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Clinical significance of signet-ring cells in colorectal mucinous adenocarcinoma

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Mucin occasionally accumulates intracellularly in colorectal mucinous adenocarcinomas, resulting in signet-ring cell morphology. In the current practice of pathology, there is no definitive rule on how to report a minor component of signet-ring cells in colorectal mucinous adenocarcinomas. We hypothesized that the absence of signet-ring cell component might have a favorable effect on survival of mucinous adenocarcinoma patients. To assess the biological characteristics of colorectal mucinous adenocarcinoma, we analyzed its clinicopathological features, microsatellite instability status, and survival outcomes and compared them with those of colorectal signet-ring cell carcinoma. A total of 266 consecutive colorectal mucinous adenocarcinoma patients and 65 signet-ring cell carcinoma patients were included. Mucinous adenocarcinomas, by comparison with signet-ring cell carcinomas, were characterized by development at an older age, less frequent vascular invasion and lymph node metastasis, and lower TNM stage at presentation. A total of 21 (22%) of 95 mucinous adenocarcinomas and 12 (19%) of 63 signet-ring cell carcinomas were high-frequency microsatellite instability. Patients with mucinous adenocarcinoma had significantly better survival than those with signet-ring cell carcinoma ($P<0.0001$) or than those with signet-ring cell carcinoma showing >50% extracellular mucin by volume ($P<0.0001$). In univariate analysis, absence of signet-ring cell component ($P=0.0197$), absence of vascular invasion, decreased invasion depth, no lymph node metastasis, and lower TNM stage had a favorable effect on survival of mucinous adenocarcinoma patients. Absence of vascular invasion, no lymph node metastasis, and lower TNM stage had a favorable effect on survival of signet-ring cell carcinoma patients. Multivariate analysis showed that higher TNM stage and T stage 4 were independent predictors of poor outcome in patients with mucinous adenocarcinoma. Our observations strongly suggest that pathologists should report the percentage of signet-ring cell component in colorectal mucinous adenocarcinomas and mucinous adenocarcinoma has different biologic behavior compared with signet-ring cell carcinoma.
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Although colorectal adenocarcinoma has a relatively better prognosis than other gastrointestinal malignancies with the same stage, specific histological types of colorectal carcinoma such as mucinous adenocarcinoma and signet-ring cell carcinoma have a poor prognosis.[1–3] Colorectal mucinous adenocarcinoma and signet-ring cell carcinoma are adenocarcinomas in which the cancer cells produce excess mucin. A unique pathologic feature of signet-ring cell carcinoma is the presence of signet-ring cells, which are single tumor cells with intracytoplasmic mucin that displaces their nuclei. The infiltrating cells spread diffusely throughout the bowel wall. In contrast, mucinous adenocarcinoma is characterized by abundant extracellular mucin produced by tumor cells. Mucinous adenocarcinoma shares some clinical characteristics with signet-ring cell carcinoma, such as affecting younger patients,[4,5] lymph node metastases,[2] and advanced stage at presentation.[2,4,5] Both colorectal mucinous adenocarcinoma and signet-ring cell carcinoma are associated with high-frequency microsatellite instability.[6–8] We also believe that there are clinicopathological differences between mucinous adenocarcinomas and signet-ring cell carcinomas, especially in the aggressiveness of biological behavior. Colorectal signet-ring cell carcinoma has an adverse prognostic significance independent of the

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stage at presentation.[9] However, the literature is controversial regarding mucinous adenocarcinoma. Some studies found colorectal mucinous adenocarcinoma to be an independent prognostic factor for poor outcomes,[10,11] whereas other studies found that poor outcomes seen for mucinous adenocarcinoma are more related to tumor stage or specific tumor location (eg, rectum), suggesting that this histologic subtype is not an independent adverse prognostic factor.[5,9,12,13]

Signet-ring cell carcinomas usually have some extracellular mucin production. Occasionally, mucin accumulates intracellularly in mucinous adenocarcinomas, resulting in signet-ring cell morphology. Signet-ring cells are usually present as single cells or in loose clusters, which implies a disruption in cell–cell adhesion. This could explain their aggressive behavior with regard to invasion and metastasis. Borger *et al*[14] reported that the presence of signet-ring cells in mucinous adenocarcinoma correlated with increased T-stage and poor prognosis. In the current practice of pathology, there is no definitive rule on how to report a minor component of signet-ring cells in colorectal mucinous adenocarcinomas. We hypothesized that the absence of signet-ring cell component might have a favorable effect on survival of mucinous adenocarcinoma patients. To assess the biological characteristics of colorectal mucinous adenocarcinoma, we analyzed its clinicopathological features, microsatellite instability status, and survival outcomes and compared them with those of colorectal signet-ring cell carcinoma.

Materials and methods

Patient Population

A total of 266 consecutive primary colorectal mucinous adenocarcinomas and 65 consecutive primary colorectal signet-ring cell carcinomas were collected from Samsung Medical Center from January 1995 to December 2006. When the carcinoma was less than 3 cm in size, all the carcinomas were sectioned and embedded. When the carcinoma was larger than 3 cm, at least four sections were taken for the pathologic examinations and the mean number of blocks was one for 1 cm of tumor diameter. In accordance with the World Health Organization criteria,[15] signet-ring cell carcinoma was defined by the presence of $>50\%$ of tumor cells with prominent intracytoplasmic mucin and mucinous adenocarcinoma was defined as carcinoma with $>50\%$ of the tumor volume showing extracellular mucin. We did not find any pure signet-ring cell carcinoma without extracellular mucin in the signet-ring cell carcinomas. None of the patients had a synchronous carcinoma of the colon or stomach, and received preoperative irradiation or chemotherapy. Clinical parameters, including age, sex, date of surgery, tumor size, and tumor location were obtained from the pathology reports. Tumors in the cecum, ascending colon, and transverse colon were classified as proximal and those in the descending colon, sigmoid colon, and rectum were distal. Clinical charts were reviewed to obtain information about distant metastases, preoperative irradiation or chemotherapy, and synchronous carcinoma of the colon or stomach. Of the 266 mucinous adenocarcinomas, 243 cases were followed up to June 2007 and were suitable for survival analysis. At the time of analysis, the median (range) follow-up period was 45.7 (2–144) months and 73 (30%) patients had died from cancer. Of the 65 signet-ring cell carcinomas, 54 cases were followed up to June 2007 and were suitable for survival analysis. At the time of analysis, the median (range) follow-up period was 26.5 (1–119) months and 36 (67%) patients had died from cancer. All patients provided written informed consent according to the institutional guideline and this study was approved by the institutional review board.

Histopathologic Evaluation

The histologic sections of tumors were examined and the following features were recorded: depth of tumor invasion, vascular invasion, lymph node metastasis, percentage of signet-ring cell component of the tumor cells, and percentage of extracellular mucin content of the tumor volume. Depth of tumor invasion, lymph node metastasis, and clinical information were used to assign a tumor stage using the TNM classification described in the AJCC Cancer Staging Manual.[16]

Analysis of Microsatellite Instability

In 95 cases of mucinous adenocarcinoma and 63 cases of signet-ring cell carcinoma, tumor and corresponding normal tissue were obtained from formalin-fixed and paraffin-embedded tissue samples by microdissection. DNA extracted from the microdissected tissues was analyzed by PCR at five microsatellite loci: BAT 25, BAT 26, D2S123, D5S346, and D17S250.[17] All primer pairs were end-labeled with fluorochromes, FAM, HEX, or NED. The PCR was performed in 10 μl reaction volumes containing $10\times$ PCR Gold Buffer (Applied Biosystems, Tokyo, Japan), 2.5 mM $MgCl_2$, 200 μM deoxynucleotide triphosphates mixture, 0.5 μM of each primer, 20–40 ng of extracted DNA, and 0.4 units of Amplitaq Gold DNA polymerase (Applied Biosystems). The DNA was amplified in a thermal cycler (GeneAmp PCR system 9700; Perkin-Elmer, Waltham, MA, USA) and PCR was performed according to the following protocol: 10 min at 95°C for polymerase activation; 40 cycles at 94°C for 30 s, 56°C for 1 min, and 72°C for 1 min; then an additional 30 min at 70°C. After denaturation by heating at 95°C for 5 min, PCR products were

electrophoresed and analyzed on an automated sequencer (3100 ABI Genetic Analyzer; Applied Biosystems), and the fluorescent signals from the different-sized alleles were recorded and analyzed using GENESCAN V.3.1 and GENOTYPER V.2.1 softwares.

We classified tumors as microsatellite instability positive when the PCR product of tumor DNA revealed at least one peak that was not visible in the PCR product of the corresponding normal tissue DNA (Figure 1). We used the criteria of the National Cancer Institute Workshop to classify microsatellite instability and microsatellite stability using the five primers that are commonly accepted in estimating microsatellite instability status.[17] High-frequency microsatellite instability is determined if two or more of the five markers exhibit instability, and low-frequency microsatellite instability is determined if only one of the five markers does so. A previous study indicated that microsatellite stability and low-frequency microsatellite instability tumors have a common molecular background,[18] so tumors that showed high-frequency microsatellite instability were classified as microsatellite instability and the others were classified as microsatellite stability.

Statistical Analyses

Statistical analyses were performed with SPSS software (version 11.0, SPSS; Chicago, IL). χ^2-Square or Fisher's exact test was used when comparing frequencies between groups. All numerical data are expressed as means ± s.d. and differences between means of groups were compared by independent sample *T*-test. The period from the date of resection to the date of death or last contact (if alive) was used for survival analysis. Outcome analysis was based on patients who were alive or had died of colorectal cancer. The log-rank test was used to compare Kaplan–Meier survival curves. The covariates were then included in the multivariate analysis using a Cox proportional hazards regression model; the hazard ratio and its 95% confidence interval were assessed for each factor. All tests were two-sided and *P*-value less than 0.05 was considered statistically significant.

Results

Mucinous Adenocarcinoma *vs* Signet-Ring Cell Carcinoma

The clinical and pathologic features of the 266 mucinous adenocarcinomas and 65 signet-ring cell carcinomas are shown in Table 1. Compared with signet-ring cell carcinomas, mucinous adenocarcinomas developed at an older age ($P=0.0035$), were less frequently lymph node positive ($P<0.0001$), and presented with a lower AJCC stage ($P<0.0001$). Vascular invasion was less frequent ($P<0.0001$) in mucinous adenocarcinomas than in signet-ring cell

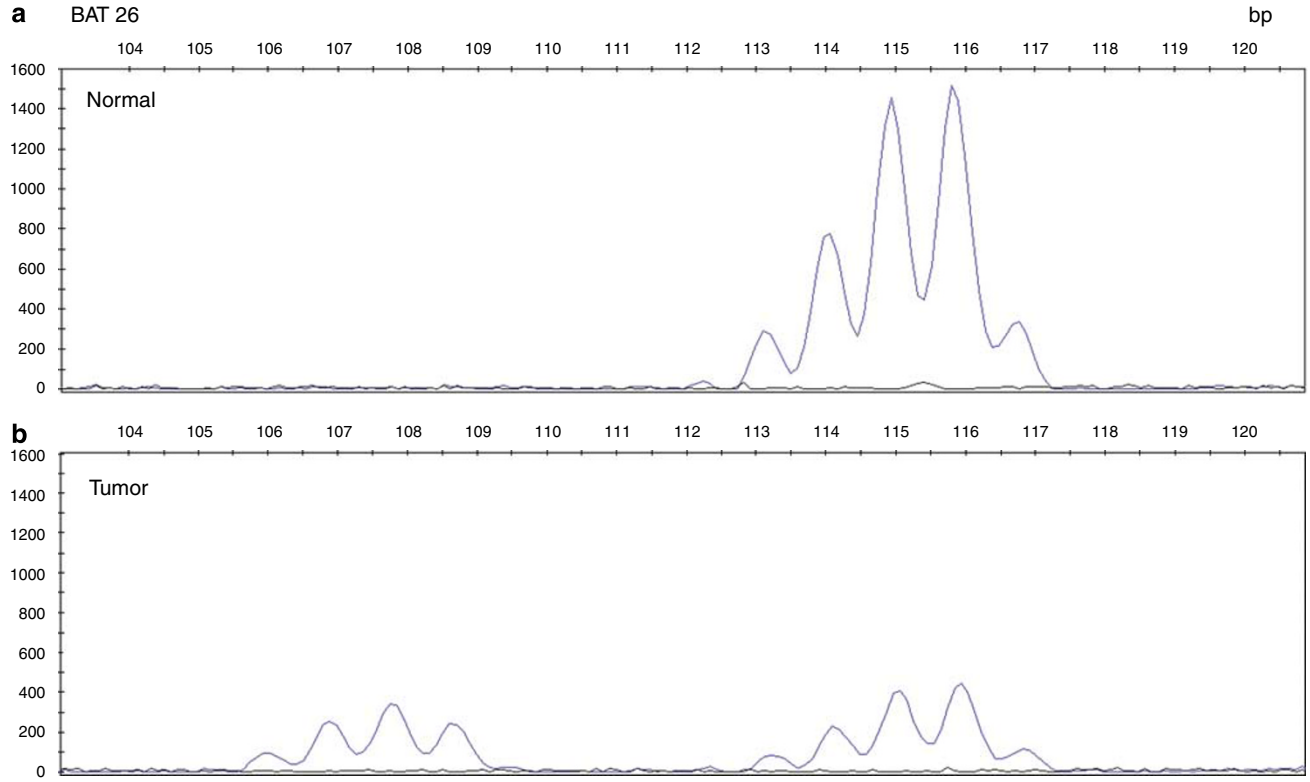

Figure 1 An example of a case showing microsatellite instability at the locus BAT 26. There are extra bands in the tumor (**b**) compared with bands in the normal (**a**). The horizontal axis represents base-pair size.

Table 1 Clinicopathological features of colorectal signet-ring cell carcinomas and mucinous adenocarcinomas

	Signet-ring cell carcinoma (n = *65*)	*Mucinous adenocarcinoma* (n = *266*)	P-*value*
Age (years)	50.8 ± 17.2	57.7 ± 13.5	0.0035[a]
Gender			
Female	24 (37%)	109 (41%)	0.55
Male	41 (63%)	157 (59%)	
Tumor size (cm)	6.64 ± 2.4	10.35 ± 55.2	0.608
Tumor location			
Proximal	23 (35%)	129 (48%)	0.0572
Distal	42 (65%)	137 (52%)	
Vascular invasion			
Absent	7 (11%)	129 (48%)	<0.0001[a]
Present	58 (89%)	137 (52%)	
Invasion depth			
T1	0	4 (1%)	0.0668
T2	1 (1%)	10 (4%)	
T3	50 (77%)	226 (85%)	
T4	14 (22%)	26 (10%)	
Lymph node status			
N0	8 (12%)	136 (51%)	<0.0001[a]
N1	7 (11%)	55 (21%)	
N2	50 (77%)	75 (28%)	
AJCC stage			
I	0	10 (4%)	<0.0001[a]
II	7 (11%)	118 (44%)	
III	45 (69%)	108 (41%)	
IV	13 (20%)	30 (11%)	

AJCC, America's Joint Committee on Cancer.
[a]Statistically significant.

carcinomas. There were no significant differences between patients with mucinous adenocarcinomas and signet-ring cell carcinomas for gender, tumor size, tumor location, or invasion depth.

Microsatellite Instability

High-frequency microsatellite instability was found in 21 of 95 cases (22%) of mucinous adenocarcinoma and 12 of 63 cases (19%) of signet-ring cell carcinoma. We compared patients who had high-frequency microsatellite instability tumors with those who had microsatellite stability tumors (Table 2). There were no significant differences between patients with high-frequency microsatellite instability and microsatellite stability mucinous adenocarcinomas for clinicopathological factors or overall survival ($P = 0.3037$). High-frequency microsatellite instability signet-ring cell carcinomas were associated with larger tumor size ($P = 0.0396$) and proximal colon location ($P = 0.0223$). We found no significant differences between patients with high-frequency microsatellite instability and microsatellite stability signet-ring cell carcinomas for age, gender, vascular invasion, invasion depth, lymph node metastasis, or TNM stage. Overall survival was not significantly different for high-frequency microsatellite instability signet-ring cell carcinomas *vs* microsatellite stability signet-ring cell carcinomas ($P = 0.1740$).

Survival Analysis

The overall mean survival for patients with mucinous adenocarcinoma and signet-ring cell carcinoma was 102.7 and 48.4 months, respectively. The cumulative survival rates for mucinous adenocarcinomas were 91, 74, and 69% at 1, 3, and 5 years, respectively. The cumulative survival rates for signet-ring cell carcinomas were 80, 55, and 33% at 1, 2, and 3 years, respectively. Patients with mucinous adenocarcinoma had significantly better survival than those with signet-ring cell carcinoma ($P < 0.0001$) (Figure 2) or than those with signet-ring cell carcinoma showing >50% extracellular mucin by volume ($P < 0.0001$) (Figure 3).

In univariate analysis of mucinous adenocarcinomas, absence of signet-ring cell component

Table 2 Clinicopathological features of colorectal signet-ring cell carcinomas and mucinous adenocarcinomas stratified by microsatellite instability

	Sigent-ring cell carcinoma (n = *63*)			*Mucinous adenocarcinoma* (n = *95*)		
	MSI-H (n = *12*)	*MSS* (n = *51*)	P-*value*	*MSI-H* (n = *21*)	*MSS* (n = *74*)	P-*value*
Age (years)	55.6 ± 13.2	49.7 ± 17.8	0.2337	58.5 ± 14.2	59 ± 12.8	0.8837
Gender						
Female	6 (50%)	17 (33%)	0.3282	11 (52%)	32 (43%)	0.4578
Male	6 (50%)	34 (67%)		10 (48%)	42 (57%)	
Tumor size (cm)	7.8 ± 2.3	6.4 ± 2.3	0.0396[a]	7.2 ± 3.3	18.9 ± 104.6	0.2994
Tumor location						
Proximal	8 (67%)	15 (29%)	0.0223[a]	13 (62%)	36 (49%)	0.2834
Distal	4 (33%)	36 (71%)		8 (38%)	38 (51%)	
Vascular invasion						
Absent	2 (17%)	4 (8%)	0.3201	13 (62%)	36 (49%)	0.2834
Present	10 (83%)	47 (92%)		8 (38%)	38 (51%)	
Invasion depth						
T1	0	0	1.0000	0	1 (1%)	0.2402
T2	0	1 (2%)		2 (9%)	1 (1%)	
T3	9 (75%)	39 (76%)		18 (86%)	64 (87%)	
T4	3 (25%)	11 (22%)		1 (5%)	8 (11%)	
Lymph node status						
N0	2 (17%)	5 (10%)	0.4699	15 (71%)	37 (50%)	0.1885
N1	2 (17%)	5 (10%)		1 (5%)	11 (15%)	
N2	8 (66%)	41 (80%)		5 (24%)	26 (35%)	
AJCC stage						
I	0	0	0.4629	1 (5%)	2 (3%)	0.2209
II	2 (17%)	4 (8%)		13 (62%)	30 (40%)	
III	7 (58%)	37 (72%)		4 (19%)	29 (39%)	
IV	3 (25%)	10 (20%)		3 (14%)	13 (18%)	

AJCC, America's Joint Committee on Cancer; MSI-H, high-frequency microsatellite instability; MSS, microsatellite stability.
[a]Statistically significant.

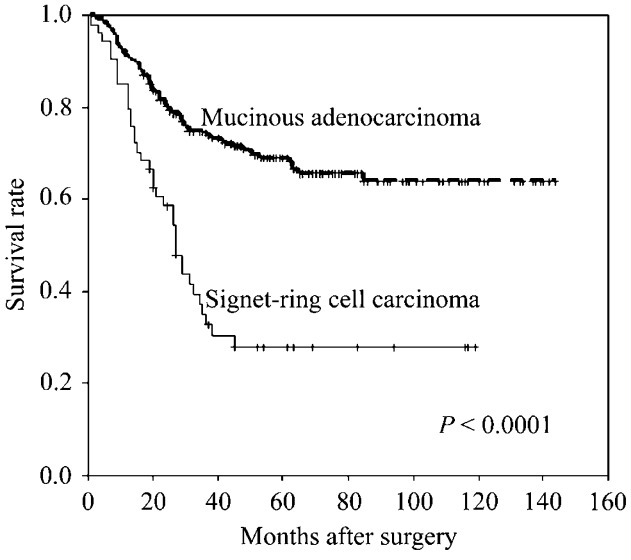

Figure 2 Kaplan–Meier survival curves showing disease-specific survival of the patients with mucinous adenocarcinoma and signet-ring cell carcinoma.

($P = 0.0197$) (Figure 4), absence of vascular invasion ($P < 0.0001$), decreased invasion depth ($P = 0.0037$), no lymph node metastasis ($P < 0.0001$), and lower TNM stage ($P < 0.0001$) showed a favorable influence on survival. Survival in patients with mucinous adenocarcinoma was not associated with gender, tumor size, tumor location, or extracellular mucin content (Table 3). In multivariate analysis of mucinous adenocarcinomas, T stage 4 ($P = 0.012$) and higher TNM stage ($P < 0.001$) were independent predictors of poor outcome (Table 4).

In univariate analysis of signet-ring cell carcinomas, absence of vascular invasion ($P = 0.0155$), no lymph node metastasis ($P = 0.0457$), and lower TNM stage ($P = 0.0347$) showed a favorable influence on survival. Survival in patients with signet-ring cell carcinoma was not associated with gender, tumor size, tumor location, extracellular mucin content, signet-ring cell component, or invasion depth (Table 3). In multivariate analysis of signet-ring cell carcinomas, female patient ($P = 0.034$) was an independent predictor of poor outcome (Table 4).

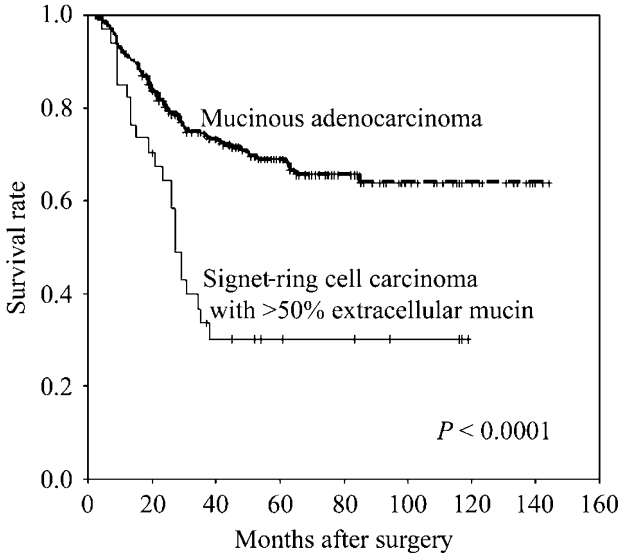

Figure 3 Kaplan–Meier survival curves showing disease-specific survival of the patients with mucinous adenocarcinoma and signet-ring cell carcinoma with >50% extracellular mucin by volume.

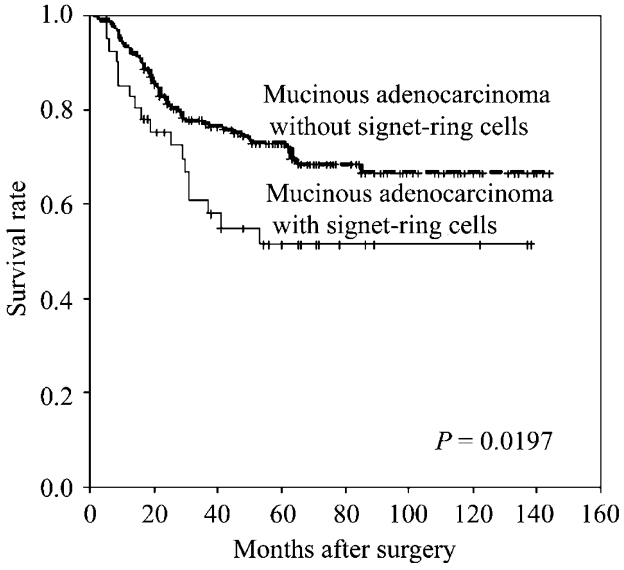

Figure 4 Kaplan–Meier survival curves showing disease-specific survival of the patients with mucinous adenocarcinoma according to the presence of signet-ring cells.

Discussion

A frequently lower TNM stage of mucinous adenocarcinoma at the time of diagnosis, compared with signet-ring cell carcinoma, was confirmed by our own and a previous study.[9] Vascular invasion and lymph node involvement were significantly less frequent than in signet-ring cell carcinoma. The aggressiveness of infiltrating growth in signet-ring cell carcinoma may be partially explained by the high incidence of vascular invasion and lymph node involvement. In this study, the mean age of 57.7 years in patients with mucinous adenocarcinoma was significantly higher than that of 50.8 years in patients with signet-ring cell carcinoma, which is consistent with a previous report.[9]

Colon cancers with high-frequency microsatellite instability have a better prognosis than other colon cancers.[19] This gives rise to a paradoxical situation: high-frequency microsatellite instability colon cancers have favorable prognosis, but can often show signet-ring morphology, a well-documented adverse prognostic factor. We found that 22% of mucinous adenocarcinoma and 19% of signet-ring cell carcinoma were high-frequency microsatellite instability. There were no significant differences between patients with high-frequency microsatellite instability and microsatellite stability mucinous adenocarcinomas for all clinicopathological factors and overall survival. These findings are in contrast to most studies that have shown a proximal colon location and a survival benefit for patients with high-frequency microsatellite instability mucinous adenocarcinoma over those with microsatellite stability mucinous adenocarcinoma.[20,21] However, a recent multivariate analysis indicated that microsatellite instability status of mucinous adenocarcinoma was not an independent predictor of survival, whereas older age, higher grade, higher stage, and absence of Crohn's-like infiltrate were independent predictors of poor outcome.[21] In signet-ring cell carcinoma, high-frequency microsatellite instability tumors were significantly more frequent in the proximal colon than in the distal colon; this finding is in agreement with a previous report.[6] There was no significant difference in overall survival between patients with high-frequency microsatellite instability and microsatellite stability signet-ring cell carcinomas, which is consistent with the result of a previous report.[6]

Colorectal signet-ring cell carcinoma has adverse prognostic significance independent of the stage at presentation.[9] Mucinous histology is an independent adverse prognostic factor in some studies,[10,11] but not in others.[5,9,13] Wu *et al*[5] proposed that differences in survival of colorectal mucinous adenocarcinomas could be related to differences in the stage at presentation rather than to histologic type. The current study clearly indicated that mucinous adenocarcinoma did have better overall survival compared with signet-ring cell carcinoma, which is consistent with the result of a previous report.[9] Colorectal signet-ring cell carcinoma was sometimes labeled as a variant of mucinous adenocarcinoma, in which mucin accumulates intracellularly. In the recent WHO classification, signet-ring cell carcinoma was classified as a separate variant of colorectal adenocarcinoma. In this study, patients with mucinous adenocarcinoma by the WHO classification had significantly better overall survival than patients with signet-ring cell carcinoma showing >50% extracellular mucin by volume; this finding

Table 3 Univariate analysis of overall survival in colorectal signet-ring cell carcinomas and mucinous adenocarcinomas

	Sigent-ring cell carcinoma (n = *54*)			*Mucinous adenocarcinoma* (n = *243*)		
	Number	*Mean overall survival (months)*	P-*value*	*Number*	*Mean overall survival (months)*	P-*value*
Gender						
Female	21 (39%)	28	0.2086	100 (41%)	105	0.5091
Male	33 (61%)	53		143 (59%)	99	
Tumor size						
≤5 cm	16 (30%)	51	0.9683	63 (26%)	100	0.9742
>5 cm	38 (70%)	47		180 (74%)	103	
Tumor location						
Proximal	16 (30%)	32	0.6911	122 (50%)	103	0.8999
Distal	38 (70%)	50		121 (50%)	99	
Extracellular mucin						
≤50%	20 (37%)	32	0.4684			
>50%	34 (63%)	51				
≤75%				162 (67%)	98	0.2471
>75%				81 (33%)	108	
SRC component						
≤75%	24 (44%)	48	0.9049			
>75%	30 (56%)	48				
Absent				202 (83%)	106	0.0197[a]
Present				41 (17%)	82	
Vascular invasion						
Absent	6 (11%)	104	0.0155[a]	117 (48%)	127	<0.0001[a]
Present	48 (89%)	41		126 (52%)	79	
Invasion depth						
T1–T2				13 (5%)	125	0.0037[a]
T3	44 (81%)	53	0.1987	205 (85%)	105	
T4	10 (19%)	21		25 (10%)	57	
Lymph node status						
N0	7 (13%)	92	0.0457[a]	124 (51%)	128	<0.0001[a]
N1	7 (13%)	25		55 (23%)	107	
N2	40 (74%)	43		64 (26%)	46	
AJCC stage						
I–II	6 (11%)	87	0.0347[a]	118 (49%)	132	<0.0001[a]
III–IV	48 (89%)	43		125 (51%)	74	

AJCC, America's Joint Committee on Cancer; SRC, signet-ring cell.
[a]Statistically significant.

indicates that colorectal signet-ring cell carcinoma showing >50% extracellular mucin by volume is not a variant of mucinous adenocarcinoma and must be differentiated from mucinous adenocarcinoma.

In agreement with previous reports,[20,21] univariate analysis demonstrated that lower TNM stage and absence of vascular invasion had a favorable effect on survival of mucinous adenocarcinoma patients. Decreased invasion depth and no lymph node metastasis also had a favorable effect on survival of mucinous adenocarcinoma patients. Our mucinous adenocarcinoma patients without signet-ring cell component had significantly better survival than those with signet-ring cell component. However, the signet-ring cell component was not an independent predictor of poor outcome in multivariate analysis of mucinous adenocarcinoma. Borger *et al*[14] reported that the presence of signet-ring cells in mucinous adenocarcinoma correlated with increased T-stage and poor prognosis and these cells showed disruption of the E-cadherin/β-catenin complex. Signet-ring cells are usually present as single cells or in loose clusters, which implies a disruption in cell–cell adhesion. Because of reduced cell–cell adhesion, signet-ring cells can loosen contact with the surrounding structure and spread diffusely. In light of our observations, signet-ring cell component can be evaluated with routine pathologic techniques in colorectal mucinous adenocarcinomas. Higher TNM stage was an independent predictor of poor outcome in patients with mucinous adenocarcinoma, which is in accordance with other studies.[20,21]

Table 4 Multivariate Cox proportional hazards model predicting death in colorectal signet-ring cell carcinomas and mucinous adenocarcinomas

Variable	*Signet-ring cell carcinoma* (n = *54*)			*Mucinous adenocarcinoma* (n = *243*)		
	Hazard ratio	*95% confidence interval*	P-*value*	*Hazard ratio*	*95% confidence interval*	P-*value*
Gender						
Female *vs* male	2.472	1.017–5.707	0.034	0.890	0.543–1.460	0.645
Tumor size						
≤5 *vs* >5 cm	0.960	0.453–2.034	0.915	1.039	0.595–1.815	0.892
Tumor location						
Proximal *vs* distal	1.015	0.447–2.307	0.971	0.795	0.493–1.281	0.346
Extracellular mucin						
≤50 *vs* >50%	2.036	0.766–5.410	0.154			
≤75 *vs* >75%				1.315	0.788–2.195	0.295
SRC component						
≤75 *vs* >75%	1.121	0.462–2.721	0.801			
Absent *vs* present				0.844	0.479–1.487	0.557
Vascular invasion						
Absent *vs* present	0.108	0.009–1.327	0.082	1.262	0.461–3.455	0.651
Invasion depth						
T3 *vs* T4	0.677	0.256–1.784	0.430	0.403	0.218–0.746	0.012
T1–T2 *vs* T3				1.521	0.349–6.623	1.000
T1–T2 *vs* T4				0.265	0.057–1.239	0.273
AJCC stage						
I–II *vs* III–IV	0.712	0.109–4.660	0.723	0.102	0.033–0.311	<0.001

AJCC, America's Joint Committee on Cancer; SRC, signet-ring cell.

In univariate analysis, lower TNM stage had a favorable effect on survival of signet-ring cell carcinoma patients; this finding is consistent with other reports.[3,6] The vast majority of signet-ring cell carcinoma presents as a diffusely infiltrating carcinoma, which therefore is described by some authors as linitis plastica or lymphangiosis-type colorectal carcinoma.[22,23] The relatively long period of intramural growth without penetrating the mucosa may be one explanation for the advanced stage at diagnosis of signet-ring cell carcinoma. The absence of vascular invasion had a favorable effect on survival of signet-ring cell carcinoma patients, which is in contrast to previous reports.[6,24] The effects of the absence of vascular invasion may underlie the favorable effect of no lymph node metastasis. Survival was not significantly influenced by the percentage of signet-ring cells, which is in agreement with the result of a previous report.[24]

On the basis of our observations, we recommend that pathologists report the percentage of signet-ring cell component in colorectal mucinous adenocarcinomas. Further study in the molecular biology could help explain the biological significance of characteristics such as oncogene or tumor suppressor gene expression in mucinous adenocarcinomas.

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