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ORIGINAL ARTICLE

Retrospective Study

Self-expanding metal stent placement and pathological alterations among obstructive colorectal cancer cases

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Abstract

BACKGROUND

Experimental studies suggest that self-expanding metal stents (SEMSs) enhance the aggressive behavior of obstructive colorectal cancer. The influence of SEMS placement on pathological alterations remains to be elucidated.

AIM

To determine whether SEMS placement is associated with molecular or pathological features of colorectal carcinoma tissues.

METHODS

Using a nonbiased molecular pathological epidemiology database of patients with obstructive colorectal cancers, we examined the association of SEMS placement with molecular or pathological features, including tumor size, histological type, American Joint Committee on Cancer (AJCC)-pTNM stage, and mutation statuses in colorectal cancer tissues compared with the use of transanal tubes. A multivariable logistic regression model was used to adjust for potential confounders.

RESULTS

SEMS placement was significantly associated with venous invasion ($P < 0.01$), but not with the other features examined, including tumor size, disease stage, mutation status, and lymphatic invasion. In both the univariable and mult-

ivariable models with adjustment for potential factors including tumor location, histological type, and AJCC-pT stage, SEMS placement was significantly associated with severe venous invasion (P < 0.01). For the outcome category of severe venous invasion, the multivariable odds ratio for SEMS placement relative to transanal tube placement was 19.4 (95% confidence interval: 5.24–96.2). No significant differences of disease-free survival and overall survival were observed between SEMS and transanal tube groups.

CONCLUSION
SEMS placement might be associated with severe venous invasion in colorectal cancer tissue, providing an impetus for further investigations on the pathological alterations by SEMSs in colorectal cancer development.

Key Words: Bridge to surgery; Colorectal carcinoma; Obstruction; Stent; Venous invasion

Core Tip: This study aimed to determine whether self-expanding metal stent (SEMS) placement is associated with molecular or pathological features of colorectal carcinoma tissues. As a result, SEMS placement was significantly associated with venous invasion (P < 0.01), but not with the other features examined, including tumor size, disease stage, mutation status, and lymphatic invasion. In both the univariable and multivariable models with adjustment for potential factors including tumor location, histological type, and American Joint Committee on Cancer-pT stage, SEMS placement was significantly associated with severe venous invasion (P < 0.01). For the outcome category of severe venous invasion, the multivariable odds ratio for SEMS placement relative to transanal tube placement was 19.4 (95% confidence interval: 5.24–96.2).

INTRODUCTION

Colorectal cancer is the third most common cancer in both men and women worldwide[1]. Despite remarkable advances in conventional multidisciplinary therapies for colorectal cancer, including surgery[2], radiotherapy, chemotherapy, and immunotherapy, improvements in clinical outcomes have been limited. Further developments of innovative treatment strategies are aggressively being sought, especially for colorectal cancer with complications, such as obstruction, perforation, and hemorrhage [3]. A considerable number of colorectal cancer patients present with a colonic obstruction, and the incidence is reported as high as 30%[4]. As colonic obstruction might endanger the life of patients, emergent decompression is urgently required. Emergency surgery might be associated with increased morbidity, mortality, stoma rate, and oncological suboptimal resection[4-6]. Therefore, a bridge to surgery approach could be a reasonable treatment strategy to allow for one-stage, or elective resection for obstructive colorectal cancer patients[7].

Self-expanding metal stents (SEMSs) have been used worldwide to rescue intestinal obstruction caused by colorectal cancer as well as benign diseases. Accumulating evidence suggests that SEMS placement results in marked advantages in short-term outcomes including the primary anastomosis rate, postoperative complications, and hospital stay after elective surgery because of patients' good general condition and adequate bowel preparation before surgery[8-11]. SEMSs might have a critical role of serving as a bridge to surgery for resectable colorectal carcinomas. Despite the efficacy and feasibility of SEMS placement in patients with obstructive colorectal cancer, there are several clinical concerns regarding SEMS placement. One of the major concerns is the risk of worse molecular or pathological malignancy by mechanical damage and pressure to the primary tumor by SEMS placement. In an *in vivo* experiment, peritoneal carcinomatosis and liver metastasis were more frequently observed in the stent group[12]. Additionally, human studies have indicated increased numbers of circulating tumor cells after SEMS placement but not after transanal decompression tube placement[13-15]. Based this evidence, we hypothesized that SEMS placement is associated with molecular or pathological malignancy in colorectal carcinoma tissues.

To test this hypothesis, we used a nonbiased molecular pathological epidemiology database of patients with obstructive colorectal cancer, and examined the molecular and pathological features of tumor tissue according to the decompression methods. Unlike previous studies[16,17], we first diagnosed lymphatic invasion (absent, minimal, moderate, or severe) and venous invasion (absent, minimal, moderate, or severe) in detail based on the Japanese Classification of Colorectal Carcinoma [18], and investigated the association between SEMS placement and molecular or pathological malignancy. We argue that the use of transdisciplinary integrated analyses to obtain a better understanding of the interaction between the decompression technique and tumor tissue characteristics will significantly help in the development of new treatment strategies for obstructive colorectal cancer.

MATERIALS AND METHODS

Study population

This study included 102 consecutive patients with obstructive colorectal cancer who underwent emergent colonic decompression at the National Hospital Organization Kumamoto Medical Center from July 2012 to December 2020. The main inclusion criteria were an age of > 18 years, histological confirmation of colorectal adenocarcinoma before or after the operation, no other active malignancy, and performance of emergent colonic decompression followed by surgery. The exclusion criteria were neoadjuvant chemotherapy and/or radiotherapy, perforation, peritonitis. The decompression method for each case was determined by tumor board. SEMS or transanal decompression tube placement was performed under both endoscopic and fluoroscopic guidance for obstructive colorectal cancer (CROSS scale 0, 1, or 2)[19]. Patients underwent cleansing enema for bowel preparation and received analgesia and sedation. The stent size and length were chosen according to the measured length of the obstruction. Tumor staging was performed according to the American Joint Committee on Cancer (AJCC) TNM classification (7th edition)[20]. Two institutional pathologists diagnosed histopathological differentiation (well, moderate, or others), lymphatic invasion (absent, minimal, moderate, or severe), and venous invasion (absent, minimal, moderate, or severe) based on the Japanese Classification of Colorectal Carcinoma[18]. Postoperative complications were recorded and graded as defined by the Clavien–Dindo classification system[21]. The term "prognostic marker'' is used throughout this article according to the REMARK Guidelines[22].

This study was approved by the Human Ethics Review Committee of the National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan (institutional ethics committee number: 1061). The requirement for written informed consent was waived in view of the retrospective nature of the study.

Statistical analysis

All statistical analyses were conducted using the JMP program (version 10, SAS Institute, Cary, NC, United States). All P values were two-sided, and the two-sided α level of 0.05 was used for all testing.

Our primary analysis (hypothesis testing) involved examination of the associations of the decompression method used (SEMS *vs* transanal tube; as a predictor variable) with lymphatic invasion and venous invasion. All other analyses, including assessments of odds ratios (ORs), represented secondary analyses. We performed multivariable logistic regression analyses to control for potential confounders. The multivariable logistic regression model included variables showing a univariable association ($P < 0.05$) with lymphatic invasion or venous invasion from the decompression method (transanal tube *vs* SEMS), age (continuous), sex (female *vs* male), tumor location (cecum to transverse colon *vs* descending to sigmoid colon *vs* rectum), waiting period (continuous), tumor size (continuous), histological type (well differentiated *vs* moderately differentiated *vs* others), AJCC-pT (T2/T3 *vs* T4), and mutation (absent *vs* present).

To compare characteristics across strata of decompression methods, we used the chi-square test for categorical variables, and an analysis of variance, assuming equal variances for continuous variables. Each of the cross-sectional analyses was secondary.

Overall survival was defined as the time between the operation date and the date of death. Disease-free survival was defined as the time between the operation date and the date of recurrence. The survival time distributions were determined by the Kaplan–Meier method using a log-rank test.

RESULTS

Decompression methods and clinical, pathological, and molecular characteristics

Among the 102 patients with obstructive colorectal cancer in the nonbiased independent database, 53% were women and the median age was 72.6 years. The most frequent tumor location was descending to sigmoid colon (65 patients, 64%), followed by the rectum (21 patients, 21%) and cecum to transverse colon (16 patients, 16%). Table 1 summarizes the clinical, pathological, and molecular features of the

Table 1 Clinical and pathological features of patients with colorectal cancer according to decompression methods

Characteristic[1]	All cases (*n* = 102)	Decompression methods		*P* value[2]
		Transanal tube (*n* = 76)	SEMS (*n* = 26)	
Sex, *n* (%)				0.91
Female	54 (53)	40 (53)	14 (54)	
Male	48 (47)	36 (47)	12 (46)	
Age, mean ± SD (years)	72.6 ± 12.5	71.7 ± 12.9	75.1 ± 11.1	0.24
Tumor location, *n* (%)				0.24
Cecum to transverse colon	16 (16)	13 (17)	3 (12)	
Descending to sigmoid colon	65 (64)	45 (59)	20 (77)	
Rectum	21 (21)	18 (24)	3 (12)	
Tumor size, mean ± SD (mm)	40.7 ± 16.2	39.0 ± 14.9	45.4 ± 19.3	0.086
Time from decompression to operation, mean ± SD (days)	13.6 ± 12.9	12.0 ± 7.6	18.2 ± 21.7	0.035
Histological type, *n* (%)				0.35
Well	29 (28)	19 (25)	10 (38)	
Moderate	67 (66)	53 (70)	14 (54)	
Mucinous, poor, or signet-ring cell	6 (5.9)	4 (5.3)	2 (7.7)	
T stage (depth of tumor invasion), *n* (%)				0.57
T1 (submucosa)	-	-	-	
T2 (muscularis propria)	1 (1.0)	-	1 (3.9)	
T3 (subserosa)	67 (66)	54 (71)	13 (50)	
T4 (serosa or other organs)	34 (33)	22 (29)	12 (46)	
N stage (number of positive lymph nodes), *n* (%)				0.54
N0 (0)	49 (48)	36 (47)	13 (50)	
N1 (1-3)	39 (38)	28 (37)	11 (42)	
N2 (4-)	14 (14)	12 (16)	2 (7.7)	
AJCC disease stage, *n* (%)				0.40
I	1 (1.0)	-	1 (3.9)	
II	42 (41)	31 (41)	11 (42)	
III	36 (35)	27 (36)	9 (35)	
IV	23 (23)	18 (24)	5 (19)	
Mutation status, *n* (%)				0.51
KRAS mutated	34 (43)	26 (47)	8 (33)	
NRAS mutated	3 (3.8)	2 (3.6)	1 (4.2)	
BRAF mutated	0 (0)	0 (0)	0 (0)	
Absent	42 (53)	27 (49)	15 (63)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.
[2]We used the chi-square test to compare categorical variables and analysis of variance to compare continuous variables. We adjusted the two-sided α level to 0.05.
AJCC: American Joint Committee on Cancer; SEMS: Self-expanding metal stent.

patients stratified according to decompression methods. Seventy-six (75%) patients underwent transanal tube placement, and 26 (25%) patients underwent SEMS placement. SEMS placement was significantly associated with a longer time between decompression and surgery (*P* = 0.035), but not with the other features examined, including tumor size, disease stage, and mutation status (all *P* > 0.08).

Table 2 summarizes the perioperative features of the patients stratified according to decompression methods. SEMS placement was significantly associated with a higher chance of reconstruction (*P* = 0.011), but not with the other features examined, including operation method, procedure, lymph node dissection, and short-term outcomes (all *P* > 0.07).

Decompression methods and lymphatic or venous invasion

Table 3 shows the distribution of patients according to the decompression methods and lymphatic invasion or venous invasion. SEMS placement was significantly associated with severe venous invasion (*P* < 0.0001). Table 4 shows the distribution of colorectal cancer cases according to decompression methods (transanal tube *vs* SEMS) and lymphatic or venous invasion in strata of AJCC-pT stage or tumor location. A similar association of SEMS placement with severe venous invasion was observed (*P* < 0.11).

Logistic regression analyses between decompression methods and venous invasion

To test our primary hypothesis, we used a logistic regression analysis to assess the association of the decompression method (SEMS *vs* transanal tube) with the degree of venous invasion (Table 5). In both the univariable and multivariable models, SEMS placement was significantly associated with severe venous invasion (*P* < 0.0001). For the outcome category of venous invasion, the univariable OR was 20.9 [95% confidence interval (CI): 5.78–101] for SEMS placement relative to transanal tube placement, and the multivariable OR was 19.4 (95%CI: 5.24–96.2). Similar findings were observed in the sensitivity analyses, in which we performed a multivariable analysis with adjustment for potential factors including tumor location, histological type, and AJCC-pT stage (multivariable OR: 36.7; 95%CI: 7.89–259; *P* < 0.0001). AJCC-pT was significantly associated with severe venous invasion in only the univariable model (*P* = 0.021), and the univariable OR was 3.72 (95%CI: 1.22–12.2) for AJCC-pT4 relative to AJCC-pT2/T3.

Among SEMS group, the waiting period for surgery did not have any association with venous invasion. For the outcome category of venous invasion, the univariable OR was 0.86 (95%CI: 0.46–1.14; *P* = 0.32) for waiting period (for 1-wk increment).

Exploratory analyses for the influence of stent diameter on lymphatic and venous invasion

As an exploratory analysis, we determined the influence of stent diameter on lymphatic and venous invasion (Table 6). A larger stent was significantly associated with venous invasion (*P* < 0.0001), and was possibly associated with lymphatic invasion (*P* = 0.055).

Decompression methods and long-term survival

As exploratory analyses, a Kaplan-Meier analysis was conducted to assess the influence of SEMS placement on long-term survival. No significant differences of disease-free survival and overall survival were observed (*P* = 0.56 for disease-free survival, *P* = 0.60 for overall survival).

DISCUSSION

Evidence indicates marked advantages in short-term outcomes by SEMS placement in patients with obstructive colorectal cancer because of these patients' good general condition and adequate bowel preparation before surgery[8,9]. Notably, other emerging evidence points to a link between SEMS placement and an increase in the number of circulating tumor cells by mechanical damage and pressure to the primary tumor[12-15]. However, the associations of SEMS placement with the molecular and pathological features of colorectal carcinoma tissues remain to be elucidated. The present study was performed to test the hypothesis that SEMS placement is associated with molecular or pathological malignancy in colorectal carcinoma tissues. We used a nonbiased molecular pathological epidemiology database of patients with obstructive colorectal cancer, and showed for the first time that SEMS placement is independently associated with severe venous invasion in colorectal cancer tissue. Although no significant differences of prognoses were observed, our findings suggest a possible influence of SEMS placement on pathological findings.

A growing body of evidence highlights associations between SEMS placement and short-term clinical outcomes among patients with obstructive colorectal cancer. A systematic review of randomized controlled trials showed that 81% of SEMS placements were technically successful, with 76% of patients achieving restoration of gastrointestinal function[23]. Additionally, a meta-analysis showed that SEMS placement helped to maintain quality of life by allowing food intake and temporal discharge, promoted laparoscopic one-stage surgery without stoma creation, and had morbidity and mortality rates equivalent to those of transanal decompression tube placement[9]. SEMS placement might decrease the rate of permanent stomas, especially in elderly patients[8]. Emerging evidence indicates the safety and feasibility of minimally invasive surgery combined with stent insertion for malignant colonic obstruction[24]. Collectively, colonic stenting followed by laparoscopy is safe and effective with high success rates and low complication rates. However, several points remain to be investigated, such as

Table 2 Perioperative features of patients with colorectal cancer according to decompression methods

Characteristic[1]	All cases (*n* = 102)	Decompression methods		P value[2]
		Transanal tube (*n* = 76)	SEMS (*n* = 26)	
Operation method, *n* (%)				0.31
Open	54 (53)	38 (50)	16 (62)	
Laparoscopy	48 (47)	38 (50)	10 (38)	
Conversion to laparotomy, *n* (%)				0.072
Absent	47 (98)	38 (100)	9 (90)	
Present	1 (2.1)	-	1 (10)	
Procedure, *n* (%)				0.17
Colectomy	58 (57)	44 (58)	14 (54)	
Anterior resection	37 (36)	25 (33)	12 (46)	
Hartmann procedure	5 (4.9)	5 (6.6)	-	
Abdominoperineal resection (Miles' operation)	2 (2.0)	2 (2.6)	-	
Lymph node dissection, *n* (%)				0.35
D1	3 (2.9)	3 (4.0)	-	
D2	10 (9.8)	8 (11)	2 (7.7)	
D3	89 (87)	65 (86)	24 (92)	
Reconstruction (except 2 abdominoperineal resection cases), *n* (%)				0.011
Absent	10 (10)	10 (14)	-	
Present	90 (90)	64 (86)	26 (100)	
Number of harvested lymph nodes, mean ± SD	21.6 ± 12.0	21.5 ± 11.8	21.7 ± 12.6	0.97
Operation time, mean ± SD (min)	241 ± 80	234 ± 79	263 ± 79	0.12
Blood loss, mean ± SD (g)	224 ± 364	229 ± 375	212 ± 336	0.84
Clavien-Dindo classification, *n* (%)				0.22
0	78 (76)	58 (76)	20 (77)	
1	5 (4.9)	5 (6.6)	-	
2	11 (11)	8 (11)	3 (12)	
3	7 (7.7)	5 (6.6)	2 (7.7)	
4	-	-	-	
5	1 (1.0)	-	1 (3.9)	
Postoperative hospitalization, mean ± SD (days)	18.8 ± 15.1	19.3 ± 17.0	17.2 ± 6.7	0.53
Postoperative chemotherapy, *n* (%)				0.36
Absent	51 (50)	36 (47)	15 (58)	
Present	51 (50)	40 (53)	11 (42)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.

[2]We used the chi-square test to compare categorical variables and analysis of variance to compare continuous variables. We adjusted the two-sided α level to 0.05.

SEMS: Self-expanding metal stent.

postoperative chemotherapy[25], the SEMS-related perforation rate (5.0%–8.9%)[8,23,26], perforation-related recurrence[26], the SEMS diameter[27], and the optimal timing from stent placement to surgery [28,29].

Long-term survival of patients with complicated colorectal cancer remains poor despite advances in surgical techniques. Additionally, how SEMS placement impacts long-term survival compared with

Table 3 Pathological features of patients with colorectal cancer according to decompression methods

| Characteristic[1] | All cases (*n* = 102) | Decompression methods | | P value[2,3] |
		Transanal tube (*n* = 76)	SEMS (*n* = 26)	
Lymphatic invasion, *n* (%)				0.12 (0.020)
Absent	11 (11)	10 (13)	1 (3.9)	
Minimal	41 (40)	33 (43)	8 (31)	
Moderate	32 (31)	23 (30)	9 (35)	
Severe	18 (18)	10 (13)	8 (31)	
Venous invasion, *n* (%)				< 0.0001 (0.0002)
Absent	19 (19)	17 (22)	2 (7.7)	
Minimal	45 (44)	37 (49)	8 (31)	
Moderate	23 (23)	19 (25)	4 (15)	
Severe	15 (15)	3 (4.0)	12 (46)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.

[2]We used the chi-square test to compare as categorical variables. We adjusted the two-sided α level to 0.05.

[3]We used the Mann-Whitney U test to compare as nonparametric continuous variables. We adjusted the two-sided α level to 0.05.

SEMS: Self-expanding metal stent.

other procedures, including diverting stomas, transanal tubes, and emergency surgery, remains controversial. A retrospective single- or multicenter observational study and two meta-analyses showed no significant difference in long-term survival between the SEMS group and emergency surgery group among patients with obstructive left-sided colorectal cancer[30-33]. Additionally, one randomized controlled trial showed no prognostic difference between the two groups[34]. One retrospective observational study revealed no significant differences in long-term outcomes between patients with obstructive colorectal cancer who underwent SEMS placement and transanal decompression tube placement as a bridge to surgery[35]. In the current study, no significant differences of disease-free survival and overall survival were observed between SEMS and transanal tube groups. A national, population-based cohort study using propensity score matching suggested that SEMS placement has intermediate-term oncologic outcomes similar to those of a decompressing stoma as a bridge to resection of left-sided obstructive colon cancer[36]. While, a French surgical association multicenter cohort study utilizing a propensity score analysis suggested that SEMS placement might be associated with a worse prognosis than a diverting stoma or immediate surgery for obstructive left-sided colorectal cancer[37,38]. The CODOMO study showed that transanal decompression tube placement might be associated with a worse prognosis than surgery for obstructive left-sided colorectal cancer[30]. For obstructive right-sided colorectal cancer, another population-based observational study demonstrated that the prognosis was significantly better in the decompression tube group than in the SEMS group [39]. SEMS-related perforation or an increased bridging interval to surgery might be a significant risk factor for systemic recurrence[26,29]. With respect to operation methods, laparoscopic surgery after stent placement for obstructive colon cancer might be performed safely with long-term outcomes comparable with those of open surgery[40]. The diameter of the colonic stent might not impact long-term survival[27]. Further research is warranted to investigate the prognostic role of SEMS placement in obstructive colorectal cancer compared with other procedures.

Dissemination of tumor cells has been a major concern in patients who undergo SEMS placement for obstructive colorectal cancer, and several experimental studies have focused on circulating tumor cells in the bloodstream. In 2007, an increase in the level of CK20 mRNA in the peripheral circulation was confirmed after endoscopic colonic stent insertion in patients with colorectal cancer[41]. In an *in vivo* study using a mouse model, peritoneal carcinomatosis and liver metastasis were more frequently observed in the stent group[12]. Moreover, in patients with obstructive colorectal cancer, the plasma levels of cell-free DNA and circulating tumor DNA increased after SEMS placement but not after transanal decompression tube placement; this suggests an oncological risk of SEMS placement in terms of molecular analysis[13-15]. The no-touch isolation technique, which was first proposed in 1952[42], gives first priority to central vascular ligation followed by mobilization of the tumor-bearing segment of the colon. This technique might reduce the spread of circulating tumor cells from the primary tumor site to other organs by ligation of blood vessels first. One retrospective study showed prognostic improvement by the no-touch isolation technique[43], but a large-scale randomized controlled trial failed to confirm the superiority of the no-touch isolation technique in patients with colorectal cancer [44]. In the current study, we found an association of SEMS placement with high severe invasion, but we

Table 4 Pathological features of patients with colorectal cancer according to decompression methods in strata of American Joint Committee on Cancer-pT stage or tumor location

Characteristic[1]	All cases (*n* = 102)	Decompression methods		*P* value[2,3]
		Transanal tube (*n* = 76)	SEMS (*n* = 26)	
Lymphatic invasion				
AJCC-pT2/T3 cases, *n* (%)				0.024 (0.036)
Absent	8 (12)	8 (15)	-	
Minimal	31 (46)	25 (46)	6 (43)	
Moderate	20 (29)	17 (31)	3 (21)	
Severe	9 (13)	4 (7.4)	5 (36)	
AJCC-pT4 cases, *n* (%)				0.53 (0.56)
Absent	3 (8.8)	2 (9.1)	1 (8.3)	
Minimal	10 (29)	8 (36)	2 (17)	
Moderate	12 (35)	6 (27)	6 (50)	
Severe	9 (26)	6 (27)	3 (25)	
Venous invasion				
AJCC-pT2/T3 cases, *n* (%)				0.0031 (0.0025)
Absent	13 (19)	12 (22)	1 (7.1)	
Minimal	37 (54)	32 (59)	5 (36)	
Moderate	12 (18)	9 (17)	3 (21)	
Severe	6 (8.8)	1 (1.9)	5 (36)	
AJCC-pT4 cases, *n* (%)				0.0077 (0.042)
Absent	6 (18)	5 (23)	1 (8.3)	
Minimal	8 (24)	5 (23)	3 (25)	
Moderate	11 (32)	10 (45)	1 (8.3)	
Severe	9 (26)	2 (9.1)	7 (58)	
Lymphatic invasion				
Cecum to transverse colon cases, *n* (%)				0.21 (0.088)
Absent	3 (19)	3 (23)	-	
Minimal	7 (44)	6 (46)	1 (33)	
Moderate	4 (25)	4 (31)	-	
Severe	2 (13)	-	2 (67)	
Descending to rectum, *n* (%)				0.40 (0.096)
Absent	8 (9.3)	7 (11)	1 (4.4)	
Minimal	34 (40)	27 (43)	7 (30)	
Moderate	28 (33)	19 (30)	9 (39)	
Severe	16 (19)	10 (16)	6 (26)	
Venous invasion				
Cecum to transverse colon cases, *n* (%)				0.10 (0.078)
Absent	5 (31)	5 (38)	-	
Minimal	6 (38)	5 (38)	1 (33)	
Moderate	2 (13)	2 (15)	-	
Severe	3 (19)	1 (7.7)	2 (67)	

Descending to rectum, *n* (%)				0.0001 (0.0012)
Absent	14 (16)	12 (19)	2 (8.7)	
Minimal	39 (45)	32 (51)	7 (30)	
Moderate	21 (24)	17 (27)	4 (17)	
Severe	12 (14)	2 (3.2)	10 (43)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.

[2]We used the chi-square test to compare as categorical variables. We adjusted the two-sided α level to 0.05.

[3]We used the Mann-Whitney U test to compare as nonparametric continuous variables. We adjusted the two-sided α level to 0.05.

AJCC: American Joint Committee on Cancer; SEMS: Self-expanding metal stent.

Table 5 Logistic regression analyses to assess the association of decompression method (predictor) with severe venous invasion (outcome)

Model for severe venous invasion (*n* = 102, as a binary outcome variable)	Univariable		Multivariable[1]		Multivariable[2]	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Decompression methods						
Transanal tube	1 (reference)	< 0.0001	1 (reference)	< 0.0001	1 (reference)	< 0.0001
SEMS	20.9 (5.78-101)		19.4 (5.24-96.2)		36.7 (7.89-259)	
Age (for 10-yr increment)	1.29 (0.82-2.20)	0.28				
Sex						
Female	1 (reference)	0.60				
Male	1.34 (0.44-4.14)					
Tumor location						
Cecum to transverse colon	1 (reference)	0.27			1 (reference)	0.27
Descending to sigmoid colon	0.88 (0.23-4.31)				0.38 (0.05-2.60)	
Rectum	0.22 (0.01-1.90)				0.11 (0.003-1.58)	
Waiting period (for 1-wk increment)	0.91 (0.47-1.22)	0.64				
Tumor size (for 10-mm increment)	1.10 (0.78-1.49)	0.55				
Histological type						
Well	1 (reference)	0.21			1 (reference)	0.065
Moderate	2.65 (0.65-17.9)				7.27 (1.27-64.5)	
Mucinous, poor, or signet-ring cell	6.75 (0.66-72.0)				10.7 (0.48-342)	
AJCC-pT						
T2/T3	1 (reference)	0.021	1 (reference)	0.084	1 (reference)	0.082
T4	3.72 (1.22-12.2)		3.17 (0.86-12.6)		3.76 (0.85-19.4)	
Mutation						
Absent	1 (reference)	0.81				
Present (*KRAS, NRAS*)	1.16 (0.33-4.07)					

[1]The multivariable logistic regression model included the decompression method (transanal tube *vs* SEMS), and AJCC-pT (T2/T3 *vs* T4).

[2]The multivariable logistic regression model included the decompression method (transanal tube *vs* SEMS), tumor location (cecum to transverse colon *vs* descending to sigmoid colon *vs* rectum), histological type (well-differentiated vs. moderately differentiated *vs* others), and AJCC-pT (T2/T3 *vs* T4).

AJCC: American Joint Committee on Cancer; CI: Confidence interval; OR: Odds ratio; SEMS: Self-expanding metal stent.

observed no significant differences of long-term survivals between two groups. Our findings need to be confirmed in future multicenter studies with a larger cohort.

Table 6 Pathological features of patients with colorectal cancer according to decompression methods (transanal tube *vs* 18-mm stent *vs* 22-mm stent)

Characteristic[1]	All cases (*n* = 102)	Decompression methods			*P* value[2,3]
		Transanal tube (*n* = 76)	18 mm stent (*n* = 11)	22 mm stent (*n* = 15)	
Lymphatic invasion, *n* (%)					0.055 (0.0060)
Absent	11 (11)	10 (13)	1 (9.1)	-	
Minimal	41 (40)	33 (43)	5 (45)	3 (20)	
Moderate	32 (31)	23 (30)	4 (36)	5 (33)	
Severe	18 (18)	10 (13)	1 (9.1)	7 (47)	
Venous invasion, *n* (%)					< 0.0001 (0.0006)
Absent	19 (19)	17 (22)	2 (18)	-	
Minimal	45 (44)	37 (49)	3 (27)	5 (33)	
Moderate	23 (23)	19 (25)	1 (9.1)	3 (20)	
Severe	15 (15)	3(4.0)	5 (45)	7 (47)	

[1]Percentage indicates the proportion of patients with a specific clinical characteristic among all patients or in strata of decompression methods.

[2]We used the chi-square test to compare as categorical variables. We adjusted the two-sided α level to 0.05.

[3]We used the Mann-Whitney U test to compare as nonparametric continuous variables. We adjusted the two-sided α level to 0.05.

We acknowledge several limitations in our study. First, the sample size was small, and this was a retrospective observational study at a single center. However, our findings are quite significant despite of small sample size. Because the optimal treatment strategy for obstructive colorectal cancer has not been established, our findings should be verified with a larger cohort in a multi-institutional study. Second, the current study was cross-sectional in nature, and the exact mechanisms that underlie the relationship between SEMS placement and severe venous invasion remain uncertain. Our hypothesis was based on several lines of experimental and population-based evidence indicating that mechanical damage and pressure to the primary tumor by SEMS placement increase venous invasion. Comparison of the pathological features between before and after SEMS placement is quite challenging, and the current study which considered the tumor stage and molecular and pathological features must be valuable. Third, we did not investigate the relationship between venous invasion and circulating tumor cells in the bloodstream. Fourth, the pathological findings including the degree of venous invasion were diagnosed based on the Japanese Classification of Colorectal Carcinoma by two pathologists[18], but the diagnosis is assessed by subjective methods. That is another limitation. Future studies are needed to confirm our findings and examine the association of SEMS placement with molecular and pathological features and long-term survival of patients with obstructive colorectal cancer.

A major strength of our study is that it used a molecular pathological epidemiology[45,46] database of patients with colorectal cancer, forming an independent cohort. This database integrates epidemiologic data, clinicopathologic features, and tumor molecular features including the *KRAS*, *BRAF*, or *NRAS* mutation status in colorectal cancer tissue. Our multidisciplinary integrated study based on this human-population colorectal cancer database enabled us to rigorously investigate the association of SEMS placement with the molecular and pathological features of colorectal cancer tissues; we utilized multivariable logistic regression models after controlling for multiple potential confounders such as disease stage, tumor location, and tumor molecular features.

CONCLUSION

In conclusion, we have herein shown that SEMS placement might be associated with severe venous invasion in colorectal cancer tissue, providing an impetus for further investigation of the potential interactive roles of SEMS placement and pathological alterations in colorectal cancer tissues. Validation of our findings may provide insights for further investigations on strategies for obstructive colorectal cancer.

ARTICLE HIGHLIGHTS

Research background

Experimental studies suggest that self-expanding metal stents (SEMSs) enhance the aggressive behavior of obstructive colorectal cancer.

Research motivation

The influence of SEMS placement on pathological alterations remains to be elucidated.

Research objectives

This study aimed to determine whether SEMS placement is associated with molecular or pathological features of colorectal carcinoma tissues.

Research methods

Using a nonbiased molecular pathological epidemiology database of patients with obstructive colorectal cancers, we examined the association of SEMS placement with molecular or pathological feature.

Research results

SEMS placement was significantly associated with venous invasion ($P < 0.01$), but not with the other features examined, including tumor size, disease stage, mutation status, and lymphatic invasion. In both the univariable and mult-ivariable models with adjustment for potential factors including tumor location, histological type, and American Joint Committee on Cancer-pT stage, SEMS placement was significantly associated with severe venous invasion ($P < 0.01$).

Research conclusions

SEMS placement might be associated with severe venous invasion in colorectal cancer tissue.

Research perspectives

Future studies are needed to confirm our findings and examine the association of SEMS placement with pathological features and long-term survival of patients with obstructive colorectal cancer.

FOOTNOTES

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