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ORIGINAL ARTICLE

Higher rate of perineural invasion in stent–laparoscopic approach in comparison to emergent open resection for obstructing left-sided colon cancer

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Abstract
Purpose We compared oncologic outcomes of laparoscopic surgery following self-expandable metallic stent (SEMS) insertion with one-stage emergency surgical treatment of obstructive left-sided colon and rectal cancers.
Methods From April 1996 to October 2007, 95 consecutive patients with left-sided obstructive colorectal cancers were included: 25 underwent preoperative stenting and elective laparoscopic surgery (SLAP) and 70 underwent emergency open surgery with intraoperative colon lavage (OLAV). Long-term oncologic outcomes were analyzed on an intention-to-treat basis.
Results There were no significant differences in baseline characteristics of patients between groups. Perineural invasion of the primary tumor was more frequent with SLAP (76 vs. 51.4 %, p=0.033). The median follow-up was 51 months (range, 4–139 months). There were no significant differences between groups in 5-year overall survival rates (SLAP vs. OLAV, 67.2 vs. 61.6 %, p=0.385). Five-year disease-free survival rates were also similar between groups (SLAP vs. OLAV, 61.2 vs. 60.0 %, p=0.932).
Conclusions Laparoscopic surgery after SEMS was feasible and safe for patients with obstructive left-sided colorectal cancer, and oncologic outcomes were comparable to emergency open surgery with intraoperative colon lavage. These results support the continued use of SLAP in this setting. Further large-scale study is needed to investigate any clinical impact attached to the higher rates of perineural invasion observed in SLAP.

Keywords Self-expandable metallic stent · Laparoscopic surgery · Perineural invasion · Colorectal cancer

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Introduction

About 8–29 % of patients with primary colorectal cancer present with an acute large bowel obstruction at the time of diagnosis [1, 2]. Traditional treatments for patients with left-sided obstructive colon cancer have been multistage operative procedures, so that the risks of anastomotic leakages from inadequate bowel preparation are minimized. Although intraoperative colon lavage or subtotal colectomy—as a more recent advance—have enabled primary anastomosis with tumor resection in selected patients [3–5], emergency open surgery was associated with electrolyte imbalance and dehydration associated with the bowel obstruction, leading to high morbidity and mortality [6–8]. Therefore, a technique for alleviating the obstructed bowel and delaying the operation, enabling a safer primary anastomosis, would be beneficial.

Dohomoto first described the placement of a self-expandable metallic stent (SEMS) in 1991 [9, 10]. At that time, a SEMS was used for palliation to avoid surgery in the case of large bowel obstructions. A step forward in the use of these stents was their application for transient colon decompression in cases of potentially curable colorectal cancer obstruction prior to definite surgery [11, 12]. SEMS insertion can decrease the morbidity and mortality before an emergency operation and allow for adequate bowel preparation. As a result, the rate of primary anastomosis was increased, along with a lower rate of stoma formation. It also permitted proximal colon evaluation by colonoscopy for assessing tumor stage. This approach also resulted in a reduced hospital stay [13–15].

SEMS insertion also enabled the surgeon to perform laparoscopic surgery as a bridging procedure in a controlled setting. Therefore, elective laparoscopic surgery can be performed after SEMS insertion to provide better results. We have previously reported shorter mean operative times, faster recovery of normal bowel movements, and shorter postoperative hospital stays for this combined approach, compared with emergency open surgery in patients with left-sided colon obstruction who underwent primary anastomosis [14]. Although only a few patients were enrolled subsequently, as the randomized controlled trial was reported, the SEMS proved its benefits and safety as a bridge to surgery [16]. However, while stenting is becoming a more frequent treatment modality, the potential of stent-related tumor metastasis and the oncologic safety for patients undergoing stenting, combined with laparoscopic surgery, are unknown. To our best knowledge, there were limited studies of the oncologic outcomes of stent–laparoscopy (SLAP). Therefore, the aim of this study was to compare the oncologic outcomes of laparoscopic surgery following the use of SEMS with those of one-stage emergency open surgery using intraoperative colonic lavage.

Methods

From April 1996 to October 2007, 125 of 2,049 patients with left-sided colon and rectal cancers presented with acute bowel obstruction. Twenty-three patients and seven patients were excluded from this study because of a staged operation and a subtotal or total colectomy, respectively. Patients with bowel perforations or hemodynamic instability at the time of diagnosis were also excluded. The SLAP group included 25 patients who underwent laparoscopic colorectal resection after successful colon stenting, whereas the open lavage (OLAV) group included 70 patients who underwent primary anastomosis with resection of the colon or rectum after intraoperative colonic lavage (Fig. 1).

A SEMS was inserted using colonoscopy under fluoroscopic guidance as described previously [11, 17]. To confirm the stent expansion and position, plain abdominal X-rays were taken 24 h after the procedure. Technical success was defined as the satisfactory deployment of the stent at the location of the stenosis and clinical success was defined as alleviation of clinical obstructive symptoms. The patients with the SEMS after a week underwent elective laparoscopic colorectal resection after the mechanical bowel preparation. Operative details for the SLAP group and the open surgery with on-table lavage were described in our previous report [14].

Patients were followed up every 3 months for 2 years, every 6 months for the next 3 years, and once annually thereafter. Clinical examinations were performed and the serum level of carcinoembryonic antigen was monitored at each visit. Chest X-rays and abdominal computed tomography scans were obtained every 6 months. Full colonoscopy was also performed 6 months after surgery and then once every 3 to 5 years thereafter. Positron emission tomography scans were ordered selectively when abnormalities on other examination surfaced. For adjuvant chemotherapy, patients with stage II–IV cancer received oral tegafur–leucovorin or infusions of 5-fluorouracil–leucovorin for 6–12 months. Oral capecitabine or infused 5-fluorouracil added to oxaliplatin

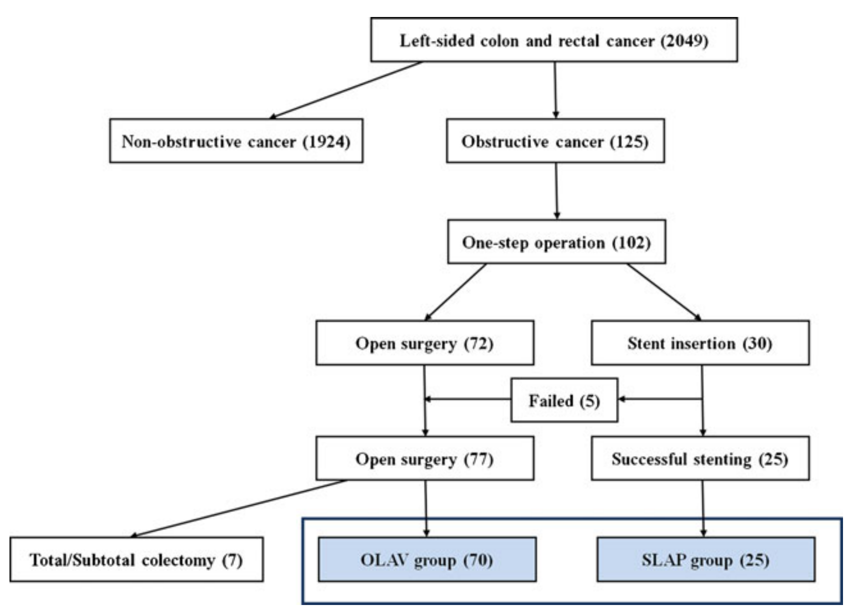

Fig. 1 Algorithm for selecting patients included in the study

was also used for patients with high-risk stage II and III or metastatic colorectal cancers. Tumor recurrence was classified as clinical, radiological, and/or pathological evidence of a tumor. The sites of the recurrence were classified as locoregional, distant, or peritoneal seeding. Tumors in areas contiguous to the primary resection bed or at the anastomotic site constituted local recurrence.

Data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Student's t test was used for comparing means and the χ^2 test was used for frequencies where appropriate. Survival curves were generated using the Kaplan–Meier method; factors were compared using the logrank test and $p<0.05$ was considered statistically significant.

Results

SEMS insertion was attempted prior to the operation in 30 patients and was successful in 25 of them with a clinical and technical success rate of 83.3 %. The procedure was unsuccessful in four patients because the guide wire could not pass through the tumor because of a complete obstruction, and one patient with a sigmoid colon cancer obstruction had developed a colonic perforation during stent insertion. These five patients underwent emergency open surgery with the intraoperative lavage followed by the resection and primary anastomosis.

There were no significant differences between groups in the patients' baseline characteristics (Table 1). Furthermore, both groups were similar with respect to the extent of the primary tumor, lymph node status, and TNM stage (AJCC sixth edition). However, perineural invasion (PNI) of the primary tumor was significantly more frequent in the SLAP group (p=0.033).

Overall survival and cancer-related survival

The median follow-up was 51 months (range, 4–139 months): 43 months in the SLAP group and 54 months in the OLAV group (p=0.106). Adjuvant chemotherapy was administered to 21 patients (84 %) of the SLAP group and 46 patients (65.7 %) of the OLAV group (p=0.085). The 5-year overall survival rate was not significantly different between groups, with 67.2 % in the SLAP group and 61.6 % in the OLAV group (p=0.385, Fig. 2a). Moreover, the 5-year cancer-related survival was not significantly different between groups: 77.0 % in the SLAP group and 65.0 % in the OLAV group (p=0.233, Fig. 2b). Six patients died from unrelated causes of tumor progression: two acute myocardial infarction in SLAP group and two traffic accidents, one hepatic failure as a result of liver cirrhosis, and one pneumonia during chemotherapy in OLAV group.

Table 1 Clinicopathological characteristics of the patients

	SLAP group (n=25)	OLAV group (n=70)	p value
Age, years[a]	61.6 (46–80)	61.7 (23–90)	0.95
Sex, no. (%)			0.62
Male	15 (60.0)	47 (62.7)	
Female	10 (40.0)	23 (37.3)	
Tumor location, no. (%)			0.52
Splenic flexure	1 (4.0)	6 (8.0)	
Descending colon	0	11 (14.7)	
Sigmoid colon	17 (68.0)	31 (41.3)	
Rectum	7 (28.0)	21 (36.0)	
Differentiation, no. (%)			0.452
Well	0	9	
Moderately	21	52	
Poorly	2	4	
Mucinous	1	2	
Signet ring cell	1	3	
Extent of primary tumor[b], no. (%)			0.169
T2	0	3 (4.3)	
T3	13 (54.2)	48 (68.6)	
T4	11 (45.8)	19 (27.1)	
Lymph node metastasis[b], no. (%)			0.769
N0	13 (52.0)	34 (48.6)	
N1-2	12 (48.0)	36 (51.4)	
TNM stage[b], no. (%)			0.74
I	0	1 (1.3)	
II	11 (44.0)	30 (42.9)	
III	9 (36.0)	30 (42.9)	
IV	5 (20.0)	9 (12.9)	
No. of retrieved lymph node[a]	28.9 (2–75)	24.4 (4–92)	0.25
Lymphatic invasion, no. (%)	15 (60.0)	46 (65.7)	0.609
Perineural invasion, no. (%)	19 (76.0)	36 (51.4)	0.033
Lymphocyte infiltration, no. (%)	19 (76.0)	58 (82.9)	0.453
Adjuvant chemotherapy, no. (%)	21 (84.0)	46 (65.7)	0.085

[a] Values in parentheses are mean (range)

[b] According to the AJCC sixth edition

Disease-free survival and tumor recurrence rates

The overall rate of tumor recurrence for patients with stage I, II, and III disease was 27.3 %. Seven patients (35 %) in the SLAP group experienced recurrence. The site of the first recurrence was a distant organ including liver, lung, and multiple organs in six patients and the peritoneum in one patient. There was no locoregional recurrence in any of the cases. Of the OLAV group, 21 patients (35 %) experienced recurrences. One patient developed locoregional recurrence in

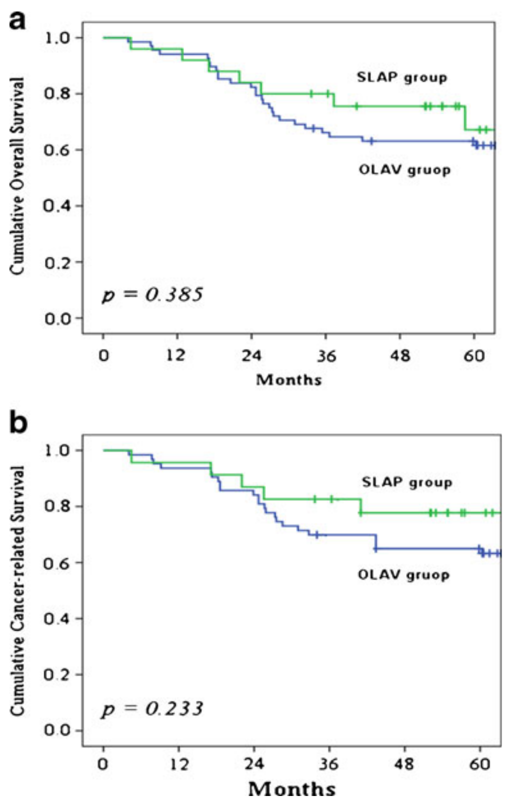

Fig. 2 Kaplan–Meier survival analyses of 5-year overall (**a**) and cancer-related survival rates for patients with obstructive left-side colorectal cancer (**b**)

the pelvic cavity and distant metastases including the liver, lung, bone, and multiple organs developed in 12 patients, in the peritoneum in 7 patients, and the rectus abdominis muscle in 1 patient. Peritoneal metastasis was more common in the OLAV group, although the site of recurrence was not statistically significant between groups (Table 2). The 5-year disease-free survival rates of 61.2 % for the SLAP group and 60.0 % for OLAV group showed no significant difference (p=0.932, Fig. 3).

Table 2 Tumor recurrences in patients with curative resection of obstructing left-sided colorectal cancer

	SLAP group (n=20)	OLAV group (n=60)	p value
Tumor recurrence, no. (%)	7 (35.0)	21 (35.0)	1.000
Type of recurrence, no.			0.572
Locoregional recurrence	0	1	
Distant metastasis	6	12	
Liver	2	4	
Lung	3	1	
Bone	0	1	
Multiple	1	3	
Peritoneal seeding	1	7	
Others[a]	0	1	

[a] Rectus muscle metastasis

Overall survival and disease-free survival among patients with stage II and III disease

Forty-one patients had stage II disease. Of these, seven patients in the OLAV group died and 11 developed a recurrence, which included three patients in the SLAP group and eight in the OLAV group. The 5-year overall survival and 5-year disease-free survival rates were comparable (p=0.103 and p=0.404, respectively, Table 3). Among the 39 patients with stage III disease, 14 in the OLAV group and four in the SLAP group were dead at 5 years, while tumor recurrence developed in four patients in the SLAP group and 13 patients in the OLAV group. The 5-year overall survival and disease-free survival rates were similar between groups (p=0.948 and p=0.394, respectively, Table 3).

Overall survival in patients with stage IV disease

Fourteen patients with stage IV disease underwent surgery. The median follow-up was 23.3 months (range 2–85) and the 5-year overall survival was 28.6 %. Four patients are currently alive, with or without disease. One patient underwent liver resection for hepatic metastasis 7 months after primary colorectal resection in the OLAV group. Within the SLAP group, two patients underwent synchronous liver resections for hepatic metastases and one patient underwent synchronous metastatectomy for a lung metastasis. Of these four patients, three patients are still alive, although one patient underwent a second operation, laparoscopic hysterectomy with bilateral salpingo-oophorectomy for an ovarian metastasis.

Positive vs. negative perineural invasion

As mentioned before, PNI was more frequent in the SLAP group. Regardless of surgical methods, 55 (57.9 %) patients

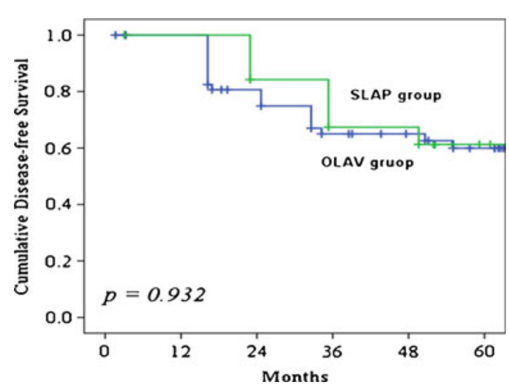

Fig. 3 Kaplan–Meier survival analyses of 5-year disease-free survival rates for patients with obstructive left-sided colorectal cancer

Table 3 Kaplan–Meier survival analyses of 5-year overall and disease-free survival rates in stage II disease and 5-year overall and disease-free survival rates in stage III disease

	SLAP group	OLAV group	*p* value
5-year overall survival rate[a], %	100.0	77.9	0.103
5-year disease-free survival rate[a], %	72.7	63.6	0.404
5-year overall survival rate[b], %	66.7	54.8	0.948
5-year disease-free survival rate[b], %	45.0	54.5	0.394

[a] Stage II disease

[b] Stage III disease

were classified as PNI positive and 45 (42.1 %) as PNI negative. Lymphatic invasion was closely related to being PNI positive but PNI positivity showed no significant association with age, gender, tumor stage, or venous invasion (Table 4). Forty-one patients (74.5 %) who were PNI positive and 26 patients (65.0 %) who were PNI negative received chemotherapy ($p=0.366$). The 5-year overall survival and disease-free survival rates relative to PNI status were not significantly different ($p=0.527$ and $p=0.084$, respectively).

One patient with stent-induced perforation

One patient suffering from colonic perforation during stent insertion underwent emergency open anterior resection with intraoperative colonic lavage but did not require the formation of a stoma. This patient is currently alive 62 months postoperatively and remains disease-free.

Discussion

This present study showed that SLAP was oncologically comparable to emergency open surgery for the treatment of patients with left-sided obstructive colorectal cancers, although perineural invasion was more frequent in the SLAP group. These results document the oncologic safety of this procedure and add to our previous study reporting its feasibility [14] by providing details on successful early postoperative outcomes.

The traditional treatment of patients with an obstructive left-sided colon cancer was a multistage operation with temporary or permanent colostomy aiming to minimize anastomotic disruption. However, as SEMS was introduced in the early 1990s [9], this new therapeutic option for malignant colon obstruction has changed previous treatment concept confined to emergent or multistage open surgeries. SEMS was initially used as a palliative treatment for patients with advanced obstructing carcinomas, [10], but several years later, it is being used as a “bridge to surgery” to decompress the colon before definitive surgical treatment in cases of potentially curable colorectal cancer obstructions [11, 12, 18]. The technical safety and efficacy of SEMS for left-sided colorectal obstruction have been reported in three review articles [13, 19, 20]. According to their results, the reported technical and clinical success rates were 85–100 %, with acceptable rates of complications such as perforations, bleeding, stent migration, re-obstruction, and pain. The most

Table 4 Clinicopathological characteristics and oncologic outcomes of the patients according to perineural invasion positivity

	PNI (−) (*n*=40)	PNI (+) (*n*=55)	*p* value
Age, years[a]	61.6 (38–84)	61.0 (23–90)	0.823
Sex, no. (%)			0.831
Male	24 (60.0)	35 (63.6)	
Female	16 (40.0)	20 (36.4)	
Tumor location, no. (%)			0.111
Colon	32 (80.0)	35 (63.6)	
Rectum	8 (20.0)	20 (36.4)	
Extent of primary tumor[b], no. (%)			0.089
T2	3 (7.5)	0	
T3	23 (57.5)	38 (70.4)	
T4	14 (35)	16 (29.6)	
Lymph node metastasis[b], no. (%)			0.810
N0	20 (50.0)	24 (43.6)	
N1–2	20 (50.0)	31 (56.4)	
TNM stage[b], no. (%)			0.077
I	1 (2.5)	0	
II	20 (50.0)	20 (36.4)	
III	17 (42.5)	23 (41.8)	
IV	2 (5.0)	12 (21.8)	
Lymphatic invasion, no. (%)			0.001
L0	22 (64.7)	12 (35.3)	
L1	18 (29.5)	43 (70.5)	
Venous invasion, no. (%)			0.295
V0	38 (95.0)	48 (87.3)	
V1	2 (5.0)	7 (12.7)	
Adjuvant chemotherapy, no. (%)	26 (65.0)	41 (74.5)	0.366
Tumor recurrence[c], no. (%)	10 (26.3)	17 (39.5)	0.243
5-year overall survival rate	69.2 %	61.9 %	0.527
5-year disease-free survival rate[c]	73.4 %	49.5 %	0.084

PNI perineural invasion

[a] Values in parentheses are mean (range)

[b] According to the AJCC 6th edition

[c] Among 95 patients, 38 patients in PNI (−) group and 43 patients in PNI (+) group to be enabled curative resection were analyzed

serious complication was a perforation with the risk for dissemination of tumor cells was reported to be 0–16 %. In the present study, the clinical and technical success rate was 83.3 % and the perforation rate was 3.3 %, comparable to previous studies [13, 19, 20].

Regardless of several advantages of stent insertion prior to surgery, when we applied SEMS to patients with obstructive colorectal cancer, its impact on oncologic outcomes and the long-term results of SLAP have not yet been fully clarified [21]. Three previous studies have been conducted, focusing on elective open surgery after SEMS insertion and analyzing long-term survival compared with emergency open surgery [8, 22, 23]. Saida et al. [22] demonstrated no significant difference in 5-year overall survival rates between emergency surgery and elective surgery after stent insertion (44 vs. 40 %). However, a primary anastomosis was not incorporated uniformly in any of these studies, and in most cases, elective open surgery was performed. Therefore, this study is a meaningful report in which oncologic outcomes have been examined in patients undergoing laparoscopic surgery after SEMS insertion compared with emergency open surgery with primary anastomosis.

The 5-year overall and cancer-related survival rates in the SLAP group in this study were equivalent to those of the OLAV group, and the disease-free survival and recurrence rates were also comparable between groups. Furthermore, rates for cancer-related and disease-free survival trended higher with SLAP, although not to a statistically significant extent. When we subclassified the patients according to stage II and III disease, the 5-year overall survival and disease-free survival rates were also not significantly different between the two groups.

We achieved better 5-year overall and disease-free survival rates in both groups with an aggressive operative and postoperative approach compared with another previous study [21, 24]. Except for patients with stage IV tumors, all patients we underwent curative resection. Sixty-seven patients (70.5 %) received chemotherapy but the remainder did not complete the chemotherapy course because of its complications, economic problem, or patients' refusal. Fourteen patients with stage IV disease were included in our study, all having had resection of advanced primary tumors. The overall survival at 20–67 months was reported in a published series [25, 26], for our patients with stage IV disease, the median survival was 34 months (range 1–105). Three patients underwent synchronous resections for lung and liver metastases in the SLAP group with the aim of curative treatment by performing exact preoperative staging. Their overall survival was 39 months; two of the patients are still alive, although one patient required a second operation for a recurrent ovarian tumor.

We observed four patients with clinical failure and one with a perforation who underwent emergency open resection with primary anastomosis. This single instance of a perforation during stent insertion was an acceptable complication of the stent procedure compared with the high postoperative mortality and morbidity associated with emergency operations. Furthermore, one patient who suffered a colon perforation 62 months after the surgery has not experienced any tumor recurrence and is still alive. However, it is difficult to demonstrate the effect of complications on survival or recurrence because of the low overall complication rate with this small study. Therefore, a larger study is needed to evaluate the impact on the survival of this complication associated with SEMS insertion.

The impact of SEMS on oncologic outcomes also had not been demonstrated in previous studies examining potential tumor dissemination into the surrounding lymphatics caused by radial stent expansion. Interestingly, we found more PNI in the stent insertion group with no difference in the degree of lymphatic invasion. Whether PNI is a definite prognostic factor remains controversial, as several reports have suggested that PNI influences the prognosis after colorectal cancer resection [27, 28]. Leibig et al. [29] demonstrated that PNI is associated with decreased survival on multivariate analysis and established that PNI is an independent predictor of outcome in patients with colorectal cancer. Multivariate analysis also revealed that patients with PNI-positive tumors were approximately twice as likely to die from their colorectal cancer. Another study demonstrated that, in patients with malignant colon obstruction, poor outcome is associated with the presence of neural invasion [30]. In our study, the PNI-positive rate was more frequent in patients with lymphatic invasion, but it did not influence the 5-year overall or disease-free survival rates. PNI-positive patients did not receive chemotherapy significantly more frequently, but no effect of chemotherapy on oncologic outcome could be demonstrated. Although we fail to the effect of PNI on oncologic outcomes according to the SEMS insertion, it is a very meaningful discovery in terms of more PNI positive on stent insertion patients. Although higher positivity of PNI could come from previous stent insertion, it might have an adverse effect during preoperative 7 days only. Therefore, in our opinion, it is too short to be translated into clinical oncologic outcomes. Long-term follow-ups on larger studies are needed to investigate the effects of perineural invasion on oncologic outcomes following stenting.

This study had several limitations. There could have been selection bias in choosing the patients who underwent SEMS insertion. Thus, insertion was not attempted in patients who had completely obstructive disease, as in such cases, the procedure was very difficult. Therefore, selection of patients for SEMS insertion might have benefited the operative outcomes in the SLAP group by eliminating the most difficult cases. In addition, this study was a retrospective cohort even though it was based on a prospectively collected database. Therefore, subjective considerations could have intervened in analyzing the data. As described above, the median follow-up was 51 months for these relatively few patients, so we could not demonstrate the impact of PNI in the SLAP group or document the influence of technical stent complications because of lower perforation rate during stent insertion. Therefore, large-scale studies and further long-term follow-up are needed. Despite these limitations, the present study has provided meaningful data about the safety and efficacy of laparoscopic surgery after stent insertion. It is the first study to evaluate oncologic outcomes in a group of patients with obstructive left-sided colorectal cancers when treated with SEMS plus laparoscopy compared with emergency open surgery.

In conclusion, our data showed that placement of SEMS before elective laparoscopic surgery is safe and achieves a high success rate for patients with obstructing left-sided colon obstruction. The oncologic outcomes were similar between the two groups, although PNI-positive findings were more frequent in the SEMS insertion group. Therefore, we argue that stent placement followed by a laparoscopic resection might be an acceptable first-line therapy for appropriate patients who present with evidence of acute left-sided malignant colon obstruction.

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Conflict of interest Hye Jin Kim, Gyu-Seog Choi, Jun Seok Park, Soo Yeun Park, and Soo Han Jun have no conflicts of interest or financial relationships to disclose.

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