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Outcomes of stent insertion and mortality in obstructive stage IV colorectal cancer patients through 10 year duration

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Abstract

Background Colorectal stents are frequently used in patients with stage IV colorectal cancer with obstruction. However, there are only few studies on changes in outcomes of these patients and on the effect of stents on outcome over a long period of time with ongoing changes in therapeutic strategy, including chemotherapy.

Methods We retrospectively evaluated 353 patients with bowel obstruction in stage IV colorectal cancer who underwent colonic stenting between years 2005 and 2014. The study population was divided into three groups based on time periods: 2005–2008, 2009–2011, and 2012–2014.

Results The frequency of colorectal stent insertion procedure increased over the time periods (13.8%, 18.3%, and 20.8%, respectively). There were no changes in success rate and total complication rate. However, the early complication rate in the 3rd period was significantly lower than in the other periods (15.4% vs. 17.1% vs. 7.2%; $P=0.039$). In the multivariate analysis, carcinomatosis (hazard ratio, 1.478; 95% confidence interval, 1.016–2.149; $P=0.041$) and covered or partial-covered stent (hazard ratio, 1.733; 95% confidence interval, 1.144–2.624; $P=0.009$; hazard ratio, 1.988; 95% confidence interval, 1.132–3.493; $P=0.017$, respectively) were associated with increased complication rate. Stent-related perforation was an independent risk factor related with increased mortality. Although survival duration increased over time ($P=0.042$), the mortality rate was unchanged across the three time periods.

Conclusions Over 10 years, the targeted agent use and survival duration increased, and early complication rate was decreased, without change in late complication rate or mortality rate during the three time periods in patients with obstructive stage IV colorectal cancer and stent insertion.

Keywords Colon stent · Colorectal neoplasm · Stage IV · Outcome · Mortality

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Abbreviations

CRC	Colorectal cancer
SEMS	Self-expandable metal stent
5-FU	5-Fluorouracil
CEA	Carcinoembryonic antigen
ECOG	Eastern cooperative oncology group
VEGF	Vascular endothelial growth factor
IQR	Interquartile range
HRs	Hazard ratios
CIs	Confidence intervals
LV	Leucovorin

Colorectal cancer (CRC) is one of the most common cancers worldwide, [1, 2] and 8–29% of patients with CRC have colonic obstruction at diagnosis, [2] which may present with additional acute manifestations, including abdominal pain, nausea, vomiting, intestinal ischemia, intestinal rupture,

sepsis, and even death [3]. Since the introduction of the self-expandable metal stent (SEMS) in 1991, [4] this method of treating CRC obstruction has been utilized for various purposes, from palliation of unresectable CRC obstruction to curative aim as a bridge to surgery [5]. However, the use of SEMS for patients with incurable CRC remains controversial [6].

Following the European Society of Gastrointestinal Endoscopy guideline in 2014, SEMS placement is recommended for palliative purposes for colonic obstructions, but not as a bridge to elective surgery in patients with malignant colonic obstructions [1]. However, stent placement may be considered as an alternative to emergency surgery in those with increased risk of post-operative mortality [1]. Thus far, the use of stents in patients with stage IV CRC with obstruction has been recommended; [7, 8] however, following the development of new devices and anti-cancer therapies, physicians' skills, chemotherapy, and radiotherapy have improved. The development of chemotherapy has been crucial in increasing survival in patients with incurable CRC. However, all of the factors related to the survival and the effects of stent complication in obstructive stage IV CRC patients are unknown in stent-inserted stage IV CRC patients.

Chemotherapy is an important therapy in stage IV CRC patients. Since 1950, 5-fluorouracil (5-FU) is still one of the most important chemotherapeutic agents for CRC [9]. However, the introduction of other cytotoxic agents such as oxaliplatin or irinotecan, as well as targeted drugs such as bevacizumab or cetuximab, has changed treatment strategies and contributed greatly to the survival of metastatic CRC patients [10]. In addition, the types and materials of colonic stents have improved over time. Stents were developed from enteral Wallstent (Boston) [11] to uncovered SEMs, [12] covered stent, dual stents [13], and covered ComVi stents [14].

Because of these improvements in stent technology and CRC treatment, we investigated the trends in outcome of colorectal stenting over 10 years in a single tertiary center. Additionally, we aimed to investigate the factors affecting the complication and mortality rates in obstructive stage IV CRC patients with colorectal stent through the 10-year period.

Materials and methods

Patients

Four hundred thirty patients underwent colonic stenting with CRC stage IV between January 2005 and December 2014 at the Severance Hospital, Seoul, Korea. We retrospectively analyzed the medical chart review. Patients with stent cannulation failure ($n=29$), no definite occlusion ($n=38$), fistula ($n=5$), only through-the-scope dilatation ($n=3$), and other compounding factors, such as intussusception ($n=2$), were excluded. Finally, 353 patients with colorectal obstruction in stage IV CRC who underwent colonic stenting were enrolled (Fig. 1). To compare the flow over time, the study population was classified into three groups: 91 patients underwent stenting in 2005–2008 (1st period), 123 patients in 2009–2011 (2nd period), and 139 patients in 2012–2014 (3rd period). This study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and approved by the institutional review board of Severance Hospital.

Baseline characteristics

The baseline characteristics of the patients were obtained, including demographics; comorbidities; site of metastases, including liver, lung, carcinomatosis, distant metastatic node, and others; laboratory findings such as carcinoembryonic antigen (CEA); chemotherapy or radiotherapy; obstruction site; obstruction status; stent type; Eastern Cooperative Oncology Group (ECOG) status; and type of operation.

Definitions

Disease

Stage IV CRC was associated with synchronous distant metastasis to any of the organs [15]. Colonic obstruction was defined by radiologic and clinical findings, including obstructive symptoms such as nausea, vomiting, abdominal discomfort, abdominal distention, and diarrhea [6].

The site of obstruction was recorded as the right side colon (ascending colon, hepatic flexure, or transverse colon), left side colon (splenic flexure, descending, sigmoid, or rectosigmoid colon), rectum, or anastomosis

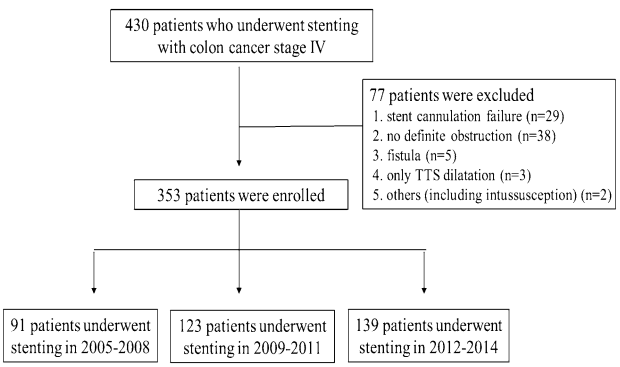

Fig. 1 Patients enrollment in obstructive stage IV colorectal cancer patients with colorectal stent insertion

recurrence site at the location of the initial bowel resection surgery [8].

Colorectal SEMS insertion

The SEMS was placed for palliation of impending or established colonic obstruction precipitated by CRC in patients with unresectable CRC [8]. Additionally, some patients underwent the SEMS procedure as a bridge to surgery to decompress a colonic obstruction and improve their medical condition in patients with resectable stage IV CRC [16]. The procedure was performed by expert gastroenterologists with more than 5 years of experience.

Under sedation, gastroenterologists found the stricture site following the guidewire, and the intraluminal wire position was confirmed with fluoroscopy. Then, the physicians decided the stent type and length. Stent length was determined by allowing at least 2 cm to be exposed proximally and distally from the strictured segment [8]. The stent was placed over the guidewire through the working channel of the endoscope and deployed under direct endoscopic vision with the aid of fluoroscopy [8].

Technical success of colonic stenting was defined as successful placement and deployment of the stent. Clinical success was defined as colonic decompression and relief of obstructive symptoms within 48 h of stent placement with no need for re-intervention [17].

Complications and survival

Complications were classified as early (within 30 days after the procedure) or late (more than 30 days after the procedure) events. Stent-related complications included perforation, re-obstruction, migration, and bleeding, and were managed by either endoscopic re-intervention or surgical treatment. Survival outcomes were measured from the time of SEMS insertion to the time of death [18].

Chemotherapy and targeted therapy

We divided the types of chemotherapy by non-targeted agents and targeted agents. We investigated non-targeted conventional chemotherapeutic agents for metastatic CRC including 5-fluorouracil/leucovorin and oxaliplatin (FOLFOX) and 5-fluorouracil/leucovorin and irinotecan (FOLFIRI) [19]. The targeted agents we examined included the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab, and the anti-epidermal growth factor receptor monoclonal antibody cetuximab [19].

Surgical therapy

The patients who underwent surgery were divided based on the aim of operation in patients underwent colonic stenting with CRC stage IV. Curative aim was defined by the patients who received surgery as a final treatment option including primary tumor with metasectomy such as liver, lung metastasis. It includes the patients who received the stenting as a "bridge to surgery," expecting surgery later. Palliative aim was defined by the patients who had the primary cancer is not curable due to fact that the area is unresectable, but surgery had been done for the following reasons; unexpected situations such as perforation, uncontrolled massive bleeding by endoscopic hemostasis, or unresolved bowel obstruction despite endoscopic stenting.

Statistical analysis

Variables are expressed as median (interquartile range, IQR) or *n* (%). The baseline characteristics were compared using independent Student's *t*-tests (or Mann–Whitney tests) for continuous variables, and χ^2 tests (or Fisher's exact tests) were used for categorical variables, as appropriate. Independent predictors of complication and mortality among the time periods classification (1st to 3rd periods) were analyzed using the Cox proportional hazard regression analysis. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were calculated. In addition, in order to find association of complication free duration, the multiple linear regression analysis was performed. Data analysis was performed with SPSS software (version 20.0; SPSS Inc., Armonk, NY, USA). The trend of colon stent type, management, and complication were presented by grouped-graph using GraphPad Prism 6.0 (GraphPad Software, La Jolla, CA, USA). A P value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 353 patients with stage IV CRC who presented with bowel obstruction underwent colonic stenting from January 2005 to December 2014 at the Severance Hospital, Seoul, Korea.

The study population was stratified into three groups: 2005–2008, 2009–2011, and 2012–2014 (1st, 2nd, and 3rd periods, respectively). A total of 91 patients (13.8% in total 661 patients of stage IV CRC) received colorectal stent insertion from 2005 to 2008, 123 patients (18.3% in total 673 patients) from 2009 to 2011, and 139 patients (20.8% in total 669 patients) from 2012 to 2014 ($P < 0.001$),

indicating an increase in the colorectal stent insertion rate (Supplementary Fig. 1). The baseline patient characteristics are presented in Table 1. The median age (62 years [IQR 48–71] vs. 62 years [IQR 54–70] vs. 66 years [IQR 57–73]; $P = 0.028$) and the use of uncovered and partial-covered stents significantly increased across the three time periods, with decreasing use of covered stents (uncovered, 60.4% vs. 60.2% vs. 79.1%; partial-covered, 0% vs. 8.1% vs. 14.4%; covered, 39.6% vs. 31.7% vs. 6.5%, $P < 0.001$) (Table 1, Supplementary Fig. 2). Sex, underlying disease, metastatic lesion, laboratory findings, chemotherapy, radiation therapy, and obstruction site and status were not statistically significant among the three time periods (Table 1).

Table 1 Baseline characteristics of patients in the three time periods

Variables	Total ($n = 353$)	2005–2008 group ($n = 91$, 25.8%)	2009–2011 group ($n = 123$, 34.8%)	2012–2014 group ($n = 139$, 39.4%)	P value*
Male sex	210 (59.5)	56 (61.5)	74 (60.2)	80 (57.6)	0.820
Age	64 (54–72)	62 (48–71)	62 (54–70)	66 (57–73)	0.028
Underlying disease					
Cardiovascular disease	25 (7.1)	7 (7.7)	5 (4.1)	13 (9.4)	0.242
Diabetes	68 (19.3)	15 (16.5)	18 (14.6)	35 (25.2)	0.072
Hepatitis	13 (3.7)	3 (3.3)	3 (2.4)	7 (5.0)	0.524
Chronic renal disease	15 (4.2)	3 (3.3)	2 (1.6)	10 (7.2)	0.073
Site of metastases					
Liver	268 (75.9)	73 (80.2)	97 (78.9)	98 (70.5)	0.155
Lung	102 (28.9)	22 (24.2)	30 (24.4)	50 (36.0)	0.061
Carcinomatosis	128 (36.3)	28 (30.8)	48 (39.0)	52 (37.4)	0.433
Distant metastatic node	148 (41.9)	31 (34.1)	61 (49.6)	56 (40.3)	0.066
Others (bone, brain, ovary)	47 (13.3)	10 (11.0)	16 (13.0)	21 (15.1)	0.662
Laboratory findings					
CEA	31.3 (7.7–204.3)	26.1 (3.7–162.2)	31.3 (9.2–195.2)	40.0 (8.3–262.3)	0.114
Chemotherapy	298 (84.4)	73 (80.2)	107 (87.0)	118 (84.9)	0.325
Radiotherapy	64 (18.1)	12 (13.2)	29 (23.6)	23 (16.5)	0.123
Obstruction site					0.781
Right.side colon[a]	211 (59.8)	59 (64.8)	71 (57.7)	81 (58.3)	
Left.side colon[b]	72 (20.4)	13 (14.3)	28 (22.8)	31 (22.3)	
Rectum	63 (17.8)	17 (18.7)	21 (17.1)	25 (18.0)	
Anastomotic recurrence	7 (2.0)	2 (2.2)	3 (2.4)	2 (1.4)	
Obstruction status					0.219
Partial	172 (48.7)	46 (50.5)	66 (53.7)	60 (43.2)	
Total	181 (51.3)	45 (49.5)	57 (46.3)	79 (56.8)	
Stent type					< 0.001
Uncovered	239 (67.7)	55 (60.4)	74 (60.2)	110 (79.1)	
Covered	84 (23.8)	36 (39.6)	39 (31.7)	9 (6.5)	
Partial covered	30 (8.5)	0 (0)	10 (8.1)	20 (14.4)	
ECOG					
0–2	345 (97.7)	89 (97.8)	120 (97.6)	136 (97.8)	0.987
3–4	8 (2.3)	2 (2.2)	3 (2.4)	3 (2.2)	
Operation					0.365
Curative aim	94 (51.9)	22 (47.8)	31 (47.7)	41 (58.6)	
Palliative aim	87 (48.1)	24 (52.2)	34 (52.3)	29 (41.4)	

Data are expressed as median (interquartile range, IQR) or *n* (%)

CEA carcinoembryonic antigen, *ECOG* Eastern cooperative oncology group

[a]Transverse colon, ascending colon, cecum

[b]Sigmoid colon, descending colon

*P value for comparing patients with 2005–2008 group, 2009–2011, and 2012–2014 group

Colonic stenting outcomes and complications over 10 years

Table 2 shows the procedure outcomes and complications in all three groups. Three hundred twenty-nine patients (93.2%) achieved clinical success, with an increasing tendency for success with time, but not statistically significant (90.1% for the 1st period vs. 92.7% for the 2nd period vs. 95.7% for the 3rd period; $P = 0.250$). After the procedure, the total complication rate was not statistically different among the three time periods (37.4% vs. 39.8% vs. 30.2%; $P = 0.241$); however, the early complication rate of the 3rd period was significantly lower than that of the 1st period (15.4% vs. 17.1% vs. 7.2%; $P = 0.039$) (Table 2, Supplementary Fig. 3). The most common type of early complication in the 3rd period was bowel perforation (5/10). After re-obstruction or migration, most patients received stent reinsertion (63.5%) as an additional intervention. There was no significant difference in complication-free duration among the three groups (median, 141 vs. 148 vs. 232 days; $P = 0.376$).

Management and chemotherapy

The trends of management in obstructing stage IV CRC patients with stent insertion are shown in Supplementary Fig. 4. The number of patients who received combination chemotherapy with targeted agents significantly increased over time (20.9% vs. 29.3% vs. 44.6%; $P < 0.001$) (Supplementary Table 1, Supplementary Fig. 4). Among the 181 patients who received surgery (Supplementary Table 4), when comparing surgical purpose, curative aim treatment increased and palliative aim decreased across the three periods (Supplementary Fig. 5).

Bevacizumab therapy, which can increase the risk of intestinal perforation when used with colonic stent, [20] increased in frequency (14.3% vs. 24.4% vs. 38.1%; $P < 0.001$) (Supplementary Table 1). To clarify the relationship between bevacizumab use and perforation, we performed the analysis on our study population. In the 3rd period, bevacizumab was more frequently administered both before (1.1% vs. 5.7% vs. 9.4%; $P = 0.035$) and after (13.2% vs. 18.7% vs. 28.8%; $P = 0.013$) colonic stenting, compared with the 1st period (Supplementary Table 1).

Table 2 Outcomes and complications of stent in obstructive stage IV colorectal cancer patients over 10 years

Variables	Total ($n = 353$)	2005–2008 group ($n = 91$, 25.8%)	2009–2011 group ($n = 123$, 34.8%)	2012–2014 group ($n = 139$, 39.4%)	P value*
Clinical success	329 (93.2)	82 (90.1)	114 (92.7)	133 (95.7)	0.250
Complications	125 (35.4)	34 (37.4)	49 (39.8)	42 (30.2)	0.241
Early	45 (12.7)	14 (15.4)	21 (17.1)	10 (7.2)	0.039
Perforation	17 (37.8)	8 (57.1)	4 (19.0)	5 (50.0)	
Obstruction	16 (35.6)	4 (28.6)	8 (38.1)	4 (40.0)	
Migration	4 (8.9)	0 (0)	4 (19.0)	0 (0)	
Bleeding	3 (6.7)	1 (7.1)	1 (4.8)	1 (10.0)	
Others[a]	5 (11.1)	1 (7.1)	4 (19.0)	0 (0)	
Late	86 (24.4)	22 (24.2)	29 (23.6)	35 (25.2)	0.954
Perforation	8 (9.3)	2 (9.1)	2 (6.9)	4 (11.4)	
Obstruction	67 (77.9)	16 (72.7)	26 (89.7)	25 (71.4)	
Migration	5 (5.8)	3 (13.6)	0 (0)	2 (5.7)	
Bleeding	5 (5.8)	1 (4.5)	1 (3.4)	3 (8.6)	
Others[a]	1 (1.2)	0 (0)	0 (0)	1 (2.9)	
Additional intervention after complications	115 (32.6)	31 (34.1)	44 (35.8)	40 (28.8)	0.137
Operation	26 (22.6)	10 (32.3)	10 (22.7)	6 (15.0)	
Re-stent insertion	73 (63.5)	20 (64.5)	28 (63.6)	25 (62.5)	
Others[b]	16 (13.9)	1 (3.2)	6 (13.6)	9 (22.5)	
Complication free duration (days)	176 (49–607)	141 (32–608)	148 (47–632)	232 (75–584)	0.376
Survival duration (days)	367 (148–797)	337 (96–780)	367 (132–888)	378 (173–697)	0.042
Mortality	301 (85.3)	81 (89.0)	106 (86.2)	114 (82.0)	0.322

Data are expressed as n (%)

[a]Anal pain, tenesmus

[b]Balloon dilatation, observation

*P value for comparing patients with 2005–2008 group, 2009–2011, and 2012–2014 group

There was no significant difference in perforation frequency among the three time periods [11.0% (10/91) vs. 4.9% (6/123) vs. 6.5% (9/139); $P = 0.213$]. In addition, when we compared with bevacizumab users ($n = 96$) and non-users (n = 257), there was no significant difference in perforation [7.3% (7/96) vs. 7.0% (18/257); $P = 0.925$].

Relative risk factors of stent complications

In the univariate analysis, the stent type [covered vs. uncovered (HR 1.683; 95% CI 1.132–2.504; $P = 0.010$), partial-covered vs. uncovered (HR 2.066; 95% CI 1.200–3.556; $P = 0.009$)], balloon dilatation under endoscopy (HR 3.943; 95% CI 1.246–12.478; $P = 0.020$), and anastomotic recurrence (HR 3.016; 95% CI 1.100–8.273; $P = 0.032$) were significantly associated with more complications (Table 3). In the multivariate analysis, along with sex, age, underlying

Table 3 Relative risk of complications in obstructive stage IV colorectal cancer patients with colorectal stent insertion

Variable	Uni-variate analysis		Multi-variate analysis	
	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Sex (male)	1.139 (0.794–1.635)	0.479	1.064 (0.729–1.553)	0.747
Age	1.005 (0.991–1.019)	0.476	1.013 (0.996–1.030)	0.125
Underlying disease				
Cardiovascular disease	1.074 (0.748–1.541)	0.700	1.113 (0.745–1.662)	0.601
Diabetes	0.669 (0.414–1.079)	0.099	0.675 (0.410–1.110)	0.121
Chronic renal disease	0.663 (0.211–2.087)	0.483	0.652 (0.200–2.120)	0.477
Metastatic lesion				
Carcinomatosis	1.369 (0.954–1.965)	0.088	1.478 (1.016–2.149)	0.041
Others*	1.019 (0.618–1.680)			
High CEA	1.144 (0.727–1.800)	0.561		
ECOG				
0–2	1.0 (Ref.)		1.0 (Ref.)	
3–4	2.956 (0.927–9.424)	0.067	1.326 (0.313–5.613)	0.701
Obstruction status				
Partial	1.0 (Ref.)		1.0 (Ref.)	
Total	0.885 (0.623–1.257)	0.495	0.952 (0.659–1.376)	0.795
Stent type				
Uncovered	1.0 (Ref.)		1.0 (Ref.)	
Covered	1.683 (1.132–2.504)	0.010	1.733 (1.144–2.624)	0.009
Partial covered	2.066 (1.200–3.556)	0.009	1.988 (1.132–3.493)	0.017
Obstruction site				
Right side[a]	1.0 (Ref.)		1.0 (Ref.)	
Left side[b]	0.621 (0.368–1.049)	0.075	0.617 (0.363–1.048)	0.074
Rectum	1.019 (0.641–1.620)	0.935	1.085 (0.669–1.759)	0.742
Anastomotic recurrence	3.016 (1.100–8.273)	0.032	1.887 (0.467–7.621)	0.373
Balloon dilatation under endoscopy	3.943 (1.246–12.478)	0.020	3.022 (0.606–15.077)	0.178
Chemotherapy	1.194 (0.640–2.228)	0.577	1.220 (0.618–2.405)	0.567
Radiotherapy	0.992 (0.639–1.539)	0.971	1.094 (0.676–1.770)	0.715
Target agent	0.820 (0.566–1.188)	0.294		
Time periods (2005–2008 vs. 2009–2011 vs. 2012–2014)				
2005–2008	1.0 (Ref.)			
2005–2008 vs. 2009–2011	1.028 (0.664–1.593)	0.900		
2005–2008 vs. 2012–2014	0.708 (0.450–1.113)	0.135		

HR hazard ratio, *CI* confidence interval, *CEA* carcinoembryonic antigen, *ECOG* Eastern cooperative oncology group

[a]Transverse colon, ascending colon, and cecum

[b]Sigmoid colon and descending colon

*Metastatic lesions including liver, lung, stage IV lymph node, bone, brain, and ovary

disease, ECOG status, obstruction status, obstruction site, balloon dilatation under endoscopy, chemotherapy, and radiation therapy, we found that carcinomatosis (HR 1.478; 95% CI, 1.016–2.149; $P=0.041$), covered stent [(HR 1.733; 95% CI 1.144–2.624; $P=0.009$), and partial-covered stent (HR 1.988; 95% CI 1.132–3.493; $P=0.017$)] were associated with a higher complication rate (Table 3).

In order to evaluate the factors associated with complication-free periods, we performed the linear regression modeling, and similar results were obtained. The univariate and multivariate linear regression are summarized in Supplementary Table 2. The analyses for complication-free duration for each complication type are shown in Supplementary Table 3. On the multiple linear regression model, carcinomatosis and the rectum and anastomotic recurrence as obstruction sites were negative predictive factors (β values) that influenced the length of the complication-free period (all $P<0.05$) (Supplementary Table 2). However, there were no significant differences in the complication rate among the three time periods by multivariate linear regression ($P=0.192$) (Supplementary Table 2).

Survival and relative risk factors of mortality

The overall mortality rate was 85.3%; there was no statistical difference among the three time periods (89.0% vs. 86.2% vs. 82.0%; $P=0.322$). However, when we compared the survival duration among the three time periods, there was a statistically significant difference (median, 337 vs. 367 vs. 378 days; $P=0.042$) (Table 2).

In the multivariate analysis, we found that carcinomatosis (HR 1.588; 95% CI 1.228–2.052; $P<0.001$), high CEA (HR 1.468; 95% CI 1.069–2.017; $P=0.018$), poor ECOG status (HR 10.856; 95% CI 4.748–24.822; $P<0.001$), the rectum (HR 1.532; 95% CI 1.115–2.106; $P=0.009$), and anastomotic recurrence (HR 11.295; 95% CI 4.995–25.540; $P<0.001$) as obstruction sites, and perforation (HR 2.097; 95% CI 1.282–3.431; $P=0.003$) were significant independent factors for mortality. Chemotherapy (HR 0.464; 95% CI 0.315–0.683; $P<0.001$), administration of targeted agents (HR 0.626; 95% CI 0.473–0.829; $P=0.001$), operation (HR 0.255; 95% CI 0.188–0.347; $P<0.001$), and re-obstruction (HR 0.651; 95% CI 0.485–0.873; $P=0.004$) were associated with decreased mortality (Table 4). Time was not associated with mortality risk (1st period vs. 2nd period, $P=0.444$; 1st period vs. 3rd period, $P=0.993$).

Discussion

CRC is among the most common malignant diseases, and malignant colorectal obstruction has been reported in 8–29% of patients with CRC [2]. Our study shows the changes in management of obstructive stage IV CRC patients and estimates the clinical factors that affect stent-related complications and mortality in these patients. Over time, the early complication rate decreased, and targeted agent usage and survival increased. Carcinomatosis and stent type significantly affected the complication rate. In addition, carcinomatosis, poor ECOG status, high CEA, obstruction site, and perforation were independent factors for increased mortality.

Several studies have reported the effectiveness of SEMSs as initial therapy for the relief of obstructive symptoms in patients with unresectable CRC; [21–24] however, most compared the effects of SEMS and surgery. As a bridge to surgery or for palliative care, SEMS placement achieves more favorable short-term outcomes than does emergency surgery [25]. Lee et al. reported the efficacy of SEMS as a palliation for colorectal obstruction over palliative surgery, with a clinical success rate for SEMS placement of 95.8% and a median stent patency of 137 days. Moreover, the overall complication rate was significantly lower in the SEMS group compared with the surgery group (15.5% vs. 32.9%), and the re-obstruction rate was 12% (range 1–92%) [6]. In our study, the re-obstruction rate was 22.4%, and there were more cases of late complications (77.9%) than early complications (35.6%). In a multi-center prospective study in 2011, short-term complications occurred less often in patients who underwent palliative surgery, while late complications were more frequent in patients who received palliative SEMS placement [26]. We hypothesized that increasing survival of obstructive stage IV CRC patients due to the development of new treatment options could lead to more complications from inserted stents. However, there have been no longitudinal studies. This study included many cases of obstructive stage IV CRC with stent insertion over a 10-year period, and showed the real experience of colon SEMS placement and the low rate of early stent-related complication over time. This might be related to the recent development of colorectal stents with better flexibility and conformability, and the increased usage of uncovered stents. Additionally, we could not see any changes in the late complication rate during the three time periods, which might be related to the increasing tendency of operation with curative aim, which is more common since the introduction of targeted agents.

Since the 2000s, cytotoxic agents such as irinotecan and oxaliplatin have shown excellent efficacy in adjuvant and palliative chemotherapy [10]. Recently, targeted therapy including bevacizumab and cetuximab has contributed to improvements in survival [10, 27–29]. However, in patients with CRC, especially obstructive CRC with stent insertion, gastrointestinal perforation is a rare but important side effect of bevacizumab, one of the targeted agents,[30, 31] a VEGF inhibitor that can block tumor angiogenesis [32]. In our study, among bevacizumab users, there was no significantly increased perforation risk. There were 25 patients

Table 4 Relative risk of mortality in obstructive stage IV colorectal cancer patients with colorectal stent insertion

Variable	Uni-variate analysis		Multi-variate analysis	
	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Sex (male)	0.877 (0.697–1.104)	0.263	0.863 (0.670–1.112)	0.254
Age	1.020 (1.010–1.030)	< 0.001	1.008 (0.997–1.018)	0.142
Underlying disease				
Cardiovascular disease	1.237 (0.981–1.560)	0.072	1.109 (0.845–1.455)	0.455
Diabetes	0.748 (0.555–1.008)	0.056	0.659 (0.478–0.910)	0.011
Chronic renal disease	2.279 (1.352–3.841)	0.002	1.047 (0.585–1.875)	0.878
Metastatic lesion				
Carcinomatosis	1.739 (1.372–2.205)	< 0.001	1.588 (1.228–2.052)	< 0.001
Other*	1.899 (1.065–3.387)	0.030	1.847 (0.980–3.482)	0.058
High CEA	1.569 (1.163–2.116)	0.003	1.468 (1.069–2.017)	0.018
ECOG				
0–2	1.0 (Ref.)		1.0 (Ref.)	
3–4	5.797 (2.837–11.848)	< 0.001	10.856 (4.748–24.822)	< 0.001
Obstruction site				
Right side[a]	1.0 (Ref.)		1.0 (Ref.)	
Left side[b]	1.663 (1.247–2.218)	0.001	1.182 (0.862–1.620)	0.298
Rectum	1.519 (1.124–2.053)	0.007	1.532 (1.115–2.106)	0.009
Anastomotic recurrent	3.403 (1.587–7.297)	0.002	11.295 (4.995–25.540)	< 0.001
Chemotherapy	0.272 (0.200–0.371)	< 0.001	0.464 (0.315–0.683)	< 0.001
Radiotherapy	0.641 (0.473–0.870)	0.004	1.212 (0.868–1.693)	0.260
Target agent	0.564 (0.441–0.722)	< 0.001	0.626 (0.473–0.829)	0.001
Bevacizumab	0.616 (0.475–0.800)	< 0.001		
Cetuximab	0.467 (0.314–0.694)	< 0.001		
Operation	0.266 (0.208–0.342)	< 0.001	0.255 (0.188–0.347)	< 0.001
Complication				
Migration	1.556 (0.800–3.024)	0.193	1.796 (0.898–3.594)	0.098
Bleeding	2.630 (1.294–5.348)	0.008	1.832 (0.871–3.851)	0.110
Perforation	0.925 (0.593–1.442)	0.731	2.097 (1.282–3.431)	0.003
Re-obstruction	0.999 (0.762–1.309)	0.995	0.651 (0.485–0.873)	0.004
Time periods (2005–2008 vs. 2009–2011 vs. 2012–2014)				
2005–2008	1.0 (Ref.)			
2005–2008 vs. 2009–2011	0.893 (0.668–1.194)	0.444		
2005–2008 vs. 2012–2014	0.999 (0.748–1.333)	0.993		

HR hazard ratio, *CI* confidence interval, *CEA* carcinoembryonic antigen, *ECOG* Eastern cooperative oncology group

[a]Transverse colon, ascending colon, cecum;

[b]Sigmoid colon, descending colon

*Metastatic lesions including liver, lung, stage IV lymph node, bone, brain, and ovary

who had perforation, 7 of whom received bevacizumab, but most started bevacizumab therapy 1 month after stent insertion. When SEMS was inserted during 30 days before and after the start of bevacizumab therapy and the stent was inserted while continuing bevacizumab therapy, only 2 of 96 patients had perforation. Moreover, bevacizumab users showed longer survival than non-users (median, 585 vs. 299 days; $P = 0.001$), and bevacizumab therapy was not an independent factor for perforation ($P = 0.806$) [data not shown]. However, bevacizumab therapy was negatively associated with mortality in metastatic CRC patients (HR 0.616; 95% CI 0.475–0.800; $P < 0.001$) (Table 4). Because the role of chemotherapy including bevacizumab could be important in patients with metastatic CRC, more detailed guidelines for the administration of bevacizumab are needed for obstructive stage IV CRC patients who need colorectal stent insertion instead of surgery.

We found that peritoneal carcinomatosis and stent type were significant risk factors for stent complications. Peritoneal carcinomatosis leads to fixed intestinal segments,

and multi-focal strictures to colonic immobilization and adhesions, which precipitate improper stent insertion, low success rate, and complications such as re-obstruction or migration [18]. Covered stents were associated with more complications than were uncovered stents (44.0% vs. 30.1%), and migration was more frequently seen in patients with covered stents (18.9% vs. 1.4%). However, perforation rates were similar between the two stent types (21.6% vs. 22.2%). Therefore, when selecting stent type, the patient's cancer status and risk stratification should be considered. As covered stents were associated with more complications than uncovered stents, our results also suggest the decreased usage of covered stents. However, our study has limitations due to the retrospective study design. Further well-designed studies comparing only the stent types with palliative aim or bridge to surgery patients will be needed.

There have been only few data on risk factors associated with mortality in obstructive stage IV CRC patients with colorectal stent insertion. In our study, patients with peritoneal metastases, poor ECOG status, high CEA level, obstruction of the rectum or anastomotic recurrence, and perforation had a higher risk of mortality. However, although perforation was a poor prognostic factor, re-obstruction was related with lower mortality in our study. We think that more re-obstructions by stent migration and restenosis can be caused by chemotherapy-induced tumor shrinkage and fibrotic change, [33] which could be related to increased survival. In addition, most of the re-obstructions due to migration and tumor ingrowth were solved by reinsertion of the stent, and were not directly related to definite progression of metastatic lesions.

From these results, our study showed the trend of 10 years' management and complications, and we suggest careful selection of decompression treatment in obstructive stage IV CRC patients and follow-up management including targeted chemotherapy, considering risk factors of complication and mortality. However, this study was retrospective in a single center and could have shown a selection bias with heterogeneity in the study population, which might have influenced the statistical limitation.

In conclusion, throughout 10 years, the frequency of use of targeted agent and survival duration increased, while the early complications of stent insertion decreased. Considering the risk factors associated with complications and mortality, colonic stenting should be carefully performed in patients with metastatic CRC with bowel obstruction.

Compliance with ethical standards

Disclosures Yong Eun Park: acquisition of data, analysis and interpretation of data, drafting of the manuscript. Yehyun Park: critical revision of the manuscript for important intellectual content. Soo Jung Park, Jae Hee Cheon, and Won Ho Kim: critical revision of the manuscript for important intellectual content. Tae Il Kim: acquisition of data; study concept and design; critical revision of the manuscript for important intellectual content. All authors approved the final version of the article, including the authorship list. Dr. Yong Eun Park, Dr. Yehyun Park, Dr. Soo Jung Park, Dr. Jae Hee Cheon, Dr. Won Ho Kim, and Dr. Tae Il Kim have no conflict of interest or financial ties to disclose.

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