Colonic perforation with intraluminal stents and bevacizumab in advanced colorectal cancer: retrospective case series and literature review

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Background: Self-expanding metal stents (SEMS) are increasingly used in the treatment of malignant large bowel obstruction in the setting of inoperable colorectal cancer. Perforation is a well-known complication associated with these devices. The addition of the vascular endothelial growth factor inhibitor bevacizumab is suspected to increase the rate, but the extent of the increase is not known.

Methods: We retrospectively reviewed the records of patients receiving SEMS in tertiary hospitals in Calgary, Alta., between October 2001 and January 2012.

Results: We reviewed the records of 87 patients with inoperable colorectal cancer who received SEMS during our study period. Nine perforations occurred in total: 4 of 30 (13%) patients who received no chemotherapy, 3 of 47 (6%) who received chemotherapy but no bevacizumab, and 2 of 10 (20%) who received chemotherapy and bevacizumab. These two patients received bevacizumab with FOLFIRI after SEMS placement, and they had peritoneal disease.

Conclusion: Our case series and other studies suggest that bevacizumab may increase the risk of colonic perforation in the setting of SEMS. Caution should be used when combining these therapies.

Contexte : Les endoprothèses métalliques auto-expansibles (EMAE) sont de plus en plus utilisées pour le traitement de l'obstruction colique d'origine maligne dans le contexte d'un cancer colorectal inopérable. La perforation est une complication bien connue de ces dispositifs et on soupçonne que l'ajout de l'inhibiteur du facteur de croissance de l'endothélium vasculaire bevacizumab en accroît le taux, mais l'ampleur de cette augmentation est inconnue.

Méthodes : Nous avons passé en revue de manière rétrospective les dossiers de patients traités par EMAE dans des hôpitaux de soins tertiaires de Calgary, en Alberta, entre octobre 2001 et janvier 2012.

Résultats : Nous avons examiné les dossiers de 87 patients atteints d'un cancer colorectal inopérable ayant reçu une EMAE durant la période de notre étude. En tout, 9 perforations ont été enregistrées, soit chez 4 patients sur 30 (13 %) qui n'avaient pas reçu de chimiothérapie, chez 3 patients sur 47 (6 %) traités par chimiothérapie sans bevacizumab et chez 2 patients sur 10 (20 %) ayant reçu une chimiothérapie et du bevacizumab. Ces 2 patients avaient été traités par bevacizumab avec FOLFIRI après la pose de l'EMAE et présentaient une atteinte péritonéale.

Conclusion : Selon notre série de cas et d'autres études, le bevacizumab pourrait accroître le risque de perforation du côlon dans le contexte de l'EMAE. La prudence s'impose lorsqu'on utilise ces traitements concomitamment.

Colorectal cancer (CRC) accounted for approximately 13% of new cases of cancer in Canada in 2012.[1] Approximately 15% of patients with CRC present with large bowel obstruction,[2] and obstruction will develop in 8% at some point in the course of advanced disease.[3] In the past, therapeutic options included emergency surgery with tumour resection and primary anastomosis or a Hartmann procedure with colostomy creation. Owing to the potential for postsurgical complications, including wound

infections and anastomotic leaks, and to mortality exceeding 10%,[4] the development of alternative treatment strategies have been explored.

Self-expanding metallic stents (SEMS) have been increasingly used in malignant colorectal obstruction, particularly in patients with advanced-stage cancers in whom resection is often not a feasible means of palliation. In addition, the use of SEMS as a bridge to surgery is gaining popularity in the management of resectable obstructions. Advantages include technical and clinical success rates exceeding 90%,[5] stent-related mortality of less than 1%[5] and possibly improved quality of life compared with palliative surgery.[6,7] The potential complications of SEMS placement include stent migration, reobstruction and, the most worrisome, colonic perforation. The incidence of the latter approaches 4%[5] and is a serious concern for clinicians because mortality after emergency surgery for a perforated CRC has been found to be approximately 20%–30% in recent studies.[8,9]

Although it does not appear that chemotherapy alone increases the risk of gastrointestinal (GI) perforation,[10] there is debate as to whether the risk of perforation is increased when chemotherapy is administered to patients with stents.[11–15] Of particular concern is the concurrent use of the vascular endothelial growth factor inhibitor bevacizumab with SEMS. While the addition of this agent to standard fluoropyrimide-based chemotherapy regimens has improved survival outcomes in patients with metastatic colorectal carcinoma, it has also been associated with a significantly increased risk of GI perforation, with a reported incidence of 1.9%.[16]

It could be expected that the combination of bevacizumab, chemotherapy and SEMS would be associated with even higher perforation rates; however, there is a paucity of literature on this topic. To investigate this possible association, we undertook a retrospective case series to determine the incidence of colonic perforation in patients with advanced-stage or locally advanced, unresectable CRC treated with SEMS in 3 tertiary hospitals in Alberta, Canada. We also performed a literature review with a particular interest on the rates of this complication with chemotherapy alone and with the addition of bevacizumab.

Methods

Consecutive patients admitted between October 2001 and January 2012 were identified using an existing database of SEMS procedures in 3 hospitals in Calgary, Alberta. The electronic medical records for these individuals were accessed, and those who had experienced a large bowel obstruction in the setting of stage 4 or locally recurrent colorectal adenocarcinoma were included in this analysis. Patients receiving stents as a bridge to surgery as well as 1 patient who was lost to follow-up in the 6-month period following insertion were excluded. In addition to demographic details, we collected data pertaining to the stent insertion, complications, specific chemotherapy used, vital statistics outcomes and additional interventions. We obtained approval from our local research ethics committee before data collection.

Statistical analysis

For comparisons between groups, we performed a Fisher exact test using STATA statistical software version 13.1.

Results

Of the 87 patients meeting our inclusion criteria, 30 had not received chemotherapy, 47 had received chemotherapy but not bevacizumab (18 before SEMS, 28 after, 1 unknown), and 10 received chemotheraphy and bevacizumab (3 before, 6 after, 1 unknown; Table 1). The patients who did not receive chemotherapy tended to be older and had worse performance status and lower baseline carcinoembryonic antigen (CEA) values. In the bevacizumab group, a relatively large proportion of patients had peritoneal involvement (40%), with both perforations in this group occurring in the setting of peritoneal disease.

Perforations occurred in 4 (13%) patients with SEMS who did not receive chemotherapy, 3 (6%) with SEMS who received chemotherapy but not bevacizumab, and 2 (20%) with SEMS who received chemotherapy and bevacizumab (Table 2). We found no differences in perforation rates between the chemotherapy plus bevacizumab and the chemotherapy alone groups (p = 0.21), between the chemotherapy plus bevacizumab and the no chemotherapy groups (p = 0.63), or between the chemotherapy alone and the no chemotherapy groups (p = 0.42). Perforations occurred in 4 of 36 (11%) patients who received chemotherapy with or without bevacizumab after stenting compared with 1 of 18 (6%) patients who had received systemic therapy before the procedure. Total complication rates (including reobstructions and migrations) were 16% in the no chemotherapy group, 27% in the chemotherapy without bevacizumab group and 50% in the chemotherapy plus bevacizumab group.

Mean survival times since stenting were 101 days in the no chemotherapy group, 277 days in the chemotherapy without bevacizumab group and 226 days in the chemotherapy plus bevacizumab group (Table 3). The chemotherapy regimens administered to 5 patients with perforations included 5-fluorouracil/folinic acid (FU/FA; n = 1), FOLFOX (n = 2) and FOLFIRI plus bevacizumab (n = 2).

Data pertaining to the 2 patients with perforations who received FOLFIRI plus bevacizumab are presented in Table 4. Features in common include peritoneal involvement and a history of exposure to FOLFIRI plus bevacizumab chemotherapy within the previous 2 weeks. Patient 2 perforated during her first treatment cycle. Location of stricture, initial CEA, time from stenting until perforation and outcome were markedly different between these patients.

Discussion

Multiple studies have established that an increased risk of perforation exists with the addition of bevacizumab to chemotherapy in patients with CRC.[16–18] A recent meta-analysis of randomized controlled trials encompassing more than 3000 patients with metastatic CRC showed a perforation rate of 15 of 1491 (1.0%) in patients treated with and 2 of 1508 (0.1%) in patients treated without bevacizumab added to standard 5-FU-based chemotherapy regimens.[17] A large observational cohort study of nearly 2000 patients treated with bevacizumab reported a perforation rate of 1.9%.[16] In another meta-analysis, Geiger-Gritsch and colleagues[18] reported a 4-fold higher risk of GI hemorrhage or perforation with bevacizumab. In a phase II NSABP C-10 trial,[19] perforation occurred in 1 of 86 (1.2%) patients; this patient had an intact primary tumour and received mFOLFOX6 chemotherapy with bevacizumab.

In patients with SEMS, the overall perforation rate was found to be 3.76% in a large pooled analysis encompassing 54 studies (1198 patients) in the pre-bevacizumab era.[5] This study included patients stented for palliation as well as patients stented as a bridge to surgery. In comparison, we found (excluding patients treated with bevacizumab) a much higher rate of perforation (9%) in the present study. This higher rate could be related to the selected population including only palliative and poor surgical risk patients. Other healthier patients and those with a lower burden of disease having a stent as a bridge to surgery were not included in our series. Similarly, patients who did not receive chemotherapy had a higher perforation rate than those who received chemotherapy (13% v. 6%). Generally, patients who are unfit for chemotherapy are older and have worse performance status and possibly more advanced primary tumours. In the setting of palliative chemotherapy, several small studies have reported similar results (Table 5).

Since both bevacizumab and SEMS are associated with colonic perforations, it would be expected that the combination of bevacizumab, chemotherapy and the use of SEMS would be associated with even higher perforation rates. In 1 case series including 9 patients treated with SEMS and chemotherapy, the only 2 patients to receive bevacizumab were the only individuals to experience perforations.[21] Small and colleagues[22] reported in a retrospective study that 4 perforations occurred in 23 (17.4%) patients who received the drug after SEMS insertion compared with 14 in 207 (6.8%) patients who did not receive it; however, this difference was not statistically significant ($p = 0.06$). In addition, another study revealed a 50% perforation rate in 8 patients who received bevacizumab with

Table 1. Baseline demographic and clinical characteristics of the study sample

Characteristic	Group, no. (%)*		
	No chemotherapy ($n = 30$)	Chemotherapy with no bevacizumab ($n = 47$)	Chemotherapy with bevacizumab ($n = 10$)
Median age at time of stent, yr	75.3	68.0	55.3
Median BMI	22.4	25.2	22.9
Median ECOG performance status	2	1	0.8
Median CEA at initial diagnosis or at time of recurrence, μg/L	90.7	56.5	25.3
Male sex	50 (15)	60 (28)	50 (5)
Nature of obstruction			
Intraluminal	93 (28)	85 (40)	80 (8)
Extraluminal	0 (0)	2 (1)	20 (2)
Unknown	7 (2)	13 (6)	0 (0)
Stage			
Metastatic	90 (27)	81 (38)	100 (10)
Local recurrence	10 (3)	19 (9)	0 (0)
Primary in situ	90 (27)	81 (38)	80 (8)
Peritoneal disease	27 (8)	13 (6)	40 (4)
Location of obstruction			
Rectosigmoid	53 (16)	72 (34)	60 (6)
Descending colon	17 (5)	2 (1)	10 (1)
Transverse colon	13 (4)	6 (3)	10 (1)
Splenic flexure	7 (2)	9 (4)	0 (0)
Hepatic flexure	7 (2)	9 (4)	0 (0)
Ascending colon	3 (1)	0 (0)	20 (2)
Radiotherapy (for rectal tumours)	7 (2)	11 (5)	10 (1)

BMI = body mass index; CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group.
*Unless otherwise indicated.

a stent in situ.[23] Our finding of 2 perforations in 10 patients fits within the range found in these prior studies.

In our series the 2 patients who experienced a perforation while treated with bevacizumab had peritoneal disease. It remains unclear if peritoneal disease increases the risk of GI perforation with bevacizumab in the setting of CRC. In patients with ovarian cancer, GI perforations occur at a rate of more than 5%.[24] As these patients frequently have abdominal carcinomatosis, some groups[24,25] have hypothesized that bevacizumab-related perforation occurs more frequently in these individuals because of peritoneal disease. Proposed mechanisms include necrosis of the tumour deposited in the intestinal wall, microperforation due to bowel obstruction[24] and aggressive surgical cytoreduction causing injury.[25] Some of these mechanisms would apply to CRC as well. Intuitively, radial pressure on the bowel wall from a stent could lead to erosion and, subsequently, perforation.

Table 2. Complications of patients with SEMS

Complication	Group, no. (%)		
	No chemotherapy	Chemotherapy with no bevacizumab	Chemotherapy with bevacizumab
Perforation	13 (4)*	6 (3)	20 (2)
Reobstruction	3 (1)	17 (8)	30 (3)
Migration	0 (0)	4 (2)	0 (0)

*One perforation occurred during the stenting procedure.

Table 3. Mean survival (d) of patients from insertion of SEMS

Survival	Group; mean, d (no. patients)		
	No chemotherapy	Chemotherapy with no bevacizumab	Chemotherapy with bevacizumab
Mean, d	101	277	226
No perforation	98 (n = 26)	264 (n = 44)	214 (n = 8)
Perforation	115 (n = 4)	462 (n = 3)	271 (n = 2)

SEMS = self-expanding metal stents.
*Unless otherwise indicated.

Table 4. Demographic and clinical characteristics of patients who experienced a perforation with bevacizumab

Characteristic	Patient 1	Patient 2
Age, yr	68.6	55.2
Sex	Male	Female
BMI	20.9	18.8
ECOG PS	1	1
Stage	Metastasis to liver and peritoneum	Metastasis to liver and peritoneum
CEA at initial diagnosis, µg/L	3.9	3087
Location of stricture	Sigmoid	Transverse colon
Primary in situ	Yes	Yes
Chemotherapy regimen	FOLFIRI-bevacizumab	FOLFIRI-bevacizumab
Timing of first chemotherapy	79 d after stenting	29 d after stenting
Time between stenting and perforation	126 d	40 d
Time between last chemotherapy and perforation	5 d	11 d
Outcome after perforation	Emergency surgery (diverting ileostomy); subsequently resumed chemotherapy	Patient died of intra-abdominal sepsis
Time from stenting to death	488 d	54 d

BMI = body mass index; CEA = carcinoembryonic antigen; ECOG PS = Eastern Cooperative Oncology Group performance scale.

The timing of administration of systemic therapy in relation to SEMS insertion may influence the risk of perforation. In patients receiving chemotherapy with or without bevacizumab after stenting, perforations occurred in 11% compared with only 6% in patients who had received systemic therapy before the procedure. This finding could be due to tumour response, resulting in the stent eroding through a weakened bowel wall. However, this mechanism could also apply to systemic therapy given before stenting. All of the patients who received chemotherapy with or without bevacizumab before stenting in our study had last been treated 50 or more days before stenting; many patients who received chemotherapy with or without bevacizumab after stenting were treated within a month of stenting. Thus, it may be the proximity in time of the chemotherapy in relation to the procedure that may be most important. Further studies are required to investigate this possibility.

Limitations

The small number of patients with SEMS who received chemotherapy and bevacizumab limits our study, as in other reports on this topic. Owing to these small numbers and the retrospective nature of our study, we were unable to control for measured (and unmeasured) variables that may have increased the perforation risk. However, the use of bevacizumab in this clinical setting is

Table 5. Selected studies of perforation following SEMS insertion for advanced colorectal cancer

Study	*N*	Population	Perforation rate
Sebastian et al.[5]	1198	Unselected patients	3.76
Bielawska et al.[12]	8	Chemotherapy	0
Karoui et al.[13]	19	Chemotherapy	11
Fernandez-Esparrach et al.[14]	26	Chemotherapy	8
Karoui et al.[15]	22	Chemotherapy	9
van Hooft et al.[20]	6	Chemotherapy	66
Cennamo et al.[21]	2	Chemotherapy + bevacizumab	100
Small et al.[22]	23	Chemotherapy + bevacizumab	17.4
Manes et al.[23]	8	Chemotherapy + bevacizumab	50

SEMS = self-expanding metal stent.

increasing, and the risk of perforation remains a major concern. Further, our study involved only 1 health region in Canada, which may limit the generalizability of our results.

Conclusion

Self-expanding metallic stents are part of the armatorium for malignant colorectal obstruction, especially in a palliative setting. However, the risk of perforation remains a major concern. Our study adds further evidence of a higher risk of colonic perforation when bevacizumab is administered to patients in this setting. Further studies involving larger numbers of patients and multiple centres are needed to confirm this risk. Oncologists should carefully consider the perforation risk associated with bevacizumab, especially in patients with SEMS.

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References

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. *Canadian Cancer Statistics 2013*. Canadian Cancer Society; 2013. Available: www.cancer.ca/statistics (accessed 2013 June 5).
2. Ohman U. Prognosis in patients with obstructing colorectal carcinoma. *Am J Surg* 1982;143:742-7.
3. Poultsides GA, Servais EL, Saltz LB, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J Clin Oncol* 2009;27:3379-84.
4. Targownik LE, Spiegel BM, Sack J, et al. Colonic stent vs. emergency surgery for management of acute left-sided malignant colonic obstruction: a decision analysis. *Gastrointest Endosc* 2004;60:865-74.
5. Sebastian S, Johnston S, Geoghegan T, et al. Pooled analysis of the efficacy and safety of self-expanding metal stenting in malignant colorectal obstruction. *Am J Gastroenterol* 2004;99:2051-7.
6. Nagula S, Ishill N, Nash C, et al. Quality of life and symptom control after stent placement or surgical palliation of malignant colorectal obstruction. *J Am Coll Surg* 2010;210:45-53.
7. Davies RJ, D'Sa IB, Lucarotti ME, et al. Bowel function following insertion of self-expanding metallic stents for palliation of colorectal cancer. *Colorectal Dis* 2005;7:251-3.
8. Zielinski MD, Merchea A, Heller SF, et al. Emergency management of perforated colon cancers: How aggressive should we be? *J Gastrointest Surg* 2011;15:2232-8.
9. Alvarez JA, Baldonedo RF, Bear IG et al. Presentation, treatment, and multivariate analysis of risk factors for obstructive and perforative colorectal carcinoma. *Am J Surg* 2005;190:376-82.
10. Asmis TR, Capanu M, Kelsen DP, et al. Systemic chemotherapy does not increase the risk of gastrointestinal perforation. *Ann Oncol* 2007;18:2006-8.
11. Datye A, Hersh J. Colonic perforation after stent placement for malignant colorectal obstruction; causes and contributing factors. *Minim Invasive Ther Allied Technol* 2011;20:133-40.
12. Bielawska B, Hookey LC, Jalink D. Large-diameter self-expanding metal stents appear to be safe and effective for malignant colonic obstruction with and without concurrent use of chemotherapy. *Surg Endosc* 2010;24:2814-21.
13. Karoui M, Roudot-Thoraval F, Mesli F, et al. Primary chemotherapy with or without colonic stent for management of irresectable stage IV colorectal cancer. *Eur J Surg Oncol* 2010;36:58-64.
14. Fernández-Esparrach G1, Bordas JM, Giráldez MD, et al. Severe complications limit long-term clinical success of self-expanding metal stents in patients with obstructive colorectal cancer. *Am J Gastroenterol* 2010;105:1087-93.
15. Karoui M, Charachon A, Delbaldo C, et al. Stents for palliation of obstructive metastatic colon cancer: impact on management and chemotherapy administration. *Arch Surg* 2007;142:619-23.
16. Kabbinavar FF, Flynn PJ, Kozloff M, et al. Gastrointestinal perforation associated with bevacizumab use in metastatic colorectal cancer: results from a large treatment observational cohort study. *Eur J Cancer* 2012;48:1126-32.
17. Cao Y, Tan A, Gao F et al. A meta-analysis of randomized controlled trials comparing chemotherapy plus bevacizumab with chemotherapy alone in metastatic colorectal cancer. *Int J Colorectal Dis* 2009;24:677-85.
18. Geiger-Gritsch S, Stollenwerk B, Miksad R, et al. Safety of bevacizumab in patients with advanced cancer: a meta-analysis of randomized controlled trials. *Oncologist* 2010;15:1179-91.
19. McCahill LE, Yothers G, Sharif S, et al. Primary mFOLFOX6 plus bevacizumab without resection of the primary tumor for patients presenting with surgically unresectable metastatic colon cancer and an intact asymptomatic colon cancer: definitive analysis of NSABP trial C-10. *J Clin Oncol* 2012;30:3223-8.
20. van Hooft JE, Fockens P, Marinelli AW et al. Early closure of a multicenter randomized clinical trial of endoscopic stenting versus surgery for stage IV left-sided colorectal cancer. *Endoscopy* 2008;40:184-91.
21. Cennamo V, Fuccio L, Mutri V, et al. Does stent placement for advanced colon cancer increase the risk of perforation during bevacizumab-based therapy? *Clin Gastroenterol Hepatol* 2009;7:1174-6.
22. Small AJ, Coelho-Prabhu N, Baron TH. Endoscopic placement of self-expandable metal stents for malignant colonic obstruction: long-term outcomes and complication factors. *Gastrointest Endosc* 2010;71:560-72.
23. Manes G, de Bellis M, Fuccio L, et al. Endoscopic palliation in patients with incurable malignant colorectal obstruction by means of self-expanding metal stent: analysis of results and predictors of outcomes in a large multicenter series. *Arch Surg* 2011;146:1157-62.
24. Han ES, Monk BJ. What is the risk of bowel perforation associated with bevacizumab therapy in ovarian cancer? *Gynecol Oncol* 2007;105:3-6.
25. Abu-Hejleh T, Mezhir JJ, Goodheart MJ, et al. Incidence and management of gastrointestinal perforation from bevacizumab in advanced cancers. *Curr Oncol Rep* 2012;14:277-84.