Safety and Oncological Outcomes of Bevacizumab Therapy in Patients With Advanced Colorectal Cancer and Self-expandable Metal Stents

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Abstract

Colorectal cancer can present with bowel obstruction, and self-expandable metal stents can be an alternative to surgery. Data on the safety of stents during bevacizumab treatment are lacking. The major early risk is perforation that can increase up to 12% during bevacizumab treatment. In patients that would benefit from self-expandable metal stents, we should consider the risks associated with systemic therapies, taking into account the improvement in survival with bevacizumab.

Background: Malignant bowel obstruction can occur in 18% of cases. Self-expandable metal stents (SEMS) can be an alternative to surgery. Bevacizumab (BV) has been associated with bowel perforation, but data on the safety of SEMS for occlusive colon cancer during BV-containing regimens are lacking. **Material and Methods:** This is a retrospective analysis of 78 patients with malignant bowel obstruction who underwent placement of SEMS as a palliative intent for stage IV disease. Chemotherapy and BV-containing regimens, stent-related complications, and outcomes were recorded. **Results:** Overall, major stent-related complications were observed in 27 (35%) patients: Re-obstruction occurred in 14 (52%) patients, and there were 7 (26%) perforations, 4 (15%) minor bleeding, and 2 (7%) migrations. Sixteen patients received BV; 2 (12.5%) had a perforation. No differences were observed between chemotherapy alone and BV in overall complications. Univariate analysis did not show that BV was more likely to develop perforations, although the incidence was higher in this subset of patients. Kaplan-Meier analysis showed a significant association with longer overall survival for patients treated with systemic therapy (27 vs. 11 months; $P \leq .00001$). Also, there is a significant benefit of BV compared with chemotherapy alone (43 vs. 39 months; $P = .02$). **Conclusion:** Placement of SEMS is effective and relatively safe but with an overall complication rate of 35% in the metastatic setting. The major early risk is perforation, which can increase up to 12% during BV treatment. In patients with obstructing advanced colorectal cancer that would benefit from SEMS, we should consider the risks associated with systemic therapies, taking into account the improvement in survival observed with BV.

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Introduction

Colorectal cancer (CRC) is the third most common cancer in males and the second in females worldwide.[1] Large-bowel obstruction caused by advanced colon cancer occurs in 8% to 13% of patients.[2] In approximately 30%, curative resection is not feasible because of advanced disease and comorbidities.[3] Morbidity and mortality rates for patients who undergo emergency surgery have been quoted at 30% to 65% and 15% to 35%, respectively,

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and up to 40% of those patients are left with a permanent colostomy.[3] Patients with a permanent stoma frequently report complications and poorer health-related quality of life than do patients without colostomy.[4]

Enteral stents are used increasingly as a non-surgical alternative for the treatment of acute obstruction in luminal gastrointestinal neoplasms.[5] In tertiary care centers, self-expandable metal stent (SEMS) placement achieves more than 90% to 95% technical and clinical success rates.[6] Moreover, sustained relief of obstructive symptoms from SEMS implantation until patient death is achieved in about 85% of patients, who are able to avoid surgery and maintain an improved quality of life until death.[6]

However, approximately 25% of patients develop stent-related complications, such as perforation, occlusion, and migration, which usually occur within 72 hours.[7] Proximal colon stenting, stricture predilation, obstruction from extracolonic malignancies, and inexperienced endoscopists are factors that have been related to the development of unfavorable outcomes.[7] Colonic perforation is infrequent and generally occurs in early postprocedure phases[8] with a median rate of 4.5%,[9] whereas delayed perforations rarely have been described.[10]

Bevacizumab (BV) is a recombinant, humanized monoclonal antibody that binds to and blocks the activity of vascular endothelial growth factor-A, a member of a family of vascular endothelial growth factor receptor-activating ligand. BV is used in combination with 5-fluorouracil-based chemotherapy regimens for first-line and second-line treatment of metastatic CRC.[11] Gastrointestinal perforation is a well-documented side effect of BV and occurs at a rate of 1% to 2%,[12] but data on the safety of SEMS for occlusive colon cancer during chemotherapy and antiangiogenic therapies are lacking.

The aim of the present study was to evaluate the short-and long-term efficacy of SEMS in patients with advanced CRC, assess risk factors for severe complications, analyze the safety of SEMS during treatment with BV-containing regimens, and evaluate the impact of these treatments in overall survival (OS).

Material and Methods

Patients

This was a retrospective analysis of the medical records of patients with obstructive metastatic CRC who underwent endoscopic stent placement between January 2012 and December 2017 in 2 tertiary hospitals: Hospital de La Princesa and Hospital Ramon y Cajal in Madrid. A total of 78 patients were included. We modified our therapeutic strategy according to the published European Society of Gastrointestinal Endoscopy (ESGE) guidelines on October 2014.[13]

Eligible patients were aged 18 years or older. Acute colorectal obstruction was diagnosed by the absence of any flatus or bowel movements for less than 1 week, abdominal distension, and/or the presence of dilated colonic loops on abdominal radiograph. All patients underwent computerized tomography before the endoscopic procedure to confirm the presence of obstruction, define the level of the stenosis, and exclude perforation, as well as local and distant staging.

Patients included in the study were considered inoperable or incurable owing to tumor metastasis (stage IV), including patients candidate for antiangiogenic drugs such as BV. Patients included in the study were treated with SEMS as a palliative intent for advanced disease and did not go on to bowel resection.

Patients with the following characteristics were excluded: (1) potentially curable malignant colorectal obstruction; (2) rectal cancer < 5 cm from the anal verge; (3) clinical evidence of bowel perforation, peritonitis, or free intraperitoneal air on abdominal imaging; (4) Patients with other causes of colonic obstruction rather than CRC.

Age, general physical condition, or advanced disease were not considered exclusion criteria for stenting as most cases occurred before the publication of ESGE guidelines.[13]

Endoscopic Procedure

All colonic SEMS were inserted endoscopically under fluoroscopic guidance with placement using through-the-scope/over-the-guidewire technique. Biopsies of the tumor were obtained in case of previously unknown diagnosis. The extent of the stenosis was measured with the stone extraction balloon or estimated through fluoroscopy. Under endoscopic and fluoroscopic guidance, the stents were positioned above the structure and proximally deployed. Abdominal radiographs were taken afterwards to check full deployment of the stent and colonic decompression.

Technical success was defined as successful stent deployment across the obstructing tumor with radiographic confirmation of flaring of the stent both proximally and distally. Clinical success was defined as colonic decompression with visible flatus or stool passage within 48 hours after the procedure.

Data Collection

All the patients underwent colonoscopic biopsy for histologic confirmation of the primary tumor. The presence of distant metastasis was studied by chest and abdomen computerized tomography. Demographic characteristics, including age, gender, primary disease, stage of the tumor, obstruction location, and date of last follow-up or death were collected and retrospectively reviewed. Technical success and complications of the procedures were also recorded. Patients with unresectable disease were referred for consideration of chemotherapy according to international guidelines.[14]

Stent-related complications and mortality as well as details of further interventions performed after stenting (such as stent reinsertion, surgery, or systemic treatment such as chemotherapy and antiangiogenic agents) were recorded. Stent-related complications were defined as those leading to new symptoms, characterized by perforation, re-obstruction, and stent migration that occurred after 2 weeks of the stent insertion.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (version 22.0). All continuous variables were described as median, whereas categorical variables were expressed as frequency and percentage. Missing follow-up data were regarded as missing at random.

To explore univariate associations in the distribution of categorical data, the χ^2 test or Fisher exact test was used as appropriate. Associations between SEMS and systemic treatments (chemotherapy and BV-containing regimens) were analyzed using the χ^2

test. Multivariate analysis was performed with an analysis of variance test, P value for significance $< .05$, to predict the independent contribution of different factors in overall complications. For this model, variables that in the univariate had shown a $P < .1$ were included. Differences in OS and time to complications were assessed by the Kaplan-Meier log-rank test.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008. The appropriate institutional review board of our institution approved this study on February 8, 2018 (Registry number 3333).

Results

During a 5-year period, 78 patients (29 men; median age, 76 years) were enrolled. The 78 patients included were considered unfit for surgical procedures or showed advanced metastatic disease at the subsequent workup, requiring SEMS placement with a palliative intention. In 73 (94%) patients, the stenosis was localized on the left side, in particular, in 50 (68%) patients in the superior rectum-sigmoid colon and 23 (32%) in the descending colon. In 5 (6%) patients, the obstruction was at the level of the right colon located at the transverse colon. RAS status: 29 (37%) unknown, 29 (37%) mutated, and 20 (26%) native (Table 1). Technical success was achieved in 76 (97%) of 78 patients. Clinical success with resolution of bowel obstructions was achieved in 75 (96%) of 78 patients. The median stent patency was 10 months in stage IV disease.

Patients were also stratified by treatment received: 31 (39.5%) received chemotherapy alone, 31 (39.5%) did not receive treatment, and 16 (21%) received BV-containing regimens (Table 1). Patients treated with BV showed a higher percentage of patients with mutated RAS in comparison with the no therapy and chemotherapy cohorts. However, tumor stage and sidedness was similar between groups. Median OS for the metastatic group was 11 months in patients who did not receive systemic therapy, 20 months for patients treated with chemotherapy alone, and 43 months for patients treated with a BV-containing regimen (Table 1).

Table 1 Clinical and Demographics Characteristics of the Study Group

Clinical Features	N (%)		
	No Treatment	Chemotherapy Alone	BV-based Regimen
Gender			
Male	13 (16)	13 (34)	3 (19)
Primary Tumor Stage			
cT1-cT3	6 (19)	3 (9)	3 (19)
cT4	14 (45)	12 (39)	5 (31)
Unknown	11 (36)	16 (52)	8 (50)
Sidedness			
Left colon	29 (94)	29 (94)	16 (100)
Right colon	2 (6)	2 (6)	0 (0)
RAS Status			
Native	2 (6)	13 (42)	5 (31)
Mutated	6 (20)	13 (42)	10 (62.5)
Unknown	23 (74)	5 (16)	1 (6.5)
Median OS (mo)	11	20	43

Abbreviations: BV = bevacizumab; OS = overall survival.

Table 2 Overall Complications According to Treatment

Complications	N (%)		
	No Treatment (n = 31)	Chemotherapy Alone (n = 31)	BV-based Regimen (n = 16)
Perforation	2 (6)	3 (9.7)	2 (12.5)
Re-obstruction	5 (16)	7 (22.5)	2 (12.5)
Minor bleeding	0	2 (6.5)	2 (12.5)
Stent migration	1 (3)	1 (3)	0
Total	8 (26)	13 (42)	6 (37.5)

Abbreviation: BV = bevacizumab.

Complications

Overall, major stent-related complications were observed in 27 (35%) patients: 14 (18%) had re-obstructions, 7 (9%) perforations, 4 (5%) minor bleeding, and 2 (2.5%) migration. In the no chemotherapy group (n = 31): 5 (16%) had a re-obstruction, 2 (6%) had a perforation, and 1 (3%) migration. In the group of patients that received chemotherapy alone (n = 31), there were 7 (22.5%) re-obstructions, 3 (9.7%) perforations, 2 (6.5%) minor bleeding, and 1 (3%) migration.

In the BV-based regimen group (n = 16), there were 2 (12.5%) perforations, 2 (12.5%) re-obstructions, and 2 (12.5%) minor bleeding (Table 2). In this group of 16 patients, we observed 2 (12.5%) perforations: 1 patient had a perforation after the first dose of BV, which was 9 months after the insertion of SEMS, and 1 patient had a perforation after 4 doses of BV, which was 6 months after the insertion of SEMS. Both perforations occurred with a median time of 21 days after the last dose of BV.

Statistical Analysis

Univariate analysis of factors related to overall stent-related complications (Table 3) identified chemotherapy as a significant risk factor. Variables that in the univariate analysis showed a P-value $< .7$ were included in the multivariate analysis (Table 4). We observed that patients who received systemic therapy (chemotherapy alone or BV-containing regimens) are almost twice more

Table 3 Univariate Analysis of Factors Related to Overall Complications

Variable	OR (95% CI)	*P* Value
Male gender	1.10 (0.42-2.88)	.52
cT3-cT4	0.54 (0.20-1.44)	.27
RAS-native	0.90 (0.28-2.88)	.54
Chemotherapy	2.39 (1.06-5.38)	.029[a]
BV-based regimen	1.24 (0.39-3.95)	.46

Abbreviations: BV = bevacizumab; CI = confidence interval; OR = odds ratio.
[a]Statistically significant.

Table 4 Multivariate Analysis of Factors Related to Overall Complications

Variable	OR (95% CI)	*P* Value
RAS-native	0.79 (0.27-2.28)	.67
Chemotherapy	1.84 (1.29-6.22)	.007[a]
BV-based regimen	1.80 (0.69-5.37)	.29

Abbreviations: BV = bevacizumab; CI = confidence interval; OR = odds ratio.
[a]Statistically significant.

likely to develop stent-related complications (odds ratio [OR], 1.84; 95% confidence interval [CI], 1.29-6.22; $P = .007$). No statistically significant differences were observed between chemotherapy alone and BV-based regimens in overall complications (42% vs. 37.5%; $P = .6$).

Univariate analysis of factors related to perforations did not show that patients receiving BV-containing regimens were more likely to develop perforations (OR, 1.76; 95% CI, 0.35-8.99; $P = .38$) (Table 5). Nevertheless, the incidence of perforation was higher with BV-containing regimens compared with patients who received chemotherapy alone (12.5% vs. 8%; $P = .47$), although these differences were not statistically significant. On the other hand, the univariate analysis showed that patients with cT1 to cT3 tumor stages were less likely to develop a perforation (OR, 0.20; 95% CI, 0.11-0.38; $P = .014$).

Patients with stent-related complications showed an association with OS in the Kaplan-Meier analysis in comparison with those patients who did not have a complication (12 months vs. 23 months); these differences were clinically but not statistically significant (log rank, 0.12; $P = .7$) (Figure 1). In addition, we also observed clinically significant differences in OS in patients with metastatic disease who had a perforation in comparison with patients who did not have a complication (8 months vs. 21 months; log rank, 0.95; $P = .33$).

In addition, patients treated with systemic therapy (chemotherapy alone or BV-containing regimens) showed an association with OS compared with patients who did not receive treatment (27 months vs. 11 months; log rank, 12.67; $P \leq .00001$) (Figure 2); these differences were statistically significant. No differences were observed in the median duration to the onset of complications in patients with stage IV disease treated with systemic therapy in comparison with patients not treated (log rank, 0.35; $P = .6$).

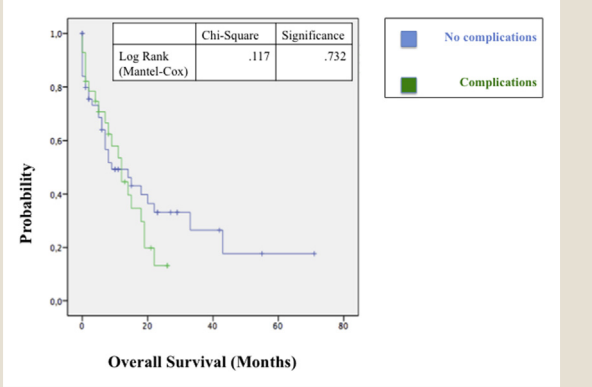
There is a clinical benefit of treatment with BV-containing regimens in patients with stage IV disease compared with chemotherapy alone (43 months vs. 39 months); this association was

Table 5 Univariate Analysis of Factors Related to Perforations

Variable	OR (95% CI)	*P* Value
Male gender	1.53 (0.28-8.46)	.48
cT1-cT3	0.20 (0.11-0.38)	.014[a]
RAS-native	0.85 (0.17-4.32)	.58
Chemotherapy	1.82 (0.33-10.07)	.39
BV-based regimen	1.79 (0.31-10.23)	.40

Abbreviations: BV = bevacizumab; CI = confidence interval; OR = odds ratio.
[a]Statistically significant.

Figure 1 Kaplan-Meier Analysis Showed Clinically Significant Association With Overall Survival in Patients With Stage IV Disease Who had Stent-related Complications, although These Differences Were Not Statistically Significant



statistically significant (log rank, 5.26; $P = .02$) (Figure 3). Furthermore, no differences were observed in the median duration to the onset of complications in patients with stage IV disease treated with chemotherapy alone in comparison with patients treated with BV-containing regimens (log rank, 0.24; $P = .63$).

Discussion

There are 2 major indications for colonic stenting in patients with CRC: palliation of advanced disease and preoperative decompression.[15] Stent placement has shown to be an effective procedure to manage obstructive CRC.[8,16] Reports of the immediate efficacy of SEMS placement for malignant colonic obstruction have been published widely.[8,13,17,18] However, most reports are from small numbers of patients without long-term follow-up. Although short-term efficacy of SEMS has been demonstrated, the

Figure 2 Kaplan-Meier Analysis Showed a Statistically Significant Association With Overall Survival of Patients With Stage IV Disease Treated With Systemic Therapy (Chemotherapy Alone or Bevacizumab-containing Regimens) Compared With Patients With Stage IV Disease that did not Receive Treatment

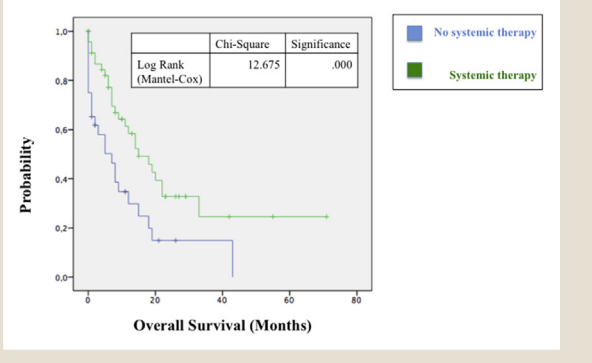
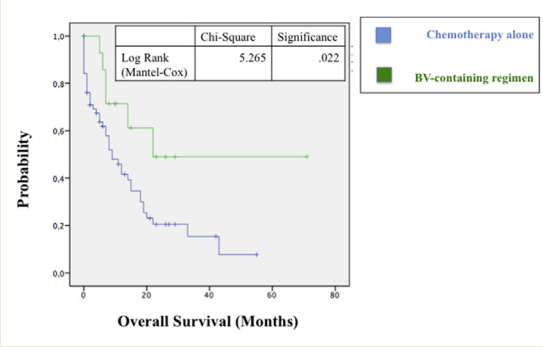


Figure 3 Kaplan-Meier Analysis Showing a Clinically Significant Benefit of Treatment With Bevacizumab-containing Regimens in Patients With Stage IV Disease With Self-expandable Metal Stents Compared With Chemotherapy Alone



Abbreviation: BV = bevacizumab.

long-term results are still debated,[19] and the role of SEMS in the treatment of malignant colonic obstruction remains controversial. Technical success and clinical success rates of colorectal SEMS placement range from 75% to 100% and 84% to 100%, respectively.[13,17,18] A recent prospective multicenter study of 513 cases of obstructive CRC showed a technical and clinical success rate superior to 95%.[16]

Regarding the use of SEMS with a palliative aim, there are many contrasting findings. According to ESGE guidelines,[15] in patients with metastatic obstructive CRC, SEMS placement is preferred because stoma formation, early complications (< 30 days), hospitalization, and 30-day mortality rates are lower after stent placement compared with palliative surgical treatment.[20] Two randomized controlled trials comparing the clinical efficacies of SEMS and colostomy showed favorable outcomes for SEMS.[21,22] However, a recent multicenter randomized controlled trial was ended early owing to the unexpectedly high rate of perforation in the SEMS group of patients treated with palliative intent.[19] In our study, we observed that patients with metastatic disease with SEMS had a significantly shorter duration to the onset of complications.

Findings of published reports show procedure-related and stent-related complications in 5% to 23% of patients, with an average of stent-related perforations in 5%.[7,13,23,24] After palliative stenting, the majority of patients receive chemotherapy or BV-containing regimens. This treatment may change the natural history of the tumor and determine tumor shrinkage; thus it can weaken the colonic wall. Stent migration and colon perforation have been described in patients treated with chemotherapy.[7,19,25] In the study of Karoui et al,[25] there was a 6% perforation rate in patients undergoing chemotherapy after SEMS placement, similar to our results. Van Hooft et al[19] observed that 4 of the 7 patients with stents treated with chemotherapy developed colonic perforation.

Van Hooft et al,[26] in their trial, reported technical and clinical success rates of 90%, but in the 11 patients of the SEMS group, the authors reported 6 cases of stent-related perforation: 2 developed 12 days after placement, and there were 4 cases at 30 days. Also, among patients who received chemotherapy after stenting, 4 experienced stent-related perforations. During follow-up, stent obstruction occurred at a rate of 20%. Of the 10 patients in the surgery group, 6 underwent resection with primary anastomosis. With these results, the authors suggested that surgery should be considered the first-line treatment for patients who are candidates for chemotherapy, and the use of SEMS should be avoided in patients treated or considered for treatment with antiangiogenic drugs.[26]

In our study, chemotherapy did not increase the risk of perforation in comparison with the average stent-related perforations documented in the literature.[7,13,23,24] Conversely, 2 (12.5%) of 16 patients who received BV developed a perforation, which suggests an increased risk for perforation in this subset of patients. We observed an association between patients with stage IV disease who had a perforation and OS. These results are in accordance with the results found in the literature.[7,27-29] However, our univariate analysis did not show that patients receiving BV were more likely to develop perforations when compared with other risk factors, although the incidence is higher in this subset of patients.

Chemotherapy and BV-containing regimens are the first-line treatments for most patients diagnosed with metastatic colon cancer because of higher response rates and increase in OS.[11,14,29] ESGE clinical guidelines[15] recommend that patients who have undergone palliative stenting can be safely treated with chemotherapy without antiangiogenic agents, given the high risk of perforation observed in low-quality published evidence.[3,7,27] After thoroughly reviewing the published literature on the subject, to our knowledge, none of the studies have evaluated the impact on survival of the complications observed in patients with advanced colon cancer treated with BV-containing regimens after the insertion of SEMS.

Therefore, in our study, we aimed to evaluate OS in patients treated with systemic therapy, including BV, and the prognostic significance of stent-related complications in these patients. In metastatic colon cancer, we observed a significant increase in OS for patients treated with systemic therapy (chemotherapy alone or BV), which is in accordance with the literature,[11,14,29] even though these patients showed more stent-related complications than patients who did not receive treatment. Furthermore, there is a significant increase in OS for patients with advanced colon cancer treated with BV-containing regimens compared with chemotherapy alone, in accordance to the literature as well.[11,29] In addition, when we compared the median time to the onset of complications in patients treated with chemotherapy alone versus BV-containing regimens, we observed no differences. Consequently, the present study constitutes the first cohort of patients with malignant colonic obstruction managed by SEMS placement that have been evaluated for stent-related complications derived from systemic therapy and the impact on OS of the complications observed according to the chemotherapy regimen received.

Gastrointestinal perforations have been related to several risk factors, such as intact primary tumors and a history of colonoscopy within 1 month of initiating BV therapy.[29] BV is broadly used in patients with advanced CRC, and gastrointestinal perforations represent a well-known but infrequent complication, occurring in every 60 to 200 treated patients.[11,12,29] Patients with occlusive

colon cancer treated with stent placement and scheduled for BV-based therapy may have an increased risk of colon perforation,[27,28] with SEMS placement representing an additional factor that further increases such risk.

However, despite observing more stent-related complications in patients treated with BV-based regimens, patients with metastatic colon cancer benefit from chemotherapy and antiangiogenic agents after SEMS implantation, showing an association with survival. Our findings could help physicians assess BV-associated risks and benefits in patients with advanced CRC and SEMS. Consequently, long-term stent complications should not be automatically an argument for not treating patients with metastatic colon cancer with chemotherapy and BV, taking into account the response rates and the association with OS observed with these systemic therapies.

Limitations

Our study design has some limitations; its retrospective nature, the small sample size, and the short follow-up may limit our conclusions in terms of oncologic outcome. Patients were enrolled for 5 years, which is shorter than in other studies.[7] The multicenter design also deserves some considerations. Participating physicians were expert endoscopists who had already placed numerous SEMS.

The main limitation is the heterogeneity of the data that originates from 2 different centers and may differ in terms of endoscopic technique, patient selection, SEMS used, the choice of systemic treatment, and the modality of follow-up. One advantage could be that the results are likely applicable to the clinical routine of tertiary endoscopic centers. The fact that demographic and clinical characteristics, as well as outcomes, did not differ significantly among the participating centers seems to minimize the problem.

Conclusions

Placement of SEMS is effective and relatively safe but with an overall complication rate of 35% in the metastatic setting. The long patency rate of most colorectal SEMS suggests that selection of the appropriate patient and stent is crucial for achieving the best results in the management of malignant bowel obstruction. The major early risk is perforation that can increase up to 12% during BV treatment. However, despite observing more stent-related complications in patients with metastatic colon cancer treated with BV, these patients may benefit from BV-containing regimens after SEMS implantation, showing an association with survival. In patients with obstructing advanced CRC who would benefit from SEMS implantation, we should consider the risks associated with systemic therapies, taking into account the improvement in survival with BV. Future large controlled trials should consider and report data on the subgroup of patients with malignant bowel obstruction carrying SEMS that are candidates for BV-based therapies.

Clinical Practice Points

- Findings of published reports show procedure-related and stent-related complications in 5% to 23% of patients, with an average of stent-related perforations in 5%. After palliative stenting, the majority of patients receive chemotherapy or BV-containing regimens.
- In our study, chemotherapy did not increase the risk of perforation in comparison with the average stent-related perforations documented in the literature, but 12% of patients who received BV developed a perforation. However, despite observing more stent-related complications in patients treated with BV-based regimens, patients with metastatic colon cancer may benefit from chemotherapy and antiangiogenic agents after SEMS implantation, showing an increase in survival.
- Our findings could help physicians assess BV-associated risks and benefits in patients with advanced CRC and SEMS. Consequently, long-term stent complications should not automatically be an argument for not treating patients with metastatic colon cancer with chemotherapy and antiangiogenic agents.
- In patients with obstructing advanced CRC that would benefit from SEMS implantation, we should consider the risks associated with systemic therapies, taking into account the improvement in survival with BV-containing regimens.

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