of HER2 signal to CEP17 signal <2.0 was considered negative according to the 2016 ASCO/CAP gastric cancer criteria in **Fig. 1** [27]. If there are three or more CEP17 signals, on average, with a ratio <2, then the presence of more than 6 HER2 signals, on average, is interpreted as positive for *HER2* amplification in **Fig. 1**.

3. Statistics

One-way analysis of variance with Welch test analysis was performed for comparison of continuous pathological characteristics and HER2 negative, low, and high expression, and chi-square tests were performed in categorical and ordinal variables as appropriate. Univariate and multivariate logistic regression analyses were done to investigate the correlation between characteristics and survival outcomes. Hazard ratios and 95% confidence intervals (CIs) were calculated with the Cox proportional hazard regression model. Kaplan-Meier survival curves for overall survival (OS) were evaluated with a log-rank test. OS was defined as the interval between diagnosis and the date of death of any cause or the last follow-up. For statistical purposes, the stage was classified into stage I and II versus stage III and IV as well as HER2 expression into negative (HER2 IHC score 0), low expression (HER2 IHC score 1+), and

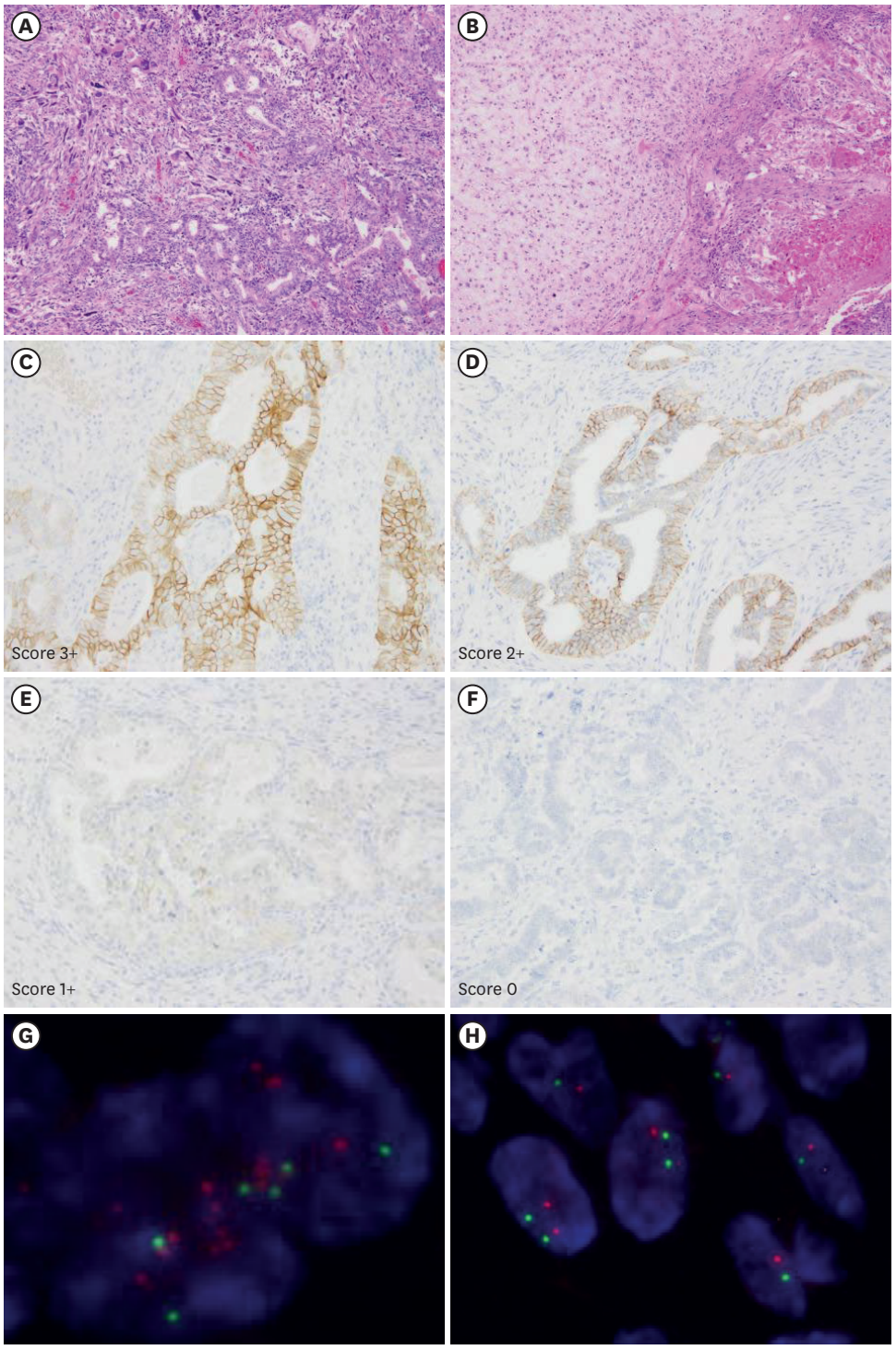

Fig. 1. Representative microphotographs of uterine carcinosarcoma expressing HER2.
(A, B) Histological findings of uterine carcinosarcoma (hematoxylin and eosin staining, ×100). (C-F) Immunohistochemistry for HER2 in uterine carcinosarcoma (×200). Fluorescence in situ hybridization for HER2 (red signal) and CEP17 (green signal). A case with (G) and without (H) *HER2* gene amplification. (G) HER2/CEP17 ratio 3.9 (184/47) (Case 44). (H) HER2/CEP17 ratio 1.1 (80/73) (Case 45).
CEP17, chromosome enumeration probe 17; HER2, human epidermal growth factor receptor 2.

https://doi.org/10.3802/jgo.2025.36.e14

high expression (HER2 IHC score 2+ and 3+). Analyses of survival outcomes were performed among 147 patients with the available survival data. Data were analyzed using IBM® SPSS® Statistics Base Edition 27.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

One hundred and forty-eight patients with UCS were included in the study. Patient and clinicopathological characteristics are shown in **Table 1**. HER2 IHC score was negative in 41/148 (27.7%) patients, low expression of 1+ was observed in 57/148 (38.5%) patients, and HER2 high expression was observed in 50/148 (33.8%) patients (2+ in 38 and 3+ in 12 patients, respectively). There were no significant statistical differences in clinicopathological characteristics based on HER2 protein expression status.

FISH was performed in 72 patients within the National Cancer Center Hospital cohort and *HER2* gene amplification was detected in 9 patients HER2 IHC score and FISH score are shown in **Table 2**. HER2 FISH positivity were 4.8% in HER2 IHC score 1+, and 15%, and 50% in HER2 IHC score 2+, and 3+, respectively.

Table 1. Clinicopathological characteristics of patients with uterine carcinosarcoma according to HER2 immunohistochemistry status

Characteristics	HER2 negative IHC score 0	HER2-low IHC score 1+	HER2-high IHC score 2+/3+	Total	p-value
Total patients	41 (27.7)	57 (38.5)	50 (33.8)	148	
Age (yr)					0.828
≥63	18 (25.4)	28 (39.4)	25 (35.2)	71	
<63	23 (29.9)	29 (37.7)	25 (32.5)	77	
ECOG PS					0.967
0	38 (27.9)	52 (38.2)	46 (33.8)	136	
1	3 (25.0)	5 (41.7)	4 (33.3)	12	
2, 3	0 (0.0)	0 (0.0)	0 (0.0)	0	
FIGO stage (2008)					0.561
I	17 (25.4)	29 (43.3)	21 (31.3)	67	
II	3 (33.3)	4 (44.4)	2 (22.2)	9	
III	11 (26.2)	12 (28.6)	19 (45.2)	42	
IV	10 (34.5)	11 (37.9)	8 (27.6)	29	
Unknown	0 (0.0)	1 (100.0)	0 (0.0)	1	
Lymph node metastasis					0.189
Negative	33 (28.4)	46 (39.7)	37 (31.9)	116	
Positive	8 (25.8)	10 (32.3)	13 (41.9)	31	
Unknown	0 (0.0)	1 (100.0)	0 (0.0)	1	
Adjuvant chemotherapy					0.057
No	30 (35.3)	29 (34.1)	26 (30.6)	85	
Yes	11 (17.5)	28 (44.4)	24 (38.1)	63	
Depth of invasion					0.290
Myometrium <50%	21 (26.3)	31 (38.8)	28 (35.0)	80	
Myometrium ≥50%	18 (31.0)	20 (34.5)	20 (34.5)	58	
Unknown	2 (20.0)	6 (60.0)	2 (20.0)	10	
Cervical stromal involvement					0.240
Negative	26 (24.3)	42 (39.3)	39 (36.4)	107	
Positive	13 (40.6)	9 (28.1)	10 (31.3)	32	
Unknown	2 (22.2)	6 (66.7)	1 (11.1)	9	
Pelvic cytology					0.820
Negative	24 (30.0)	28 (35.0)	28 (35.0)	80	
Positive	15 (25.4)	23 (39.0)	21 (35.6)	59	
Unknown	2 (22.2)	6 (66.7)	1 (11.1)	9	

Results were considered significant with a 2-sided p-value of <0.05
ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

https://doi.org/10.3802/jgo.2025.36.e14

Table 2. Concordance between HER2 immunohistochemistry score and fluorescent in situ hybridization (n=73)

HER2 IHC score*	FISH		Positivity (%)
	Positive HER2/CEP17 ≥2.0 (%)	Negative HER2/CEP17 <2.0 (%)	
Score 0 (n=27)	3 (11.1)	24 (88.9)	11
Score 1+ (n=21)	1 (4.8)	20 (95.2)	5
Score 2+ (n=20)	3 (15.0)	17 (75.0)	15
Score 3+ (n=4)	2 (50.0)	2 (50.0)	50

Percentages were calculated using the number of patients in the total column as the denominator.
CEP17, chromosome enumeration probe 17; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.
*Scoring based on the 2016 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) gastric cancer criteria.

The median follow-up time was 26.6 months (range, 0.7–215.9 months). Univariate analysis and multivariate analysis in HER2 IHC score and prognosis are shown in **Table 3**. Univariate analysis showed an association between OS, age (≥63 years), stage IV, lymphovascular invasion, cervical stromal invasion, myometrium invasion, and pelvic cytology. Multivariate analysis using these parameters showed an association with OS in age and stage IV. Kaplan-Meier curves

Table 3. Univariable and multivariable analysis of survival outcome

Characteristics	No.	Univariate			Multivariate		
		HR	95% CI	p-value	HR	95% CI	p-value
HER2 status							
Negative	41	1					
Low	57	0.88	0.51–1.54	0.672			
High	49	0.47	0.25–0.90	0.022	0.59	0.32–1.09	0.098
Age (yr)							
<63	71	1					
≥63	76	2.14	1.34–3.58	0.002	2.48	1.44–4.27	0.001
ECOG PS							
0	135	1					
≥1	12	1.47	0.63–4.43	0.358			
Stage							
I	67	1					
II	9	1.82	0.68–4.86	0.230			
III	41	1.95	1.05–3.60	0.033			
IV	29	5.54	2.96–10.35	<0.001	2.83	1.45–5.51	0.002
Sarcomatous component							
Homologous	76	1					
Heterologous	65	1.39	0.85–2.25	0.181			
Unknown	6						
Lymphovascular invasion							
Negative	62	1					
Positive	71	2.21	1.29–3.76	0.003	1.60	0.87–2.96	0.129
Unknown	14						
Cervical stromal invasion							
Negative	107	1					
Positive	31	1.73	1.01–2.97	0.045	0.94	0.52–1.70	0.849
Unknown	9						
Myometrium invasion							
<50%	80	1					
≥50%	57	2.05	1.24–3.37	0.005	1.40	0.79–2.47	0.240
Unknown	10						
Pelvic cytology							
Negative	80	1					
Positive	58	2.07	1.26–3.41	0.004	1.54	0.88–2.68	0.123
Unknown	9						

Results were considered significant with a 2-sided p-value of <0.05.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hazard ratio.

https://doi.org/10.3802/jgo.2025.36.e14

in stage I/II and stage III/IV are shown in **Fig. 2**. Median OS was 26 months in all patients, in stage I/II, 34 months in HER2 negative and low group, and 57 months in HER2 high group, which was the only group that showed a survival benefit with statistical significance. There was no significant difference in OS among HER2 status in stage III/IV. Kaplan-Meier curve in HER2 IHC score 2+/3+ and FISH positive and HER2 IHC score 0 or FISH negative group are shown in **Fig. 3**. There was no significant difference in OS among the above, regardless of stage.

DISCUSSION

We examined HER2 protein expression and *HER2* gene amplification in 148 and 72 patients of UCS using IVD HER2 testing kits to clarify the prognostic significance of HER2 status in patients with UCS and clinicopathological characteristics of UCS with HER2-low expression.

We identified HER2 IHC scores 0, 1+, 2+, and 3+, in 41 (27.7%), 57 (38.5%), 38 (25.7%), and 12 (8.1%) cases, respectively, which was comparable with previous reports using the same interpretation criterion and threshold (membranous staining and ≥10% positive tumor cells) [18]. A total of 107/148 (72.3%) UCS cases with HER2 expression were observed, indicating the majority of the patients with UCS would be candidates for anti-HER2 ADC therapy. Unexpectedly, no correlation was observed between HER2 expression status and clinicopathological factors, and the HER2-low and HER2-high groups could not be characterized according to age, stage distribution, or pathological features. Although UCS cases with HER2 IHC score 3+ has been found in the range between 0% and 25% in UCS cases [19-21,29], it has been suggested that this wide range may in part reflect the lack of standardized methodologies and common interpretation criterion used in the various studies to assess the HER2 status. We believe that our data, obtained with the IVD kit and evaluated in a well-defined manner, may serve as a reliable reference for future studies examining HER2 expression in UCS.

FISH analysis was performed only in 72 cases within the National Cancer Center Hospital cohort. In IHC score 2+ and 3+ cases, 15.0% (6/40) and 50.0% (6/12) showed FISH positivity, respectively. Although there had been few reports on the concordance between IHC results and *HER2* gene amplification in patients with UCS, IHC score 2+ and 3+ cases have shown 19%–45% and 25%–100% FISH-positive results, respectively [18,19]. Similar to the previous reports, concordance between IHC and FISH scores was low, particularly in the IHC score 2+ and 3+ group, compared to breast cancer and gastric cancer, in which HER2 protein expression and *HER2* gene amplification is more concordant. The precise cause of this discordance is unknown, but HER2 protein expression may occur through a different mechanism than *HER2* gene amplification in some UCS. Intratumoral heterogeneity can be denied because FISH was performed on tumor cells marked as HER2 high by IHC score beforehand. There also were no significant differences in the clinicopathologic feature between the FISH negative and positive groups (**Table S1**), and stratification of UCS is difficult using the *HER2* gene amplification. Likely to the previous The Cancer Genome Atlas study, *HER2* gene amplification was not a prognostic factor in our study [19,20]. Furthermore, the HER2 testing system based on a combination of IHC and FISH results, which is applied for breast and gastric cancer, revealed no significant difference in the prognosis of patients with UCS (**Fig. 3**). Our findings suggest that IHC results for HER2 protein expression do not always correlate with *HER2* gene amplification in UCS and that *HER2* gene amplification and HER2 protein expression should be treated qualitatively separately in UCS.

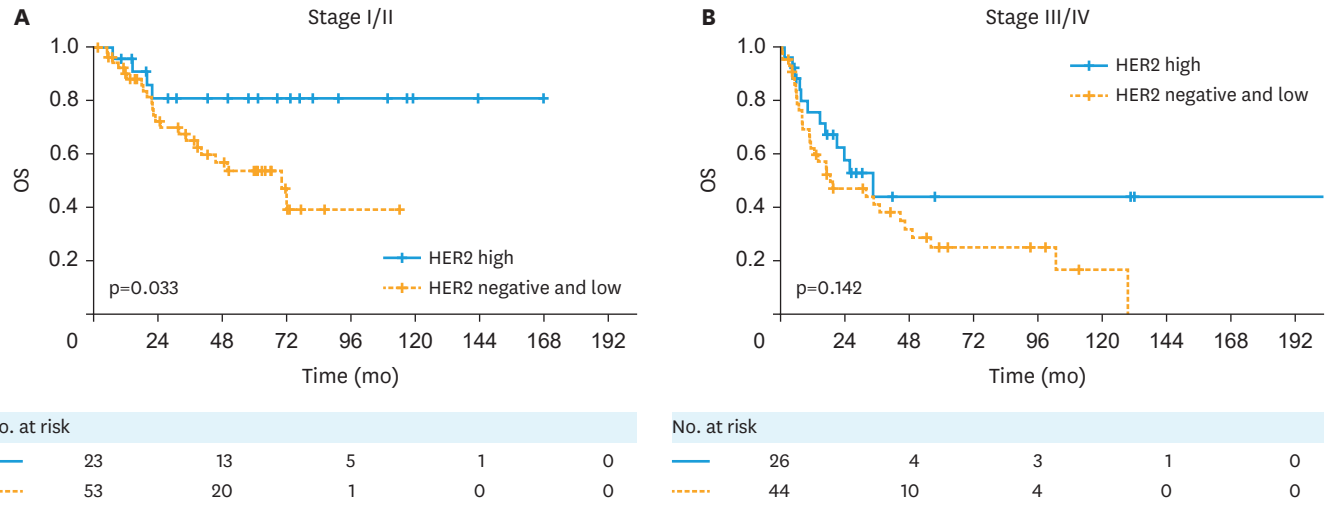

Fig. 2. HER2 status (HER2 low and HER2 high) for OS (n=148).
Log-rank test for p-values. Survival curves are shown based on (A) stage I/II, (B) stage III/IV. OS of uterine carcinosarcoma expressing HER2 in stage I/II and stage III/IV. Median OS 26 months in all patients, in stage I/II, 40 months in HER2 negative group, 31 months in HER2 low group, and 57 months in HER2 high group.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival.

We assessed HER2 status only with an IHC score instead of a combination of IHC and FISH scores. Compared among stage I/II UCS patients with HER2 IHC scores of 0 (negative), 1+ (low), 2+, and 3+ (high) group, HER2 IHC negative and low groups showed worse prognosis than HER2 high group (**Table 3**, **Fig. 2**). This result indicated that existing HER2 testing using a combination of IHC and FISH, ASCO/CAP criteria for gastric cancer and breast cancer was not suitable for the prognostic analysis for UCS. We have evaluated the HER2 IHC score with the scoring system that accepts lateral/basolateral staining patterns proposed in the previous report [18]. UCS with a predominant sarcomatous component, which reflects epithelial-mesenchymal transition (EMT) phenotype, reportedly have a worse prognosis [6], but at

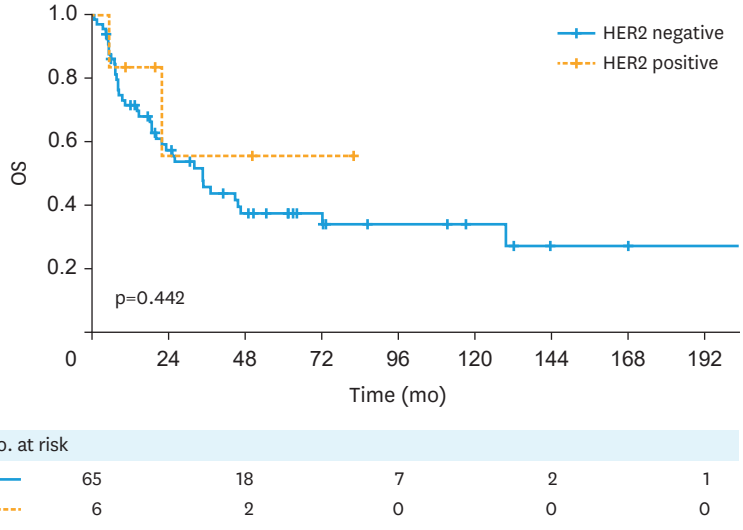

Fig. 3. OS of HER2 positive (HER2 IHC score 2/3 and FISH positive) and HER2 negative (HER2 IHC score 0 or FISH negative) uterine carcinosarcoma. There were no significant differences in OS among FISH status.
FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; OS, overall survival.

https://doi.org/10.3802/jgo.2025.36.e14

the same time, HER2-positive tumor cells are known to be less common in the sarcomatous component [18]. This suggests that UCS with HER2 negative or low scores have a predominant sarcomatous component, which may be one of the reasons for the worse prognosis.

In contrast, there was no significant difference in the prognosis of patients with stage III/IV UCS according to HER2 status. Patients with stage III/IV UCS had a poor prognosis regardless of HER2 expression. Although the reason for HER2 as a non-prognostic factor in advanced disease is unclear, decreased HER2 expression indicating EMT in the primary tumor, may not play a major role in advanced-stage UCS. Alternatively, in advanced-stage cases, the HER2 status of the metastatic site may be relevant, though we could not evaluate them in this study.

According to our knowledge, we have demonstrated for the first time that the HER2 IHC score is negative and the low group has a poor prognosis in patients with stage I/II UCS. Unfortunately, the clinical characteristics of patients with HER2-low UCS are not well defined, and thus IHC is currently required to identify these patients. Based on our result, the early stage of HER2 low UCS could be a potential area to develop anti-HER2 therapy. Although HER2 was not a prognostic factor in UCS in the advanced stage, it is important as a predictive factor for anti-HER2-ADC therapy, as they are effective and safe in patients with unresectable/metastatic UCS [25]. This study showed not only promising efficacy of ADC in UCS with groups high and low group, but demonstrated no apparent difference in the PFS, and OS. One of the reasons for this effectiveness is thought to be a bystander effect to cells neighboring HER2-positive cells, due to a highly membrane-permeable payload of T-DXd [30]. Hence, distinguishing HER2 IHC score 1+ from 0 will be important when considering treatment strategies for unresectable or metastatic UCS. Collectively, the HER2 IHC score was a prognostic factor in stage I/II UCS and reportedly a predictive factor of HER2-ADC in patients with unresectable/metastatic UCS, respectively. Thus, it would be essential to assess the HER2 IHC score in all patients with UCS.

A major limitation of the study is that this study was a retrospective study and the sample size might have been insufficient for analysis for each group depending on the HER2 status. We assume confirmation with a prospective study with a more sufficient number of patients will be necessary for the future, however, regarding the rarity of UCS, conducting such a prospective study is surely a challenge.

Concordance between HER2 IHC and FISH scores is low and combining these results was not efficient as a prognostic factor in UCS. In contrast, the HER2 IHC score alone was a prognostic factor in stage I/II UCS. HER2 low group did not show specific clinicopathologic features. Since the HER2 IHC score both low and high in advanced UCS is a predictive factor, stratification of UCS using HER2 IHC score for HER2 IHC score low group and developing adjuvant therapy may be proposed in the near future.

ACKNOWLEDGEMENTS

The authors thank Kasumi Yamamoto, Rui Kitadai, Tatsunori Shimoi, Kazuki Sudo, Maiko Miwa, Sho Sato, Daisuke Shintani, Mitsutake Yano, and Akihiro Hirakawa for advice on conceptualization, investigation, and also thank review and support of Daiichi Sankyo Company, Limited.

SUPPLEMENTARY MATERIAL

Table S1

Clinicopathological characteristics of patients with uterine carcinosarcoma according to FISH status

REFERENCES

1. Cimbaluk D, Rotmensch J, Scudiere J, Gown A, Bitterman P. Uterine carcinosarcoma: immunohistochemical studies on tissue microarrays with focus on potential therapeutic targets. Gynecol Oncol 2007;105:138-44. PUBMED | CROSSREF
2. Jonson AL, Bliss RL, Truskinovsky A, Judson P, Argenta P, Carson L, et al. Clinical features and outcomes of uterine and ovarian carcinosarcoma. Gynecol Oncol 2006;100:561-4. PUBMED | CROSSREF
3. Harano K, Hirakawa A, Yunokawa M, Nakamura T, Satoh T, Nishikawa T, et al. Prognostic factors in patients with uterine carcinosarcoma: a multi-institutional retrospective study from the Japanese Gynecologic Oncology Group. Int J Clin Oncol 2016;21:168-76. PUBMED | CROSSREF
4. Ebata T, Yonemori K, Nishikawa T, Sudo K, Shimomura A, Noguchi E, et al. Treatment outcome of second-line chemotherapy for gynecologic carcinosarcoma. Oncology 2020;98:699-705. PUBMED | CROSSREF
5. Cantrell LA, Blank SV, Duska LR. Uterine carcinosarcoma: a review of the literature. Gynecol Oncol 2015;137:581-8. PUBMED | CROSSREF
6. Matsuo K, Takazawa Y, Ross MS, Elishaev E, Podzielinski I, Yunokawa M, et al. Significance of histologic pattern of carcinoma and sarcoma components on survival outcomes of uterine carcinosarcoma. Ann Oncol 2016;27:1257-66. PUBMED | CROSSREF
7. Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, et al. Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/neu. J Clin Oncol 2018;36:2044-51. PUBMED | CROSSREF
8. Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, et al. Breast cancer. Nat Rev Dis Primers 2019;5:66. PUBMED | CROSSREF
9. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-97. PUBMED | CROSSREF
10. Schwab CL, English DP, Black J, Bellone S, Lopez S, Cocco E, et al. Neratinib shows efficacy in the treatment of HER2 amplified carcinosarcoma in vitro and in vivo. Gynecol Oncol 2015;139:112-7. PUBMED | CROSSREF
11. Nicoletti R, Lopez S, Bellone S, Cocco E, Schwab CL, Black JD, et al. T-DM1, a novel antibody-drug conjugate, is highly effective against uterine and ovarian carcinosarcomas overexpressing HER2. Clin Exp Metastasis 2015;32:29-38. PUBMED | CROSSREF
12. 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
13. Cortés J, Kim SB, Chung WP, Im SA, Park YH, Hegg R, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med 2022;386:1143-54. PUBMED | CROSSREF
14. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med 2020;382:610-21. PUBMED | CROSSREF
15. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med 2020;382:2419-30. PUBMED | CROSSREF
16. Li BT, Smit EF, Goto Y, Nakagawa K, Udagawa H, Mazières J, et al. Trastuzumab deruxtecan in *HER2*-mutant non-small-cell lung cancer. N Engl J Med 2022;386:241-51. PUBMED | CROSSREF
17. Tsurutani J, Iwata H, Krop I, Jänne PA, Doi T, Takahashi S, et al. Targeting HER2 with trastuzumab deruxtecan: a dose-expansion, phase I study in multiple advanced solid tumors. Cancer Discov 2020;10:688-701. PUBMED | 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. Rottmann D, Snir OL, Wu X, Wong S, Hui P, Santin AD, et al. HER2 testing of gynecologic carcinosarcomas: tumor stratification for potential targeted therapy. Mod Pathol 2020;33:118-27. PUBMED | CROSSREF
20. Saglam O, Husain S, Toruner G. AKT, EGFR, C-ErbB-2, and C-kit expression in uterine carcinosarcoma. Int J Gynecol Pathol 2013;32:493-500. PUBMED | CROSSREF
21. Swisher EM, Gown AM, Skelly M, Ek M, Tamimi HK, Cain JM, et al. The expression of epidermal growth factor receptor, HER-2/Neu, p53, and Ki-67 antigen in uterine malignant mixed mesodermal tumors and adenosarcoma. Gynecol Oncol 1996;60:81-8. PUBMED | CROSSREF
22. Raspollini MR, Susini T, Amunni G, Paglierani M, Taddei A, Marchionni M, et al. COX-2, c-KIT and HER-2/neu expression in uterine carcinosarcomas: prognostic factors or potential markers for targeted therapies? Gynecol Oncol 2005;96:159-67. PUBMED | CROSSREF
23. Amant F, Vloeberghs V, Woestenborghs H, Debiec-Rychter M, Verbist L, Moerman P, et al. ERBB-2 gene overexpression and amplification in uterine sarcomas. Gynecol Oncol 2004;95:583-7. PUBMED | CROSSREF
24. Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med 2022;387:9-20. PUBMED | CROSSREF
25. 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
26. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO classification of tumours of female reproductive organs. WHO Classification of Tumours, 4th Edition, Volume 6. Lyon, France: International Agency for Research on Cancer; 2014.
27. Bartley AN, Washington MK, Colasacco C, Ventura CB, Ismaila N, Benson AB 3rd, 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
28. Yoshida H, Yamamoto N, Taniguchi H, Oda I, Katai H, Kushima R, et al. Comparison of HER2 status between surgically resected specimens and matched biopsy specimens of gastric intestinal-type adenocarcinoma. Virchows Arch 2014;465:145-54. PUBMED | CROSSREF
29. Livasy CA, Reading FC, Moore DT, Boggess JF, Lininger RA. EGFR expression and HER2/neu overexpression/amplification in endometrial carcinosarcoma. Gynecol Oncol 2006;100:101-6. PUBMED | CROSSREF
30. Ogitani Y, Hagihara K, Oitate M, Naito H, Agatsuma T. Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody-drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. Cancer Sci 2016;107:1039-46. PUBMED | CROSSREF