Oncological outcomes of colonic stents as "bridge to surgery" versus emergency surgery for obstructive colorectal cancer: A portuguese comparative study

Outcomes oncológicos da colocação de próteses metálicas auto-expansíveis como "ponte para cirurgia" versus cirurgia emergente na oclusão intestinal por cancro colorectal: Um estudo comparativo português

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RESUMO

Introdução: Os resultados a curto prazo da utilização de próteses metálicas do cólon seguida de cirurgia eletiva (ponte para cirurgia, PPC) na oclusão intestinal por cancro colorectal são bem conhecidos. Os resultados oncológicos a longo prazo permanecem alvo de discussão e levaram a que, recentemente, as sociedades internacionais de endoscopia não recomendassem esta estratégia como primeira linha.

Objetivo e Métodos: Realizámos um estudo longitudinal observacional de coorte com base nos dados clínicos dos doentes tratados na nossa instituição entre 2006 e 2012 (7 anos). Analisámos a sobrevida livre de doença (SLD), a sobrevida global (SG) e a recidiva como *end-points* primários. Os dados demográficos, o estádio da doença e a morbi-mortalidade peri-operatórias foram também comparados.

Resultados: Incluímos 126 doentes, 79 (62,7%) foram tratados seguindo uma estratégia PPC (grupo 1) e 47 (37,3%) foram submetidos a cirurgia emergente (grupo 2). A distribuição por sexo, idade (70,9+/-11,4 anos) e estádio TNM foi semelhante. O tempo de *follow-up* médio foi de 49,2 +/- 3,6 meses. Não houve diferenças estatisticamente significativas em relação a complicações peri-operatórias (p=0,23) ou realização de quimioterapia adjuvante (p=0,53). A incidência de estoma definitivo foi superior no grupo 2(p<0,001). A recidiva não foi significativamente diferente, apesar de ter sido superior no grupo 2 (34,5% *vs*. 42,5%,p=0,492). A SLD (22,2 *vs*. 19,7 meses;p=0,652) e a SG (43,2 vs. 31,9 meses, p=0,096) também não foram significativamnete diferentes, embora tenham sido ligeiramente superiores no grupo 1.

Conclusões: Os resultados do nosso estudo vão ao encontro das meta-análises mais recentes sugerindo que a estratégia PPC poderá ser uma alternativa promissora à cirurgia emergente. São necessários ensaios clínicos e estudos prospetivos que o comprovem.

ABSTRACT

Introduction: *The short-term results of colonic stenting followed by elective surgery (bridge to surgery, BTS) for malignant large-bowel obstruction (MLBO) have been well described. However long-term oncological outcomes are still debated and international endoscopy societies have recently not recommended it as a first-line approach.*

Aims & Methods: *A longitudinal observational cohort study was performed based on clinical data review from patients treated in our center between 2006 and 2012 (7 years). We analysed disease-free survival (DFS), overall survival (OS) and recurrence as primary end-points. We also reviewed demographic data, disease staging and peri-operatory morbility and mortality.*

Results: *A total of 126 patients were included: 79 (62,7%) were treated with a BTS strategy (group 1) and 47 (37,3%) underwent an emergent surgery (group 2). The distribution by sex, age (70,9+/-11,4 years) and TNM stage was similiar. The median follow-up time was 49,2 +/- 3,6 months. There was no significant difference in peri-operatory complications (p=0,23) and adjuvant chemotherapy (p=0,53). The need for a definite stoma was higher in group 2 (p<0,001). The recurrence did not differ significantly between the two groups, although it was superior in group 2 (34,5% vs. 42,5%,p=0,492). DFS (22,2 vs 19,7 months; p=0,652) and OS (43,2 vs. 31,9 months, p=0,096) also did not differ signficantly between the two groups, being slightly longer in group 1.*

Conclusion: *Results of our study on oncological outcomes, as stated in most recent meta-analysis, as well as well-described short-term outcomes, suggest that BTS could be a promising alternative strategy for MLBO. Larger prospective studies and randomized clinical trials are definetely needed in the future.*

INTRODUCTION

Approximately 10% of patients with colorectal cancer (CRC) initially present with malignant large-bowel obstruction (MLBO), which in turn accounts for 85% of colonic emergencies.[1,2]

In Portugal, CCR accounted for 14,9% of all oncological related mortality in 2012 (second cause overall), with an incidence of 33,15 /100.000 inhabitants, according to the National Oncology Regist (RON 2014). Also, 10-30% of the cases presented with MLBO.[3]

The standard for management of malignant

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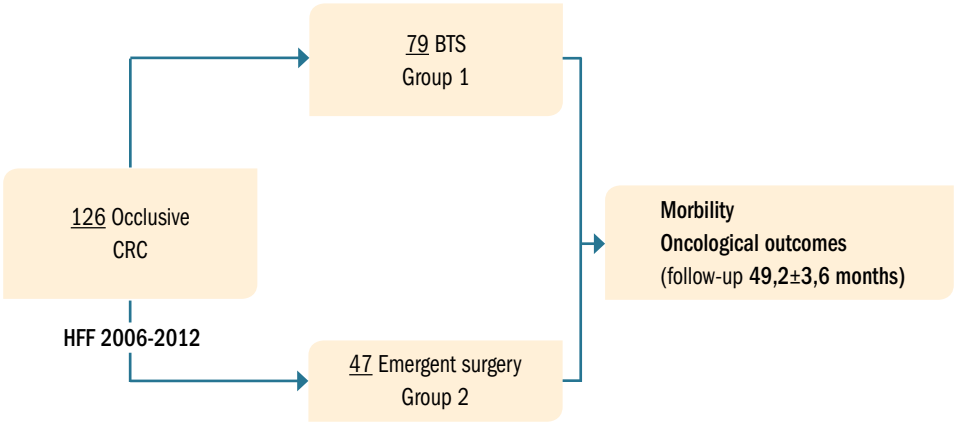


FIGURE 1. Flow-chart of patients

large-bowel obstruction (MLBO) is emergency surgery, which frequently requires stoma creation. However, emergency colorectal surgery continues to be associated with significant mortality and morbidity.[4] Furthermore, patients who undergo emergency surgery are reported to have poorer oncological prognoses than those who undergo elective surgery, even for equivalent disease stages.[5,6] Dohmoto *et al.* first described the placement of a self-expandable metallic colonic stent (SEMS) for the relief of colonic obstruction in 1991.[7,8] The SEMS is now considered to be a safe and effective alternative modality for decompressing MLBO, as several meta-analyses have demonstrated favorable short-term outcomes of SEMS insertion followed by surgery, "bridge to surgery (BTS),"compared with emergency surgery.[9–11] Preoperative SEMS insertion can prevent high--risk emergency surgery and may allow elective radical surgery following full preoperative staging, screening for synchronous proximal lesions, and appropriate bowel preparation.[12–14] In theory, SEMS insertion could have deleterious effects on both tumor progression and metastasis, mainly due to manipulation of the tumoral mass or even undetectable complications (such as microperforations) but the effect of SEMS on the long-term oncological outcome of patients whose disease is potentially curable is still unclear.[15,16] Until very recently, studies evaluating long-term oncological effects of BTS were sparse; however, several long--term studies were published after 2013 and have boosted further debate.[17–22]. This debate and all the concerns about possible worse oncological outcomes in patients following a BTS strategy ended up driving some international societies of endoscopy to ellaborate and publish clinical guidelines advising caution when using colonic SEMS in a BTS strategy, and pointing them as not the first choice in patients believed to be good surgical candidates (such as those that are young and with low risk according to the American Society of Anesthesiologists (ASA) Physical Status classification system).[23]

AIMS

The purpose of this study was to compare two different strategies when treating obstructive colorectal cancer (colonic stenting as BTS and emergency surgery) in terms of oncological outcomes. Disease-free survival (DFS), overall survival (OS) and recurrence were considered primary end--points. As secondary end-points peri-operative morbidity and mortality were performed and compared between the two groups.

METHODS

We conducted a longitudinal observational cohort study based on clinical data review from patients with MLBO treated in our center with a curative intent between January 2006 and December 2012 (seven years) to assess the impact of the two strategies regarding long-term oncological outcomes. Duration of follow-up time and outcomes were taken into account until the end of June 2015.

Patients with signs of perforation and peritonitis, with middle and distal rectal cancers or right colon cancers (proximal to the distal tranverse colon) were excluded as they would not be suitable for colonic stent placement according to

TABLE 1
Distribution according to gender, age and tumor location

	Group 1 (n=79)	Group 2 (n=47)	
Sex (M/F)	63,3% / 36,7%	57,4/ 42,6%	*ns*
Age (years)	69,3% ± 11,0	72,5 ± 11,7	*ns*
Tumor location			*ns*
· Distal transverse /splenic flexure	24,0%	31,9%	
· Descending colon	15,2%	10,6%	
· Sigmoid colon	55,7%	53,2%	
· Proximal rectum	5,1%	4,3%	

current guidelines.[23]

The data were collected from medical records, procedure and pathology reports.

The age and gender of the patients were recorded as well as the location of colorectal cancers.

Colonic stent placement was performed in an emergency setting by certified gastroenterologists and using standard endoscopic equipment after previous clinical and radiological evaluation. Colonoscopes used were CFQ160AL, Olympus Optical Co.®, Tokyo, Japan and the stents used were uncovered self-expandable metal stents Wallflex, Boston Scientific®. The diameter and length of the stents varied depending on the malignant strictures characteristics (location, length) and according to the endoscopist preference.

No sedation or sedation using intravenous midazolam (performed by a gastroenterologist) was administered on a case-to-case basis.

Patient surgical risk was stratified based on American Society of Anesthesiology – Physical status (ASA) and tumor staging was classified according to American Joint Comittee on Cancer – TNM system. Peri-operative mordibidity and mortality were evaluated according to Clavien--Dindo Classification.[24]

Regarding colonic stent placement, technical success was defined as being able to deploy the stent adequately across the malignant stricture as for clinical sucess we considered resolving the obstruction without the need of additional measures or treatment.

An oncological surgical resection was performed according to a protocol varying to the location of the tumor and was decided by the surgeon. Follow-up protocol for patients after surgery was performed according to current guidelines. The need for adjuvant chemotherapy was decided according to pathological staging, histological type of the tumor and patient characteristics (co-morbidities) in a case-to-case basis after multidisciplinary meeting. Stoma reversion surgery was performed in selected cases, as a second stage surgery, after adjuvant chemotherapy.

Recurrence after curative resection was defined as locally or regionally recurrent disease in the anastomosis, tumor bed, mesentery, draining lymphatics, surgical scar, or port sites. Distant metastasis was defined as the spread of the disease outside the surgical field to organs such as the liver, lungs, bones or brain.

Global recurrence rate during follow-up, type of recurrence and OS (survival time from surgery until the end of follow-up) as well as DFS (survival time without recurrence from surgery until the end of follow-up) were assessed and compared between the groups.

Statistical analysis was performed using IBM SPSS version 20.0. X^2 test and Mann-Whitney tests were used to assess the differences between the two groups. P values less than 0.05 were considered statistically significant. Kaplan-Meier curves were designed to assess survival diferences between the 2 groups.

RESULTS

Between January 2006 and December 2012, 126 patients with MLBO were treated at our instituition with a curative intent. These accounted for 11,8% of all patients with colorectal cancer treated during that given time.

79 patients (62,7%) were treated with colonic

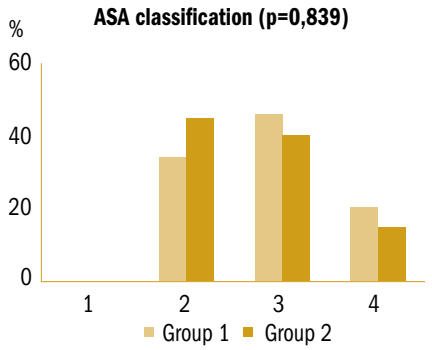


FIGURE 2. Distribution of cases according to ASA classification

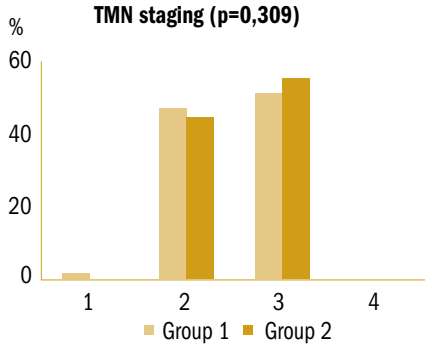


FIGURE 3. Distribution of tumor staging according to AJCC TNM classification

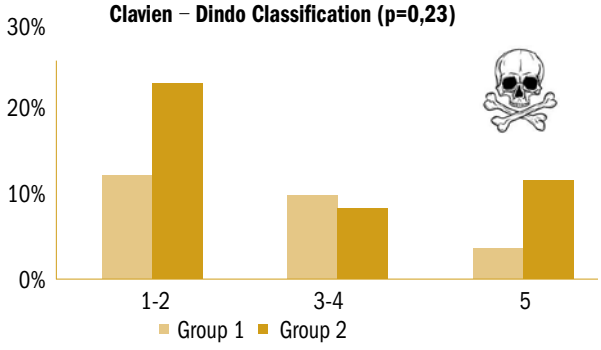


FIGURE 4. Distribution of cases according to Clavien-Dindo Classification regarding postoperative complications (I – Any deviation from the normal postoperative course withou the need for pharmacological treatment or surgical, endoscopic or radiological interventions; II – Requiring pharmacological treatment; III – Requiring surgical, endoscopic or radiological intervention; IV – Life threatning complications requiring admission in intermediate / intensive care unit; V- Death)

stent placement following a BTS strategy (Group 1) and in 47 cases (37,3%) emergency surgery was performed (Group 2). Outcomes were assessed until June 2015 with a mean period of follow-up of 49,2 +/- 3,6 months (median follow-up longer than 2 years) (Figure 1).

TABLE 2
Results regarding colonic stent placement

	Group 1 (n=79)
Technical success	98,7%
Clinical success	89,9%
Complications - Perforation - Migration	8,8% 5,0% (n=4) 3,8% (n=3)
Mortality related to the procedure	1,37% (n=1)
Mean time to surgery (days)	8,6 ± 4,9 (in 3 cases > 30 days)

Demographic characteristics of the patients and tumor distribution according to the location are showed in Table I. In both groups there was a small predominance of male sex, mean age was around 70 years old and the majority of tumors were located in the sigmoid colon. There was no significant difference between the two groups regarding sex, age and tumor location (p=ns).

Distribution of the patients regarding surgical risk (ASA) and TNM staging are showed in Figures 2 and 3. There was also no significant difference between the two groups (p=ns).

Regarding colonic stent placement (Table II), technical and clinical success were achieved, respectively, in 98,7% and 89,9%. Complications occured in a total of 7 cases (8,8%) and included 4 cases of perforation (5%) and 3 cases of stent migration (3,8%). Two perforations occured immediately and there were two late perforations (9 and 10 days after procedure). There was one immediate migration and two late migrations (10 and 12 days after the procedure).

All complications were managed surgically. There was one death related to the procedure (1,37%), following perforation and septic shock (which was excluded from survival analysis).

Mean time to surgery was 8,6+/-4,9 days (in-hospital stay). In three cases, surgery was performed more than 30 days after stent placement due to clinical instability and high surgical risk.

Following surgery, in group 1, a primary anastomosis was achieved in 88% of patients and the mean in-hospital stay was 14,4 days and mortality

	Group 1 (n=76)	Group 2 (n=40)	
Recurrence	34,5%	42,5%	p = 0,492

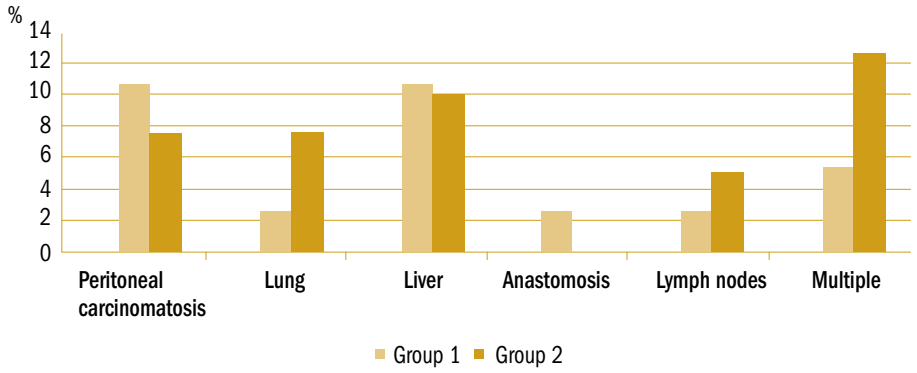


FIGURE 5. Total recurrence rate and prevalence of recurrence by type in each group (*ns*)

TABLE 3
Postoperative results

	Group 1 (n=79)	Group 2 (n=47)	
Rate of primary anastomosis	88%	29,8%	**p < 0,005**
In - hospital stay (days)	14,4	24,7	**p < 0,01**
In-hospital mortality	3,8%	11,7%	**p < 0,01**
Adjuvant chemotherapy	53,9%	60%	p < 0,530
Definitive stoma	13,9%	40,4%	**p < 0,005**

was 3,8%. All patients underwent surgery during the first admission. 53,9% of patients were offered chemotherapy and a definitive stoma was created in 13,9%. As for Group 2, primary anastomosis was possible in 29,8% of patients, mean in--hospital stay was 24,7 days and mortality 11,7%. 60,0% of patients were offered chemotherapy and a definitive stoma was created in 40,4%. Comparing the two groups, when colonic stent was placed in a BTS strategy, there was a statistacally significant higher primary anastomosis rate, lower in-hospital stay and mortality and less definitive stoma creation (Table III).

Apart from mortality, as previously mentioned, there were no statistically significant diferences between groups after distribution according to Clavien- -Dindo Classification (Figure 4).

Regarding oncological outcomes, global recurrence of disease was 34,5% in Group 1, lower than in Group 2 (42,5%), although this difference was not statistically significant (p = 0,492). Distribution by type of recurrence among the two groups is showed in Figure 5 and was similar between the two groups in terms of relative incidence.

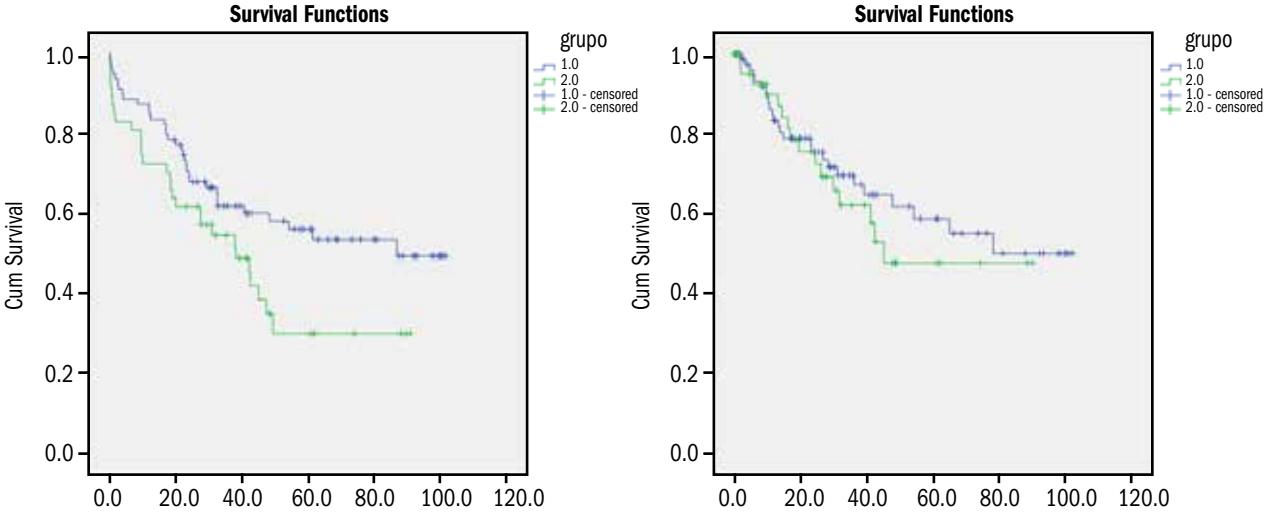
Both DFS and OS were superior in Group 1 (22,2 and 43,2 months, respectively) when compared with Group 2 (19,7 and 31,9 months), although this difference didn't reach statistic significance. OS at the first year was 89% in Group 1 versus 83% in Group 2. OS at 3 years was 63% versus 57% and at 5 years 55% versus 31% (Table IV and Figures 6 and 7).

DISCUSSION

Group 1 (BTS strategy) was larger than Group 2 which probably has to do with the experience our hospital as gained in colonic stenting in recent years. Treatment was generally decided by surgical and gastroenterology teams. However, factors as time of the day of the admission, admission on

TABLE 4
Mean survival analysis and Kaplan- Meier curves for DFS (left) and OS (right) (*ns*)

	Group 1	Group 2	
Mean DFS (months)	22,2	19,7	p=0,652
Mean OS (months)	43,2	31, 9	p=0,096



FIGURES 6 AND 7. Mean survival analysis and Kaplan- Meier curves for DFS (left) and OS (right) (*ns*)

weekends and availability of a gastroenterologist proficient in stent placing could have had an important role and were not possible to analyse. Both groups were comparable regarding distribution by gender, age, tumor location, disease staging and acess to adjuvant chemotherapy.

Regarding complications of colonic stenting, the complication incidence is similiar or lower to those reported before.[9-11] As for perforation and migration, and since there were two late perforations and two late migrations happening one week after the procedure, we can expect that this incidence can be lowered if surgery is performed in the first week. However, and due to the size of our sample, we cannot assume that according to statistical analysis. On the other hand, patient condition not always allows performing surgery as early as wished.

Postoperative results suggest a benefit from the BTS strategy in terms of primary anastomosis rate, in-hospital stay and mortality as well as definitive stoma creation. This was expected according to short-term results previously published and reflect a significative impact in patient quality of life, especially if we have into account that these patients have already a reduced life expectancy and poor outcomes due to advanced stage disease.

Regarding oncological outcomes, recurrence did not significantly differ between the two groups both in terms of global recurrence and as recurrence by location. Based on previous suspicion about the deleterious effect of colonic stenting regarding tumor manipulation and complications we could expect some differences in local recurrence (anastomosis or peritoneal carcinomatosis alone). However, peritoneal recurrence alone only occured in 10,5% of cases in Group 1 compared with 7,5% in Group 2. On the other hand, there were only two cases of anastomotic recurrence in Group 1 (compared to none in Group 2). Interestingly, none of the cases in Group 1 with local recurrence happened to have had a perforation following stent placement. These data suggest that postoperative recurrence and the kind of recurrence may depend on many other factors and that stenting alone may play a not so important role.

Long-term survival of our sample was poor as expected due to advanced disease staging (more than 50% were stratified as stage TNM III). Our results showed a tendency for longer DFS but

especially longer OS in Group 1, although these differences were not statistically significant.

In our experience, SEMS can have a very important role in treating occlusive CRC with a curative intent and benefit peri-operatory results without compromising oncological outcomes. Our results show a good technical and clinical success combined with less peri-operatory mortality and less need for definite stoma with positive impact in patient quality of life.

Our study has some limitations regarding its design (retrospective study) which can account for some unavoidable selection bias (mainly involving the decision process regarding the treatment and availability for stent placement). Also, there are several important questions that can imply worsening of oncological outcome and that could not be evaluated during our study protocol such as the existence of micro-perforations, biological factors of bad prognosis and the time "door to operating--room" in an emergency setting.

However, we should emphasize the fact that we got a good sample size and the existence of a relevant percentage of patients younger than 70 years-old (42,8%; n=54) and ASA < III (> 40%), which in theory account for the patients that should undergo emergency surgery, according to the recent guidelines.

This study represents a real-life setting case--based study and, to the best of our knowledge, it is the largest Portuguese report in which long--term results have been compared between BTS and emergency surgery for MLBO. Also, and according to the available literature, it is the third largest published study with more than two years of mean follow-up regarding this issue.[22]

The question this study imposes, especially regarding similar data on the long-term outcomes for SEMS in a BTS strategy, is if there is still enough evidence to recommend against SEMS placement as a first approach to LBMO due to occlusive CRC.

CONCLUSION

Results of our study on oncological outcomes, as stated in most recent meta-analysis and as well as well-described short-term outcomes, suggest that BTS can be a promising alternative strategy for MLBO. Larger prospective studies and randomized clinical trials would be beneficial in order to assess impact regarding oncological outcomes. However, these studies are very difficult to perform and would still need a very long follow-up period of time. As for now, we believe these results can be better evaluated in each center and there is probably insuficient evidence to generally recommend against BTS strategy for MLBO, as long as there is enough experience with colonic SEMS placement and good technical and clinical results can be guaranteed. ■

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