Article

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Long-Term Outcomes of the Self-Expandable Metallic Stent as a Bridge to Surgery versus Elective Surgery without Stent Placement for Colorectal Cancer: A Retrospective Cohort Study

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Background: The uncertainty surrounding whether delaying surgery after self-expandable metal stent (SEMS) placement for neoplastic stricture can yield similar oncologic outcomes as elective surgery remains. This study aims to investigate the impact of elective surgery following SEMS placement for obstructive colorectal cancer (OCC) on patients.
Methods: Patients diagnosed with stage I to III colorectal cancer (CRC) were recruited and randomly allocated into two groups: group A, receiving elective surgery after SEMS placement for obstructive colon cancer, and group B, undergoing elective surgery for non-obstructive colorectal cancer. Following a 1:2 matching process based on age, gender, tumor location, tumor depth, pathological stage, and adjuvant chemotherapy, group A comprised 95 patients, while group B consisted of 190 patients for comparative analysis.
Results: The 5-year disease-free survival (DFS) rate and overall survival (OS) rate were worse in group A (62.3% vs. 70.9%, *p* = 0.086) and (65.6% vs. 75.8%, *p* = 0.093) compared with group B, although these differences were not statistically significant. This discrepancy in long-term oncologic outcomes did not reach significance when the analysis was stratified by tumor perineural invasion (PNI) status. Univariate analysis revealed that SEMS placement was not a poor prognostic factor for DFS (*p* = 0.086).
Conclusions: Elective surgery for obstructive colorectal cancer (OCC) following SEMS placement may exhibit poorer long-term oncologic outcomes compared to elective surgery for non-obstructive colorectal cancer, particularly due to the higher rate of PNI associated with OCC. Upon stratification of patients in each group by PNI status, the observed differences became marginal.

Keywords: colorectal cancer; bowel obstruction; colonoscopy; stenting procedure; SEMS; PNI

Introduction

Colorectal cancer (CRC) ranks among the most prevalent malignant tumors globally. Its incidence has markedly risen in China over recent years [1,2]. Roughly 15–20% of colorectal cancer patients present with symptoms of acute intestinal obstruction upon consultation [3], necessitating emergency surgery to alleviate the obstruction. However, research indicates that emergency surgery carries a complication incidence of 40–50%, with a mortality rate ranging from 15–20%, while elective surgery demonstrates a significantly lower mortality rate, between 0.9% and 6% [4]. Even among patients with the same cancer stage, those undergoing emergency surgery for intestinal obstruction exhibit a poorer prognosis and a heightened risk of metastasis compared to those opting for elective surgery [5]. This disparity may stem from the compromised general condition and nutritional status of obstructed patients, the impact of emergency surgery on their well-being, and the less favorable prognosis anticipated by surgeons at the time [6]. Furthermore, studies reveal that over 51% of patients undergoing emergency surgery necessitate colostomy, with 35.2% requiring a permanent colostomy [7], significantly diminishing patients' quality of life. Hence, whenever feasible, avoiding emergency surgery is advisable.

More than two decades ago, stent placement in the colon was introduced as a "bridge to surgery (BTS)" [8], aiming to supplant emergency surgery with an elective procedure. The 2020 update of the The National Institute for Health and Care Excellence (NICE) guideline acknowledges self-expandable metal stent (SEMS) placement as an effective approach for managing left colorectal cancer with obstruction. Recent meta-analyses suggest that compared to emergency surgery, stent placement as a BTS strategy can enhance the rate of primary anastomosis, decrease the incidence of permanent stoma, lower the occurrence of wound infection, and concurrently reduce surgical mortality and postoperative complication rates [7,9]. Long-term survival investigations indicate that there is no statistically significant difference in 5-year disease-free survival and overall survival between elective surgery following SEMS placement and emergency surgery [10].

Moreover, concerning the prognosis of obstructive colorectal cancer (OCC), studies have elucidated that obstruction contributes to both survival outcomes and postoperative recurrence in colorectal cancer patients. Compared to non-obstructive colorectal cancer, patients with obstructive colorectal cancer exhibit poorer overall survival and a heightened rate of postoperative recurrence [11]. However, certain research has indicated that obstruction's adverse effects on colorectal cancer might be limited to the perioperative phase [12,13]. Furthermore, tumor stage, histological type, and various clinical and surgical factors significantly influence the prognosis of obstructive colorectal cancer (OCC) patients, while obstruction itself may not serve as a significant predictor of survival [14,15]. Nonetheless, patients with OCC who undergo emergency surgery experience a bleaker long-term prognosis compared to those with non-obstructive CRC who opt for elective surgery. To enhance the treatment outcomes of patients with OCC, who necessitate emergency surgery to save their lives, numerous medical scientists are diligently working to find solutions. SEMS placement stands as one such outcome, aiming to transition from emergency surgery to an elective approach. Its objective is to continually enhance the treatment efficacy of OCC, enabling it to achieve comparable treatment outcomes to non-obstructive colorectal cancer at equivalent cancer stages. Therefore, we conducted this study to ascertain whether SEMS placement as a BTS for obstructive neoplastic strictures can yield similar long-term oncologic outcomes as elective resections.

Materials and Methods

Study Design and Patient Selection

We conducted a retrospective analysis involving 203 patients with OCC who underwent SEMS placement and 507 patients with non-obstructive CRC in stages I to III who underwent elective surgery at the Department of Department of Colorectal (Tumor) Surgery, Guangdong Provincial Hospital of Chinese Medicine between June 2012 and April 2019. Patients with stage III CRC were selected for the study. Exclusion criteria included: (1) palliative surgery; (2) emergency operation, and (3) clinical failure of SEMS placement. Patients were categorized into two groups: those who underwent elective surgery after SEMS placement for OCC (group A) and those who underwent elective surgery for non-obstructive CRC (group B). Propensity score matching was employed to mitigate the impact of confounding variables. Propensity scores were computed using the following variables: adjuvant chemotherapy, pathological stage, tumor location, depth, and age. Patients with clinical failure of SEMS placement were excluded from the study due to potential complications that could affect prognosis and long-term outcomes. Ultimately, 95 patients remained in group A, while 190 patients were in group B.

This study scrutinized clinicopathologic variables, stoma formation, and complications, conducting a comprehensive analysis to compare and assess disease-free and overall survival. Disease-free survival was defined as the duration (in months) from the initial resection to either tumor recurrence or death. Overall survival was delineated as the number of months from the first resection to the patient's demise or last known whereabouts if they were still alive. Patients without recorded events at the time of analysis were censored at the most recent assessment date. The Clavien-Dindo classification was utilized to grade the severity of postoperative complications [16].

In our study, the left side of the colon encompassed the splenic flexure, sigmoid colon, and descending colon, while the right side included the cecum, ascending colon, hepatic flexure, and transverse colon. Patients underwent routine follow-up during the initial year, involving phone interviews and office visits every three months, followed by visits every six months thereafter. Follow-up procedures included physical examination, chest and abdominopelvic CT scans, measurement of carcinoembryonic antigen (CEA) levels, and colonoscopy. The median follow-up period was 60.0 months (ranging from 9 to 108 months) in group A and 58.0 months (ranging from 8 to 99 months) in group B, as of April 1, 2022.

This research adheres to the requirements outlined in the Declaration of Helsinki and has received approval from the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (Approval No.: ZE2022-199). In addition, informed consent has been obtained from all participants involved in the study.

SEMS Placement and Surgical Technique

A dedicated team of professionals, experienced in utilizing fluoroscopy and endoscopy for guidance and confirmation, performed all SEMS placements endoscopically. Upon identifying the obstructive lesion, a guidewire was carefully inserted and advanced to the site of the stricture. Guidewires were then employed to traverse the stricture and securely position the stent delivery catheters. Following complete implantation of the stent, the stent delivery catheter was removed. Subsequently, contrast agent injection through the endoscope facilitated the assessment of stent patency, expansion, and potential complications, such as perforation.

We defined SEMS placement as technically successful when the stent traversed the neoplastic stricture without encountering complications such as perforation, reobstruction, displacement, or similar issues. Clinical success was characterized by colic decompression and symptom alleviation persisting until surgery following SEMS placement.

Table 1. Patients' characteristics.

	Group A	Group B	χ^2	Z	p
	N = 95	*N = 190*			
Gender			0.479		0.489
Male	62 (65.3%)	116 (61.1%)			
Female	33 (34.7%)	74 (38.9%)			
Age			1.086		0.297
≥65 years	64 (67.4%)	116 (61.1%)			
<65 years	31 (32.6%)	74 (38.9%)			
Pathological stage			0.063		0.802
II	46 (48.4%)	95 (50.0%)			
III	49 (51.6%)	95 (50.0%)			
Tumor depth			1.585		0.208
T3	67 (70.5%)	147 (77.4%)			
T4	28 (29.5%)	43 (22.6%)			
pN-stage				0.282	0.778
N0	46 (48.4%)	95 (50.0%)			
N1a	11 (11.6%)	22 (11.6%)			
N1b	19 (20.0%)	36 (18.9%)			
N1c	7 (7.4%)	15 (7.9%)			
N2a	4 (4.2%)	9 (4.7%)			
N2b	8 (8.4%)	13 (6.8%)			
Tumor differentiation			3.399		0.065
Moderate	72 (75.8%)	161 (84.7%)			
Poor/mucinous	23 (24.2%)	29 (15.3%)			
Tumor location			0.994		0.803
Right colon	26 (27.4%)	49 (25.8%)			
Left colon	25 (26.3%)	42 (22.1%)			
Sigmoid colon	37 (38.9%)	82 (43.2%)			
Rectum	7 (7.4%)	17 (8.9%)			
Adjuvant chemotherapy			0.253		0.615
Yes	46 (48.4%)	98 (51.6%)			
No	49 (51.6%)	92 (48.4%)			
Lymphatic invasion			2.423		0.120
Negative	61 (64.2%)	139 (73.2%)			
Positive	34 (35.8%)	51 (26.8%)			
Perineural invasion			7.712		0.005
Negative	54 (56.8%)	139 (73.2%)			
Positive	41 (43.2%)	51 (26.8%)			

Upon relief of obstructive symptoms post-SEMS placement, elective surgery was scheduled based on the patient's physical well-being. Similar to the elective surgery group, the choice between laparoscopic or open surgery depended on tumor size and location. The decision regarding the necessity of a stoma was made during intraoperative exploration. All surgical procedures were performed by specialized colorectal surgeons.

Statistical Analysis

Statistical analyses were conducted using SPSS software (IBM Corp., Armonk, NY, USA, released in 2017, Version 25.0). Categorical variables were presented as numbers and percentages. The chi-square test or Mann-Whitney U test was utilized to compare categorical variables. Survival outcomes were compared using the Kaplan-Meier method with log-rank tests. Multivariate analysis was performed using the Cox proportional hazard model. Statistical significance was defined as $p < 0.05$.

Results

Between June 2012 and April 2019, a total of 203 patients with malignant intestinal obstruction underwent SEMS placement, and 197 patients successfully completed the procedure, resulting in a technical success rate of 97.0%. Among these, 172 patients experienced relief from intestinal obstruction, yielding a clinical success rate of 87.3%.

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Of these 172 patients, 95 met the inclusion criteria for this study and were assigned to group A. Concurrently, 507 patients with non-obstructive colorectal cancer underwent elective surgery. Following 1:2 matching based on age, gender, tumor location, tumor depth, pathological stage, and adjuvant chemotherapy, 190 patients were included in group B for comparison with the 95 patients from group A.

Table 1 presents a summary of the characteristics shared by the two cohorts. Age, gender, pathological stage, tumor depth, pN-stage, tumor differentiation, tumor location, lymphatic invasion, and adjuvant chemotherapy were comparable between the two groups. However, patients in group A exhibited a higher rate of perineural invasion compared to those in group B (43.2% vs. 26.8%, $p = 0.005$).

As depicted in Table 2, there were no significant disparities in surgical outcomes between the two groups, except for the rate of diverting stoma construction. Twenty-one patients in group A required a stoma, with one necessitating a permanent stoma (colostomy due to pelvic local tumor recurrence). In contrast, in group B, 22 out of 190 patients required a temporary stoma, and there were no instances of permanent stomas in this group. The statistical difference between the groups was significant ($p = 0.018$). Eighty-two patients (86.3%) in group A underwent a minimally invasive operation compared to 174 patients (91.6%) in group B ($p = 0.166$). Postoperative complications (Clavien-Dindo classification grade II or higher) occurred in 19 cases (20.0%) in group A and 25 cases (13.2%) in group B ($p = 0.132$). However, all complications were resolved with conservative treatment, and neither group experienced postoperative mortality.

In group A, there was a declining trend in 5-year disease-free survival (DFS) and 5-year overall survival (OS) rates compared to group B (DFS: 62.3% vs. 70.9%, $p = 0.086$, Fig. 1; OS: 65.6% vs. 75.8%, $p = 0.093$, Fig. 2). Subgroup analysis (Figs. 3,4) showed no significant difference in the 5-year DFS rate between patients positive or negative for perineural invasion (PNI) (PNI-positive: 47.9% vs. 53.9%, $p = 0.396$; PNI-negative: 73.3% vs. 77.0%, $p = 0.528$). Similarly, the rates of 5-year OS were insignificantly different between the groups (PNI positive: 50.9% vs. 64.6%, $p = 0.306$; PNI negative: 76.6% vs. 79.7%, $p = 0.721$; Figs. 5,6).

Univariate analysis revealed that age, pathological stage, tumor depth, lymphatic invasion, and perineural invasion significantly affected DFS in CRC patients ($p < 0.05$) (Table 3). Additionally, multivariate analysis using the Cox proportional hazards model showed that age ≥65 years, stage III cancer, stage T4 cancer, positive lymphatic invasion, and PNI positivity were all associated with poor DFS (Table 4).

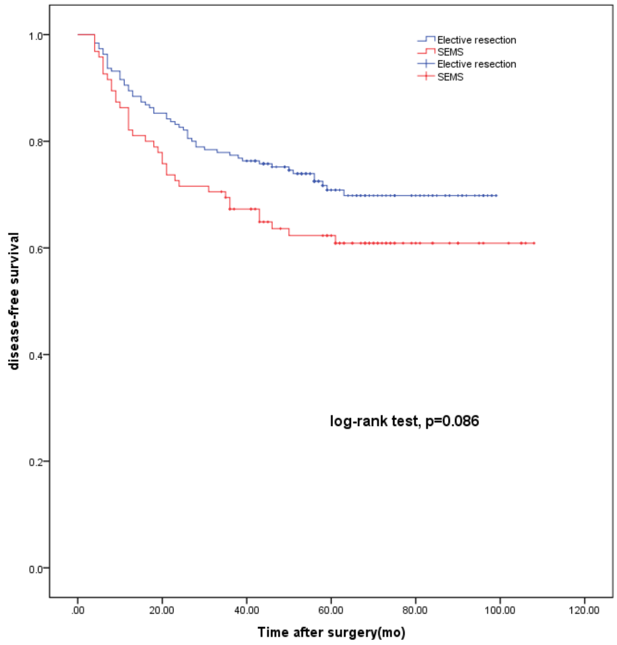

Fig. 1. Kaplan-Meier probability of disease-free survival (DFS). The blue line represents patients with non-obstructive colorectal cancer (CRC) who underwent elective surgery and the red represents patients with obstructive colorectal cancer (OCC) who underwent self-expandable metal stent (SEMS) placement.

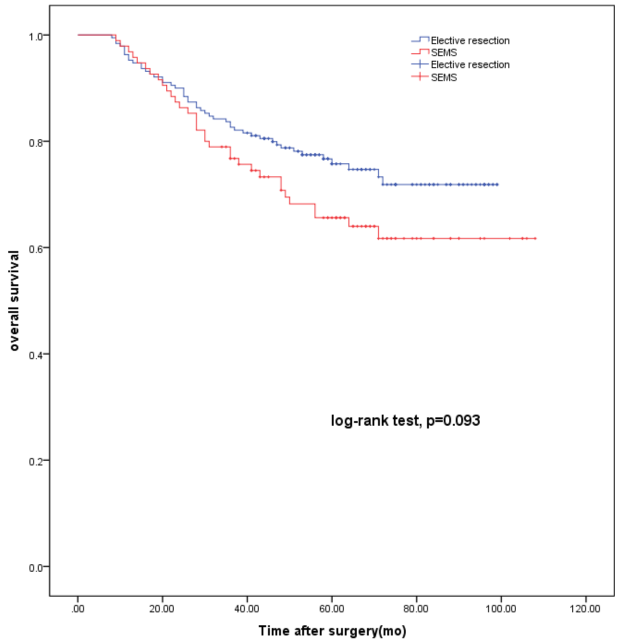

Fig. 2. Kaplan-Meier probability of overall survival (OS).

Discussion

In the present study, patients with OCC who underwent SEMS placement prior to surgery exhibited lower rates of both OS and DFS compared to patients who underwent other elective surgeries without SEMS insertion. However, these differences did not reach statistical signifi-

Table 2. Surgical characteristics and outcomes.

	Group A	Group B	χ^2	p
	$N = 95$	$N = 190$		
Surgery			1.919	0.166
Laparoscopy	82 (86.3%)	174 (91.6%)		
Open	13 (13.7%)	16 (8.4%)		
Surgical procedure			3.108	0.540
Right hemicolectomy	26 (27.4%)	48 (25.3%)		
Left hemicolectomy	25 (26.3%)	42 (22.1%)		
Sigmoid colectomy	34 (35.8%)	81 (42.6%)		
Anterior resection	7 (7.4%)	17 (8.9%)		
Hartmann's procedure	3 (3.2%)	2 (1.1%)		
Stoma			5.582	0.018
No stoma	74 (78%)	168 (88.4%)		
Stoma	21 (22%)	22 (11.6%)		
Postoperative complications (CD $\geq$ grade II)			2.271	0.132
Positive	19 (20.0%)	25 (13.2%)		
Negative	76 (80.0%)	165 (86.8%)		
30-day mortality Negative	0	0	0	1
Postoperative hospital stay			0.760	0.383
$\leq$8 days	64 (67.4%)	118 (62.1%)		
>8 days	31 (32.6%)	72 (37.9%)		

CD, Clavien-Dindo classification.

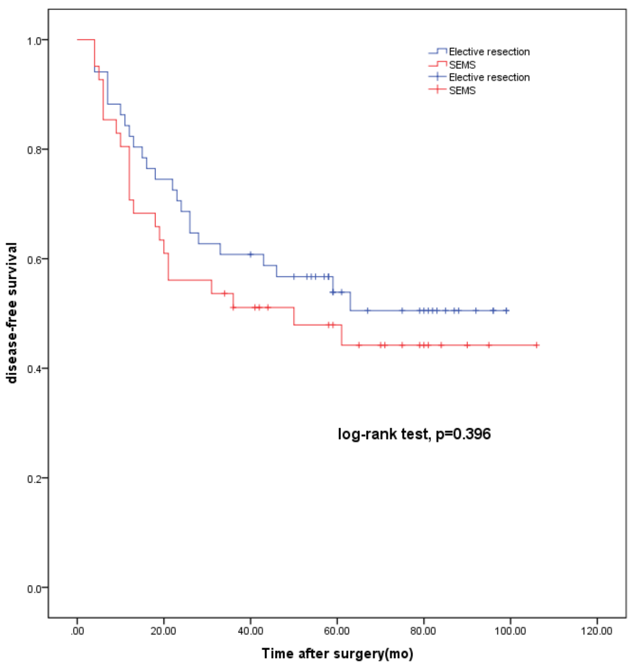

Fig. 3. Kaplan-Meier probability of DFS of patients with perineural invasion (PNI)-positive.

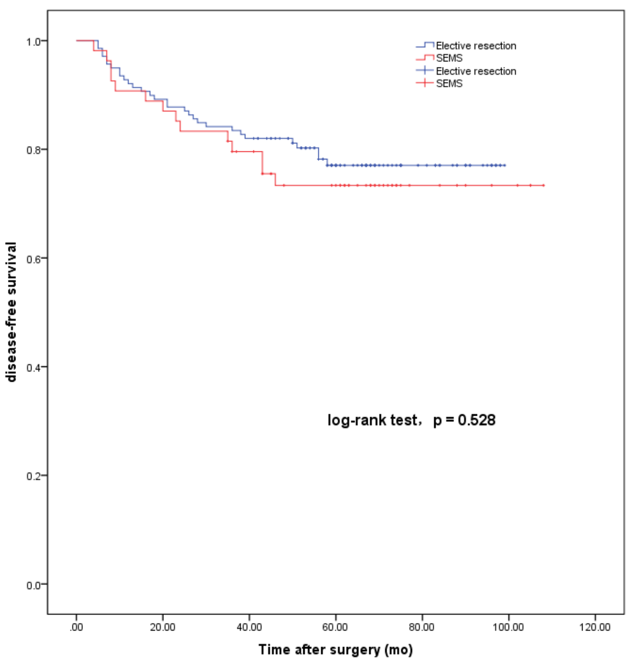

Fig. 4. Kaplan-Meier probability of DFS of patients with PNI-negative.

cance. This finding may be attributed to the higher prevalence of tumor perineural invasion in the SEMS group. Notably, when examining PNI-positive and PNI-negative patient populations separately, both groups demonstrated comparable long-term oncologic outcomes.

Regarding surgical technique, endoscopic surgery rate, postoperative complications, 30-day postoperative mortality, and length of postoperative inpatient stay, there were no significant statistical differences between the two groups. However, the elective surgery group had a lower

Table 3. Univariate analyses of factors for 5-year DFS.

	n	5-year DFS n (%)	χ^2	p
Surgical Procedure			0.168	0.682
Non-stent	128	75 (58.6)		
Stent	79	44 (55.7)		
Gender			0.048	0.827
Female	72	41 (56.9)		
Male	135	79 (58.5)		
Age			7.398	0.007
<65 years	71	50 (70.4)		
≥65 years	136	69 (50.7)		
Pathological stage			22.695	<0.001
II	101	75 (74.3)		
III	106	44 (41.5)		
Tumor depth			20.285	<0.001
T3	155	103 (66.5)		
T4	52	16 (30.8)		
Tumor differentiation			2.754	0.097
Moderate	168	102 (60.7)		
Poor/mucinous	39	18 (46.2)		
Tumor location			1.311	0.252
Right colon	58	37 (63.8)		
Left colon/sigmoid/rectum	149	82 (55.0)		
Adjuvant chemotherapy			0.219	0.640
Yes	98	58 (59.2)		
No	109	61 (56.0)		
Lymphatic invasion			13.477	<0.001
Negative	145	96 (66.2)		
Positive	62	24 (38.7)		
Perineural invasion			14.362	<0.001
Negative	133	90 (67.7)		
Positive	74	30 (40.5)		

DFS, disease-free survival.

Table 4. Multivariate analyses of factors for 5-year DFS.

Prognostic factors	p	Hazards ratio (95% CI)
Age (≥65 years <65 years)	0.002	2.185 (1.340–3.564)
Pathological stage (III/II)	0.014	1.841 (1.129–3.003)
Tumor depth (T4/T3)	0.002	1.966 (1.270–3.043)
Lymphatic invasion (positive/negative)	0.023	1.682 (1.075–2.630)
Perineural invasion (positive/negative)	0.003	1.915 (1.246–2.945)

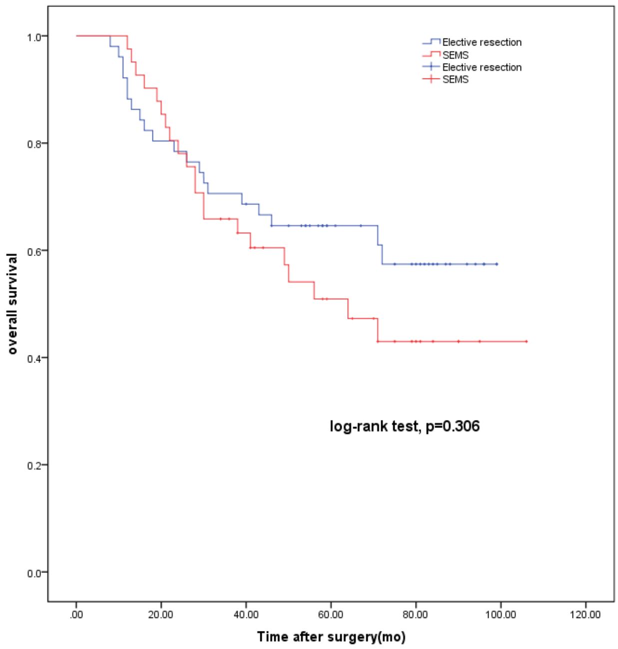

Fig. 5. Kaplan-Meier probability of OS of patients with PNI-positive.

rate of postoperative prophylactic stoma placement compared to the stent implantation group.

Colostomy stent implantation, also known as "bridge to surgery (BTS)", serves as an alternative to emergency surgery [8]. Mauro *et al.* [17] advocated endoluminal SEMS placement in patients with OCC for two main reasons: (a) providing long-term colonic decompression in patients with unresectable OCC, and (b) offering temporary colonic decompression in patients with resectable OCC to facilitate laxative preparation and enable a single-stage surgical resection. Recent meta-analyses have shown that SEMS placement as a BTS can reduce the incidence of wound infection, enhance primary anastomosis rates, decrease the need for permanent stomas, and lower operative mortality and postoperative complications compared to emergency surgery [7,9].

Patients with non-obstructive CRC undergoing elective surgery generally experience better long-term prognoses compared to those with OCC necessitating emergency surgery [18,19]. This discrepancy is attributed, on one hand, to a higher incidence of multiple tumors, more aggressive histopathological features of the tumor, and more advanced stages in patients requiring emergency surgery [20]. On the other hand, in emergency situations, the colon is often distended with a significant amount of feces, and intestinal edema is pronounced, which can impede surgical maneuverability. This not only increases the likelihood of serious postoperative complications but also compromises the thoroughness of lymph node dissection and tumor excision. Moreover, it promotes the dissemination of tumor cells to the peritoneal cavity, lymphatic vessels, and vasculature, leading to tumor recurrence.

Therefore, decompression of the dilated bowel via surgical or non-surgical means is a critical step for individuals with obstructive colorectal cancer. Following SEMS placement, relief of intestinal obstruction enables the transition from emergency to elective surgery, affording surgeons time to comprehensively evaluate and stabilize the patient's condition and physiological state. The optimal surgical team can then perform laparoscopic surgery and complete intestinal reconstruction electively, thus reducing

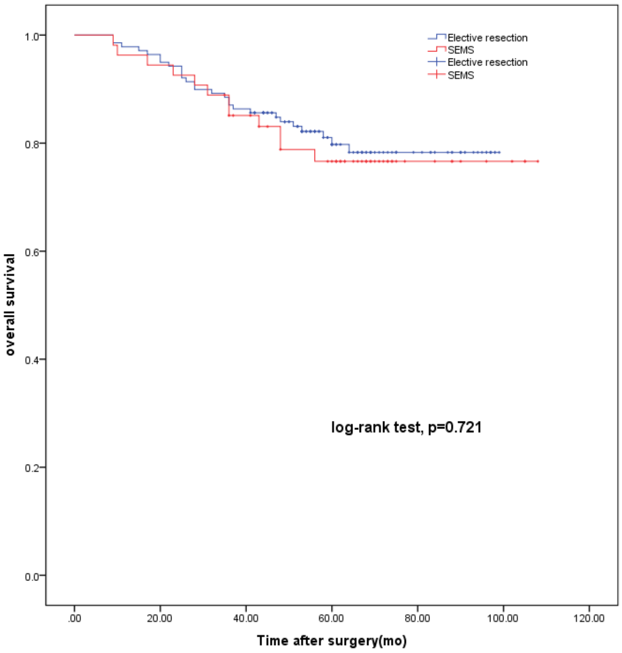

Fig. 6. Kaplan-Meier probability of OS of patients with PNI-negative.

the incidence of perioperative complications and the risk of mortality. This approach aligns with the current principles of damage control surgery [21].

The application of SEMS in the management of malignant tumor-related intestinal obstruction has a history of over 20 years. In recent years, numerous high-quality studies and meta-analyses have consistently indicated that SEMS placement does not result in worse long-term oncological outcomes compared to immediate emergency surgery [22–25]. Moreover, when comparing SEMS placement with concurrent elective surgery for non-obstructive colorectal cancer, two studies highlighted that the long-term results of SEMS placement as a BTS were satisfactory [26,27].

However, Kim *et al.* [28] reported conflicting findings, suggesting that SEMS implantation had a detrimental impact on 5-year overall survival compared to elective surgery for non-obstructive cancer (38.4% vs. 65.6%; p = 0.025). Although these findings did not reach statistical significance, they suggested that SEMS placement as a BTS might be associated with poorer DFS and OS rates compared to elective surgery. This study further delved into the impact of perineural invasion (PNI) on long-term oncological outcomes.

PNI represents a crucial pathway for tumor metastasis alongside lymphatic metastasis, vascular metastasis, and implantation metastasis. In 2009, Liebig *et al.* [29] defined PNI as the presence of tumor cells within the perineural space or inside any layer of the nerve sheath covering at least one-third of the nerve circumference. Positive PNI status has consistently been associated with poorer long-term survival following surgical resection for colorectal cancer [30–34]. Although SEMS placement may potentially increase the rate of perineural tumor invasion [35], recent studies have shown no direct association between preoperative colonic stenting and PNI [36–38]. While PNI may be correlated with obstruction [39], SEMS placement itself is not.

In our study, the SEMS group exhibited a significantly higher incidence of PNI compared to the non-SEMS group (43.2% vs. 26.8%, p = 0.005), which could be attributed to obstruction or SEMS placement. We posit that the increased incidence of perineural tumor invasion in the SEMS group might contribute to their inferior disease-free survival and overall survival, a notion supported by our findings. Upon further comparison of patients with PNI-positive or PNI-negative status in the SEMS and non-SEMS groups, respectively, the disparity between the two groups was notably reduced.

Regarding patients with OCC, univariate analysis revealed that SEMS placement alone was not a significant predictor of poorer DFS. Instead, age ≥65 years, stage III tumor, T4 tumor, positive lymphatic invasion, and PNI-positive status were identified as independent risk factors for poorer DFS.

Cases of malignant tumors in the right colon were included in this study. Traditionally, emergency surgery with primary anastomosis was considered safe for patients with right-sided obstructive colonic cancer. However, recent research suggests that this approach can have a mortality rate of emergency surgery as high as 34% [40–42]. A comparison between right-sided and left-sided OCC conducted by the French Surgical Association revealed that patients with right-sided OCC were typically older and more likely to have comorbidities, a history of cancer, or prior laparotomy. Additionally, a substantial percentage (up to 17%) of patients with right-sided OCC required emergency surgery to establish a definitive stoma [42].

A Dutch study examining the mid-term and long-term effects of various therapies on 1860 patients with right-sided OCC found that the preoperative stent placement group had a significantly lower incidence of complications (27.3%) compared to the emergency surgery group (39.6%), along with a lower 30-day mortality rate [40]. Recent meta-analyses have also confirmed that preoperative stent implantation for right-sided OCC yields similar short-term outcomes to those observed for left-sided OCC, and it can effectively reduce postoperative complications and mortality [43].

In terms of long-term oncological outcomes, recent studies have indicated that preoperative stenting does not worsen OS and DFS in patients with right-sided OCC [44]. Our study findings also corroborate that tumor location and stent placement were not associated with a poor prognosis. Therefore, SEMS placement is recommended for patients with right-sided OCC as well.

Several limitations are associated with this study. Firstly, being a retrospective study conducted at a single center, there is a possibility of selection bias in the patient cohort. Secondly, the study had a relatively small sample size, which may limit the generalizability of the findings. Thirdly, the potential adverse oncological outcomes in patients with clinical failure of SEMS placement were not investigated further in this study.

Conclusions

In the context of long-term oncological outcomes, elective surgery following SEMS installation for obstructive colorectal cancer may exhibit less favorable results compared to elective surgery for non-obstructive colorectal cancer, primarily due to a higher risk of perineural invasion. However, when patients from each group were stratified by PNI status, the observed difference diminished considerably. We uphold the safety and reliability of SEMS implantation in the treatment of obstructive colorectal cancer. Nonetheless, prospective randomized controlled studies with large sample sizes are imperative in the future to validate the relationship between SEMS placement and the incidence of perineural tumor invasion, as well as to assess the efficacy of SEMS installation in the management of obstructive colorectal cancer.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

Conceptualization, BZ and DD; Methodology, BZ and DD; Validation, JL, WL and JW; Formal analysis, BZ and JL; Investigation, BZ and WL; Resources, DD; Data curation, HL, XY and XF; Writing—Original Draft Preparation, BZ, JL, WL, JW and XF; Writing—Review and Editing, DD, HL and XY; Visualization, BZ; Supervision, DD; Project administration, DD; Funding acquisition, DD. All authors have read and approved the final version and are accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This research adheres to the requirements outlined in the Declaration of Helsinki and has received approval from the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (Approval No.: ZE2022-199). In addition, informed consent has been obtained from all participants involved in the study.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

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