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ORIGINAL ARTICLE

Cancer-induced spiculation on computed tomography: a significant preoperative prognostic factor for colorectal cancer

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Abstract

Purpose Cancer-induced spiculation (CIS) on computed tomography, which is reticular or linear opacification of the pericolorectal fat tissues around the cancer site, is generally regarded as cancer infiltration into T3 or T4, but its clinicopathological significance is unknown. This study examines the correlation between CIS and clinicopathological findings to establish its prognostic value.

Methods The subjects of this retrospective study were 335 patients with colorectal cancer (CRC), who underwent curative surgery between January, 2010 and December, 2011, at the National Defense Medical College Hospital in Saitama Prefecture, Japan.

Results The level of interobserver agreement in the evaluation of CIS was substantial (83%; kappa value, 0.65). The presence of CIS was specific for T3/T4 disease (positive predictive value, 88.3%), and was significantly associated with tumor size and venous invasion. The 5-year relapse-free survival rate was significantly lower in patients with CIS than in those without CIS (68.6% and 84.0%, respectively, $p=0.001$). Subgroup analysis revealed remarkable prognostic differences in patients with stage III and T3 disease. Multivariate analysis revealed that CIS was a significant independent prognostic factor.

Conclusions CIS was a significant preoperative prognostic factor and could be useful in the selection of preoperative therapy for patients with CRC.

Keywords Colorectal cancer · Preoperative prognostic factor · Cancer-induced spiculation · Computed tomography images

Introduction

A preoperative T-staging diagnosis is important for selecting the appropriate treatment strategy for colorectal cancer (CRC). This is currently performed comprehensively based on endoscopic findings, barium enema X-ray, and computed tomography (CT). T staging is generally diagnosed based on the relationship between the intestinal wall and adipose tissue on CT. Previous studies have found that reticular or linear opacification of pericolorectal fat tissues around CRC, referred to as "cancer-induced spiculation" (CIS), is associated with tumor invasion of T3 or T4 [1–3]. Although investigations of CIS have historically focused on the T-staging diagnosis, it remains unknown whether CIS is correlated with prognosis. If CIS has prognostic capability, the identification of patients with worse prognostic features may help in selecting treatment options such as preoperative chemotherapy.

Preoperative chemotherapy is now used widely for esophageal cancer and gastric cancer [4, 5]. However, there is still no consensus on its use for CRC, although several clinical trials have been conducted to validate its use [6–8]. In a prospective randomized controlled trial (the "FOxTROT trial"), reported in 2012 [6], preoperative chemotherapy was given to patients with T4 invasion or T3 subserosal invasion of ≥5 mm. However, these criteria were based on a cohort study of relatively few (126) subjects at a single institution [9]; therefore, the evidence level was not considered high.

We conducted the present study to investigate the prognostic value of CIS and its utility for designing future studies on the validation of preoperative chemotherapy for CRC.

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Methods

Patients

The subjects of this retrospective study were 335 patients who had consecutively undergone curative surgery for primary CRC at the National Defense Medical College Hospital between January, 2010 and December 2011. Patients who received preoperative chemotherapy or chemoradiotherapy were excluded from the analysis. This study was approved by the relevant institutional review board.

CT procedure

CT scans were obtained from all 335 patients in the study, including 284 who had scanning done at our hospital and 51 who had scanning done at other hospitals. The CT protocol used at our hospital was as follows:

All patients underwent CT scanning within 1 month before surgery, in the supine position, with a 64-multidetector CT scanner (Aquilion 64, Toshiba, Tokyo, Japan). The patients received an intravenous injection of an iodinated contrast agent at a rate of 2 ml/s, delivered by a mechanical injector. In 11 patients who had an allergic reaction to the contrast agent, plain CT was conducted. The CT parameters utilized were beam collimation, 90 mm; table speed, 45 mm/rotation; gantry rotation time, 0.5 s; 120 kVp; and 100–400 mAs. The raw dataset was reconstructed at a thickness of 5 mm.

Image analysis

Two examiners (one surgeon and one radiologist) with at least 10 years of experience in abdominal imaging examined the abdominal CT images on a picture archiving and communication system workstation. They examined all images in December, 2012. Two-dimensional images, including the original axial images and multiplanar reconstruction images were viewed. Examiners were blinded to clinical information obtained via colonoscopic examinations and histologic examinations, and prognostic information. CIS was defined as reticular or linear opacification of pericolorectal fat tissues around the cancer site (Fig. 1). CIS was diagnosed independently, and in cases of discrepancy, a consensus was reached via reevaluation.

Variables examined

Prognostic data were collected prospectively, and survival analyses were performed in 2018, more than 5 years after completing the categorization of CIS. CIS was analyzed in conjunction with medical records, including operative, pathological, and follow-up reports. We also estimated relapse-free survival (RFS) and cancer-specific survival (CSS) after primary resection.

Histologic evaluation

For assessing CIS from a pathological standpoint, ten CIS-positive cases and ten CIS-negative cases were randomly selected, and the hematoxylin–eosin-stained specimens from these patients were examined.

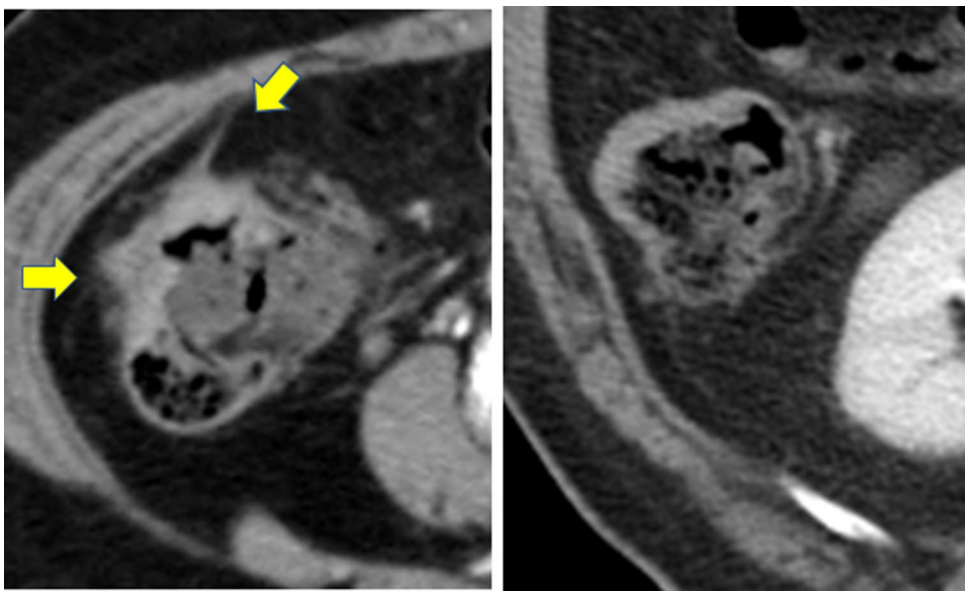

Fig. 1 Cancer-induced speculation (CIS) was defined as reticular or linear opacification of pericolorectal fat tissues around the cancer site (arrows)

Statistical analysis

JMP® Pro 13 software (SAS Institute, Cary, NC, USA) was used for all statistical analyses. Differences between groups were assessed using the Chi square test or Fisher's exact test. When two distributions were compared statistically, the Wilcoxon rank sum test was used. Multivariate logistic regression analysis was performed to identify factors that were independently associated with CIS. Values of $p < 0.05$ were considered significant. RFS and CSS were analyzed using Kaplan–Meier survival curves and the log rank test.

The degree of interobserver agreement for the evaluation of CIS was assessed via the generalized kappa test for two or more observers. In accordance with the criteria proposed by Landis and Koch [10], kappa values were assigned strength of agreement scores of poor, slight, fair, moderate, substantial, and almost perfect for values of < 0.00, 0.00–0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80, and 0.81–1.00, respectively.

Results

Interobserver variability of CIS

The kappa value for interobserver variability between the two observers was 0.65, demonstrating substantial agreement for CIS.

Correlations between CIS and clinicopathological characteristics

The average age of the patients was 66.1 (range 28–88) years and 213 (63.6%) patients were male. With an average follow-up period of 67 (range 2–103) months for survivors, the RFS and CSS 5 years after surgery were 79.6% and 93.9%, respectively.

The disease was classified as CIS-positive in 94 patients. Table 1 shows the correlations between CIS and clinicopathological characteristics. The CIS-positive rates were 5%, 14%, 35%, and 53% for T1, T2, T3, and T4 disease, respectively. As the depth of invasion increased, the rate of CIS recognition increased. Based on an assumption that the presence of CIS indicated invasion to T3 or T4, the positive predictive value was 88.3%. The incidence of CIS was higher in the rectum than in the colon. CIS was significantly correlated with tumor size, venous invasion, and the serum C-reactive protein (CRP) level. Multivariate logistic regression analysis demonstrated that CIS was independently correlated with tumor size and venous invasion (Table 1). HE staining showed that patients with CIS-positivity had highly irregular linear fibrosis in the subserosal layer (Fig. 2).

CIS and postoperative recurrence and survival

CIS was significantly correlated with recurrence. The recurrence rate in the lung was higher in the CIS-positive group (13.8%) than in the CIS-negative group (3.7%; $p = 0.0008$). However, there were no significant differences in the incidences of recurrence in the liver, lymph node, peritoneum, or brain, or locally. The 5-year RFS curves in the CIS-positive (68.6%) and CIS-negative (84.0%) groups differed significantly ($p = 0.001$). With regard to the CSS curve, the CIS-positive group exhibited a significantly poorer prognosis than the CIS-negative group, with 5-year CSS rates of 85.3% and 94.9%, respectively [$p = 0.008$; (Fig. 3)].

In our analysis of 320 cases excluding patients with cT4b tumors, the 5-year RFS curves in the CIS-positive (72.5%) and CIS-negative (84.2%) groups differed significantly ($p = 0.019$). With regard to the CSS curve, the CIS-positive group exhibited a significantly poorer prognosis than the CIS-negative group, with respective 5-year CSS rates of 89.7% and 96.3%, respectively ($p = 0.035$).

The 5-year RFS rates in the CIS-positive group were 78.9% for patients with stage II disease and 48.5% for those with stage III disease, and in the CIS-negative group, they were 85.1% for those with stage II disease and 74.8% for those with stage III disease. Patients with stage III disease in the CIS-positive group had a significantly poorer prognosis ($p = 0.007$). With regard to T stage, the 5-year RFS rates in the CIS-positive group were 66.9% for pT3 and 62.5% for pT4, and in the CIS-negative group, they were 84.9% for pT3 and 49.8% for pT4. Patients with pT3 in the CIS-positive group had a significantly poorer prognosis ($p = 0.006$; Fig. 4).

Multivariate RFS analyses

Of the potential prognostic factors evaluated before surgery, those that were significantly associated with RFS were clinical N stage, the prognostic nutritional index (PNI), and CIS. Among these, multivariate analysis revealed that CIS and clinical N stage affected RFS independently (Table 2).

Discussion

Initial studies suggested that CIS reflected tumor invasion into the serosa or the pericolonic tissues (pT4) [1–3]. However, histology studies have shown that CIS does not necessarily indicate pT4 invasion as it can be caused by inflammatory reactions and extramural fibrosis [11]. The sensitivity of CIS for differentiating pT3 from pT4

Table 1 Cancer-induced spiculation and clinicopathological characteristics

Parameters	Categories	Univariate			Multivariate		
		CIS-positive (%) (*N* = 94)	CIS-negative (%) (*N* = 241)	*P*	OR	95%CI	*P*
Sex	Male	61 (28.6)	152 (71.4)	0.76	–		
	Female	33 (27.0)	89 (73.0)				
Age (years)		66.5	65.9	0.68	–		
Location	Colon	41 (22.0)	145 (78.0)	0.006			NS
	Rectum	53 (35.6)	96 (64.4)				
Tumor diameter (mm)		61.1	36.3	< 0.0001	1.05	1.04–1.06	< 0.0001
Tumor differentiation	tub1	39 (23.8)	125 (76.2)	0.22	–		
	tub2	49 (31.8)	105 (68.2)				
	por/muc/sig	6 (35.3)	11 (64.7)				
Pathological T stage	T1	3 (4.6)	63 (95.5)	< 0.0001			NS
	T2	8 (14.3)	48 (85.7)				
	T3	59 (35.1)	109 (64.9)				
	T4	24 (53.3)	21 (46.7)				
Nodal involvement	Negative	58 (25.7)	168 (74.3)	0.16	–		
	Positive	36 (33.0)	73 (67.0)				
Lymphatic invasion	ly 0/1	81 (29.1)	197 (70.9)	0.33	–		
	ly 2/3	13 (22.8)	44 (77.2)				
Venous invasion	v 0/1	44 (20.7)	169 (79.3)	< 0.0001	2.2	1.3–3.8	0.006
	v 2/3	50 (41.0)	72 (59.0)				
Tumor budding	G1	49 (24.3)	153 (75.7)	0.08	–		
	G2	19 (29.2)	46 (70.8)				
	G3	26 (38.2)	42 (61.8)				
CRP (mg/dL)[a]	≤ 0.3	49 (21.9)	175 (78.1)	0.0005			NS
	> 0.3	42 (40.4)	62 (59.6)				
CEA (ng/mL)	< 5.3	64 (26.1)	181 (73.9)	0.19	–		
	≥ 5.3	30 (33.3)	60 (66.7)				
Adjuvant chemotherapy	No	81 (33.7)	160 (66.3)	0.94	–		
	Yes	32 (34.0)	62 (66.0)				

CRP C-reactive protein, *CEA* carcinoembryonic antigen, *OR* odds ratio, *NS* not selected

[a]Among 328 patients whose preoperative CRP level was known

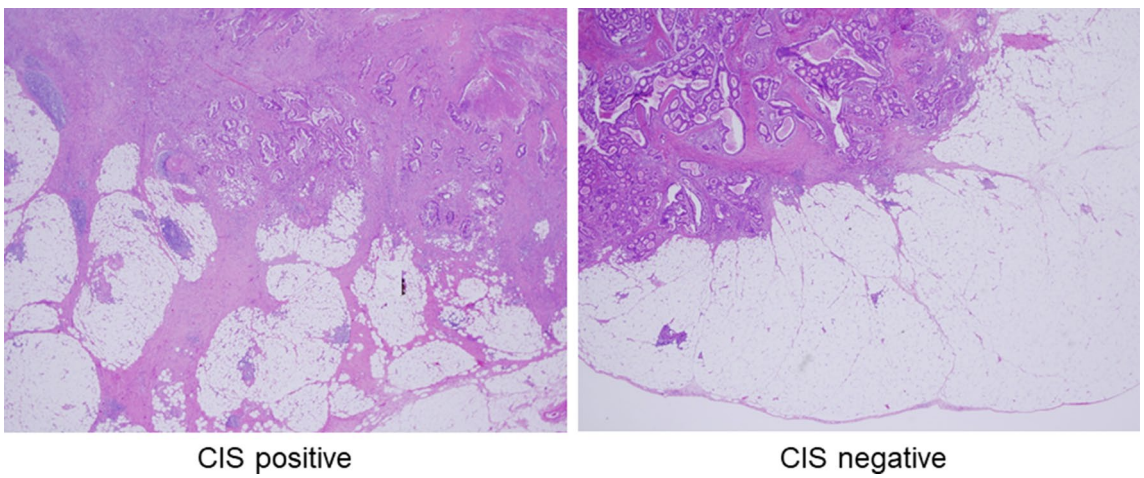

Fig. 2 Patients with CIS-positivity had highly irregular linear fibrosis in the subserosal layer

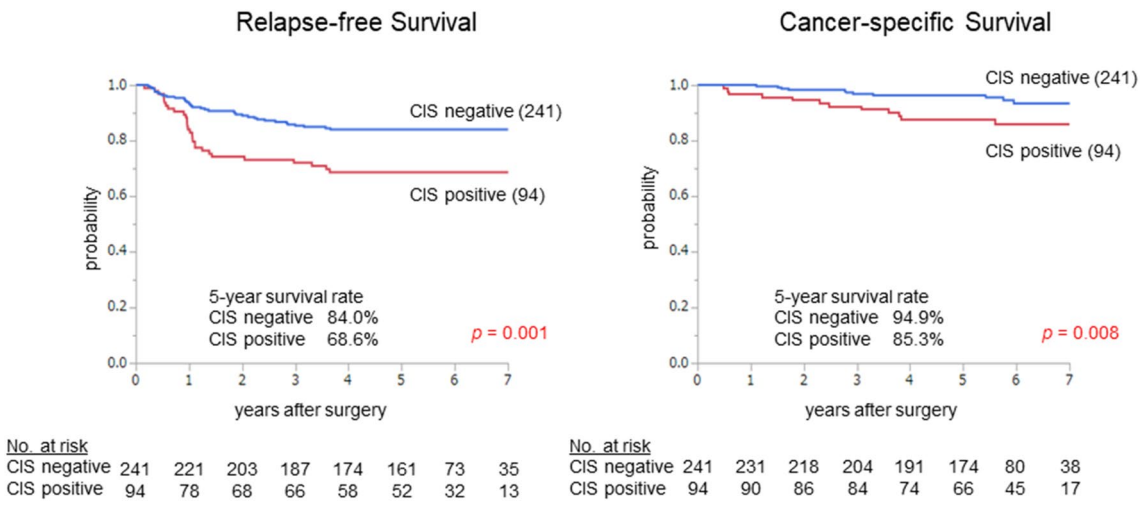

Fig. 3 Survival curves for the analyses of recurrence-free survival (RFS) and cancer-specific survival (CSS)

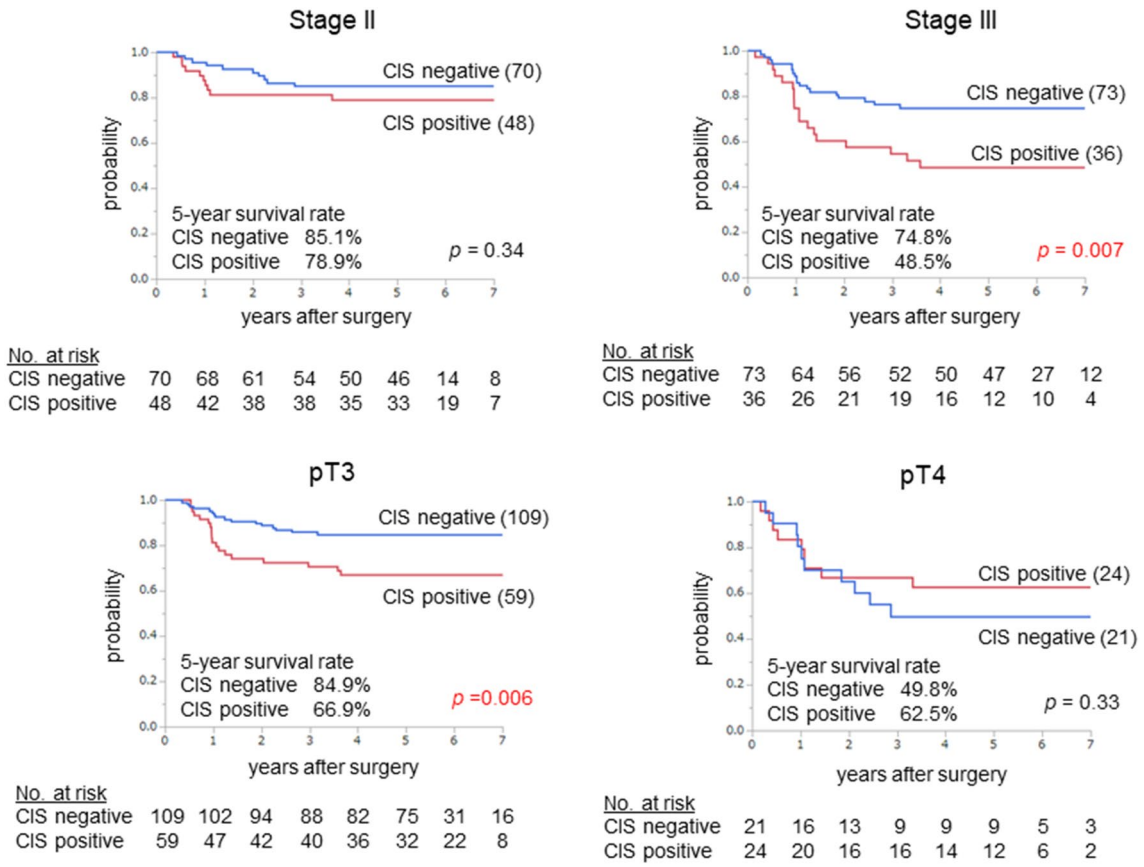

Fig. 4 Recurrence-free survival (RFS) curves according to final stage and tumor depth

is relatively low, ranging from 55 to 70% [1–3]. Utano et al. [12] reported that CIS was usually associated with a pT3/pT4 stage tumor but was not useful for distinguishing between pT3 and pT4. Concordantly, in the current study, based on an assumption that CIS indicated pT3/pT4 invasion, its positive predictive value was 88.3%. However, if we assumed that CIS was indicative of pT4, its positive predictive value was only 25.5%. Therefore, it is

Table 2 Univariate and multivariate analyses of recurrence-free survival by the Cox proportional hazards regression model

Parameters	Categories	Univariate			Multivariate		
		Number	5-year RFS	*P*	HR	(95% CI)	*P*
Location	Colon	186	81.6	0.26	–		
	Rectum	149	77.0				
Tumor diameter (mm)	< 50	209	81.1	0.38	–		
	≥ 50	126	77.2				
Biopsy histological type[a]	Adenoma	5	80.0	0.87	–		
	pap/tub1/tub2	307	79.6				
	por/muc/sig	8	87.5				
cT stage	≤ cT3	285	80.7	0.18	–		
	cT4	50	73.3				
cN stage	Negative	182	86.9	0.0006	1.0		0.02
	Positive	153	71.0		1.9	(1.1–3.3)	
CEA (ng/mL)	< 5.3	245	82.3	0.05	–		
	≥ 5.3	90	72.5				
CRP (mg/dL)[b]	≤ 0.3	224	81.6	0.26	–		
	> 0.3	104	76.8				
PNI	> 40	304	81.1	0.01			NS
	≤ 40	31	65.0				
NLR	< 2.5	217	81.6	0.27	–		
	≥ 2.5	118	75.9				
CIS	Negative	241	84.0	0.001	1.0		0.047
	Positive	94	68.6		1.6	(1.0–2.8)	

RFS relapse-free survival, *CEA* carcinoembryonic antigen, *CRP* C-reactive protein, *PNI* prognostic nutritional index, *NLR* neutrophil–lymphocyte ratio, *NS* not significant

[a]Among 320 patients who had a preoperative biopsy

[b]Among 328 patients whose preoperative CRP level was known

reasonable to consider that CIS is indicative of infiltration into the subserosal layer.

In the present study, CIS-positive CRC was associated with clinicopathological findings indicative of a high potential for malignancy. Hulsmans et al. [11] reported that CIS was indicative of subserosal fibrosis, which is in line with our findings. In recent years, many studies have indicated that tumor stroma has a strong influence on cancer progression. Tumor stroma contributes to tumorigenesis via several mechanisms, including paracrine effects on carcinoma and immune cells, and the production and degradation of extracellular matrix [13–17]. Accordingly, stromal fibroblasts increase the number of tumor-initiating cells and adversely affect the prognosis of CRC patients [18, 19]. Fibroblasts are the main cellular component of tumor stroma. West et al. [20] reported that a greater proportion of stroma is associated with poorer patient outcomes. CIS-positive CRC is considered to be associated with a high number of fibroblasts, and consequently CIS-positive patients may have a poorer prognosis.

In recent years, giving preoperative chemotherapy to patients with T4 disease has become more widely accepted. The merits of preoperative chemotherapy include improved radical resection rates through tumor shrinkage [5, 21], reduced postoperative distant metastasis rates from eradication of micro-metastatic disease [22, 23], and better tolerance than to similar treatments given after surgery [8]. It also allows for pathologic evaluation of the therapeutic effects of chemotherapy, which can provide useful guidance about postoperative drug selection. However, the method has two limitations. First, because the duration of preoperative chemotherapy is 2–3 months, there is concern that R0 surgery may become impossible if the primary tumor grows or distant metastases develop. Second, there is a possibility that the treatment options for chemotherapy will be reduced after recurrence. For these reasons, it is important to restrict the use of preoperative chemotherapy to patients with poor prognoses.

In the current study, the rates of peritoneal dissemination recurrence and local recurrence were low in the patients with CIS-positive disease, whereas their hematogenous distant metastasis recurrence rates (especially lung metastases) were high. This is because CIS is strongly associated with venous invasion. Thus, preoperative chemotherapy may reduce hematogenous recurrence and improve the prognosis of patients with CIS-positive disease.

In recent studies, the preoperative serum CRP level [24], neutrophil–lymphocyte ratio [25], and PNI were significant prognostic factors that could be evaluated preoperatively [26]. In the present study, when we examined these factors via univariate analysis, the PNI was identified as a significant prognostic factor. However, in multivariate analysis, it was not a significant independent predictor of a poorer prognosis. CIS was a more meaningful indicator for stratifying patients and for the preoperative prediction of tumors associated with a poorer prognosis.

It should be noted that we observed CIS even in the pT1 (4.6%) and pT2 (14.3%) tumors in the present study. Therefore, we consider that it is difficult to select candidates for neoadjuvant chemotherapy based only on the CIS. However, in the subgroup analysis, there were remarkable prognostic differences in patients with stage III CRC. Hence, we might be able to use the CIS status to consider adapting preoperative chemotherapy for clinically node-positive patients.

According to the results of the current study, CIS may be useful for identifying which patients with T3 invasion have a poorer prognosis, thus facilitating the performance of preoperative chemotherapy focused on highly malignant tumors. Conversely, CIS may also be useful for identifying which patients with stage III disease have a relatively good prognosis, and for whom preoperative chemotherapy may not be necessary. For these reasons, we believe that CIS is clinically meaningful.

The current study had several limitations. First, because it was a retrospective single-institutional study, we could not analyze the influence of the patients' background factors. Second, postoperative adjuvant chemotherapy and treatments for recurrence were not homogeneous. Because we did not conduct a prospective study separating patients with CIS-positive disease into a preoperative chemotherapy group and a no preoperative chemotherapy group, it is not clear whether prognosis can be improved by performing preoperative chemotherapy. However, given that there are few informative prognostic indicators that can be evaluated before surgery, it is very meaningful that CIS can be assessed using CT, which is performed almost routinely before surgery, and has prognostic power. The results of the present study need to be verified by a prospective study.

In conclusion, the findings of the current study suggest that CIS can be used to predict a high potential for malignancy, and that it is a promising preoperative prognostic factor in CRC, particularly for patients with T3 tumors and those with Stage III disease. To the best of our knowledge, this is the first study in which CIS was clearly an informative prognostic factor in CRC patients. CIS evaluation may allow us to identify patients with a high risk of postoperative cancer recurrence, before surgery, and make more informed decisions about the administration of neoadjuvant chemotherapy.

Compliance with ethical standards

Conflict of interest Tadakazu Ao and his co-authors have no conflicts of interest to declare.

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