



# Oncologic investigation of the interval from stent placement to surgery in patients with obstructive colorectal cancer

Shintaro Kanaka<sup>1</sup> · Akihisa Matsuda<sup>1</sup> · Takeshi Yamada<sup>1</sup> · Yasuyuki Yokoyama<sup>1,2</sup> · Satoshi Matsumoto<sup>3</sup> · Goro Takahashi<sup>1</sup> · Hiromichi Sonoda<sup>1</sup> · Ryo Ohta<sup>2</sup> · Kay Uehara<sup>1</sup> · Seiichi Shinji<sup>1</sup> · Takuma Iwai<sup>1</sup> · Kohki Takeda<sup>1</sup> · Kumiko Sekiguchi<sup>2</sup> · Sho Kuriyama<sup>1</sup> · Toshimitsu Miyasaka<sup>1</sup> · Hiroshi Yoshida<sup>1</sup>

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## Abstract

**Purpose** Self-expandable metallic stent (SEMS) placement is widely used as a bridge to surgery (BTS) procedure for obstructive colorectal cancer. However, evidence regarding the optimal interval between SEMS placement and elective surgery is lacking.

**Methods** We retrospectively collected data from patients with BTS between January 2013 and October 2021. Inverse probability treatment-weighted propensity score analyses were used to compare short- and long-term outcomes between the short-interval (SI) and long-interval (LI) groups, using a cutoff of 20 days.

**Results** In total, 138 patients were enrolled in this study (SI group,  $n=63$ ; LI group,  $n=75$ ). In the matched cohort, the patients' backgrounds were well balanced. The incidence of Clavien–Dindo grade  $\geq$  II postoperative complications was not significantly different between the SI and LI groups (19.0% vs. 14.0%,  $P=0.47$ ). There were no significant differences between the SI and LI groups in the 3-year recurrence-free survival (68.0% vs. 76.4%,  $P=0.73$ ) or 3-year overall survival rates (86.0% vs. 90.6%,  $P=0.72$ ).

**Conclusions** A longer interval did not deteriorate the oncological outcomes. Individual perioperative management with an appropriate interval to improve the patient's condition is required to ensure safe surgery.

**Keywords** Colorectal cancer · Stent · Surgery · Interval · Survival

## Introduction

Obstructive colorectal cancer (OCRC) accounts for 8–34% of colorectal cancer (CRC) [1–3]. Although these conditions require immediate intervention, emergency one-stage

resection for OCRC is associated with significantly higher mortality and morbidity rates than elective surgery [4, 5].

The placement of a self-expandable metallic stent (SEMS) as a bridge to surgery (BTS) procedure, followed by elective surgery, has been introduced as an alternative to emergency surgery [6]. While this BTS procedure has demonstrated improved short-term outcomes, such as primary anastomosis rates, stoma construction rates, and postoperative morbidity rates, its effects on long-term outcomes remain unclarified [7–11].

The BTS strategy for left-sided OCRC was recently recommended in the updated version of the guidelines from the European Society of Gastrointestinal Endoscopy (ESGE) in 2020 [12]. The ESGE guidelines recommend an interval of approximately 2 weeks between SEMS placement and surgery; however, the level of evidence for this recommendation is low [12]. A longer interval is reported to contribute to decreased postoperative complications owing to better intestinal decompression and improvement of the patients'

Shintaro Kanaka and Akihisa Matsuda contributed equally to this work.

✉ Akihisa Matsuda  
a-matsu@nms.ac.jp

- <sup>1</sup> Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-Ku, Tokyo 113-8603, Japan
- <sup>2</sup> Department of Digestive Surgery, Nippon Medical School Musashikosugi Hospital, 1-383 Kosugi-Cho, Nakahara-Ku, Kawasaki, Kanagawa 211-8533, Japan
- <sup>3</sup> Department of Surgery, Nippon Medical School Chiba Hokusoh Hospital, 1715 Kamagari, Inzai, Chiba 270-1694, Japan

general condition [13–16]. In contrast, some studies have warned that a longer interval is associated with the deterioration of long-term outcomes [17–19]. However, few studies have investigated the optimal BTS interval in terms of short- and long-term outcomes, and no definitive conclusions have been reached.

The present study investigated the association between the interval between SEMS placement and surgery and long-term outcomes in patients with OCRC. The primary endpoints were the 3-year recurrence-free survival (RFS) and 3-year overall survival (OS) rates, and the secondary endpoint was the postoperative complication rate.

## Materials and methods

This multicenter, retrospective study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Review Committee of Nippon Medical School (approval number: R1-07-1107). The requirement for written informed consent was waived owing to the retrospective nature of this study.

## Patients and protocol

We retrospectively collected and analyzed the data of patients who underwent curative tumor resection for OCRC after SEMS placement between January 2013 and October 2021 at three Departments of Surgery of Nippon Medical School Hospitals (Main, Chiba Hokusoh, and Musashikosugi). Patients were excluded if they showed signs of peritonitis, perforation, or other serious complications necessitating emergency surgery. Patients with benign disease, positive surgical margins, invasive malignancies other than primary CRC, or SEMS placement with a palliative intent were also excluded. None of the patients received neoadjuvant therapy, including chemotherapy or radiotherapy. SEMS placement was considered contraindicated in patients with rectal cancer < 5 cm from the anal verge, extremely long or multiple stenoses, or intestinal perforation. OCRC was diagnosed based on the following symptoms and findings: (1) abdominal pain, fullness, vomiting, and constipation; (2) contrast-enhanced computed tomography findings of colonic dilatation caused by obstructive primary CRC; and (3) endoscopic findings of obstructive primary colorectal tumor. The severity of obstruction was classified using the colorectal obstruction scoring system (CROSS) [20, 21]. A total of 138 patients with pathological stage (pStage) II/III/IV disease were enrolled in this study. Tumors were classified according to the American Joint Committee on Cancer TNM staging system. Nine patients diagnosed with pStage IV disease had synchronous liver metastasis or peritoneal

dissemination, which was resected simultaneously with the primary lesion.

## Endoscopic stenting procedure and perioperative management

SEMS placement was performed by endoscopists under fluoroscopic and endoscopic guidance in accordance with the mini-guidelines published on the website of the Japan Colonic Stent Safe Procedure Research Group (<http://colonstent.com/>). The implanted SEMS were the WallFlex™ colonic stent (Boston Scientific, Marlborough, MA, USA), Niti-S™ colonic stent (Taewoong Medical Inc., Gimpo-si, Korea), JENTLLY colonic stent (Japan Lifeline, Chiba, Japan), and HANAROSTENT® Naturfit colonic stent (Boston Scientific, Marlborough, MA, USA), all of which were uncovered. A guidewire was then passed through the malignant stenosis. The SEMS was deployed over the wire and through the scope without preprocedural balloon dilatation of colonic obstruction. The type, size, and diameter of the SEMS were selected by the endoscopist performing the procedure.

We defined technical and clinical success as proper placement of the SEMS and relief of obstruction without complications until elective surgery, respectively. In this study, we excluded cases of technical failure.

After SEMS insertion, improvement in the obstruction was monitored based on abdominal symptoms and abdominal radiography. If improvement of the obstruction was confirmed, oral intake of magnesium oxide agents was initiated. The baseline clinical and surgical variables and short- and long-term outcomes were retrospectively collected. The timing of elective surgery after SEMS placement was determined by a physician. The surgical approach (open or laparoscopic) and extent of resection were determined based on patient factors. The surgeon attempted to perform single-stage surgery with primary anastomosis. However, if this was not feasible, a diversion method with primary anastomosis was implemented.

## Postoperative follow-up

All patients were followed-up every 3 months during the first 2 years postoperatively and every 6 months thereafter. Tumor markers, including carcinoembryonic antigen and carbohydrate antigen 19-9, were examined at each follow-up visit, and computed tomography of the chest and abdomen was performed every 6 months. In accordance with Japanese guidelines, total colonoscopy was performed in the first and third postoperative years [22]. The basic policy of the participating institutions was that adjuvant chemotherapy should be offered to patients treated with a BTS procedure, regardless of their pStage. However, adjuvant chemotherapy was

not administered when treatment of other comorbidities was considered a priority or when chemotherapy was considered difficult owing to patient background characteristics, such as recovery from postoperative complications, a poor performance status, a poor organ function, and advanced age.

### Determination of cutoff values for the BTS interval

To compare the outcomes of short and long intervals between SEMS placement and surgery, the cutoff was defined by the operating characteristic (ROC) curve, which is the plot of sensitivity versus 1-specificity and the area under the curve [23]. Various opinions exist regarding the interval cutoff, and determining the optimal cutoff is currently difficult. Almost all previous studies investigating this clinical question set the cutoff without a scientific basis, such as the median value and division into three parts. Given that the oncological outcome was defined as the primary outcome in this study, we determined the cutoff based on the long-term outcome, defining the value using the ROC curve based on the RFS in this study. The ROC curve demonstrated that the optimal cutoff interval for RFS events was 20 days, with an area under the curve of 0.512. Although this ROC curve was close to a 45° straight line and was not statistically significant, we conducted analyses to determine the cutoff based on the RFS.

### Data analyses

Continuous data are expressed as the mean or median  $\pm$  standard deviation. Background and perioperative variables were collected from medical charts. Postoperative complications were defined as those that occurred within 30 days after surgery and were evaluated using the Clavien–Dindo (CD) classification system [24]. All statistical analyses were performed using R Commander and EZR [25], which is a modified version of R Commander. The  $\chi^2$  test was performed to compare frequencies between the groups. For continuous variables, differences between groups were compared using Student's *t* test. If the data did not show a normal distribution, the Mann–Whitney U test was used. The Kaplan–Meier method was used to estimate the OS and RFS, and the log-rank test was used to compare survival curves. Statistical significance was set at  $P < 0.05$ . Owing to the infeasibility of performing a randomized controlled trial due to the small sample size, inverse probability treatment-weighted (IPTW) propensity score analyses that mimic pseudo-randomized cohorts were used to improve the degree of comparability and reduce bias due to confounding variables between the long-interval (LI) and short-interval (SI) groups [26]. The IPTW method was used to generate a pseudo-population with well-adjusted covariate combinations between the groups, stabilizing the weights between

the participants without losing participant strength during matching [27]. This method can alleviate the overadjustment of bias toward the control group without decreasing the sample size. Considering the limited sample size of this study, we applied the IPTW method rather than conventional propensity score matching, which has the disadvantage of a considerable decrease in the sample size.

To estimate propensity scores, a multivariable logistic regression model was fitted using a generalized estimating equation model adjusted for age, sex, body mass index, American Society of Anesthesiologists physical status, Charlson Comorbidity Index score, blood transfusion before surgery, CROSS score before SEMS insertion, SEMS size, tumor location, synchronous CRC, pStage, and pathological features of the tumor, namely poor differentiation, T4 depth of invasion, lymphatic invasion, perineural invasion, and venous invasion.

Univariate and multivariate analyses using Cox proportional hazards models of variables with a *P* value of  $< 0.05$  in the univariate analysis and those previously reported to affect oncological outcomes were performed to examine the association between the selected variables and the RFS or OS.

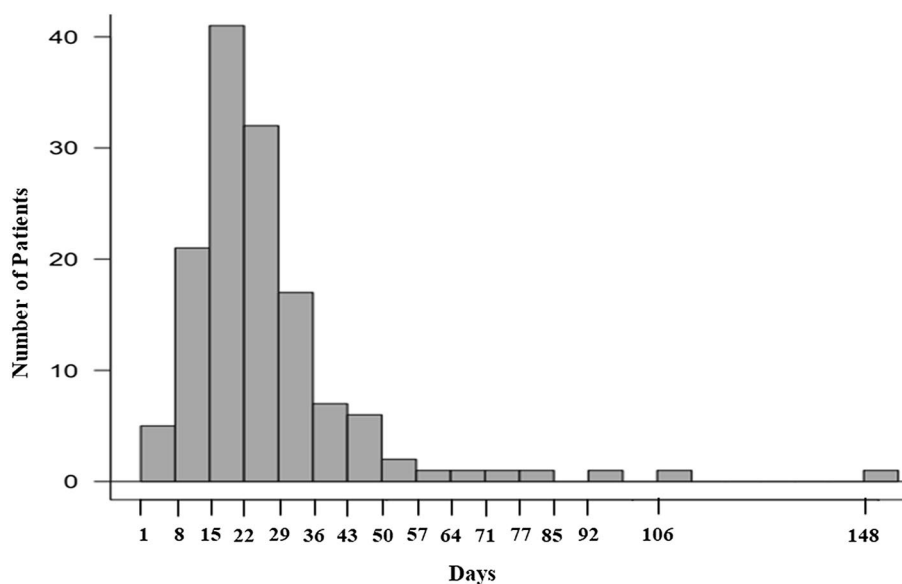
## Results

A total of 138 patients were enrolled in this study. The distribution of the interval between SEMS placement and surgery for 7 days in all included patients is shown in Fig. 1. The median interval was 15–22 (range: 1–148) days. The patients were divided into two groups: the SI group, who underwent curative surgery  $\leq 20$  days after SEMS insertion ( $n = 63$ ), and the LI group, who underwent curative surgery  $\geq 21$  days after SEMS placement ( $n = 75$ ).

The preoperative characteristics of the two groups before and after matching are presented in Table 1. There were no marked differences in the patient characteristics between the two groups after matching. The interval between SEMS placement and surgery was longer in the LI group than in the SI group ( $34.6 \pm 20.3$  days vs.  $14.4 \pm 4.0$  days,  $P < 0.01$ ). The clinical success rates of SEMS placement were 97.0% and 89.0% in the SI and LI groups, respectively ( $P = 0.15$ ). The SEMS-related complication rate was higher in the LI group than in the SI group (4.2% vs. 13.3%,  $P = 0.04$ ). Emergency surgery was performed for two patients in the SI group due to perforation and fecal impaction and for one patient in the LI group due to bleeding.

The perioperative and pathological outcomes are summarized in Table 2. All patients underwent curative resection. In the matched cohort, surgical outcomes were not significantly different between the SI and LI groups. The incidence of CD grade  $\geq$  II postoperative complications was not significantly

**Fig. 1** Histogram showing the distribution of patients by interval between self-expandable metallic stent placement and surgery for obstructive colorectal cancer



**Table 1** Patients' characteristics and preoperative outcomes

	All cohorts (n = 138)			Adjusted cohorts (n = 134.0)			SMD
	SI group (n = 63)	LI group (n = 75)	P-value	SI group (n = 60.1)	LI group (n = 73.9)	P-value	
Age (years)	71.1 ± 12.5	70.9 ± 11.2	0.94	71.6 ± 11.6	70.9 ± 11.8	0.76	0.057
Sex, M/F	39/24	48/27	0.86	39.0/21.1	46.6/27.3	0.81	0.039
BMI	21.2 ± 2.9	21.2 ± 3.3	0.92	21.0 ± 2.9	21.2 ± 3.2	0.76	0.053
ASA ≥ 3, n (%)	10 (15.6)	15 (20.0)	0.66	12.6 (20.9)	14.6 (19.7)	0.87	0.029
<i>Comorbidities</i>							
Hypertension, n (%)	19 (30.2)	33 (44.0)	0.11	21.6 (36.0)	32.7 (44.3)	0.34	0.170
Diabetes mellitus, n (%)	10 (15.9)	10 (13.3)	0.81	9.8 (16.3)	8.2 (11.0)	0.34	0.155
Dyslipidemia, n (%)	2 (3.2)	6 (8.0)	0.29	1.7 (2.7)	5.9 (7.9)	0.25	0.232
Charlson Comorbidity Index	5.2 ± 1.7	5.5 ± 1.7	0.35	5.3 ± 1.6	5.3 ± 1.6	0.80	0.043
Tumor location (right/left)	17/46	20/55	1.00	17.8/42.3	19.7/54.2	0.70	0.066
Synchronous cancer, n (%)	1 (1.6)	2 (2.7)	0.66	1.0 (1.7)	1.6 (2.1)	0.89	0.034
Preoperative blood transfusion, n (%)	1 (1.6)	9 (12.0)	0.02*	3.5 (5.8)	5.5 (7.5)	0.66	0.069
Pre-decompression CROSS score 0 or 1, n (%)	50 (79.4)	58 (77.3)	0.83	45.9 (76.3)	57.6 (78.0)	0.85	0.039
<i>SEMS outcomes</i>							
Clinical success, n (%)	60 (95.2)	68 (89.5)	0.23	58.3 (97.0)	65.7 (89.0)	0.15	0.315
Complications, n (%)	4 (6.3)	10 (13.3)	0.18	2.5 (4.2)	9.9 (13.3)	0.04*	0.327
Migration	2 (3.2)	3 (4.0)	0.80				
Re-obstruction	1 (1.6)	4 (5.3)	0.24				
Perforation	1 (1.6)	0 (0.0)	0.27				
Obstructive colitis	0 (0.0)	2 (2.7)	0.19				
Pneumatosis cystoides intestinalis	0 (0.0)	1 (1.3)	0.36				
Outside diameter of SEMS > 22 mm, n (%)	47 (74.6)	50 (66.7)	0.35	42.2 (70.2)	51.7 (70.0)	0.99	0.005
Interval until first meal (days)	2.6 ± 4.2	3.8 ± 10.2	0.40	2.5 ± 4.3	3.2 ± 8.1	0.50	0.097
Interval until surgery (days)	14.7 ± 4.2	35.9 ± 21.2	<0.01*	14.4 ± 4.0	34.6 ± 20.3	<0.01*	1.382

Values are presented as the mean ± standard deviation, number of patients, or number (percentage)

\*Statistically significant ( $P < 0.05$ )

Abbreviations: SMD standardized mean difference, BMI body mass index, ASA American Society of Anesthesiologists, SEMS self-expandable metallic stent, SI short interval ( $\leq 20$  days from SEMS placement to surgery), LI long interval ( $\geq 21$  days from SEMS placement to surgery)

**Table 2** Perioperative and pathological outcomes

	All cohorts ( <i>n</i> = 138)			Adjusted cohorts ( <i>n</i> = 134.0)			SMD
	SI group ( <i>n</i> = 63)	LI group ( <i>n</i> = 75)	<i>P</i> -value	SI group ( <i>n</i> = 60.1)	LI group ( <i>n</i> = 73.9)	<i>P</i> -value	
Laparoscopic surgery, <i>n</i> (%)	48 (76.2)	64 (85.3)	0.20	45.7 (76.0)	63.7 (86.2)	0.15	0.263
D3 lymphadenectomy, <i>n</i> (%)	55 (87.3)	71 (94.7)	0.14	50.9 (84.6)	70.0 (94.7)	0.06	0.337
Operation time (min)	242.7 ± 100.6	259.3 ± 85.1	0.34	245.7 ± 98.1	257.3 ± 86.6	0.49	0.126
Blood loss (ml)	132.1 ± 164.7	69.6 ± 124.9	0.03*	136.6 ± 175.5	74.0 ± 133.3	0.07	0.402
Combined resection, <i>n</i> (%)	5 (7.9)	9 (12.0)	0.57	5.0 (8.3)	6.9 (9.4)	0.82	0.039
Number of harvested lymph nodes	22.8 ± 10.8	26.4 ± 13.1	0.048*	23.0 ± 10.3	26.3 ± 12.3	0.09	0.288
Primary anastomosis, <i>n</i> (%)	60 (95.2)	70 (93.3)	0.73	57.1 (94.9)	69.3 (93.8)	0.90	0.050
Stoma construction, <i>n</i> (%)	7 (11.1)	9 (12.0)	1.00	5.8 (9.6)	8.1 (11.0)	0.86	0.048
Postoperative complications (CD ≥ II), <i>n</i> (%)	14 (22.2)	12 (16.0)	0.39	11.4 (19.0)	10.3 (14.0)	0.47	0.136
Postoperative complications (any)							
Anastomotic leakage, <i>n</i> (%)	3 (4.8)	2 (2.7)	0.66	1.9 (3.2)	1.4 (1.9)	0.45	0.085
Wound infection, <i>n</i> (%)	5 (7.9)	5 (6.7)	1.00	2.2 (3.6)	4.3 (5.8)	0.55	0.105
Ileus, <i>n</i> (%)	9 (14.3)	10 (13.3)	1.00	8.9 (14.7)	8.0 (10.8)	0.47	0.117
30-day mortality, <i>n</i> (%)	0 (0.0)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00	
<i>Pathological findings</i>							
Pathological stage, <i>n</i> (%)			0.63			0.92	0.084
II	22 (34.9)	32 (42.7)		21.8 (36.3)	27.8 (37.7)		
III	37 (58.7)	38 (50.7)		34.8 (57.8)	42.6 (57.6)		
IV	4 (6.3)	5 (6.7)		3.5 (5.9)	3.5 (4.7)		
Tumor size > 60 mm, <i>n</i> (%)	34 (54.0)	49 (65.3)	0.22	37.1 (61.6)	45.2 (61.2)	0.92	0.009
Well-differentiation, <i>n</i> (%)	58 (92.1)	73 (97.3)	0.27	57.2 (95.1)	71.4 (96.6)	0.79	0.075
T4, <i>n</i> (%)	26 (41.3)	36 (48.0)	0.49	25.3 (42.1)	32.5 (44.0)	0.85	0.038
Ly +, <i>n</i> (%)	49 (77.8)	55 (73.3)	0.56	45.7 (76.0)	56.5 (76.5)	0.93	0.011
Pn +, <i>n</i> (%)	39 (61.9)	52 (69.3)	0.37	39.7 (66.1)	49.5 (66.9)	0.96	0.018
v +, <i>n</i> (%)	46 (73.0)	61 (81.3)	0.31	47.1 (78.3)	58.0 (78.6)	0.99	0.007
Lymph node metastasis, <i>n</i> (%)	39 (61.9)	42 (52.0)	0.49	37.7 (62.7)	46.1 (62.4)	0.89	0.007
Liver metastasis, <i>n</i> (%)	4 (6.3)	4 (5.3)	1.00	3.5 (5.9)	2.7 (3.6)	0.79	0.106
Peritoneal dissemination, <i>n</i> (%)	0 (0.0)	1 (1.3)	1.00	0.0 (0.0)	0.8 (1.1)	0.37	0.146
Postoperative hospital stay (days)	17.1 ± 15.4	13.8 ± 11.2	0.16	15.8 ± 14.4	13.3 ± 10.7	0.26	0.191
Overall hospital stays (days)	29.7 ± 17.4	31.0 ± 18.2	0.68	30.7 ± 29.7	29.7 ± 17.0	0.77	0.054
Adjuvant chemotherapy, <i>n</i> (%)	37 (58.7)	44 (58.7)	1.00	35.8 (56.9)	45.6 (61.7)	0.92	0.044
Oxaliplatin, <i>n</i> (%)	19 (30.2)	16 (21.3)	0.25	18.4 (30.7)	17.6 (23.8)	0.36	0.155
Median follow up (days)	1099.8 ± 684.8	780.1 ± 533.3	< 0.01*	1123.2 ± 643.0	879.6 ± 524.5	0.02*	0.415

Values are presented as mean ± standard deviation, number of patients, or number (percentage)

\*Statistically significant ( $P < 0.05$ )

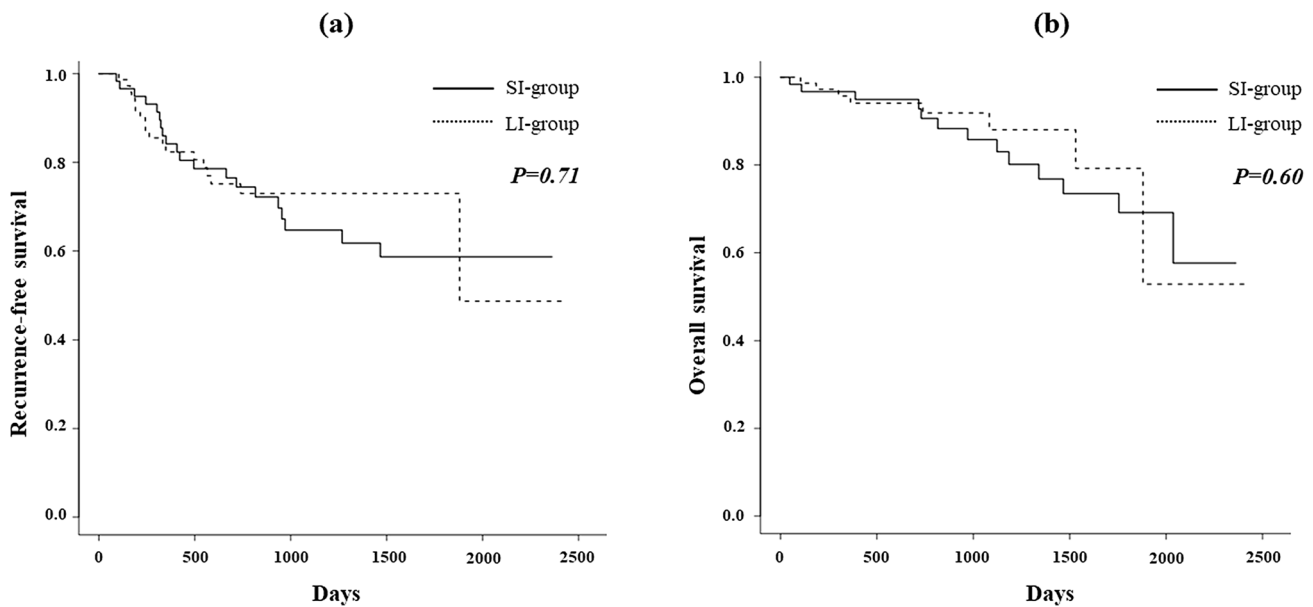
Abbreviations: *SMD* standardized mean difference, *CD* Clavien–Dindo, *Ly* lymphatic invasion, *Pn* perineural invasion, *v* venous invasion, *SI* short interval ( $\leq 20$  days from SEMS placement to surgery), *LI* long interval ( $\geq 21$  days from SEMS placement to surgery)

different between the SI and LI groups (19.0% vs. 14.0%,  $P = 0.47$ ). No 30-day mortality was observed in either group. The length of the overall hospital stay was not significantly different between the SI and LI groups. The median follow-up period was significantly longer in the SI group than the LI group (1123.2 ± 643.0 vs. 879.6 ± 524.5 days,  $P = 0.02$ ).

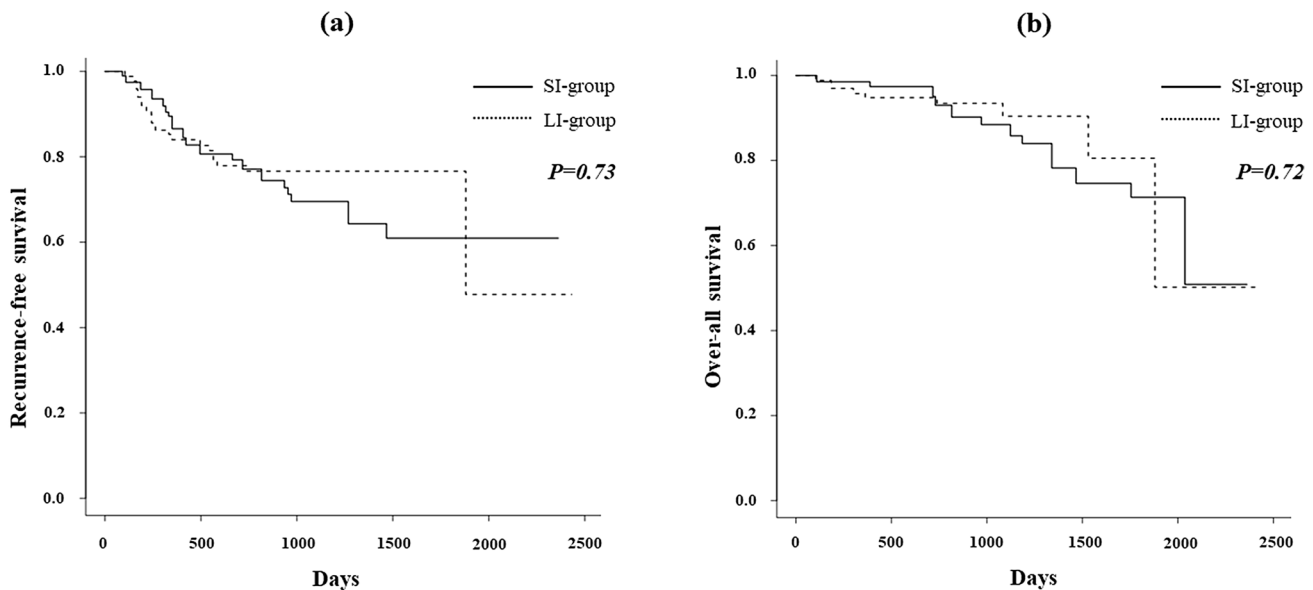
The SI and LI groups in the unadjusted cohort showed no significant differences in the 3-year RFS (69.6% vs. 78.0%,  $P = 0.71$ ) and 3-year OS rates (88.6% vs. 90.2%,  $P = 0.60$ )

(Fig. 2). There were also no significant differences between the SI and LI groups in the adjusted cohort regarding the 3-year RFS (68.0% vs. 76.4%,  $P = 0.73$ ) and 3-year OS (86.0% vs. 90.6%,  $P = 0.72$ ) (Fig. 3).

Prognostic factors for the RFS were evaluated using univariate and multivariate Cox proportional hazards models in the adjusted cohort using IPTW with propensity scores. Among the variables with a  $P$  value of  $< 0.05$ , in the univariate analyses of outcome-related factors, the independent



**Fig. 2** **a** RFS and **b** OS curves for all patients in the SI and LI groups. RFS, recurrence-free survival; OS, overall survival; SI group, short-interval group ( $\leq 20$  days from SEMS placement to surgery); LI group, long-interval group ( $\geq 21$  days from SEMS placement to surgery)



**Fig. 3** **a** RFS and **b** OS curves for the SI group and LI group in the adjusted cohort. RFS, recurrence-free survival; OS, overall survival; SI group, short-interval group ( $\leq 20$  days from SEMS placement to

surgery); LI group, long-interval group ( $\geq 21$  days from SEMS placement to surgery)

risk factors for a poor RFS were a Charlson Comorbidity Index (hazard ratio [HR] 1.25, 95% confidence interval [CI], 1.029–1.508,  $P=0.02$ ), postoperative complications of CD grade  $\geq$  II (HR 3.10, 95% CI, 1.379–6.986,  $P<0.01$ ), pT4 positivity (HR 4.90, 95% CI, 2.006–11.96,  $P<0.01$ ), venous invasion (HR 4.47, 95% CI, 1.279–15.65,  $P=0.02$ ), and the absence of adjuvant chemotherapy (HR 2.87, 95%

CI, 1.350–6.093;  $P<0.01$ ) (Table 3). Similarly, prognostic factors for the OS were evaluated. The variables identified as independent risk factors for a poor OS in the multivariate analysis were a Charlson Comorbidity Index (HR 1.36, 95% CI, 1.041–1.766;  $P=0.02$ ), an interval from SEMS placement to the first meal (HR 1.06, 95% CI, 1.014–1.117,  $P=0.01$ ), pT4 positivity (HR 5.91, 95% CI, 1.734–20.14,

**Table 3** Results of a Cox proportional hazard analysis for the recurrence-free survival in the adjusted cohort

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.02	0.986–1.053	0.26			
Sex (male)	2.07	0.894–4.787	0.08			
BMI	0.93	0.835–1.034	0.18			
Charlson Comorbidity Index	1.27	1.068–1.516	<0.01*	1.25	1.029–1.508	0.02*
Tumor location (right-sided colon)	0.73	0.298–1.769	0.48			
Pre-decompressive CROSS score 0 or 1	2.16	0.760–6.124	0.15			
Outside diameter of SEMS > 22 mm	1.29	0.590–2.814	0.53			
Preoperative blood transfusion	1.66	0.435–6.301	0.46			
Time interval until first meal	1.02	0.973–1.066	0.43			
Time interval until surgery	1.00	0.982–1.016	0.88	0.99	0.974–1.009	0.33
Clinical failure of SEMS	0.51	0.067–3.798	0.50			
Surgical time	1.00	0.998–1.006	0.28			
Blood loss	1.00	0.999–1.004	0.09			
Non-laparoscopic surgery	2.60	1.232–5.504	0.01*	1.20	0.486–2.949	0.70
Dissected lymph node number	0.98	0.944–1.018	0.30			
Less than D3 lymphadenectomy	3.08	1.063–8.940	0.04*	0.93	0.275–3.153	0.91
Postoperative complications (CD ≥ II)	3.80	1.782–8.121	<0.01*	3.10	1.379–6.986	<0.01*
Tumor size > 60 mm	0.67	0.334–1.326	0.25			
Poorly-differentiation	3.03	0.751–12.22	0.12			
T4+	5.14	2.400–11.01	<0.01*	4.90	2.006–11.96	<0.01*
Ly+	1.56	0.682–3.579	0.29			
Pn+	1.37	0.664–2.825	0.39	1.36	0.460–4.021	0.58
V+	3.78	1.300–11.01	0.01*	4.47	1.279–15.65	0.02*
Pathological stage				1.50	0.741–3.030	0.26
III	1.20	0.569–2.526	0.63			
IV	5.19	1.619–16.62	<0.01*			
Absence of adjuvant chemotherapy	3.00	1.514–5.938	<0.01*	2.87	1.350–6.093	<0.01*

\*Statistically significant ( $P < 0.05$ )

Abbreviations: *BMI* body mass index, *SEMS* self-expandable metallic stent, *CD* Clavien–Dindo, *CROSS* colorectal obstruction scoring system, *CI* confidence interval, *HR* hazard ratio, *Ly* lymphatic invasion, *Pn* perineural invasion, *V* venous invasion

$P < 0.01$ ), and the absence of adjuvant chemotherapy (HR 8.88, 95% CI, 2.851–27.63,  $P < 0.01$ ) (Table 4).

## Discussion

This study aimed to investigate the association between the interval from SEMS placement to elective surgery and long-term outcomes in patients with OCRC. These results demonstrated that a longer BTS interval did not worsen the RFS or OS.

SEMS placement for OCRC was first introduced in 1990 for palliation and has been used as a BTS procedure since 1993 [6, 28]. Since then, SEMS placement as a BTS procedure has rapidly spread as an alternative to emergency surgery for OCRC, and numerous studies on the subject have been published [8–10, 29]. There is some concern that

SEMS expansion could induce mechanical compression, which alters the biological malignant potential and subsequently worsens the prognosis [30]. However, a summary of the reports to date showed that BTS using SEMS placement improved short-term outcomes and did not worsen long-term outcomes compared to emergency surgery [31]. Thus, the abovementioned findings were reflected in the updated version of the ESGE guidelines for 2020 [12].

There is no consensus regarding the optimal BTS interval for OCRC. SEMS placement with an appropriate BTS interval is a potentially effective treatment strategy for OCRC. However, a longer interval might increase the complications associated with SEMS and worsen the oncological outcomes. Previous studies have applied various cutoff values for the BTS interval (Table 5). Broholm et al. [17] divided patients into two groups using a cutoff of 18 days, which was the median interval from SEMS placement to surgery

**Table 4** Results of a Cox proportional hazard analysis for the overall survival in the adjusted cohort

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.05	0.999–1.106	0.05			
Sex (male)	1.40	0.566–3.497	0.46			
BMI	0.93	0.776–1.104	0.39			
Charlson Comorbidity Index	1.29	1.045–1.589	0.02*	1.36	1.041–1.766	0.02*
Tumor location (right-sided colon)	1.29	0.467–3.575	0.49			
Pre-decompressive CROSS score 0 or 1	1.44	0.584–3.545	0.43			
Outside diameter of SEMS > 22 mm	1.31	0.422–4.097	0.64			
Preoperative blood transfusion	1.70	0.185–15.63	0.64			
Time interval until first meal	1.04	1.028–1.055	<0.01*	1.06	1.014–1.117	0.01*
Time interval until surgery	1.01	0.988–1.032	0.89	0.99	0.959–1.027	0.68
Clinical failure of SEMS	1.26	0.446–3.599	0.20			
Surgical time	1.00	0.998–1.010	0.19			
Blood loss	1.00	0.999–1.004	0.22			
Non-laparoscopic surgery	3.02	1.104–8.264	0.03*	0.56	0.091–3.503	0.54
Dissected lymph node number	0.99	0.926–1.049	0.65			
Less than D3 lymphadenectomy	11.01	3.550–34.120	<0.01*	4.76	0.626–36.14	0.13
Postoperative complications (CD ≥ II)	3.29	1.138–9.487	0.03*	1.91	0.452–8.111	0.38
Tumor size > 60 mm	1.72	0.643–4.593	0.28			
Poorly-differentiation	3.88	0.727–20.73	0.11			
T4+	4.26	1.647–11.01	<0.01*	5.91	1.734–20.14	<0.01*
Ly+	0.81	0.280–2.320	0.69			
Pn+	0.91	0.360–2.303	0.84	1.05	0.274–4.045	0.94
V+	1.52	0.493–4.679	0.47			
Pathological stage				1.05	0.424–2.581	0.92
III	0.77	0.278–2.121	0.61			
IV	1.97	0.635–6.096	0.24			
Absence of adjuvant chemotherapy	5.81	2.286–14.75	<0.01*	8.88	2.851–27.63	<0.01*

\*Statistically significant ( $P < 0.05$ )Abbreviations: *BMI* body mass index, *SEMS* self-expandable metallic stent, *CD* Clavien–Dindo, *CROSS* colorectal obstruction scoring system, *CI* confidence interval, *HR* hazard ratio, *Ly* lymphatic invasion, *Pn* perineural invasion, *V* venous invasion

in their study. Kye et al. [18] divided patients into weekly segments, and Veld et al. [16] divided patients according to the 2014 and 2020 ESGE guidelines [12]. Broholm et al. [17] reported a significantly increased risk of recurrence in the group with an interval of > 18 days from SEMS placement to elective surgery (odds ratio 5.1, 95% CI, 1.6–15.8,  $P = 0.005$ ). Furthermore, Sato et al. [19] suggested that elective surgery within 16 days after SEMS placement might balance short-term benefits and long-term oncologic risks. In contrast, Ho et al. [32] reported no marked differences in the OS and recurrence between the early and delayed surgery groups (> 4 weeks) of patients managed with BTS SEMS placement for OCRC. Other reports demonstrated that surgical conditions for elective resection improve at intervals of up to 4 weeks after SEMS placement, with an optimal interval of approximately 2–4 weeks [16, 33]. In the present study, there were no significant differences in short- and

long-term outcomes between patients who underwent curative surgery within 20 days versus 21 or more days after SEMS placement.

In the present study, a Charlson Comorbidity Index, postoperative complications, pT4 stage, and the absence of adjuvant chemotherapy were independent risk factors for a poor RFS and OS. A great benefit of a longer interval from SEMS placement to elective surgery is a reduction in short-term postoperative complications, which is attributed to an improvement in the patients' general and intestinal conditions. Although the difference was not statistically significant, the LI group had a lower rate of postoperative complications than the SI group in the present study. In addition, our previous study demonstrated that an interval of > 15 days is recommended to minimize postoperative complications [15]. The negative oncological impact of postoperative complications following CRC surgery has



**Table 5** Previous reports for the time interval between SEMS placement and surgery

References	Year	Country	Institution	Study design	Total cases	Interval until surgery, day (cases)	Short-term outcomes	Long-term outcomes
Lee GJ [13]	2013	Korean	Single center	RS	43	≤ 9 days (15), ≥ 10 days (28)	Anastomotic leakage rate was higher in ≤ 15 days group	–
Gianotti [14]	2013	Italy	Single center	RS	49	–	The ROC curve suggests that waiting at least 6 days	–
Broholm M [17]	2017	Denmark	multi center	RS	112	–	–	≥ 18 days was risk factor of recurrence
Matsuda A [15]	2018	Japan	Single center	RS	47	≤ 15 days (19), ≥ 16 days (28)	Postoperative complications rate was higher in ≤ 15 days group	–
Veld JV [16]	2020	Netherland	Multi center	RS	174	5–10 days (24), 11–17 days (38), ≥ 18 days (112)	No significant differences in each group	No significant differences in each group
Kye BH [18]	2020	Korean	Multi center	RS	174	≤ 7 days (75), 8–14 days (56), ≥ 15 days (43)	No significant differences in each group	Longer interval was risk factor of DFS and OS
Sato R [19]	2022	Japan	Single center	RS	92	≤ 15 days (40), ≥ 16 days (52)	–	≥ 16 days was risk factor of RFS
Ho MF [34]	2023	Hong Kong	Single center	RS	105	≤ 28 days (64), ≥ 29 days (40)	No significant differences in both groups	No significant differences in both groups

Abbreviations: *RS* retrospective study, *DFS* disease free survival, *OS* overall survival, *RFS* relapse free survival

been consistently reported. The potential mechanisms are as follows: 1) local and systemic activation of proinflammatory cytokines and mediators, which promote micrometastasis; 2) delayed and canceled adjuvant chemotherapy; and 3) abdominal implantation of intraluminal cancer cells in patients with anastomotic leakage [34–38]. Recently, we demonstrated a consistent and more powerful negative oncological impact of postoperative complications in a cohort treated using the BTS strategy than in a cohort without SEMS placement [39]. Taken together, these findings suggest that perioperative management should be conducted to avoid postoperative complications and administer adjuvant chemotherapy appropriately, rather than attempting to perform high-risk surgery within a short interval after SEMS placement.

The interval between SEMS placement and curative tumor resection may be extended because of the patients' condition. In our cohort, the LI group included patients with emergency admission due to heart failure, pneumonia, or cerebrovascular disease who were diagnosed with OCRC and underwent SEMS insertion. These patients required time

to sufficiently improve their condition to enable them to tolerate surgery. Interestingly, in the present study, it was not the interval between SEMS placement and elective surgery, but the interval between SEMS placement and the first meal was found to be an independent risk factor for a poor OS. Patients who have difficulty eating despite adequate intestinal decompression probably do not eat due to other factors, such as poor respiratory conditions and dysphagia. Clinicians should aim to improve the preoperative nutritional status of patients with OCRC during an adequate interval between SEMS placement and surgery, as preoperative malnutrition worsens the prognosis of patients with cancer [40, 41].

However, the need for adjuvant chemotherapy for OCRC remains controversial. In the present study protocol, because of the high rate of pathological T4 invasion in patients with OCRC, adjuvant chemotherapy was administered in all cases, except when treatment of other comorbidities was a priority or when the patient's background characteristics made it difficult [42]. However, chemotherapy

was administered to only 58% of patients. Han et al. [43] reported that SEMS placement followed by neoadjuvant chemotherapy prior to elective surgery appears to be safe and well tolerated in patients with OCRC. New strategies are emerging that guarantee oncologic safety while taking advantage of the long interval from SEMS placement to elective surgery.

Several limitations associated with the present study warrant mention. First, it was a retrospective study with a small number of patients. Therefore, the statistical power might have been insufficient, especially for survival analyses. To minimize this limitation, we applied the IPTW matching method instead of conventional propensity score matching because the IPTW data are closer to the clinical data. The IPTW matching method alleviated the overadjustment of bias toward the control group without decreasing the sample size. To our knowledge, this is the first study of the optimal interval of SEMS placement as a BTS procedure in OCRC to be conducted using an IPTW propensity score-matched multicenter design. Second, the follow-up period was relatively short.

In conclusion, a longer interval between SEMS placement and elective surgery did not deteriorate oncological outcomes. Therefore, individual perioperative management with neither an excessive nor an insufficient interval between SEMS placement and surgery should be conducted to improve the condition of each patient with OCRC and to increase the safety of surgery.

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## Declarations

**Conflict of interest** The authors declare no conflict of interest for this article.

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