Place of colorectal stents in therapeutic management of malignant large bowel obstructions

French recommendations. Endoscopy and Cancer committee of the French Society of Digestive Endoscopy (SFED) and the French Federation of Digestive Oncology (FFCD)

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Take home messages:

- Whatever the situation a medical-surgical discussion must take place before any treatment decision.
- The placement of a stent is not recommended in the absence of clinical and radiological signs of obstruction, even when the endoscope cannot pass through the tumour.
- If indicated, colonic stenting should be considered within 12 to 24 hours after admission.
- Stent is contraindicated in cases of perforation, clinical and/or radiological signs of colonic suffering, for cancer of the low and middle rectum, and when colonic obstruction is associated with small bowel incarceration.
- Stent must be placed endoscopically and under radiological control.
- Stent placement must be performed by a trained operator in a suitable medico-surgical unit.
- The use of polyethylene glycol (PEG) and other oral preparations is contra-indicated.
- Pre-expansion and passage through the tumour stenosis by a large-caliber endoscope must be avoided.
- In curative intent (non metastatic tumour or resectable metastases), stenting cannot be recommended as first-line intervention. It remains a therapeutic option in expert centres, pending validation by a randomized study. In the context of curative intent, the surgical treatment of occlusion is preferred.
- In the context of palliative intent (unresectable metastases, unresectable patient), stenting can be recommended as a first-line intervention. In this situation surgery is another treatment option.
- In patients with a colonic stent, using anti-angiogenic therapy may cause more frequent local complications (relative contraindication), and the placement of a stent in a patient treated with anti-angiogenic treatment is not recommended.
- The short-term efficacy data of stents are generally good. There are few data about long-term outcomes or about patients receiving chemotherapy with or without targeted therapy.

A. Introduction

With 40500 new cases per year and 17500 deaths per year in France in 2010 [1], colorectal cancer remains a major public health problem. In 8% to 29% of cases, this cancer is revealed by obstruction [2, 3], and theoretically is treated by one or two stages emergency surgeries. Approximately 35% of these obstructions occur in the context of advanced disease (metastatic or unresectable disease [4]). The high morbidity and mortality of emergency surgery in this situation led to colonic stenting being proposed as an alternative to surgery to treat the obstruction [5].

The use of a colonic stent is considered by the American Society of Gastrointestinal Endoscopy (ASGE) in two guidelines as an acceptable therapeutic option in the case of acute colonic obstruction (ASGE 2010 and 2005) [6, 7].

Colonic stenting was initially proposed with palliative intent for colorectal cancer complicated by obstruction. More recently, in the context of curative treatment, stenting was also proposed as a "bridge to surgery".

The purpose of this work is to establish French national guidelines for the use of colonic stenting in colorectal cancer complicated by obstruction, with curative and palliative intent, and to clarify the role of this technique in the oncologic management of these cancers. A literature review of the most relevant series, phase 3 trials and meta-analyses was conducted for this purpose.

Fig. 1 summarizes the different situations and presents a decision tree.

B. Placement of a colonic stent:

a) Pre-treatment assessment

Clinical examination, search for electrolyte imbalances, evaluation of medical comorbidity.

- Thoraco-abdomino-pelvic CT scan with contrast to confirm the origin of colonic obstruction, locate the tumour, achieve locoregional and metastatic staging, and identify contraindications to stent placement.
- Pre-anaesthesia check-up.
- Medical-surgical discussion in emergency situation, or by multidisciplinary digestive oncology staff. Assessment of local endoscopic and surgical resources.

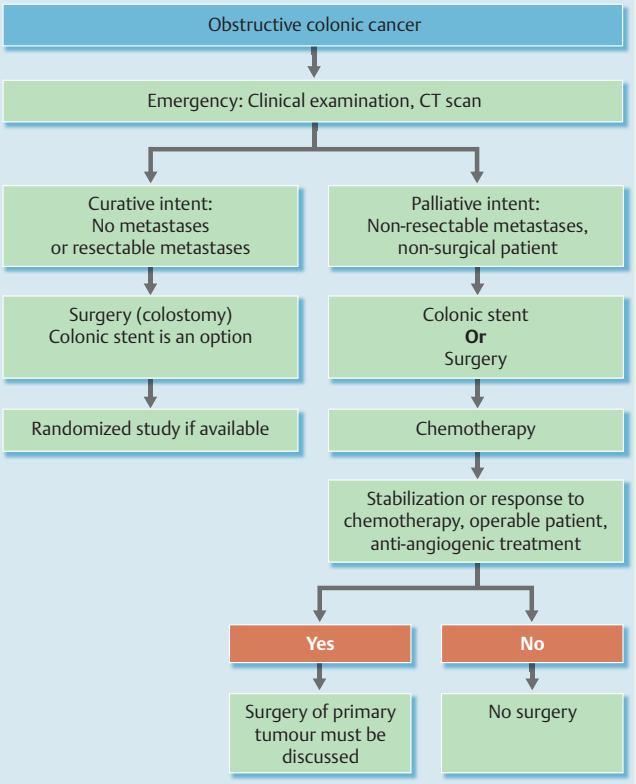

Fig. 1 Therapeutic decision tree.

b) Time limit for stent placement

No studies have specifically studied the time limit for stent placement for colonic obstruction in emergency or non-emergency situations. However, prospective randomized studies that compared stenting as a "bridge to surgery" with emergency surgery proposed that the procedure should be completed within 24 hours of admission of the patient.

The placement of a colonic stent for obstructive colorectal cancer should be considered in the 12 to 24 hours after admission of the patient (*expert opinion*). This interval is conditioned by the severity of clinical and/or radiological signs of acute obstruction, the diameter of the caecum, the intensity of obstructive symptoms, and the time taken to obtain the best anaesthetic and technical conditions for stent placement.

c) Endoscopic or radiological placement?

The placement of the stent can technically be realized under video-endoscopic and fluoroscopic control (endoscopic technique) or under fluoroscopic control only (radiological technique). The advantages of video-endoscopic control are: i) precise location of the lesion to be treated; ii) facilitates the passage of the guidewire within a sometimes tortuous sigmoid colon; iii) improves stiffness of the guidewire and deployment of the stent; iv) provides the pathological proof of cancer at the same time (biopsy) in the case of inaugural diagnoses; v) allows the opacification of the proximal colon and assessment of the appearance and length of the stenosis.

No studies have compared the success and complication rates of endoscopic and radiological techniques.

Colonic stenting must be performed endoscopically and under fluoroscopic control (*expert agreement*).

d) Environment and conditioning of the patient

The success rate of the colonic stent is conditioned by the skill of the endoscopist: success rates are better for endoscopists that regularly perform interventional endoscopy and biliopancreatic retrograde catheterization [8]. There is a known learning curve, and it is considered necessary to have completed more than 30 procedures to acquire sufficient skill for colonic stenting [9]. An experienced surgical-assistant is required and the stent placement procedure is ideally performed in the usual interventional endoscopy room of the endoscopist. These relevant data have not been included in prospective studies. General anaesthesia with intubation is preferred in most cases. The wash-out of the patient before stent placement is important. The use of rectal enemas is recommended to improve video-endoscopic progression. The use of polyethylene glycol (PEG) and any other orally administered wash-out is contraindicated. Only a few specialized centres fulfilling all these conditions can offer 24-h access to this technique.

The lack of a trained endoscopist and appropriate facilities is a contra-indication to the placement of a colonic stent. The best examination conditions should be obtained, and the preparation of the patient should be done rectally. Stent placement is preferentially performed under general anaesthesia with intubation (*expert opinion*).

e) Specific equipment and endoscopes

The use of a CO_2 inflator is highly recommended for colonic stenting: in theory this technique reduces gastrointestinal distension and the risk of perforation. No studies have been reported on the prevention of risk of complications by inflation with CO_2 versus air. In the absence of a CO_2 inflator, inflation during progression to the stenosis and during the implantation of the prosthesis must be as small as possible.

A washing pump is useful for facilitating progression to the stenosis.

The use of a CO2 inflator and a washing pump is recommended for the placement of a colonic stent (*expert agreement*).

f) Stent placement procedure

Four main steps lead to the placement of a colorectal stent: catheterization of the stenosis with a guide wire, the evaluation of the appearance and length of the stenosis to ensure selection of the correct stent, insertion of the stent into the stenosis and, finally, its deployment. To date there have been no comparative studies about the different catheterization or stent placement techniques.

- Two different situations must be distinguished

The "easy" catheterization: easy positioning of the endoscope in front of the stenosis (left colon, transverse, rectum). The use of a flexible catheter with a single or dual channel with a long (>450 cm) flexible (or fully flexible) hydrophilic guidewire tip allows the placement of the stent Through The Scope (TTS) under fluoroscopy, combining safety and efficiency.

The "difficult" catheterization: the stenosis is lateralized, or angular, or the position of the endoscope is unstable (recto-sigmoid, sigmoid colon, splenic and hepatic flexures), the stenosis is tight, or the stenosis is tortuous. These situations require the help of a pre-curved adjustable catheter, or a rotary sphincterotome, and the use of the "J" guide wire technique, or a thinner guide wire (0.018 or 0.025 inches). The materials and techniques used in this situation are the same as those used for endoscopic retrograde cholangiopancreatography (ERCP).

Prior dilatation and passage through tumour stenosis by large caliber endoscope must be avoided (*expert agreement*). The use of biliopancreatic catheterization materials and long non-traumatic hydrophilic guides is advocated. Biopsies for pathological diagnosis and possible molecular biological analyses (RAS and MSI status) are required for subsequent oncological decisions. Installing external radiopaque markers is unnecessary and should be avoided.

g) Stents

There are multiple colonic stent manufacturers. The choice of stent will mainly depend on the habits of the individual endoscopist. A meta-analysis studying the different types of stents has recently been published [10]: it showed that although covered stents prevent intra-prosthetic tumour proliferation, unsurprisingly they do not improve patency rates and lead to significantly more frequent late migration. Covered and non-covered stents do not differ in terms of technical success, clinical success and early complications (especially perforation). The choice of stent length will depend mainly on the length of the stenosis. It is necessary to obtain the best possible congruence with colonic walls. Thus, for an angular stenosis a longer stent will be required to prevent impaction of the stent tip (risk of dysfunction).

The use of non-covered self-expanding metallic stents is recommended; their length should be adapted to the length and shape of the stenosis and should always be at least 4 cm longer than the stenosis.

h) Particular situations and locations

- Right or proximal colon

The placement of a stent in the right colon segment is less frequently reported because of a lower frequency of acute right colon obstruction and easier surgical options (one-stage emergency surgery). Stenting the caecum, the ileo-caecal valve or the colonic flexures is more difficult due to limited accessibility and for technical reasons. Since 2007, the feasibility of colonic stenting in the proximal colon using Through The Scope stents has been reported in only four retrospective series including over ten patients.

- Low rectum

The results of a comparative retrospective study show that stenting a stenosis of the lower rectum (less than 3 to 5 cm from the anal verge) is associated with a significant increase in rectal pain syndrome (tenesmus) in comparison with stenting for stenosis of the middle or upper rectum [11]. The overall incidence of rectal tenesmus is estimated to be 5% after placement of a stent and incontinence occurred in 11% of cases [12].

Stenting for lower rectum cancer must be avoided (tumours located within 3 to 5 cm of the anal verge) (*grade C*).

i) Technical contraindications

Definitive:

- Clinical signs of peritonitis
- Clinical and radiological signs of perforation or colonic suffering
- Associated small intestine obstruction

Relative:

- Time required to obtain endoscopic expertise
- Peritoneal carcinomatosis
- Patient undergoing anti-angiogenic therapy or for whom anti-angiogenic treatment is being considered (see specific section)
- Cancer of the low and middle rectum

C. Success and complications of colonic stenting

a) Short-term outcomes

The short-term outcomes are defined by the technical and clinical success of the stent, and early complications evaluated between 2 and 7 days after placement of the stent whatever the indication (palliative or curative as a "bridge to surgery").

A large amount of data on the results of colonic stenting is available from large retrospective series that included a total of 3,581 patients [13–15], six randomized trials [16–21] and eight meta-analyses [22–29]. It should be noted that these meta-analyses were based in part on retrospective studies with objectives that were not always clearly defined. In addition we must report several series published in many countries and the first Hispanic-Danish prospective study on 447 patients, which provided representative results of current practice in general hospitals in these two countries [30].

Based on these very large datasets, the colorectal segments most frequently involved in the placement of a stent are the sigmoid (50–70%), the rectum (12–18%), the left colon (9–15%) and more rarely, the transverse colon and the right colon.

The safety of colonic stenting is excellent with an immediate mortality rate of below 1% in most published series (average 0.6%). Technical success rates vary from 92% to 98.2% with an average of 96.2% while the average clinical success rate is about 92%. Early complications are represented by perforation, migration and less frequently bleeding. The early rate of perforation varies between 0.8% and 4.5% (average: 3.7%). The early rate of migration varies between 0% and 13%, and the rate of bleeding between 1.8% and 0.9%. Note that the last two complications can lead to endoscopic recovery while perforation usually requires emergency surgical treatment and is the main source of early mortality. Perforation is also very pejorative on oncologic outcomes.

The good immediate results of colonic stenting reported in most uncontrolled series are closely linked to the skill of the specialized endoscopic teams and to the selection of patients and are opposed to poorer outcomes reported in randomized studies comparing colonic stent to emergency surgery. It should be noted that randomized studies are small and are sometimes critical for methodology.

b) Long-term outcomes

There are fewer data available about long-term outcomes compared to short-term outcomes. They usually relate to the results at 30 days as described in the Spanish-Danish prospective series [30,31].

The 30-day mortality rate was 9% with half of the deaths related to poor prognosis of cancer. The 30-day morbidity involved 16% to 31% of patients [32–34]. The rate of late perforations varied from 1% to 7% (average: 3.9%). The risk of late perforation appeared to be associated with the type of stent use, the presence of peritoneal carcinomatosis and the ad-

ministration of chemotherapy associated with anti-angiogenic therapy [33,34]. We must therefore take into account the increased risk of perforation for patients for whom chemotherapy is indicated after placement of a stent.

Migration of the stent can occur and this risk is related to the type of stent used. The late stent migration rate is about 2% for the non-covered Wallflex® stent, and exceeds 10% for covered stents. In the series reported by Fernandez-Esparrach et al. the rate of late migration for non-covered stents even reached 22% [31].

The rate of obstruction by tumour growth through or over the stent varies from 3.3% for covered stents to 22.3% for non-covered stents. The risk of obstruction increases with survival and the median duration of stent permeability is estimated to be about 100 days [32,34]. This complication can be overcome endoscopically via the placement of a second stent in the first, thus lengthening the duration of stent permeability to over 200 days [32]. Late bleeding occurs in less than 1% of cases.

Decisions about stent placement for obstructive colorectal cancer must consider the risks of long-term stent-related complications and must be balanced with the prognosis of the cancer and possible therapeutic strategy following the resolution of obstruction.

D. Surgical treatment

The most appropriate surgical strategy for patients with obstructive left colon cancer remains under debate. Four surgeries can be discussed: two requiring two-stage surgery, and two requiring one-stage surgery.

Two-stage surgery:

- Colostomy: this is the "easy" way to treat obstruction and is associated with low morbidity. Once the obstruction has been resolved the disease can be staged and colectomy can be performed 8 – 10 days later.
- Left colectomy without restoration of continuity (Hartmann) is associated with high morbidity and mortality, and a 30 – 40% risk of definitive stoma [35].

A prospective randomized study compared colostomy with the Hartmann procedure and showed an advantage for the first intervention in terms of infectious morbidity, transfusion and rate of definitive stoma [36]

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One-stage surgery:

- Segmental colectomy with intraoperative lavage and anastomosis without stoma is a difficult and long procedure associated with significant morbidity and mortality. It requires skill in colorectal surgery, making its realization not reproductible in emergency.
- Total colectomy with ileo-rectal anastomosis is a difficult and long procedure, and is associated with high postoperative morbidity. It enables treatment of possible synchronous lesions (5 – 10% of cases) with a poor functional outcome.

A prospective randomized study compared the two procedures and found an advantage for segmental colectomy in terms of functional outcome and definitive stoma [37].

The high mortality rates (5 – 20%) and morbidity rates (45 – 50%) reported in the literature after emergency surgery for cancer of the left colon are difficult to interpret because of the heterogeneity of surgical techniques.

Another factor that may explain the high morbidity and mortality rates after surgery for obstructive colon cancer is patient selection. Several studies have demonstrated that certain factors were associated in multivariate analysis with increased mortality after colorectal surgery. In a multicentre prospective study of 1049 patients by the French Association of Surgery (AFC), malnutrition, neurological disease history, emergency surgery and age over 70 years were independent factors associated with high postoperative mortality [38]. The mortality rates were 0.5%, 1.6%, 7.2%, 46.8% and 70% if there were 0, 1, 2, 3 or 4 risk factors. A multicentre French study on 84000 patients operated on for colorectal cancer confirmed these results [39].

In summary, there is no reason to favour one surgical procedure over another for placement of a colonic stent for the treatment of left colonic obstructive cancer. However colostomy could be advocated in an emergency because this procedure is easy to perform, is reproducible and is associated with low morbidity.

E. Colonic stent with curative intent, "as a bridge to surgery"

The goal of the stent in the context of curative intent is to treat the acute obstruction in an emergency situation and to enable delayed oncologic surgery after correction of electrolyte imbalance and staging of the cancer. In the context of curative intent the goal of treatment is survival. Six studies with this endpoint are available in the literature.

Of these studies, only one was a prospective randomized study although the primary endpoint was not survival [19], one was a retrospective analysis with a propensity score [40] and five were retrospective studies [19,41 – 45].

In 2003, Saida et al. compared 40 patients who underwent emergency surgery with 44 patients treated with colonic stent. This was not an intention-to-treat analysis. There were significantly fewer rectal tumours in the emergency surgical group compared with the colonic stent group and cancers in the colonic stent group were more likely to be advanced. Overall survival did not differ significantly between the two groups [41].

In 2008, Dastur et al. retrospectively compared 23 patients who underwent emergency surgery with 19 patients treated with a colonic stent. Patients did not differ in terms of age, sex, ASA score, tumour location or Dukes stage. The average time between the placement of the stent and colonic surgery was 70 days (range 1 – 223 days). The median survival of patients did not differ significantly between the two groups ($p=0.8$). The major bias of this study was that it involved some patients treated with palliative intent [42].

In 2011, Alcantara et al. [19] published a prospective randomized trial comparing surgery with per-operative colonic lavage to colonic stent "as a bridge to surgery". The trial intended to include 21 patients per group. The study was stopped prematurely because of a higher rate of anastomotic leakage in the surgical group. Fifteen patients were included in the stent group and 13 in the surgical group. There was no difference in overall survival between the two groups. Patients in the stent group had more recurrences but this difference was not statistically significant. The median disease-free survival was 25.5 months in the stent group versus 27.1 months in the surgical group ($p=0.096$).

In 2013, Kim et al. [43] reported a retrospective study on the survival of patients who had undergone emergency surgery ($n=70$) compared with patients treated with a colonic stent ($n=25$). The analysis was not an intention-to-treat analysis. The two groups were comparable for age, sex, tumour location, tumour differentiation, and TNM stage. The median duration

of follow-up was 51 months (4–139). There was no significant difference between the two groups in terms of 5-year overall survival (61.6% in the surgical group versus 67.2% in the colonic stent group) or 5-year recurrence-free survival (respectively 60% versus 61.2%). In this study, the rate of completion of chemotherapy did not differ significantly between the two groups, although it was higher in the colonic stent group (84.0% versus 65.7%). The authors also evaluated the pathological criteria of the primary tumour in both groups and showed that there was significantly more peri-nervous involvement after the placement of a colonic stent (76% versus 41.4%, p=0.033).

More recently Sabbagh et al. [40] published a retrospective analysis with a propensity score comparing the overall survival and disease-free survival of patients who had undergone emergency surgery with that of patients treated with a colonic stent. In this study all patients were included, regardless of TNM stage. Overall survival differed significantly between the two groups (p=0.001). There was no difference in overall survival at 1 year (81% in the stent group versus 82% in the emergency surgical group) but at 3 years (44% versus 66%, p=0.015) and 5 years (25% versus 62%, p=0.0003) the overall survival was significantly lower in the stent group. Disease-free survival did not differ significantly between the two groups. For patients without perforations or metastases, 5-year overall survival was significantly better in the surgical than the stent group (67% and 30% respectively, p=0.001).

Kim et al. [44] reported that the survival of 45 patients initially treated with a colonic stent was worse than that of 350 control patients with cancer of the left colon without obstruction who were treated by surgery: 5-year overall survival: 38.4% versus 65.6% and recurrence-free survival: 48.5% versus 75.5%. The difference in prognosis was likely due to the fact that these authors compared cancers without obstruction to cancers with obstruction.

In a recent study Kim et al. [45] compared 43 patients treated with a colonic stent "as a bridge to surgery" with 48 patients treated by emergency surgery with curative intent for obstructive tumour. No difference in 5-year overall survival or recurrence-free survival was noted (70.4% versus 76.4% and 47.2% versus 48.9% respectively).

Conclusion:

For treatment with curative intent, data from the literature suggest that there is no difference in survival between surgery and colonic stent. However, the relevant studies are mostly retrospective and involve few patients. Moreover, the results of Sabbagh et al. about the prevalence of peri-nervous involvement in the primary tumour after placement of a colonic stent must be taken into account and justify a new prospective randomized study. Expansion of the tumour stenosis by the stent could facilitate the migration of neoplasic cells. Pending new studies, the placement of a colonic stent "as a bridge to surgery" is not recommended. It is an alternative to surgery when comorbidities do not permit an emergency colostomy, which in practice is a rare situation.

Pending new studies, the placement of a colonic stent "as a bridge to surgery" is not recommended as part of a curative oncological treatment strategy grade C. However, it remains a therapeutic alternative in some rare situations.

F. Colonic stent with palliative intent

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Publications regarding colonic stenting with palliative intent are all retrospective and the main bias of these studies concerns the definition of the term "palliative".

In 2010, Vemulapalli et al. [46] retrospectively compared the duration of hospital stay, morbidity, and the early postoperative and long-term survival of patients treated with palliative intent with colonic stent (n=53) or by emergency surgery (n=70). All patients had metastatic disease but no data were available on the extent of metastatic disease. In the surgery group, surgical treatment was heterogeneous with 17 colostomies alone and 32 surgical resections of the primary tumour. The authors concluded that the hospital stay was significantly shorter in the stent group (2 versus 8 days, p<0.001). Patients in the stent group also had significantly fewer acute complications (8% versus 30%, p=0.03) and lower hospital mortality (0% versus 8.5%, p=0.04). The rate of late complications was higher in the stent group, although this difference was not statistically significant (22% versus 9%, p=0.06). There was no significant difference in overall survival between the two groups. The median survival was 24 weeks in the stent group and 23 weeks in the surgery group (NS).

In 2011, Lee et al. [47] retrospectively compared patients treated with emergency surgery to patients treated with colonic stent. Treatment was considered palliative for unresectable liver metastases or extrahepatic metastatic disease. One hundred and forty four patients were included in this retrospective study (71 in stent group, 73 in the emergency surgery group). The rate of early postoperative complications (15.5% versus 32.9%, p=0.015) and duration of hospital stay (13.2 versus 24.4 days, p<0.001) were significantly lower in the stent group compared to the emergency surgery group. The length of time between the procedure (surgery or prosthesis) and the start of chemotherapy was shorter in the stent group (16.2 versus 31.5 days, p<0.001). The rate of late complications was significantly higher in the stent group compared to the surgery group (33.8% versus 17.8%, p=0.028). Obstruction was the most frequent late complication in the stent group (29.6% of cases). A second stent was placed in 21% of cases. The authors also studied the risk factors for late complications. In multivariate analysis, an ASA score 3 (p=0.031), a stent diameter less than 20 mm (p=0.016) and the administration of chemotherapy (p=0.01) were independent risk factors for late complications. The administration of bevacizumab did not increase the risk of late complications in this study. Overall survival did not differ significantly between the two groups (10.9 vs. 13 months, p=0.771), but seemed lower in the stent group; the statistical significance of a difference of 2 months would have required inclusion of more patients. In multivariate analysis, R0 resection (p=0.034) and palliative chemotherapy (p=0.002) were associated with improved overall survival.

In 2004 Carne et al. [48] retrospectively compared the survival of palliative patients (unresectable metastases) treated with the placement of a colonic stent with that of patients treated with emergency surgery. Overall survival was 7.5 months in the stent group and 3.9 months in the emergency surgery group (p=0.2).

In 2007 Karoui et al. [49] retrospectively compared 31 patients treated with colonic stent with 27 patients treated with emergency surgery. Patients included in this study had unresectable metastases. Mortality and morbidity did not differ significantly between the two groups. The median duration of hospital stay was sig-

nificantly lower in the stent group (8 versus 13.5 days, p < 0.001), as were the rate of stoma (6% versus 37%, p = 0.002) and time to start chemotherapy (14 versus 28.5 days, p = 0.002). There was no significant difference between the two groups in terms of the percentage of patients with access to chemotherapy (71% versus 59%, NS). The median survival did not differ significantly between the two groups (13.7 months in the stent group versus 11.4 months in the surgery group, NS).

Conclusion:

In the palliative situation, colonic stent does not appear to affect the prognosis of patients. It permits earlier initiation of chemotherapy than emergency surgery (grade C). All available studies are small and retrospective; the definition of palliative criteria is heterogeneous.

Treatment with a colonic stent in the context of palliative intent is an option grade C: it reduces the rate of stoma, the duration of hospital stay, and morbidity and mortality, and permits rapid initiation of chemotherapy, so could thus reduce costs. In this situation, surgery is an option, being preferred in younger patients and those without significant comorbidity.

G. Colonic stent and anti-angiogenic treatment

The use of anti-angiogenic therapy in patients with colonic stent is controversial. The results of a meta-analysis that included several types of cancers treated with bevacizumab showed that the risk of gastrointestinal perforation increased. This risk was higher for patients treated for colorectal cancer and was related to a recent colonoscopy [50–52].

In a series of 233 patients treated for colonic obstruction with placement of a colonic stent (168 palliative and curative 65), Small et al. [8] specifically studied 26 patients treated with bevacizumab. Of these patients, 23 were treated with palliative intent and 3 with curative intent. The rate of perforations (n = 4) was higher in the group of patients treated with bevacizumab (15.4% versus 6.8%, NS). All perforations occurred in patients treated with palliative intent within a median of 21 days (range 20–26).

In 2009 Cennamo et al. [53] reported a series of nine patients with obstructive colonic cancer with synchronous metastases and treated by placement of a colonic stent followed by chemotherapy. Of these patients, two received bevacizumab. Both suffered a perforation requiring emergency surgery.

More recently, in a large series of patients treated with a colonic stent and long-term follow-up, four perforations were reported among the eight patients treated with bevacizumab [54].

No data regarding the risk of gastrointestinal perforation have been reported to date for the new anti-angiogenics prescribed in colorectal cancer (regorafenib, aflibercept). Given their similar mechanism of action, it is likely that the risk of gastrointestinal perforation induced by these new drugs is comparable to that reported for bevacizumab.

Given the increased risk of colonic perforation, the administration of anti-angiogenic treatment is not recommended in patients with a colonic stent (*expert agreement*). Similarly, placement of a colonic stent in patients treated with anti-angiogenic treatment is not recommended.

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