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ORIGINAL RESEARCH

Systemic inflammation score in locally advanced rectal cancer patients following total mesorectal excision

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Video abstract

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Objective: The objective of the study was to evaluate whether any association exists between systemic inflammation score (SIS) and adverse events (AEs) and survival of locally advanced rectal cancer patients treated with total mesorectal excision (TME) followed by adjuvant chemoradiotherapy.

Patients and methods: All of the 109 rectal cancer patients recruited between May 2008 and June 2015 were treated with TME followed by adjuvant chemoradiotherapy. The prognostic ability of SIS for overall survival (OS) was calculated by the receiver operating characteristic (ROC) curves.

Results: According to the classification of the SIS, 22 (20.2%), 59 (54.1%) and 28 (25.7%) patients were classified as a score of 2, 1 and 0, respectively. With an area under the curve (AUC) of 0.616, the SIS score of 1 was defined as the optimal cut-off value. Therefore, we divided the patients into the SIS-low group (SIS score of 1 or 0, n=87) and SIS-high group (SIS score of 2, n=22). Multivariate analysis indicated that SIS was associated with OS (HR 0.390, 95% CI 0.186–0.817, P=0.012). The 5-year OS rate in patients without adjuvant chemotherapy was lower than the patients with adjuvant chemotherapy (53.3% vs 75.8%, P=0.010). Multivariate analysis showed that adjuvant chemotherapy was associated with OS (HR 0.217, 95% CI 0.089–0.529, P=0.001). A marginal statistically significant difference was observed in terms of leukopenia during adjuvant chemoradiotherapy between the SIS-low group and the SIS-high group (P=0.05).

Conclusion: These results suggest that SIS might serve as an independent biomarker for predicting AEs and prognosis in locally advanced rectal cancer treated with TME followed by adjuvant chemoradiotherapy. Strengthening treatment may be administered to locally advanced rectal cancer with high SIS score obtained before adjuvant chemoradiotherapy.

Keywords: rectal cancer, SIS, chemoradiotherapy, acute adverse event, survival

Introduction

Neoadjuvant chemoradiotherapy followed by total mesorectal excision (TME) has been recommended for patients with locally advanced rectal cancer. However, for patients with locally advanced rectal cancer treated by primary surgery, adjuvant chemoradiotherapy is recommended.[1] Broad variations of survival and adverse events (AEs) have been reported in response to the adjuvant chemoradiotherapy.[2] In our previous studies, genetic variations in mismatch repair genes and microRNA seed regions could predict the risk of AEs and prognosis.[3,4]

Historically, radiotherapy toxicity was explained using the linear quadratic model.[5] As the seventh hallmark of cancer, the role of inflammation in radiotherapy

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toxicity needs further study.[6] The systemic inflammation score (SIS), which is based on lymphocyte-to-monocyte ratio (LMR) and serum albumin level, has been reported to be associated with the prognosis of gastric cancer, renal cell carcinoma and colorectal cancer.[7–9] Since colon cancer and rectal cancer differ in their biological behaviors, they should be analyzed separately.[10,11] The aim of this study was to evaluate whether any association exists between SIS and AEs and survival of locally advanced rectal cancer patients treated with TME followed by adjuvant chemoradiotherapy.

Materials and methods
Patients
This study was approved by the independent ethics committee, Zhejiang Cancer Hospital. Consent was waived and patient records were deidentified and anonymized prior to analysis. The study was in compliance with the Declaration of Helsinki.

All of the rectal cancer patients recruited between May 2008 and June 2015 were treated with TME followed by a total radiation dose of 45–50.4 Gy in 25–28 fractions at 1.8–2.0 Gy per daily fraction concurrently with capecitabine or capecitabine plus oxaliplatin. The details of adjuvant chemoradiotherapy were described previously.[2] Patient eligibility criteria included as following: (1) pathological stage II or III rectal adenocarcinoma; (2) R0 TME; (3) Karnofsky Performance Score (KPS) ≥70; (4) 18–75 years old; (5) with no history of cancer excluding carcinoma in situ of the uterine cervix or basal cell carcinoma of the skin; and (6) with adequate organ function. AEs were graded according to the Common Terminology Criteria for Adverse Events ver. 4.0.

Follow-up
All patients were evaluated weekly during radiotherapy, and were required to be followed-up after the completion of treatment: every 3 months for the first 2 years, and every 6 months thereafter. Each follow-up included physical examination, complete blood count, liver and renal function test and tumor markers (carcinoembryonic antigen and cancer antigen 19–9). Pelvic computed tomography (CT) or magnetic resonance imaging (MRI), chest radiography and abdominal CT and/or ultrasonography were performed every 6 months. Colonoscopic examination was repeated annually.

Data extraction
The patient demographic variables (age, sex) and clinical characteristics (KPS, surgical procedure, concurrent oxaliplatin-based chemoradiotherapy, adjuvant chemotherapy, pathological stage, distance from anal verge, results of peripheral blood tests before chemoradiotherapy and related follow-up data) were collected. All patients were staged based on the 8th edition of the American Joint Committee on Cancer staging system. Blood samples were drawn and assayed within 2 weeks before chemoradiotherapy. The laboratory parameters included serum albumin level, lymphocyte and monocyte count. Patients with a serum level ≥40 gL^{-1} and LMR ≥4.44 were classified as a score of 0; patients with either a serum albumin level <40 gL^{-1} or LMR <4.44 were classified as a score of 1; patients with both hypoalbuminemia <40 gL^{-1} and LMR <4.44 were classified as a score of 2.[5–7]

Statistical analysis
Statistical analysis was carried out using SPSS version 22.0 (IBM, Armonk, NY, USA). The prognostic ability of SIS for overall survival (OS) was calculated by the receiver operating characteristic (ROC) curves. The disease-free survival (DFS) and OS were measured from the day of surgery to the date of the event and were estimated by use of the Kaplan-Meier method. Log-rank test and Chi-square test were used to assess differences between the SIS-low and the SIS-high group. Multivariate analyses with the Cox proportional hazards model were used to test independent significance by using backward elimination of insignificant explanatory variables. Host factors (age and sex) were included as covariates in all tests. Statistical tests were based on a two-sided significance level. $P<0.05$ indicated statistical significance.

Results
Characteristics of study subjects
A total of 109 patients were enrolled; the median follow-up time was 6.6 years (range, 2.4–9.5 years). According to the classification of the SIS, 22 (20.2%), 59 (54.1%) and 28 (25.7%) patients were classified as a score of 2, 1 and 0, respectively. According to the ROC curve to predict OS, an SIS score of 1 was defined as the optimal cut-off value with an area under the curve (AUC) of 0.616 (Figure 1). Therefore, we divided the patients into the SIS-low group (SIS score of 1 or 0, n=87) and SIS-high group (SIS score of 2, n=22). The basic clinical characteristics of the patients are presented in Table 1.
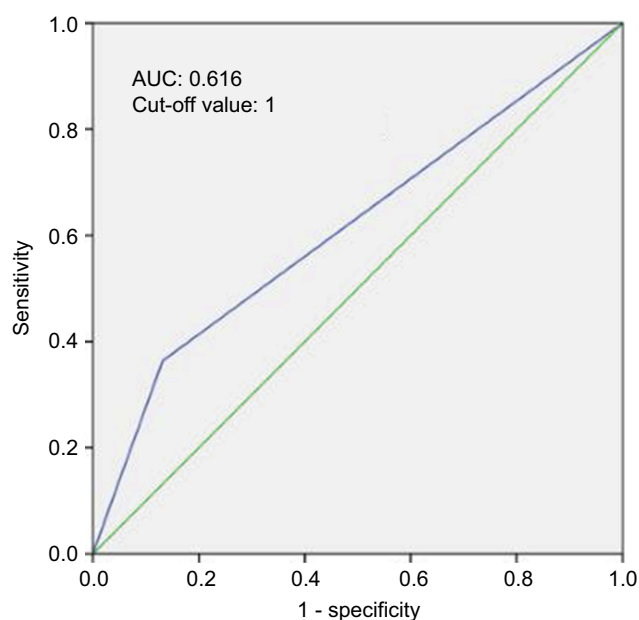
Figure 1 Receiver operating characteristic curves predicting overall survival by SIS are represented.
Abbreviations: AUC, area under the curve; SIS, systemic inflammation score.

Table 1 Clinical characteristics

Characteristic	SIS-low group	SIS-high group	*P*-value
Sex			
Male	56 (64.4)	12 (54.5)	0.396
Female	31 (35.6)	10 (45.5)	
Age			
<54	45 (51.7)	14 (63.6)	0.198
≥54	42 (48.3)	8 (36.4)	
KPS			
90–100	59 (67.8)	16 (72.7)	0.657
70–80	28 (32.2)	6 (27.3)	
Surgery			
Dixon	60 (69.0)	14 (63.6)	0.632
Mile's	27 (31.0)	8 (36.4)	
Distance from anal verge (cm)			
≤5	40 (46.0)	9 (40.9)	0.669
>5	47 (54.0)	13 (59.1)	
Pathological stage			
II	13 (14.9)	1 (4.5)	0.293
III	74 (85.1)	21 (95.5)	
Concurrent oxaliplatin-based chemoradiotherapy			
Yes	43 (49.4)	10 (45.5)	0.814
No	44 (50.6)	12 (54.5)	

(Continued)

Table 1 (Continued).

Characteristic	SIS-low group	SIS-high group	*P*-value
Adjuvant chemotherapy			
Yes	15 (17.2)	3 (13.6)	>0.999
No	72 (82.8)	19 (86.4)	

Abbreviations: SIS, systemic inflammation score; KPS, Karnofsky Performance Score.

No statistically significant difference was observed in terms of age, sex, KPS, surgical procedure, concurrent oxaliplatin-based chemoradiotherapy, adjuvant chemotherapy, pathological stage and distance from anal verge between the SIS-low group and the SIS-high group.

SIS and AEs during chemoradiotherapy

The most frequently observed acute toxicity during chemoradiotherapy was mainly grade 0 or grade 1. The incidence of acute grade ≥2 diarrhea, dermatitis and leukopenia was 36.7%, 18.3% and 24.8%, respectively. A marginal statistically significant difference was observed in terms of leukopenia during chemoradiotherapy between the SIS-low group and the SIS-high group (*P*=0.05) (Table 2).

SIS and survival

The 5-year OS rate in the SIS-high group was lower than the patients in the SIS-low group (50.0% vs 78.2%, *P*=0.011). No statistically significant difference was found in terms of 5-year DFS rate between the SIS-low and the SIS-high groups (66.0% vs 52.5%, *P*=0.281) (Figure 2). Multivariate analysis by Cox proportional-hazards model showed that SIS was associated with OS (HR 0.337, 95% CI 0.160–0.713, *P*=0.004) (Table 3). The 5-year OS rate in patients without adjuvant chemotherapy was lower than the patients with adjuvant chemotherapy (53.3% vs 75.8%, *P*=0.010). Multivariate analysis showed that adjuvant chemotherapy was associated with OS (HR 0.217, 95% CI 0.089–0.529, *P*=0.001).

Discussion

In the present study, we evaluated the association between systematic inflammation and AEs and survival of locally advanced rectal cancer patients treated with TME followed by adjuvant chemoradiotherapy. To our knowledge, the present study is the first study to evaluate the role of SIS for AEs and survival in locally advanced rectal cancer patients treated with TME followed by adjuvant chemoradiotherapy. The

Table 2 Association between SIS and acute adverse events in patients with rectal cancer receiving chemoradiation therapy

Characteristic	SIS-low group	SIS-high group	P-value
Leukopenia			
Grade ≥2	18 (20.7)	9 (40.9)	0.050
Grade <2	69 (79.3)	13 (59.1)	
Dermatitis			
Grade ≥2	15 (17.2)	5 (22.7)	0.553
Grade <2	72 (82.8)	17 (77.3)	
Diarrhea			
Grade ≥2	33 (37.9)	7 (31.8)	0.595
Grade <2	54 (62.1)	15 (68.2)	

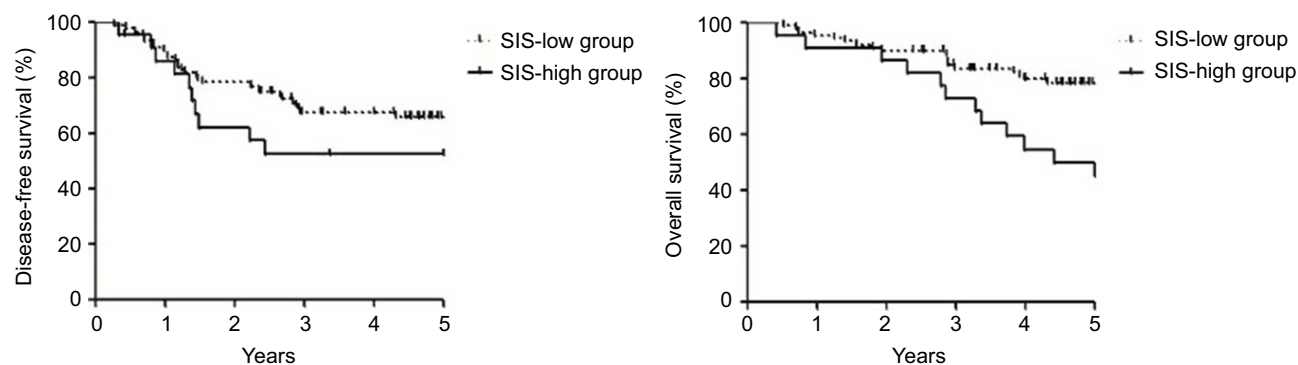**Abbreviation:** SIS, systemic inflammation score.

results suggested that SIS was an independent prognostic predictor of OS and marginal statistically significant difference was observed in terms of leukopenia between the SIS-low group and the SIS-high group during chemoradiotherapy.

As Virchow originally made links between inflammation and cancer in 1863, the role of systemic inflammation in the pathogenesis and progression of cancer has been revived in the recent years.[12,13] Lymphocyte, a surrogate marker of host immunological status, has been reported to suppress tumor progression and promote tumor immune-surveillance.[14–17] Tumor-associated macrophages, derived from monocytes, have been reported to play a critical role in the pathogenesis, progression and therapeutic resistance of cancer.[18,19] LMR was reported to be associated with the prognosis of rectal cancer with or without neoadjuvant chemoradiotherapy.[20–23] Serum albumin level is an indicator of nutritional status and systematic inflammation response,[24] associated with prognosis and postoperative morbidity in rectal cancer.[25–27]

In the study including 441 clear-cell renal cell carcinoma patients undergoing nephrectomy, SIS was firstly reported to be associated with tumor behaviors and OS after adjusting for traditional clinicopathological features and other markers of systemic inflammation responses.[7] The higher SIS score was also associated with poorer OS and DFS in gastric cancer patients after curative gastrectomy.[9] In the study of evaluating the prognostic impact of the SIS in colorectal cancer patients after curative resection, 161 (22.1%) patients with rectal cancer who did not receive neoadjuvant chemoradiotherapy or radiation therapy were included. SIS was significantly associated with more advanced stage. Furthermore, SIS was an independent prognostic factor for OS by multivariate analysis. Compared with SIS =0, the hazard ratio of SIS =1 was 1.711 (P=0.030), and that of SIS =2 was 1.944 (P=0.018).[8] In our study, the prognostic ability of SIS for OS was calculated by the ROC curves and we divided the patients into the SIS-low group (SIS score of 1 or 0, n=87) and SIS-high group (SIS score of 2, n=22) for the limited patients. No statistically significant difference was observed in terms of pathological stage between the SIS-low group and the SIS-high group; however, more patients with Stage III were classified into the SIS-high group (95.5% vs 85.1%, P=0.293). Multivariate analysis showed that SIS was an independent prognostic predictor of OS, which was similar with the previous report of colorectal cancer.

The mechanisms of radiotherapy toxicity include direct or indirect cell death, inflammation and immune reaction. Genetic analyses and radiomics had been adopted for predicting radiotherapy toxicity.[6] In our previous studies,[3,4] MSH3 rs12513549 (odds ratio, 0.68; 95% CI, 0.48–0.97; P=0.037), rs33013 (odds ratio, 0.71; 95% CI, 0.50–0.99; p=0.049) and rs6151627 (odds ratio, 1.51; 95% CI, 1.02–2.27; P=0.041) were significantly associated with grade ≥2 diarrhea; PMS1 rs1233255 A>C (odds ratio, 0.48; 95% CI,

Figure 2 Kaplan-Meier curves of overall survival and disease-free survival in the SIS-low group and the SIS-high group.
Abbreviation: SIS, systemic inflammation score.

Table 3 Multivariate analysis of overall survival by Cox proportional hazards model

Items	Overall survival		
	HR	95% CI	*P*-value
SIS (SIS-low group vs SIS-high group)	0.337	0.160–0.713	0.004*
Pathological stage (II vs III)	0.160	0.021–1.212	0.076
KPS (70–80 vs 90–100)	2.637	1.226–5.671	0.013*
Adjuvant chemotherapy (Yes vs No)	0.217	0.089–0.529	0.001*

Note: *$P < 0.05$.
Abbreviations: SIS, systemic inflammation score; KPS, Karnofsky Performance Score; CI, confidence interval; HR, hazard ratio.

0.23–0.93; $P = 0.041$) was associated with grade ≥2 dermatitis; single nucleotide polymorphism rs2273626 was associated with grade ≥2 leukopenia (odds ratio, 0.48; 95% CI, 0.31–0.74; $P = 0.0009$). In the present study, a marginal statistically significant difference was observed in terms of grade ≥2 leukopenia during radiotherapy between the SIS-low group and the SIS-high group.

The serum albumin level and white blood cell count were obtained before surgery in the previous studies of SIS.[7–9] In the present study, the serum albumin level and white blood cell count obtained before adjuvant chemoradiotherapy were used to evaluate the role of SIS for AEs and survival in locally advanced rectal cancer patients treated with TME followed by adjuvant chemoradiotherapy. In the study including 146 rectal cancer patients treated by neoadjuvant chemoradiotherapy and surgery, the cutpoint was significantly associated with OS for LMR before neoadjuvant chemoradiotherapy but not for LMR after neoadjuvant chemoradiotherapy.[22] The role of SIS before any treatment in rectal cancer should be elucidated in the future.

There were several limitations to our study. First, for the limited patients from one institution, the role of the SIS in rectal cancer should be evaluated prospectively in other populations and larger cohorts in the future. Second, although circulating white blood cell counts are thought to be an indicator of systematic immune reaction, we did not determine the relation of SIS and other immunological characteristics, such as immunoscore,[28] which has been reported to be a prognostic marker of rectal cancer. Third, despite no head-to-head comparison in the adjuvant setting, current treatment guidelines of rectal cancer recommend either XELOX or FOLFOX as standard of care treatment options.[1] Multivariate analysis showed that adjuvant chemotherapy was associated with OS in the present study. In the SIS-high group, only 3 patients received adjuvant chemotherapy; it would be inappropriate

to evaluate the role of adjuvant chemotherapy for locally advanced rectal cancer with high SIS score.

Conclusion

These results suggest that SIS might serve as an independent biomarker for predicting AEs and prognosis in locally advanced rectal cancer treated with TME followed by adjuvant chemoradiotherapy. Strengthening treatment may be administered to locally advanced rectal cancer with high SIS score obtained before adjuvant chemoradiotherapy.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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