ORIGINAL

SDF-1 expression after preoperative chemoradiotherapy is associated with prognosis in patients with advanced lower rectal cancer

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Abstract : Stromal cell-derived factor-1 (SDF-1) expression is associated with cancer progression, as a biomarker of prognosis. We clarified the significance of SDF-1 expression on chemoradiotherapy (CRT) resistance and prognosis in advanced lower rectal cancer patients. We evaluated 98 patients with advanced lower rectal cancer who underwent preoperative CRT. All patients received 40 Gy of radiation therapy, with concurrent chemotherapy containing fluorinated pyrimidines, followed by surgical resection. SDF-1 expression in surgical specimens was examined by immunohistochemistry. We divided the patients into SDF-1-positive- (n=52) and SDF-1-negative groups (n=46) and compared the clinicopathological factors and survival rates. The SDF-1-positive group was more resistant to CRT than the SDF-1-negative group (non-responder rate, 63.5% vs. 47.8%, respectively ; p=0.12). Overall survival (OS) in the SDF-1 positive group was significantly poorer vs. the SDF-1-negative group (5-year OS, 73.4% vs. 88.0%, respectively ; p=0.02), and disease-free survival (DFS) was worse (5-year DFS, 61.0% vs. 74.1%, respectively ; p=0.07). Multivariate analysis confirmed that SDF-1 expression was a significant independent prognostic predictor of OS (p=0.04). SDF-1 expression after preoperative CRT is significantly associated with a poor prognosis in advanced lower rectal cancer patients and is a promising biomarker. J. Med. Invest. 68 : 309-314, August, 2021

Keywords **:** *Rectal cancer, Stromal derived factor-1, Radiation resistance, Preoperative chemoradiotherapy*

INTRODUCTION

Preoperative chemoradiotherapy (CRT) is widely used as a major treatment modality in advanced lower rectal cancer patients to control local tumor progression, allow sphincter-sparing surgery, and improve survival (1, 2). However, the rate of distant metastasis after CRT followed by radical operation in advanced lower rectal cancer patients remains high at 15%–20% (2-4). New biomarkers are necessary to select patients with a high risk of recurrence and allow for personalized therapy.

Stromal cell-derived factor-1 (SDF-1) is a CXC chemokine and is also known as CXC motif chemokine ligand-12 (CXCL12). SDF-1 is ubiquitously expressed in almost all organs, and is essential for hematopoiesis, vascular development, cardiogenesis, and neurogenesis (5-7). CXC chemokine receptor-4 (CXCR4), which is an SDF-1 receptor, expresses on the cell surface of hematopoietic stem cells and T and B lymphocytes, and SDF-1 is implicated in the homing of these cells (8, 9). CXCR4 also express on the surfaces of malignant cells ; the SDF-1/CXCR4 axis enhances cancer cell survival, proliferation, angiogenesis, and metastasis (10, 11). In addition, high expression of SDF-1 in cancer cells attracts CXCR4-positive cells, such as cancer-associated fibroblasts (CAF) or immune cells, including myeloid-derived suppressor cells (MDSC), regulatory T cells (Treg) and tumor-associated macrophages (TAM), to the tumor sites and converts the tumor microenvironment (TME) to immune tolerance (12-14). Therefore, SDF-1 might have potential as a new therapeutic target, and could be a useful biomarker for patients with malignant tumors.

SDF-1 expression in cancer cells promotes the progression of breast cancer, lung cancer, and lymphoma, and could be a biomarker for a poor prognosis (15-17). The significance of SDF-1 expression remains unclear, and few reports have focused on SDF-1 expression in advanced lower rectal cancer (18, 19). Recently, several reports described that SDF-1 was a factor related to resistance to radiotherapy for glioblastoma, and head and neck cancer (20, 21). In this study, we evaluated whether SDF-1 expression in cancer cells could induce radiation resistance and lead to a poor prognosis in advanced lower rectal cancer patients undergoing preoperative CRT.

The aim of this study was to investigate the significance of SDF-1 expression in advanced lower rectal cancer patients undergoing preoperative CRT.

PATIENTS AND METHODS

Patients

We evaluated 98 surgically-resected specimens from advanced lower rectal cancer patients who underwent preoperative CRT followed by radical resection from April 2006 to July 2018 at Tokushima University Hospital. The indications for preoperative CRT at our institution were previously reported (22). Briefly, preoperative CRT was offered to advanced lower rectal cancer patients who were diagnosed with locally advanced (≥ T3 and/or ≥ N1) cancer or to those who were estimated to have T2 cancer close to or involving the anal sphincter. Preoperative pelvic irradiation constituted a total dose of 4000 cGy at 200 cGy per fraction daily, five times weekly. The radiation field included

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the lateral pelvic lymph nodes, and radiation therapy was administered concomitantly with chemotherapy that included fluorinated pyrimidines. The regimen constituted tegafur-uracil (UFT) or S-1 orally, only (n = 18, n = 45, respectively) ; S-1 and oxaliplatin ; bevacizumab (SOX + Bev, n = 33) ; or S-1 and CPT-11 (IRIS, n = 2).

This study was approved by the Institutional Review Board of Tokushima University (Tocms2901-1). This study was conducted according to the principles expressed in the Declaration of Helsinki. All tissue samples included in this investigation were obtained with the patients' informed consent.

Immunohistochemical staining

The immunohistochemical method was reported previously (22). Briefly, paraffin sections were cut at 4-μm thicknesses from archival formalin-fixed paraffin-embedded tissue blocks. The sections were deparaffinized using xylene and dehydrated using a series of graded ethanol solutions. Endogenous peroxidase activity was blocked by administering 0.3% hydrogen peroxidase and methanol. After washing three times for 5 minutes (each wash) with phosphate-buffered saline (PBS), the sections were processed in 10 mM EDTA buffer (pH : 9) in a microwave for antigen retrieval. After cooling at room temperature, the sections were incubated with primary mouse monoclonal antibody for SDF-1 (MAB350, dilution 1 : 50 ; R&D Systems, Minneapolis, MN, USA) at 4℃, overnight, followed by three washes. The sections were then incubated with a Dako REAL EnVision/HRP detection system (Dako, Tokyo, Japan) for 1 hour. After three washes, 3,3′-diaminobenzidine tetrahydrochloride (DAB) was used to develop the peroxidase reaction. Nuclei were counterstained with Mayer's hematoxylin solution to complete the procedure.

SDF-1 expression in cancer cells was scored by staining intensity (SI), as follows : no staining = 0 ; weak = 1 ; moderate = 2 ; and strong = 3 (23). We then categorized SDF-1 values into negative and positive groups (0, 1 : SDF-1-negative ; 2, 3 : SDF-1-positive).

Pathological evaluation

Evaluation of patients' therapeutic responses to preoperative CRT was described previously (24). Briefly, the evaluation of surgical specimens was performed according to the histopathological response criteria of the general rules for clinical and pathological studies on cancer of the colon, rectum, and anus (Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma). All specimens with SDF-1-positive grade 2 or 3 were classified as responders, and specimens with grade 0 or 1 were classified as non-responders.

Statistical analyses

All statistical analyses were performed using JMP statistical software (version 8.0.1 ; SAS Institute Inc., Cary, NC, USA). The χ2-test and Mann–Whitney U test were used to compare the clinicopathological variables between the two groups. Survival curves were created using the Kaplan–Meier method, and the curves were compared using the log-rank test. $p<0.05$ was considered statistically significant.

RESULTS

Typical immunohistochemistry images of SDF-1-positive cells in lower rectal cancer tissues are shown in Figure 1. All patients were divided into an SDF-1-positive group (n = 52) or -negative group (n = 46). The clinicopathological characteristics of each group are shown in Table 1. SDF-1 expression correlated

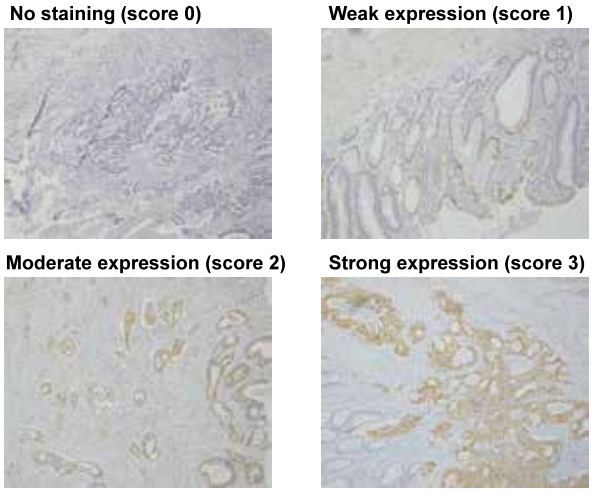

Figure 1. Representative immunohistochemical staining of stromal cell-derived factor-1 (SDF-1).
SDF-1 expression was assessed in the cytoplasm of cancer cells.

Table 1. Comparison of the clinicopathological characteristics between the SDF-1-positive and -negative groups

Variable	SDF-1-negative (n=46)	SDF-1-positive (n=52)	p-value
Age (years)	63 ± 10	66 ± 9	0.11
Sex (M / F)	30 / 16	35 / 17	0.82
Location (Ra / Rb / P)	8 / 37 / 1	7 / 42 / 3	0.58
Depth of invasion (T1–2 / T3–4)	24 / 22	21 / 31	0.24
Lymph node metastasis (− / +)	38 / 8	34 / 18	0.05
Lymphatic invasion (− / +)	30 / 9	29 / 18	0.12
Venous invasion (− / +)	20 / 19	24 / 24	0.90
Differentiation (tub1 / tub2 / others)	22 / 22 / 2	20 / 29 / 3	0.47
Stage (0 / I / II / IIIa / IIIb / IV)	6 / 18 / 11 / 5 / 4 / 2	5 / 12 / 16 / 6 / 9 / 4	0.46
Neoadjuvant chemotherapy (UFT / S-1 / IRIS / SOX+Bev)	10 / 26 / 0 / 10	8 / 19 / 2 / 23	0.02
Adjuvant chemotherapy (− / +)	40 / 6	39 / 13	0.13

SDF-1, stromal cell-derived factor-1 ; y, years ; M, male ; F, female ; Ra, rectum above the peritoneal reflection ; Rb, rectum below the peritoneal reflection ; P, proctos ; tub1, well differentiated adenocarcinoma ; tub2, moderately differentiated adenocarcinoma ; UFT, uracil/tegafur ; IRIS, irinotecan plus S-1 ; SOX, S-1 combined with oxaliplatin ; Bev, bevacizumab

with lymph node metastasis and neoadjuvant chemotherapy regimens. We investigated whether there was a correlation between SDF-1 expression and the effect of radiation therapy. Approximately 63.5% of the patients in the SDF-1-positive group and 47.8% in the SDF-1-negative were non-responders to preoperative CRT ($p = 0.12$, Fig. 2).

Overall survival (OS) in the SDF-1-positive group was significantly poorer than that in the SDF-1-negative group (5-year OS, 74.3% vs. 88.0%, respectively ; $p < 0.05$; Fig. 3A), and disease-free survival (DFS) was also poorer (5-year DFS, 61.0% vs. 74.1%, respectively ; $p = 0.07$; Fig. 3B). Univariate analysis showed that sex, pT, pN, lymphatic invasion, serum CEA concentration, and SDF-1-positive expression were significant prognostic factors for OS, and pT, pN, lymphatic invasion, and high expression of SDF-1 were prognostic factors for DFS (Table 2 and Table 3). Multivariate analysis showed that SDF-1 was a significant independent risk factor for both OS (relative risk, 2.85 ; $p = 0.04$; Table 2) and DFS (relative risk, 2.07 ; $p = 0.06$; Table 3).

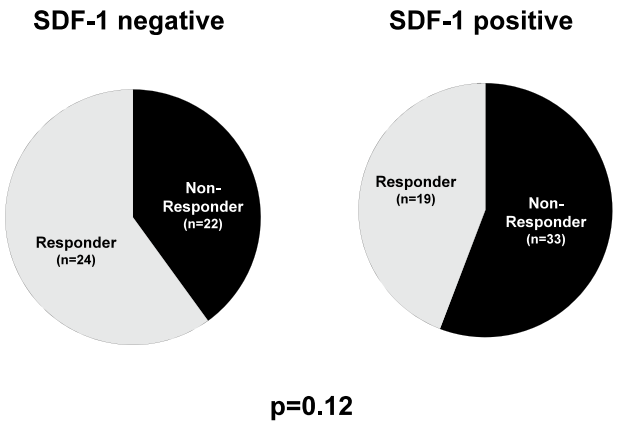

Figure 2. Pathological response to preoperative CRT after surgical resection
The Stromal cell-derived factor-1 (SDF-1)-positive group had more non-responders compared with the SDF-1-negative group.

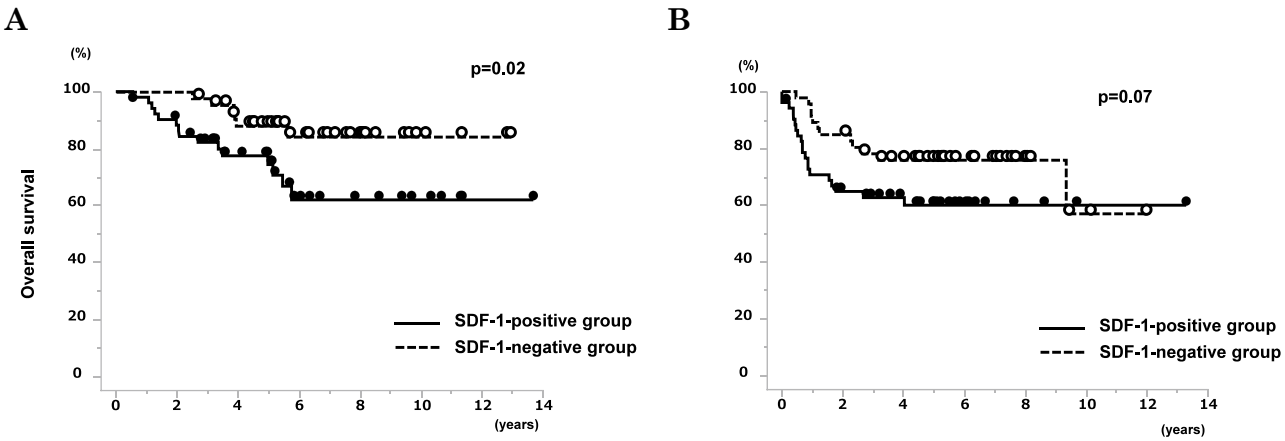

Figure 3. Kaplan–Meier analysis of overall survival (A) and disease-free survival (B) for stromal cell-derived factor-1 (SDF-1) expression.

Table 2. Univariate and multivariate analysis of the prognostic factors for overall survival (OS)

Variable	5-year OS (%)	Univariate	Multivariate	
		p-value	HR (95% CI)	p-value
Age (<60 / ≥60 years)	87.5 / 78.7	0.51	0.84 (0.25–2.82)	0.77
Sex (M / F)	81.4 / 79.1	0.70	1.15 (0.40–3.24)	0.78
Tumor differentiation (tub1, tub2 / others)	80.9 / 80.0	0.92	0.79 (0.09–6.82)	0.83
T stage (T1–2 / T3–4)	87.0 / 75.5	0.02	1.40 (0.45–4.32)	0.55
Lymph node metastasis (−/+)	88.1 / 58.8	<0.01	2.09 (0.54–8.09)	0.28
Lymphatic invasion (−/+)	88.6 / 57.3	<0.01	3.04 (0.94–9.81)	0.06
Venous invasion (−/+)	84.1 / 71.6	0.17	2.41 (0.84–6.91)	0.10
CEA (<5 ng/ml / ≥5 ng/ml)	81.3 / 71.4	0.01	4.53 (1.14–17.93)	0.03
Adjuvant chemotherapy (−/+)	83.0 / 71.2	0.19	3.27 (0.81–1.14)	0.08
SDF-1 (negative / positive)	88.0 / 74.3	0.02	2.85 (1.00–8.11)	0.04

HR, hazard ratio ; CI, confidence interval ; y, years ; M, male ; F, female ; tub1, well differentiated adenocarcinoma ; tub2, moderately differentiated adenocarcinoma ; CEA, carcinoembryonic antigen ; SDF-1, stromal cell-derived factor-1

Table 3. Univariate and multivariate analysis of the prognostic factors for disease-free survival (DFS)

Variable	5-year DFS (%)	Univariate	Multivariate	
		p-value	HR (95% CI)	p-value
Age (< 60 y / ≥ 60 y)	79.1 / 63.7	0.31	1.34 (0.51–3.54)	0.54
Sex (M / F)	67.9 / 66.3	0.79	0.58 (0.26–1.27)	0.17
Tumor differentiation (tub1, tub2 / others)	67.8 / 60.0	0.73	0.76 (0.16–3.65)	0.73
T stage (T1–2 / T3–4)	84.1 / 53.5	< 0.01	1.61 (0.59–4.34)	0.34
Lymph node metastasis (− / +)	76.9 / 42.3	< 0.01	3.02 (1.03–8.40)	0.04
Lymphatic invasion (− / +)	74.8 / 36.6	< 0.01	3.11 (1.34–7.19)	< 0.01
Venous invasion (− / +)	70.3 / 55.1	0.11	1.61 (0.70–3.71)	0.25
CEA (< 5 ng/ml / ≥ 5 ng/ml)	69.0 / 42.8	0.09	2.87 (0.82–10.06)	0.09
Adjuvant chemotherapy (− / +)	71.2 / 52.6	0.06	2.63 (0.13–1.05)	0.06
SDF-1 (negative / positive)	74.1 / 61.0	0.07	2.07 (0.94–4.55)	0.06

HR, hazard ratio ; CI, confidence interval ; y, years ; M, male ; F, female ; tub1, well differentiated adenocarcinoma ; tub2, moderately differentiated adenocarcinoma ; CEA, carcinoembryonic antigen ; SDF-1, stromal cell-derived factor-1

DISCUSSION

In the current study, we identified the significance of SDF-1 expression as a biomarker for predicting the prognosis of advanced lower rectal cancer patients undergoing preoperative CRT, using immunohistochemical staining.

SDF-1 activates the downstream signal pathways, such as PI3K/AKT/mTOR and ERK1/2, and enhances cancer cell survival, proliferation, and chemotaxis by binding to CXCR4 (25). High SDF-1 expression was associated with a poor prognosis in esophagogastric, pancreatic, and lung cancer patients in two meta-analyses (26, 27). In CRC patients, the significance of SDF-1 expression in cancer cells remains controversial because SDF-1 is reported to be both tumor promoting (28) and tumor suppressive (29). There are only a few reports of the significance of SDF-1 expression in cancer cells regarding prognosis in advanced lower rectal cancer patients (18, 19). In cancer cells, the SDF-1/CXCR4 axis activates intracellular signaling through the MEK/ERK and PI3K/AKT pathways and promotes cell survival and proliferation, and metastasis (30, 31). In addition, SDF-1 can attract CXCR4-positive cells, such as CAF, MDSC, Treg, or TAM, to the tumor sites and assist tumor progression in the TME (10, 14). Our data showed that SDF-1 expression in cancer cells after preoperative CRT was an independent prognostic factor for OS in advanced lower rectal cancer patients. Our data also showed that SDF-1 expression correlated with higher recurrence rates. Our results were compatible with previous reports, and indicate the significance of SDF-1 in advanced lower rectal cancer patients undergoing preoperative CRT.

Several researchers reported that SDF-1 expression induced resistance to radiation therapy in glioblastoma, and head and neck cancer (20, 21). Kim *et al*. reported that upregulation of SDF-1 before and after preoperative CRT was associated with radiation resistance (18). In our study, SDF-1 expression in cancer cells correlated with response to radiotherapy. To the best of our knowledge, no previous reports identified the mechanism of acquiring radiation resistance via upregulation of SDF-1 expression in advanced lower rectal cancer. Recently, converting the TME has been shown to be an important factor inducing radiation resistance in cancer cells (32-34), and several studies showed that MDSC and Treg recruitment to the TME was a major factor in radiation resistance (35, 36). As the SDF-1/CXCR4 axis plays a crucial role in recruiting MDSCs and Tregs to the TME (37, 38), we speculate that upregulation of SDF-1 expression may induce tumor radiation resistance via infiltration of these immune cells. In a future study, we will investigate the relationship between SDF-1 expression in tumors and immune cell infiltration.

Increasing experimental evidence suggests using the SDF-1/CXCR4 axis as a therapeutic target. Some researchers showed that inhibiting the SDF-1/CXCR4 axis improved tumor malignancy and survival. For example, AMD3100, an anti-CXCR4 drug, was associated with reduced proliferation and metastasis of cancer cells in ovarian cancer (39), and NOX-A12, an anti-SDF-1 aptamer, improved the survival of irradiated rats with glioblastoma (40). Other researchers have also suggested that modulating the SDF-1/CXCR4 axis could revert the tolerogenic polarization of the TME, and modulate immunotherapy with anti-CTLA-4 or anti–PD-1 antibody (13, 41).

There are limitations in our study. While almost 100 tissue specimens were included in the analysis, sample sizes were relatively small. However, SDF-1 expression correlated with CRT response. To further investigate the relationship between radiation resistance and SDF-1 expression, it will be necessary to evaluate not only the SDF-1 expression level after surgical resection, but also the SDF-1 expression level prior to preoperative CRT.

In conclusion, in advanced lower rectal cancer, cancer cells expressing SDF-1 were less sensitive to radiation therapy and more frequently associated with postoperative recurrence. Additionally, SDF-1 expression was an independent prognostic factor for OS. SDF-1 expression in cancer cells is a useful biomarker and has the potential to become a new therapeutic target.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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