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Original Research Article

Does Colorectal Stenting as a Bridge to Surgery for Obstructive Colorectal Cancer Increase Perineural Invasion?

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Abstract
Objectives: To clarify whether self-expandable metallic stent (SEMS) placement for obstructive colorectal cancer (CRC) increases perineural invasion (PNI), thereby worsening the prognosis.
Methods: In total, 1022 patients with pathological T3 or T4 colon or rectosigmoid cancer who underwent resection were retrospectively reviewed. The study patients were divided into a no obstruction group (n=693), obstruction without stent group (n=251), and obstruction with stent group (n=78), and factors demonstrating an independent association with PNI, the difference in PNI incidence and severity between groups, and the association between PNI and the duration from SEMS placement to surgery were investigated. Survival analysis was performed for each group.
Results: On multivariate analysis, SEMS placement (hazard ratio [HR]: 2.08) was independently associated with PNI whereas SEMS placement was not.
PNI occurred in 39%, 45%, and 68% of the no obstruction, obstruction without stent, and obstruction with stent group, respectively. In the obstruction with stent group, the proportion of PNI was not associated with the duration from SEMS placement to surgery. Extramural PNI, an advanced form of PNI, demonstrated no increase with increasing interval. The five-year OS was 86.3%, 76.7%, and 73.1% in no obstruction, obstruction without stent, and obstruction with stent group, respectively. On multivariate analysis, obstruction was an independent risk factor of decreased OS (HR: 1.57) whereas SEMS placement was not.
Conclusions: The prognosis was comparable between patients with SEMS placement and those with an obstruction who did not undergo SEMS placement, thus demonstrating that SEMS is a viable, therapeutic option for BTS.

Keywords
perineural invasion, colon cancer, obstruction, bridge to surgery, self-expanding metallic stent
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Introduction

Reportedly 8-13% of colorectal cancer (CRC) cases are associated with colorectal obstruction at the time of diagnosis[1-3]. Obstructive CRC accounts for 25% of functional bowel obstructions and 85% of emergency surgeries for colorectal disease[4]. The prognosis is also poorer for obstructive CRC than for CRC without obstruction and therefore is considered to be a risk factor of recurrence after resection with curative intent[5,6].

There are several treatment options for obstructive CRC: emergency surgery with one-stage bowel resection, staged surgeries consisting of bowel resection and stoma creation, and elective surgery after bowel decompression with a transanal decompression tube. In recent years, self-expandable metallic colonic stent (SEMS) placement followed by surgery, a so-called bridge to surgery (BTS), has been popularized as an alternative treatment option for obstructive CRC. In the early reports of the use of SMES as a BTS, SEMS placement was associated with a higher recurrence rate and poorer prognosis than other decompression treatments, partly owing to the high rate of treatment failure, including colonic perforation at the time of SEMS placement, resulting in the 2014 ESGE guidelines' recommendation not to use SEMS as a BTS[7].

However, SEMS placement techniques have improved, and several, recent studies have demonstrated long-term and short-term outcomes of BTS that were equivalent or superior to those of emergency surgery[8,9]. Consequently, the latest ESGE guidelines now mention stenting as a bridge to surgery as a possible treatment option[10].

A high frequency of perineural invasion (PNI) has been reported in resected specimens after SEMS placement[11-13]. Because the PNI of CRC is known to be indicative of poor, long-term prognosis[14,15], the increased PNI incidence after SEMS placement was thought to be one of the reasons for the poor prognosis of patients with BTS[16]. However, it is not clear whether SEMS placement increases PNI, thereby worsening the prognosis[17,18] or whether the baseline PNI incidence is so high in CRC with severe bowel stenosis as to require SEMS placement[19].

The present study divided CRC patients into those without colorectal obstruction (no obstruction group); those with an obstruction due to CRC but without the need for decompression by SEMS (obstruction without stent); and those with a colorectal obstruction who underwent decompression by SEMS (obstruction with stent group), and the differences in the PNI incidence and severity between groups were investigated. If SEMS placement induced PNI, an increase in the duration between SEMS placement and surgery should be reflected in an increased rate and severity of PNI. With this assumption, the association between PNI and the duration from SEMS placement to surgery was also investigated.

Methods

Patients

The present, retrospective, observational study was conducted in the Department of Colorectal Surgery at Tokyo Metropolitan Komagome Hospital. In total, 1022 consecutive patients with pathological T3 or T4 primary colon or rectosigmoid cancer without distant metastasis who underwent tumor resection with curative intent between April 2014 and January 2022 were retrospectively reviewed. The patients were divided into those with CRC without colorectal obstruction (the no obstruction group, n=693); those with a colorectal obstruction due to CRC but without decompression by SEMS (the obstruction without stent group, n=251); and those with a colorectal obstruction due to CRC who underwent decompression by SEMS preoperatively (the obstruction with stent group, n=78). The indication of emergent bowel decompression by SEMS was at the discretion of each surgeon. Colorectal obstruction was defined as a stenosis that was so severe so that a colonoscope couldn't pass through. The severity of the stenosis at the time of the first diagnosis was assessed using the Colorectal Obstruction Scoring System (CROSS) as described previously[20].

Intervention and pathological assessment

Gastroenterologists performed all the SEMS placements. Experienced gastroenterological surgeons performed the primary tumor resections and lymph node dissections with curative intent after sufficient bowel decompression was achieved by SEMS placement. Postoperative complications were assessed using the Clavien-Dindo classification, with grade IIIb or higher qualifying as a complication in the present study. Assessment of the pathological features of the resected specimens, including PNI, was performed using the TNM classification by a board-certificated pathologist. The cohort was divided into two groups based on the size of the tumor with a cut-off value of 57 mm. This particular value was determined using ROC analysis (Area under curve 0.52), where PNI positivity was set as the objective variable and tumor size was considered as the explanatory variable. PNI was classified into an intramural or extramural form in accordance with a previous report[21]. Intradural PNI was defined by the horizontal spread of the cancer along the Auerbach plexus while extramural PNI was defined by histological findings of tumor cell invasion into or along nerve fascicles external to the muscularis propria.

Postoperative follow-up

Postoperative surveillance was performed in accordance with the Japanese Society for Cancer of the Colon and Rectum guidelines[22], which recommend surveillance for five postoperative years, including diagnostic imaging studies (chest-abdominal multi-detector row computed tomography), a semiannual tumor marker (CEA, CA 19-9) assessment, and a yearly colonoscopy.

Statistical analysis

The Mann-Whitney U test was used to compare continuous variables between two groups, ANOVA was used to compare continuous variables, and the χ^2 test was used to analyze categorical data for the three groups. Univariate and multivariate analyses were performed with logistic regression to assess factors demonstrating an independent association with PNI. Any variables found to be P<0.05 on univariate analysis were included in multivariate analysis.

Survival analysis was performed using the Kaplan-Meier method and log-rank test. The difference in survival rate among all the groups was calculated using the Bonferroni correction, and P<0.017 was considered to indicate statistical significance. Univariate and multivariate analyses with Cox proportional hazards were performed to identify independent, predictive factors of OS. All statistical analyses were conducted using JMP16 (SAS Institute Inc., Cary, NC, USA). This study was approved by the institutional review board of Tokyo Metropolitan Komagome Hospital (Approval number 3130).

Results

Patient background

Table 1 shows the clinicopathological characteristics of the patients. The obstruction with stent group had the highest proportion of left-sided cancers (74%, P=0.0015), the largest tumors (65 mm, P<0.0001), the highest proportion of T4 cancer (46%, P<0.0001), and the highest proportion of node metastasis (66%, P=0.0012), suggesting that this group contained the most advanced cases. Moreover, lymphatic invasion was most frequently observed in this group (48%, P=0.031), and most importantly, perineural invasion was observed in 68% of the cases, which was markedly higher than in the other two groups (P<0.0001).

Risk factors associated with perineural invasion

On univariate analysis, PNI was significantly associated with T4 (P<0.0001), regional lymph node metastasis (P<0.0001), lymphatic invasion (p<0.0001), venous invasion (P<0.0001), obstruction due to CRC (P=0.0007), and SEMS placement (P<0.0001), whereas tumor diameter showed no correlation (p=0.12, Table 2). On multivariate analysis, T4 (hazard ratio [HR]: 2.91), regional lymph node metastasis (HR: 2.39), lymphatic invasion (HR: 1.79), venous invasion (HR: 2.17), and SEMS placement (HR: 2.08) were independent factors associated with PNI.

Relationships between the status of obstruction and PNI

Figure 1 shows the relationship between obstruction status and PNI. The obstruction with stent group was further divided into three subgroups according to the number of weeks from stent placement to surgery: <3 weeks, 3-5 weeks, and >5 weeks. PNI was found in 39%, 45%, and 68% of the no obstruction group, obstruction without stent group, and obstruction with stent group, respectively. In the obstruction with stent group, the proportion of PNI was not associated with duration to surgery (64%, 72%, and 57% for <3 weeks, 3-5 weeks, and >5weeks, respectively). In addition, extramural PNI, the most advanced PNI group, showed no increase with increasing duration (41%, 35%, and 43% for <3 weeks, 3-5 weeks, and >5 weeks, respectively). Nor was any correlation observed between PNI and the duration of stenting as a continuous variable (P=0.47).

Prognosis

The median surveillance period was 3.57 years. Five-year OS was 86.3%, 76.7%, and 73.1% in the no obstruction group, obstruction without stent group, and obstruction with stent group, respectively (Figure 2). There was no significant difference in OS between the obstruction with and without stent groups (P=0.52). Meanwhile, OS in the no obstruction group was significantly better than in the other groups (both P<0.01).

On univariate analysis, poor OS was significantly associated with age >70 years, male sex, size of the primary tumor >57 mm, T4, regional lymph node metastasis, lymphatic and venous invasion, obstruction, SEMS placement, perineural invasion, and adjuvant chemotherapy (Table 3). On multivariate analysis, obstruction was an independent risk factor of shorter OS (HR: 1.48) whereas SEMS placement was not. Other factors for poorer OS were age >70 (HR:6.77), male sex (HR: 1.58), T4 (HR: 2.03), and lymphatic invasion (HR: 1.77).

Discussion

The present study investigated the impact of SEM placement on PNI in colorectal cancer because PNI has been shown to be a stage-independent prognostic factor[23-25] and colon cancer is known to be associated with a high incidence of PNI[19]. The severity of PNI was also investigated because progression from intramural to extramural PNI is indicative of a poor prognosis[21]. Initially, factors demonstrating an association with PNI in the resected specimen (Table 2) were investigated. On multivariate analysis, SEMS insertion independently correlated with PNI together with T stage, regional lymph node metastasis, and lymphatic and vascular invasion while obstruction by colorectal cancer did not. A recent meta-analysis also demonstrated an increased

Table 1. Patient Characteristics.

Variables		No obstruction n=693	Obstruction without stent n=251	Obstruction with stent n=78	P value
Age, years	Mean ± SD	70±12.1	70±12.4	71±12.2	0.24
Sex	Male	363 (52%)	133 (53%)	40 (51%)	0.80
	Female	330 (48%)	118 (47%)	38 (49%)	
Cancer location	Right	281 (41%)	76 (30%)	20 (26%)	0.0015
	Left	412 (59%)	175 (70%)	58 (74%)	
CROSS score	0		4 (2%)	34 (43%)	
	1		14 (6%)	4 (5%)	
	2		9 (4%)	6 (8%)	
	3		129 (51%)	32 (41%)	
	4		95 (37%)	2 (3%)	
Method of decompression	Nothing		82 (32%)		
	Fasting		10 (4%)		
	Laxative		142 (56%)		
	Transnasal ileus tube		2 (1%)		
	Transanal ileus tube		6 (3%)		
	Stoma creation		9 (4%)		
Size of primary tumor, mm	Mean ± SD	45±21.4	57±21.5	65±18.5	<0.0001
Histology	Differentiated	630 (91%)	238 (95%)	74 (95%)	0.093
	Others	63 (9%)	13 (5%)	4 (5%)	
T stage	T3	598 (86%)	169 (67%)	42 (54%)	<0.0001
	T4	95 (14%)	82 (33%)	36 (46%)	
Regional LN metastasis	Absent	386 (56%)	126 (50%)	27 (34%)	0.0012
	Present	307 (44%)	125 (50%)	51 (66%)	
Lymphatic invasion	Absent	435 (63%)	155 (62%)	50 (42%)	0.031
	Present	258 (37%)	96 (38%)	69 (48%)	
Venous invasion	Absent	147 (21%)	51 (20%)	37 (47%)	0.63
	Present	546 (79%)	200 (80%)	41 (53%)	
Perineural invasion	Absent	421 (56%)	138 (55%)	25 (32%)	<0.0001
	Present	272 (44%)	113 (45%)	53 (68%)	
Adjuvant chemotherapy	Absent	429 (62%)	151 (60%)	40 (51%)	0.12
	Present	264 (38%)	100 (40%)	38 (49%)	

differentiated, well or moderately differentiated adenocarcinoma; LN, lymph node

incidence of PNI in patients with obstructive colorectal cancer who underwent SEMS placement[21]. There are two possible explanations for the increased PNI in patients with SEMS placement: one is that the stenting itself increased the incidence, and the other is that PNI was already present in patients with severe stenosis requiring stenting.

Although the 2020 European Society of Endoscopy guidelines recommend an interval of less than 14 days between SEMS placement and surgery, no definite evidence has been produced in support of this recommendation[10]. Because an interval <15 days until surgery reportedly increases the rate of postoperative complications significantly[26], the study center protocol calls for a minimum interval until radical surgery of two to three weeks; therefore, patients with an interval shorter than three weeks in the present study were categorized into a short interval group. Assuming that some pathological changes require more than two weeks to develop, the longer interval group was divided into two subgroups each reflecting an increment of two weeks. If SEMS placement induced the PNI, the PNI rate might be expected to increase as the interval after SEMS insertion and before surgery increases. However, contrary to this assumption, the interval length showed no association with PNI incidence or severity despite all the SEMS groups having a higher PNI incidence than the obstruction without SEMS insertion group (Figure 1). This finding suggested that patients requiring bowel decompression by SEMS had a more severe obstruction than those who did not require mechanical decompression, and the increased pressure in the large bowel rather than the stenting might have increased the PNI incidence. The severity of stenosis in the obstruction with and without stent groups was assessed using the

Table 2. Risk Factors Associated with Perineural Invasion.

Variables	N (%)	Univariate	Multivariate	
		P value	OR (95%CI)	P value
Age, years		0.12		
≤70	519 (50.8)			
>70	503 (49.2)			
Sex		0.81		
female	488 (47.7)			
male	534 (52.3)			
Cancer location		0.13		
left	377 (36.9)			
right	645 (63.1)			
Size of the primary tumor, mm		0.12		
≤57	676 (66.1)			
>57	346 (33.9)			
Histology		0.14		
differentiated	942 (92.2)			
others	80 (7.8)			
T stage		<0.0001		<0.0001
T3	809 (78.5)		1	
T4	213 (21.5)		2.91 (2.03-4.16)	
Regional LN metastasis		<0.0001		<0.0001
absent	539 (52.7)		1	
present	483 (47.3)		2.39 (1.79-3.17)	
Lymphatic invasion		<0.0001		0.0001
absent	627 (61.4)		1	
present	395 (38.6)		1.79 (1.33-2.40)	
Venous invasion		<0.0001		<0.0001
absent	211 (20.6)		1	
present	811 (79.4)		2.17 (1.51-3.13)	
Obstruction		0.0007		0.96
absent	693 (67.8)		1	
present	329 (32.2)		1.01 (0.73-1.40)	
SEMS		<0.0001		0.015
absent	944 (92.4)		1	
present	78 (7.6)		2.08 (1.15-3.75)	

LN, lymph node; differentiated, well or moderately differentiated adenocarcinoma; SEMS, self-expandable metallic colonic stent

CROSS. In the group without SEMS, 89.2% of the patients had a CROSS score of 3 or 4 while in the group with SEMS, only 43.6% of the patients had an equivalent CROSS score, demonstrating that the SEMS group had more severe stenosis. This fact may explain why patients with SEMS had a higher incidence of PNI. Moreover, some studies have reported that the duration of stenting does not adversely affect the prognosis[27,28], suggesting that a longer duration of stenting does not increase the PNI incidence.

Next, the impact of obstruction, SEMS insertion, and elevated PNI on the prognosis was assessed. It has been pointed out that SEMS placement may cause a gastrointestinal perforation, a subclinical perforation due to mechanical stimulation of the tumor, PNI, peritoneal seeding or long-term deterioration of the prognosis through promoting the release of cancer cells into the blood[11]. Although early studies demonstrated impaired prognosis after SEMS placement[11], several recent studies have reported that the long-term prognosis after SEMS implantation was equivalent to that after emergency surgery[8,9]. Recent improvements in SEMS placement techniques and the increase in the variety of stents to match the range of cancer characteristics[29] should contribute to reducing complications, especially bowel perforation, associated with SEMS placement.

In the present series, both bowel obstruction groups had worse OS than the no-obstruction group although stenting was not responsible for this outcome. Multivariate analysis

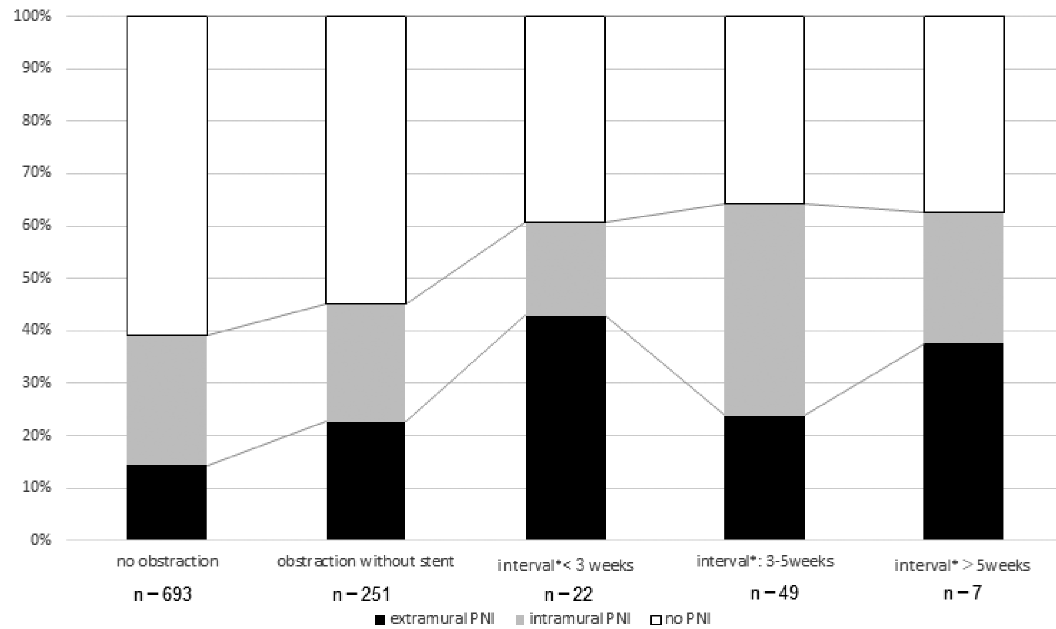

Figure 1. Relationship between obstruction status and PNI.
The obstruction with stent group was divided into three groups according to the duration from SEMS placement to surgery: 3 weeks, 3 - 5 weeks, and > 5 weeks.
Each bar demonstrates the proportion of no PNI (white box), intramural PNI (gray box), and extramural PNI (black box). * Duration from stent insertion to surgery.

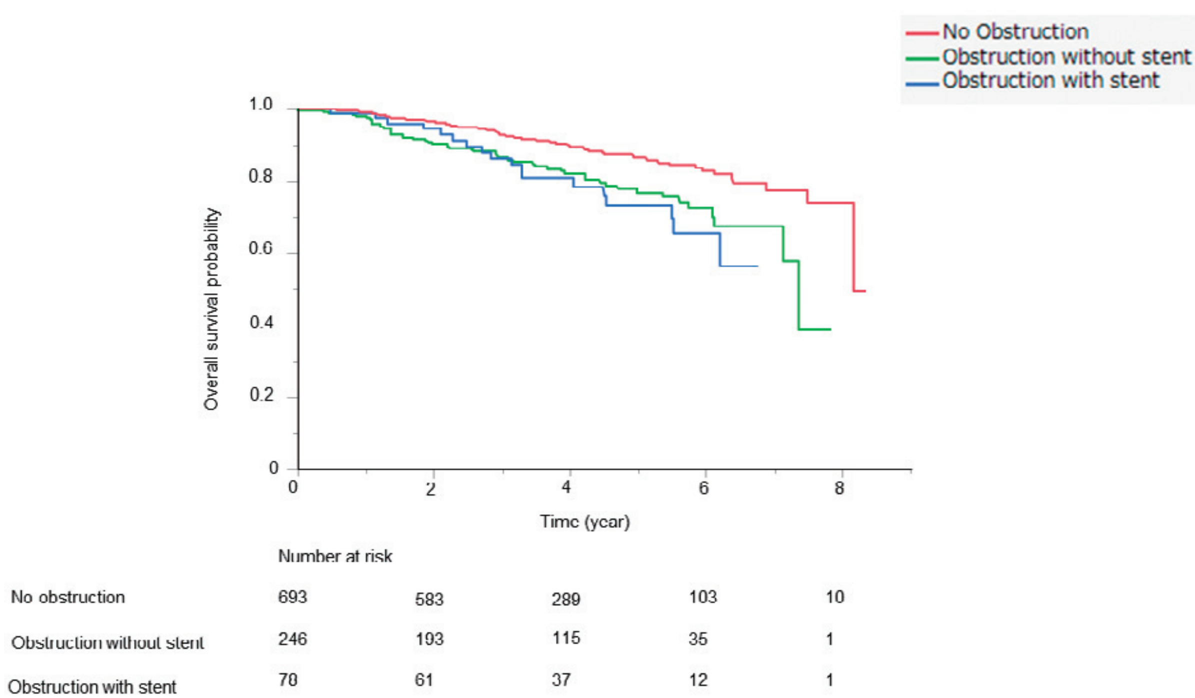

Figure 2. Kaplan-Meier curves of postoperative overall survival.
Red line: no obstruction group; green line: obstruction without stent group; blue line: obstruction with stent group.

found obstruction rather than SEMS placement or PNI to be an independent factor of poor OS. Numerous studies have demonstrated that obstruction is indicative of poor prognosis in colorectal cancer[30-32]. Because the present study did not include any cases of gastrointestinal perforation caused by stenting, the SEMS placement, which was performed by skilled GI physicians in all the cases, may have helped to avoid impairment of the prognosis after stenting.

Table 3. Prognostic Factors of Overall Survival after Curative Resection.

Variables	N (%)	Univariate	Multivariate	
		P value	HR (95%CI)	P value
Age, years		0.0002		0.0011
≤70	519 (50.8)		1	
>70	503 (49.2)		6.77 (2.14-21.4)	
Sex		0.0073		0.010
female	488 (47.7)		1	
male	534 (52.3)		1.58 (1.11-2.23)	
Cancer location		0.99		
left	377 (36.9)			
right	645 (63.1)			
Size of the primary tumor, mm		0.0081		0.17
≤57	676 (66.1)		1	
>57	346 (33.9)		1.28 (0.89-1.82)	
Histology		0.32		
differentiated	942 (92.2)			
others	80 (7.8)			
T stage		<0.0001		0.0003
T3	809 (78.5)		1	
T4	213 (21.5)		2.03 (1.38-2.98)	
Regional LN metastasis		<0.0001		0.057
absent	539 (52.7)		1	
present	483 (47.3)		1.50 (0.99-2.28)	
Lymphatic invasion		<0.0001		0.0023
absent	627 (61.4)		1	
present	395 (38.6)		1.77 (1.23-2.56)	
Venous invasion		0.00056		0.068
absent	211 (20.6)		1	
present	811 (79.4)		1.56 (0.97-2.53)	
Obstruction		<0.0001		0.049
absent	693 (67.8)		1	
present	329 (32.2)		1.48 (1.00-2.18)	
SEMS		0.031		0.41
absent	944 (92.4)		1	
present	78 (7.6)		0.79 (0.46-1.38)	
Perineural invasion		<0.0001		0.34
absent	584 (57.1)		1	
present	438 (42.9)		1.20 (0.82-1.77)	
Postoperative complication of Clavian-Dindo classification gradeIIIb or higher		0.24		
absent	998 (97.7)			
present	24 (2.3)			
Adjuvant Chemotherapy		0.0002		0.64
absent	619 (60.6)		1	
present	403 (39.4)		1.10 (0.74-1.65)	

LN, lymph node; differentiated, well or moderately differentiated adenocarcinoma; SEMS, self-expandable metallic colonic stent

The present study has several limitations. First, it was retrospective and monocentric. Because research into PNI was described in the Japanese classification only since 2013[22], the patient pool was relatively small. Further accumulation of cases will help to clarify the association of PNI with obstruction and stenting. Second, the obstruction without stent group included various clinical settings. The present study defined colorectal obstruction as stenosis of sufficient severity to render colonoscopy impossible. This group included a wide range of obstructions from mild obstructions not requiring preoperative decompression to complete obstruction requiring preoperative stoma creation. Third, PNI could have developed immediately after stent placement although it would be quite difficult to determine the period of PNI development after stent placement.

In conclusion, although the rate of PNI positivity was higher in patients with SEMS placement, the prognosis of these patients was comparable to that of patients who had an obstruction but did not receive SEMS placement, thus demonstrating the viability of SEMS placement as a therapeutic option for BTS and an alternative to conventional decompression treatments.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

All authors contributed to the study's conception and design. Hiroki Kato and Kazushige Kawai performed material preparation, data collection, and analysis. Hiroki Kato and Kazushige Kawai wrote the first draft of the manuscript. All authors critically revised the manuscript. All authors read and approved the final manuscript.

Approval by Institutional Review Board (IRB)

This study was approved by the institutional review board of Tokyo Metropolitan Komagome Hospital (Approval number 3130).

Disclaimer

Masaaki Ito is one of the Associate Editors of Journal of the Anus, Rectum and Colon and on the journal's Editorial Board. He was not involved in the editorial evaluation or decision to accept this article for publication at all.

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