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## Single Case

# Long-Term Colon Stent Patency for Obstructing Colorectal Cancer Combined with Bevacizumab

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## Keywords

Self-expanding metal stent · Colorectal cancer · Bevacizumab · Chemotherapy · Patency

## Abstract

Self-expanding metal stents can be considered as initial treatment for malignant large bowel obstruction in the palliative setting. It is suggested that systemic anti-angiogenic therapy increases the risk of stent perforation. We report a 65-year-old woman with a metastatic, obstructing colon tumor who has been successfully treated with stent placement and chemo-immunotherapy consisting of capecitabine and bevacizumab for 8 years.

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## Introduction

In the past years the incidence of colorectal cancer (CRC) increased to 14.1 million new cases worldwide in 2012 [1]. Patients diagnosed with CRC present in 8% with colorectal obstruction causing nausea, vomiting, constipation, and abdominal distension [2].

Obstructing CRC is a potentially life-threatening condition that can lead to colonic necrosis and blow-out perforations. Emergency resection or endoscopic self-expanding metal stent (SEMS) placement are the treatment options in the acute setting. Resection often requires laparotomy with stoma formation and has a high morbidity (54%) and mortality (12%) [3]. In the elderly and frail patients who have a high surgical risk as well as for patients with incurable metastatic disease, SEMS placement can be considered as initial treatment for colonic decompression [4, 5]. A randomized trial that compared SEMS placement with primary surgery for the palliation of colorectal obstruction was closed early because 6 out of 10 patients treated with SEMS placement developed a perforation. The authors speculated that the administration of systemic chemotherapy could have contributed to the risk of stent perforation [6]. Although based on low-quality evidence, the literature data suggest that in particular systemic treatment with bevacizumab, a monoclonal antibody that binds to vascular endothelial growth factor (VEGF) and thereby inhibits angiogenesis, increased the risk of stent perforations. A meta-analysis of pooled literature data found that patients treated with bevacizumab-based systemic therapy had a 12.5% risk of stent perforation [7].

First-line systemic therapy in metastatic CRC includes fluoropyrimidine-containing chemotherapy plus bevacizumab [8]. The AVEX trial [9] randomized elderly patients with metastatic CRC to receive first-line treatment with capecitabine with or without bevacizumab. Addition of bevacizumab to capecitabine significantly increased response rates and progression-free survival (9.1 vs. 5.1 months,  $p < 0.0001$ ). A meta-analysis of nine trials investigated the efficacy and safety of bevacizumab plus chemotherapy compared to chemotherapy alone in previously untreated, advanced, or metastatic CRC. Patients who received both chemotherapy and bevacizumab had higher response rates (RR = 0.89; 95% CI = 0.82–0.96;  $p = 0.003$ ) with heterogeneity, higher progression-free survival (HR = 0.69; 95% CI = 0.63–0.75;  $p < 0.00001$ ), and also higher overall survival rates (HR = 0.87; 95% CI = 0.80–0.95;  $p = 0.002$ ) with moderate heterogeneity [10], so the addition of bevacizumab to palliative chemotherapy regimens has proven its value. Systemic bevacizumab therapy in patients treated with a colorectal SEMS is however controversial because of the potentially increased risk of stent perforation [4].

In Northwest Clinics Alkmaar, a 65-year-old woman presented with a metastatic obstructing colon tumor; she was successfully treated with a colonic stent in 2009 and has been on palliative chemotherapy with bevacizumab ever since. In this case report, we aim to illustrate prolonged bevacizumab therapy in a patient with a colonic SEMS and the factors contributing to SEMS patency and safety in combination with bevacizumab.

## Case Report

In July 2009, a 65-year-old woman with early dementia presented initially to the pulmonologist with progressive dyspnea, bloody stools, abdominal pain, and distension since

4 weeks. Her medical history mentioned osteoporosis for which she used calcium and vitamin D<sub>3</sub> supplementation in combination with risedronic acid. She complained of continuous dyspnea with abdominal distension and bloody stools. She did not have fever or significant weight loss, nor any other localizing pulmonary or cardiac complaints. She had regular defecation. Physical examination was unremarkable, in particular there were no clinical signs of an ileus. Chest X-ray showed suspicious lung lesions. A PET-CT was performed and showed a PET-avid sigmoid tumor with FDG-avid lymph nodes and multiple FDG-avid pulmonary and liver lesions. In addition, increased FDG activity was seen in the proximal left humerus. Thus, PET-CT showed evidence of a metastasized sigmoid tumor with disseminated disease into the lymph nodes, liver, lungs, and possibly bone marrow (Fig. 1). Colonoscopy confirmed an obstructing tumor in the sigmoid and biopsies showed adenocarcinoma. The carcinoembryonic antigen (CEA) level was 14.1 µg/L.

During a second colonoscopy 6 days later, a colonic stent was placed as palliative treatment because of the stenosing characteristics of the tumor. An SEMS (WallFlex Enteral Colonic Stent, uncovered, diameter 25 mm, length 90 mm, Boston Scientific) was successfully placed through the 60-mm stenosis without complications or suspicion of guidewire perforation. No dilatation before or after stent placement was used. Macrogol was started to facilitate defecation and prevent fecal obstruction of the SEMS. Palliative chemoimmunotherapy with capecitabine, oxaliplatin, and bevacizumab was started 4 days after stent placement. After six cycles of systemic therapy, a CT scan showed a slight decrease in size of the pulmonary and liver metastases. After eight cycles, the patient continued with bevacizumab and capecitabine because of oxaliplatin-induced neuropathy. In January 2012, she developed hypothyroidism and levothyroxine was started. Stable disease was the best response reached, and this remained so for years until September 2014. At that time, a CT scan showed slight disease progression with growth of the known lung metastases and one newly formed metastatic lung lesion. The liver metastases had remained stable and CEA had increased to 38.6 µg/L. Since the progression of disease was minimal, treatment was not modified. Half a year later she presented with a urinary tract infection causing a severe delirium. CEA had increased again. In agreement with the patient and her family, it was decided to not perform any diagnostics and stop chemoimmunotherapy because she was in very poor condition (WHO performance status 3). After 3 months her condition improved without cancer treatment, and both the patient and her family wished to restart therapy. A CT scan showed progression in size of the known lung and liver metastases. Resumption of treatment was possible and capecitabine and bevacizumab were restarted. In June 2016, CEA had increased to 240 µg/L, and a PET-CT scan showed one progressive liver metastasis in the left liver lobe; the other metastases were stable. The patient was referred for laparoscopic resection of liver segments II and III. The pathologist reported mucinous adenocarcinoma of a 4.5-cm metastasis with vital tumor cells and one smaller sclerotic lesion with calcifications without vital tumor cells. There were no complications and the patient recovered quickly. Systemic chemotherapy with bevacizumab was continued. A PET-CT scan 4 months after liver surgery showed stable disease, and CEA had decreased to 151.0 µg/L. Hereafter, stable disease was again reached until the last follow-up on July 1, 2017.

All CT scans that followed stent placement were reviewed and showed stable colonic tumor with a patent stent in the proper position. No clinical or radiological signs of colonic perforation developed.

## Discussion

Our patient shows extraordinary stent patency, without stent-related complications and with clinical benefit for at least 96 months (8 years) while on the 128th cycle of palliative chemotherapy in combination with bevacizumab. To our knowledge, such an exceptionally long SEMS patency for the palliation of colonic obstruction has never been described before, particularly in combination with prolonged systemic bevacizumab therapy. Studies on palliative colorectal stenting have demonstrated that stent placement has a significant risk of complications, including a 10% perforation rate [5]. Therefore, there has been debate on whether colonic stenting is a good alternative to surgery in case of large bowel obstruction. In the study by van Hooft et al. [6], patients with stage IV left-sided CRC were randomized for surgery or stenting as palliative treatment. That study had to close early because of the high risk of stent perforation (6/10). Other complications of palliative colonic stenting are stent migration (9.2%) and obstruction (18.3%); bleeding, pain, incontinence, and tenesmus are reported less often [5].

In metastatic CRC, the first-line systemic therapy includes fluoropyrimidine-containing chemotherapy with or without the anti-VEGF antibody bevacizumab. Bevacizumab is a monoclonal antibody that binds to VEGF and thereby inhibits angiogenesis. A meta-analysis of nine trials investigated the efficacy and safety of bevacizumab plus chemotherapy compared to chemotherapy alone in previously untreated, advanced, or metastatic CRC. Patients who received both chemotherapy and bevacizumab had higher response, progression-free survival, and overall survival rates [10].

Since bevacizumab can negatively influence wound healing, it is advised not to start bevacizumab treatment within 1 month after surgery or if a wound is not fully healed. Moreover, addition of bevacizumab to palliative chemotherapy is known to significantly increase the risk of spontaneous gastrointestinal perforations in comparison with chemotherapy regimens without bevacizumab [10].

The literature on SEMS placement combined with palliative chemoimmunotherapy including bevacizumab is limited. Only six studies (Table 1) have reported on perforation rates of colorectal SEMS placement during palliative chemotherapy including bevacizumab, and all six suggest an increased perforation risk in patients treated with bevacizumab [7, 11–15]. The perforation rates in those small studies ranged from 11.8% (4/34) to 100% (2/2). Despite low-quality evidence, the European Society of Gastrointestinal Endoscopy Clinical Guideline strongly recommends against SEMS placement in patients who are or will be treated with bevacizumab [4].

Several factors may have contributed to the prolonged SEMS patency in our patient and could explain the variation in perforation rates in the literature. One of the hypotheses is that our patient had stable disease without tumor shrinkage. Hereby, the bowel wall keeps its integrity, which reduces the risk of perforation, migration, and tumor reobstruction. Stent perforation during bevacizumab treatment may be caused by the forces of the SEMS against weakened neoplastic tissue or a weakened bowel wall because of tumor shrinkage [11]. Further, it is suggested that it prevents the healing process of pressure-induced ulcers by the SEMS, which can lead to perforation [13]. The latter is the reason that nowadays bevacizumab is not given directly after SEMS placement. However, our patient received bevacizumab only 4 days after stenting, and possibly this is the second reason for success. The bow-

el wall could adapt to the changes induced by bevacizumab before final stent fixation. This may be more beneficial than changes to the integrity of the bowel wall after fixation of the stent and thereby result in a lower risk of perforation. Thirdly, an experienced endoscopist successfully placed the stent without acute complications. Fourthly, stent characteristics are an important factor in the prevention of complications. The large 30-mm proximal diameter of this stent can lead to more pressure and thereby a better fixation. Finally, our patient presented in a good condition (WHO performance status 1) in a nonacute situation, which allowed for multidisciplinary decision-making about optimal management.

In conclusion, our patient proves that colonic stent placement in combination with bevacizumab can lead to a very favorable course in selective cases. Contributing factors may have been stable disease (no tumor shrinkage), quick start of bevacizumab after stent placement, an experienced endoscopist, a nonacute situation at presentation, and stent characteristics.

### Statement of Ethics

Ethical approval was not required.

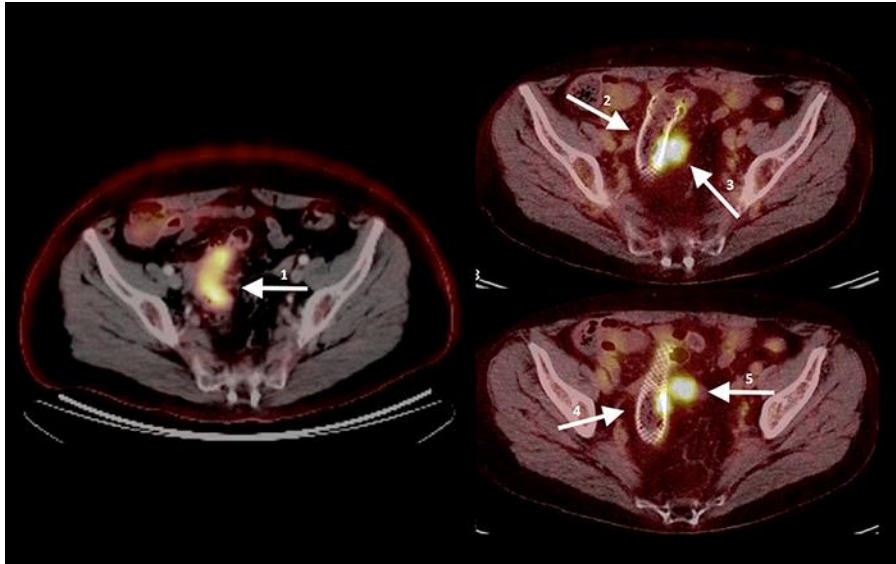
### Disclosure Statement

The authors declare that they have no conflicts of interest.

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**Fig. 1.** Initial PET-CT scan and PET-CT scan with colonic stent in situ after 89 months. Left: PET-CT in July 2009 showing intense FDG uptake of the wall thickening (arrow 1), compatible with the diagnosis sigmoid carcinoma. Right: Low-dose PET-CT in June 2016, overlaying images showing stent (arrows 2 and 4) without wall thickening and without FDG uptake of the wall. Two locoregional lymph nodes with intense FDG uptake (arrows 3 and 5) represent metastases.

**Table 1.** Perforation rate in patients with a self-expanding metal stent receiving chemoimmunotherapy including bevacizumab

Reference	Curative or palliative	Patients receiving chemoimmunotherapy including bevacizumab	Patients with perforation	Perforation rate
van Halsema et al. [7]	both	80	6	12.5% <sup>a</sup>
Manes et al. [12]	palliative	8	4	50.0%
Cennamo et al. [13]	palliative	2	2	100.0%
Imbulgoda et al. [14]	palliative	10	2	20.0%
Small et al. [15]	palliative	23	4	17.4%
Fuccio et al. [11]	palliative	34	4	11.8%

<sup>a</sup> Weighted by meta-analysis.