Influence of K-ras status and anti-tumour treatments on complications due to colorectal self-expandable metallic stents: A retrospective multicentre study

(Article begins on next page)

07 August 2024

Influence of K-ras status and anti-tumour treatments on complications due to colorectal self-expandable metallic stents: A retrospective multicentre study

- Lorenzo Fuccio[a,]
- Loredana Correale[b],
- Alberto Arezzo[c],
- Alessandro Repici[d],
- Gianpiero Manes[e],
- Cristina Trovato[f],
- Benedetto Mangiavillano[g],
- Mauro Manno[h],
- Claudio Camillo Cortelezzi[i],
- Marco Dinelli[j],
- Vincenzo Cennamo[k],
- Mario de Bellis[l]

- [a] Gastroenterology Unit, S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy
- [b] Im3D Medical Imaging Lab, Turin, Italy
- [c] Department of Surgical Sciences, University of Turin, Turin, Italy
- [d] Digestive Endoscopy Unit, Istituto Clinico Humanitas, Rozzano, Milan, Italy
- [e] Department of Gastroenterology, University Hospital L. Sacco, Milan, Italy
- [f] Endoscopy Division, European Institute of Oncology, Milan, Italy
- [g] Gastrointestinal Endoscopy Unit, Azienda Ospedaliera San Paolo, University of Milan, Milan, Italy
- [h] Gastroenterology and Endoscopy Unit, New S. Agostino Hospital, Modena, Italy
- [i] Division of Gastroenterology, Varese, Italy
- [j] Department of Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy
- [k] Unit of Digestive Endoscopy, Department of Surgery, AUSL Bologna Bellaria-Maggiore Hospital, Bologna, Italy
- [l] Endoscopy Unit, National Cancer Institute and G. Pascale Foundation, Naples, Italy

  -
    - on behalf of the KRASTENT Study Group 1
      - Annalisa Altimari[a],
      - Giulio Cariani[b],
      - Angelo Caruso[c],
      - Rita Conigliaro[c],
      - Cristiano Crosta[d],
      - Paolo Delrio[e],
      - Maria Cristina Di Marco[f],
      - Carlo Fabbri[g],
      - Michelangelo Fiorentino[h],
      - Stefania Ghersi[g],
      - Elisa Gruppioni[h],
      - Cesare Hassan[i],
      - Liboria Laterza[b],
      - Guglielmo Nasti[j],
      - Carmine Pinto[f],
      - Fabiola Rojas[f],
      - Eleonora Scaioli[b]
      - [a] Division of Pathology, S.Orsola-Malpighi Hospital, Bologna, Italy
      - [b] Gastroenterology Unit, S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy
      - [c] Gastroenterology and Endoscopy Unit, New S. Agostino Hospital, Modena, Italy
      - [d] Endoscopy Division, European Institute of Oncology, Milan, Italy
      - [e] Division of Colorectal Surgery, National Cancer Institute and G. Pascale Foundation, Naples, Italy
      - [f] Division of Oncology, S.Orsola-Malpighi Hospital, Bologna, Italy

- [g] Unit of Digestive Endoscopy, Department of Surgery, AUSL Bologna Bellaria-Maggiore Hospital, Bologna, Italy
- [h] Division of Pathology, S.Orsola-Malpighi Hospital, Bologna, Italy
- [i] Department of Gastroenterology and Digestive Endoscopy, Nuovo Regina Margherita Hospital, Rome, Italy
- [j] Division of Abdominal Medical Oncology, National Cancer Institute and G Pascale Foundation, Naples, Italy

Abstract

Background

This study aimed to explore the relationship between K-ras status, anti-tumour treatments, and the complications of colorectal self-expandable metallic stenting in colorectal cancer.

Methods

This is a retrospective, multicentre study of 91 patients with obstructive advanced colorectal cancer palliated with enteral stents between 2007 and 2011.

Results

K-ras wild-type tumours were diagnosed in 44 patients (48.4%); 82 (90.1%) received chemotherapy and 45 (49.4%) had additional biological therapy (34 bevacizumab, 11 cetuximab). Twenty-one (23.1%) experienced stent-related complications: 11 (52.4%) occurred in the K-ras mutant group ($P = 0.9$). K-ras wild-type patients were not less likely to develop adverse events than K-ras mutant patients (OR, 0.99; 95% CI: 0.4–2.7). Overall mean time to complication was 167.6 days (range 4–720 days), with no difference between the two groups (141 vs. 197 days; $P = 0.5$). Chemotherapy did not influence the risk of complications (OR, 0.56; 95% CI: 0.14–2.9), and there was no evidence that patients treated with chemotherapy and cetuximab were more likely to experience stent-related complications than patients treated with chemotherapy alone, or untreated (OR, 1.2; 95% CI: 0.2–5.9). Although perforation rates were higher with bevacizumab-based treatment (11.8% vs. 7%), this result was not statistically significant ($P = 0.69$).

Conclusions

K-ras mutation status, chemotherapy, and biological treatments should not influence colorectal stent-related complication rates.

Keywords

- Bevacizumab;
- Cetuximab;
- Colorectal cancer;
- K-ras mutation status;
- Occlusion;
- Self-expandable metal stent

1. Introduction

Colorectal cancer (CRC) is the third most common cancer in Western countries [1] and [2] and in several cases it is diagnosed after the development of obstructive symptoms [3] and [4]. Curative resection is not feasible in up to 30% of patients due to advanced disease and comorbidities [4]. For these patients, placement of a self-expandable metallic stent (SEMS) may represent an alternative to surgery [5] and [6]. SEMS placement is technically successful in most cases; however, both early and long-term complications (i.e., perforation, migration, and occlusion) have been reported in up

to 30–50% of patients [7] and [8]. Furthermore, although the initial clinical success of SEMS placement is over 90%, it tends to decline to less than 50–60% after 6 months, because of late complications [6].

Over the last decade, concerns about the use of colorectal SEMS have increased due to the clinical success of new chemotherapy regimens used for patients with stage IV CRC. Chemotherapy alone, or in combination with targeted monoclonal antibody therapies (bevacizumab, cetuximab, and panitumumab), is often given to patients with late-stage disease. Recently, chemotherapy has been associated with a 35% reduction in the risk of death for these patients, and with an improvement of median survival from 11 months to more than 20 months [9]. The risk of SEMS-related complications increases along with patients' survival, and the role of the anti-tumour therapy, which could determine the tumour shrinkage and could weaken the colonic wall, remains poorly explored.

K-ras protein is encoded by the K-ras gene, and it functions as an essential component of the epidermal growth factor receptor (EGFR) signalling cascade. Activating mutations in the K-ras gene have been detected in approximately 30–50% of CRC specimens [10]. Mutational activation of RAS oncogenes is the most important factor for determining non-responsiveness to EGFR inhibitors (cetuximab and panitumumab) [11] and [12]. Patients with wild-type K-ras CRC treated with EGFR inhibitors generally have an overall increased survival compared to patients carrying a mutated K-ras [11], [12], [13], [14], [15], [16] and [17]. Bevacizumab is a monoclonal antibody routinely used in combination with chemotherapeutic regimens for treatment of metastatic CRC, and it has been associated with an increased risk of spontaneous gastrointestinal perforation [5] and [18].

The aim of our study was to explore the relationship of K-ras mutation status, anti-tumoral therapies (chemotherapy with or without monoclonal antibody therapies) and SEMS-related complication rates in patients with obstructive CRC palliated by means of SEMS.

2. Methods

2.1. Study design

This was a multicentre, retrospective, cohort study involving 10 Italian centres (4 centres in Milan, Baggiovara, Bologna, Monza, Naples, Turin, and Varese). The study was approved by the Institutional Review Board of the coordinating centre (S. Orsola-Malpighi Hospital, University of Bologna, Bologna) and, thereafter, by the Ethics Committee of each participating centre.

2.2. Patients

Patients treated from January 2007 to December 2011 were retrospectively identified, using the prospectively collected SEMS database in each participating centre. All CRC patients with SEMS placed for palliation, with known K-ras mutation status of CRC, and with follow-up until death, stent removal due to complications, or until the end of the study observation period (December 2012) were considered eligible. Patients with colonic obstruction due to causes other than CRC, those with SEMS placed as a bridge to surgery, those with unknown K-ras mutation status, and patients lost to follow-up were excluded from the study.

The diagnosis of an obstructing CRC was made by clinical findings and radiological imaging (computed tomography). Each patient underwent lower endoscopy with biopsy of the primary tumour for histological diagnosis and K-ras analysis. All patients gave written informed consent before SEMS placement. Only patients for whom SEMS insertion was technically and clinically successful were eventually enrolled in the study. Technical success was defined as successful placement of SEMS, with its correct deployment and positioning at the level of the stenosis, assessed by radiology. Clinical success was defined as complete colonic decompression within 72 h after SEMS insertion, evaluated clinically and radiologically by means of standard abdominal X-ray. Persistent clinical success continued to be assessed until death or the last follow-up visit.

The following data were collected for each patient: demographic data, site and length of stenosis, type (covered, partially covered, or uncovered) and length of SEMS placed, number of SEMS placed in each patient during the same session, cancer stage, site of metastasis, medical history and concomitant therapies, K-ras mutation status (wild-type/mutated and type of mutation), chemotherapy (oxaliplatin-based, fluoruracil-based, irinotecan-based), biological treatment (cetuximab, panitumumab, bevacizumab), SEMS-related complications (perforation, migration, obstruction due to ingrowth or overgrowth) and timing of complications, length of follow-up, status of the patient (alive or dead) at the end of follow-up.

2.3. Stenting technique

SEMSs were inserted in the conventional manner [19]. The type of stent, as well as its length and its diameter, was selected according to the endoscopist's preference and stricture characteristics. All the procedures were carried out in high-volume, tertiary care centres by endoscopists highly experienced in both SEMS placement and interventional endoscopy.

2.4. K-ras analysis

K-ras analysis was performed on all biopsies taken from the primary tumours, according to the currently suggested methods for mutation analysis [20]. Mutations at codons 12 and 13 were routinely searched in all centres.

2.5. Follow-up and definition of endpoints

Follow-up data were obtained from chart reviews, clinical visits, and telephone calls to the patient or the closest relative. Patients were followed until death, stent removal, or last clinical follow-up.
Primary endpoint was the association between the occurrence of complications and K-ras mutation status and anti-tumour therapies. Persistence of clinical success over time, and time to death were examined as secondary endpoints. Time to maintain clinical success was defined as the time from stent placement to the occurrence of complications. Patient survival was defined as the time from stent placement to death, or patient status on the date of the last follow-up visit.

2.6. Statistical analysis

Patients' characteristics were summarised by using means ± standard deviations (SD), while medians and interquartile ranges were used for continuous variables, and percentages for categorical variables. The Chi-square test, the Fisher's exact test, or the *t*-test were used, as appropriate, to compare patients' characteristics between the 2 study groups (K-ras wild-type CRC vs. K-ras mutated CRC). Also, the logistic regression model was used to study the association between complications and different influencing variables. In this model, the dependent variable was complication result (yes/no), while the risk factors analysed were age, gender, CRC features including K-ras gene status, stent characteristics, and treatment procedures. The association was presented as odds ratios (ORs), with 95% confidence intervals (CI). Secondly, the Kaplan–Meier analysis was used to estimate clinical success over time and median survival times. The log-rank test was used to compare survival between K-ras wild-type and K-ras mutant tumours. Cox proportional hazard regression analyses were also used to estimate the effect of different risk factors, such as gender, age, and biological therapy, on the risk of clinical failure. All tests were two-sided with a significance level of $P < 0.05$.
One of the main purposes of this study was to explore the relationship between occurrence of complications from stent placement and K-ras mutation status. Since no information was available from previous studies, it was not possible to calculate the sample size. However, using logistic regression to explore the association between complications' occurrence and K-ras gene status, a sample size of 91 patients should allow the detection of ORs >2.7 with one-tailed alpha of 0.05 and power of 0.8, assuming a proportion of complications at 25%.
Statistical analyses were performed by using the R software (R Development Core Team (2009). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0).

3. Results

After reviewing the data of 795 patients in whom colorectal SEMS were placed during the study period, the inclusion criteria were met by 91 patients (Figure S1). Forty-four (48.4%) patients had K-ras wild-type tumours and 47 (51.6%) had K-ras mutated tumours. Demographic and clinical data are summarised in Table 1, while details of SEMS characteristics for the entire series and for both K-ras mutation status subgroups are summarised in Table 2. Ninety-six stents were placed in 91 patients (5 patients received 2 stents). Chemotherapy was administered to 82 patients (90.1%), and 45 of them (49.5%) received additional biological therapy (34 bevacizumab, 11 cetuximab); of note, 27 patients treated with biological therapy were in the K-ras wild-type CRC group (Table 1). Nine patients did not perform any kind of anti-tumour treatment and underwent only palliative supportive care. All 9 patients were informed of their clinical condition and they refused any other treatment. These patients were followed up for a mean period of 185 days (12–720 days) after SEMS placement, and 3 of them developed SEMS-related complications. Of these, 2 were colonic perforations that occurred 12 and 50 days after SEMS insertion, and another one was a case of stent occlusion due to tumour ingrowth, diagnosed 720 days after stent placement. All but one of these patients were dead by the end of follow-up.

Table 1.
Demographic and clinical characteristics of the study population.

Variable	All patients (*n* = 91)	Wild-type K-ras (*n* = 44)	K-ras mutation (*n* = 47)	*P* value
Mean age (years, range)	64.6 (37–92)	67.8 (45–92)	62.9 (37–89)	0.105
Male gender (%)	61 (67)	29 (65.9)	32 (68.0)	0.941
Stenosis size (cm, range)	4.58 (2–10)	4.66 (3–10)	4.50 (2–10)	0.649
Stenosis-location (%)				
Rectum	23 (25.3)	12 (27.3)	11 (23.4)	0.915
Rectum-sigmoid	7 (7.7)	4 (9.1)	3 (6.4)	0.915
Sigmoid	34 (37.4)	17 (38.6)	17 (36.2)	
Descending colon	8 (8.8)	3 (6.8)	5 (10.6)	
Splenic flexure	10 (11.0)	4 (9.1)	6 (12.7)	
Transverse colon	6 (6.6)	2 (4.5)	4 (8.5)	
Hepatic flexure	1 (1.1)	1 (2.4)	0	
Anastomosis to the rectum	2 (2.3)	1 (2.4)	1 (2.1)	
Chemotherapy (%)	82 (90.1)	38 (86.4)	44 (93.6)	0.306
Biological therapy (%)	45 (49.5)	27 (61.4)	18 (38.3)	0.036
Cetuximab	11	11	0	
Bevacizumab	34	16	18	
T3, N2, M0/stage III	8 (8.8)	3 (6.8)	5 (10.6)	0.915
Any T, any N, M1/stage IV	83 (91.2)	41 (93.2)	42 (89.4)	0.715
Mean follow-up (days, range)	251 (4–1440)	228 (12–750)	273 (4–1440)	0.351
Deaths (%)	55 (60.4)	25 (56.8)	30 (63.8)	0.526

Table options

Table 2.
Self-expandable metallic stent characteristics. Ninety-six stents were placed in 91 patients (5 patients received 2 stents).

Variable	Total SEMS (*n* = 96)	SEMS in wild-type K-ras group (*n* = 45)	SEMS in K-ras mutated group (*n* = 51)	*P*-value
Single stent (%)	86 (89.5)	39	47	0.06
Device manufacture (*n*)				
Wallflex	60	30	30	
Ultraflex Precision	11	7	4	
EGIS	1	0	1	
Bonastent	1	0	1	0.450
Evolution	12	5	7	
Hanarostent	10	3	7	
Niti-S	1	0	1	
Stent type (%)				
Covered	2 (2.1)	1	1	
Uncovered	93 (96.8)	44	49	0.623
Partially covered	1 (1.1)	0	1	
Stent length, mean (range)	9.0 (6–14)	8.7 (6–12)	9.3 (6–14)	0.215

SEMS, self-expandable metallic stent.
Table options

The two groups of patients (K-ras wild-type and mutated) were homogenous according to all the demographic and clinical variables.

3.1. Complications

The incidence of complications is shown in Table 3. Overall, there were 21 (23.1%) complications related to colorectal SEMS. Eleven (52.4%) of them were observed in the K-ras mutant subgroup. After stent insertion, the mean time to complication was 167.6 ± 186.7 days (median 90, range 4–720 days). When comparing K-ras mutant patients with K-ras wild-type patients, no difference in terms of time to complication was noted (141 vs. 197 days; $P = 0.501$). Complications included SEMS occlusion in 11 cases (12.1%), bowel perforation in 8 cases (8.8%), and stent migration in 2 cases (2.2%). SEMS occlusion occurred in 6 K-ras wild-type patients, within a mean period of $308 \pm 1\ 10$ days (median 325, range, 120–424 days) after colorectal stent placement. In K-ras mutant patients, 5 occlusions were reported within a mean of 257 ± 267 days (median 70, range 70–720 days) after SEMS placement ($P = 0.705$). Perforations occurred in 3 K-ras wild-type patients, within a mean of 20.6 ± 26 days (median 12, range 0–50 days) after stent placement. In K-ras mutated CRCs, there were 5 perforations, with a mean time to perforation of 50.4 ± 73.6 days (median 15, range 4–180 days, $P = 0.447$). Overall, K-ras wild-type patients were not less likely to develop an adverse event than K-ras mutated patients (ORs, 0.99; 95% CI: 0.4–2.7; $P = 0.939$).

Table 3.
Stent-related complications.

Variable	All patients (n = 91)	Wild-type K-ras (n = 44)	K-ras mutation (n = 47)	P-value
Overall complications (%)	21 (23.1)	10 (22.7)	11 (23.4)	0.908
Occlusion (%)	11 (12.1)	6 (13.6)	5 (10.6)	0.705
Perforation (%)	8 (8.8)	3 (6.8)	5 (10.6)	0.447
Migration (%)	2 (2.1)	1 (2.3)	1 (2.1)	1.000

Table options

Chemotherapy did not influence the risk of complications (ORs, 0.56; 95% CI: 0.14–2.9; $P = 0.446$). Forty-five patients (49.5%) received additional biological therapy; of these, 27 were in the K-ras wild-type group. Eleven patients received cetuximab, while 34 patients were treated with bevacizumab (Table 1 and Table 4). Complications occurred in 12 patients (26.7%) who received biological therapy; of these, 10 (29.4%) were reported in the bevacizumab group and 2 occurred among the 11 patients treated with cetuximab (18%). Biological therapy was not associated with an increased rate of complications (ORs, 1.6; 95% CI: 0.6–4.8; $P = 0.293$). Furthermore, although complication rates were higher in the group of patients treated with bevacizumab (29.4%), there was no statistically significant difference between this group and that of patients not treated with biological therapy (19.6%, $P = 0.309$), or patients receiving cetuximab (18%, $P = 0.469$). There was no evidence that patients treated with chemotherapy and cetuximab were more likely to experience stent-related complications than patients treated with chemotherapy alone, or untreated patients (ORs, 1.2; 95% CI: 0.2–5.9; $P = 0.856$).

Table 4.
Stent-related complications according to anti-tumour therapies.

Complications	CT only (n = 37)	CT + bevacizumab (n = 34)	CT + cetuximab (n = 11)	No treatment (n = 9)	Total (n = 91)
Overall (%)	6 (16.2)	10 (29.4)	2 (18.2)	3 (33.3)	21
Occlusion (%)	3 (8.1)	5 (14.7)	2 (18.2)	1 (11.1)	11
Perforation (%)	2 (5.4)	4 (11.8)	0	2 (22.2)	8
Migration (%)	1 (2.7)	1 (2.9)	0	0	2

CT, chemotherapy.
Table options

Development of perforations did not correlate with any of the clinical variables analysed. Furthermore, there was no evidence of a significant relationship between the occurrence of perforations and K-ras gene mutation (ORs, 2.8; 95% CI: 0.5–22; $P = 0.266$). Colonic perforation occurred in 4 bevacizumab-treated patients (Table 4). Although the perforation rate was higher among patients receiving bevacizumab than among those not treated with bevacizumab [11.8% (4/34) vs. 7%, (4/57); $P = 0.695$], there was no statistically significant difference between the two groups; the

odds of complications in patients treated with bevacizumab was 2.1 (95% CI: 0.7–6.1) compared with patients treated only with chemotherapy ($P = 0.185$).

3.2. Time to clinical success and survival

Patients were followed up for a mean of 251 ± 229 days (range 4–1440 days) until death, stent removal, or the end of the study. The mean follow-up of patients with wild-type and mutated K-ras CRCs was 228 days and 273 days, respectively ($P = 0.351$).

According to the Kaplan–Meier analysis, the cumulative probabilities of clinical success at 12 and 24 months after stent placement were 70.7% (95% CI: 58.4–85.7%) and 42.2% (95% CI: 21.4–83.2%), respectively (Fig. 1). No difference in terms of maintenance of clinical success over time was found between patients with and without K-ras mutations (RR; 0.92; 95% CI: 0.4–2.2; $P = 0.847$) (Fig. 2). Treatment with biological therapy was not a significant factor for clinical failure (RR; 1.1; 95% CI:0.5–2.7; $P = 0.763$). Furthermore, no statistically significant differences were found in terms of maintenance of clinical success over time among patients receiving bevacizumab in combination with chemotherapy, patients receiving cetuximab in combination with chemotherapy, and untreated patients (RR, 1.4; 95% CI: 0.7–3.5; $P = 0.415$). Among the subjects with K-ras wild-type CRC, patients treated with cetuximab in combination with chemotherapy did not have a risk of clinical failure greater than that of patients treated with chemotherapy alone, or untreated ($P = 0.368$).
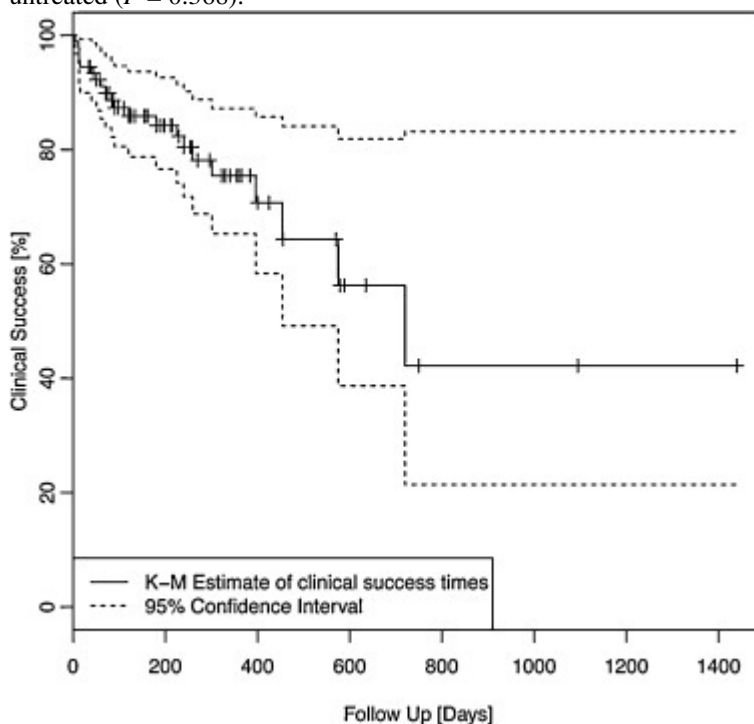

Fig. 1.
According to Kaplan–Meier analysis, the cumulative probabilities of clinical success at 12 and 24 months after stent placement was 70.7% (95% CI: 58.4–85.7%) and 42.2% (95% CI: 21.4–83.2%), respectively.
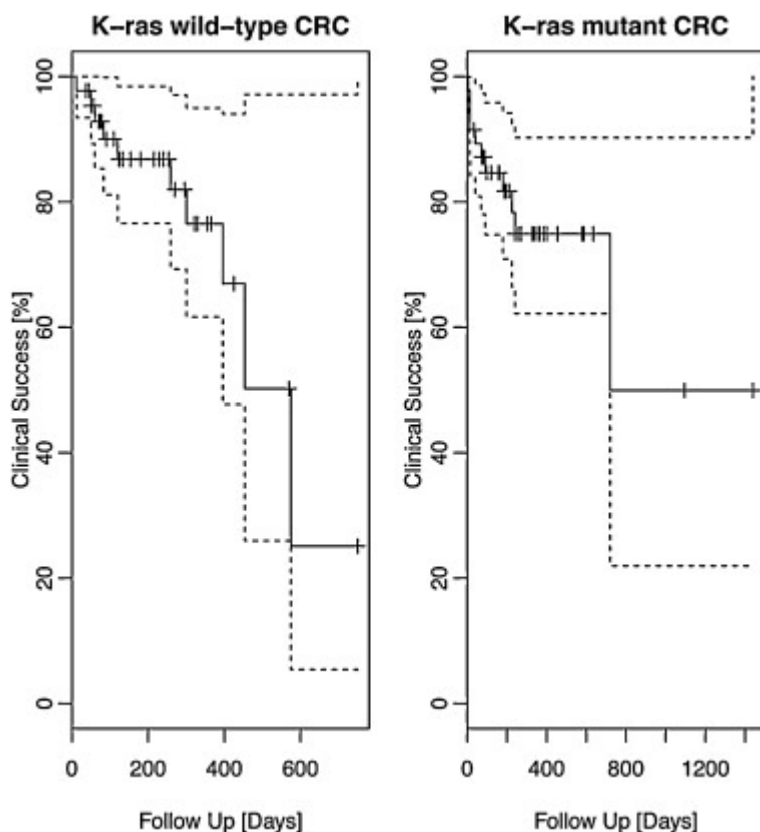Figure options

Fig. 2.

Kaplan–Meier estimated clinical success curves for K-ras wild-type colorectal cancers and K-ras mutants. Clinical success time was not different for K-ras wild-type and mutant colorectal cancers (RR 0.92; 95% CI: 0.4–2.2; $P = 0.847$).

Figure options

Thirty-six patients (39.6%) were alive at the end of follow-up. At the time of death, SEMS remained a clinical success in 43 of the 55 non-survivors (78%). Patients experiencing complications were not at greater risk of death (ORs, 1.3; 95% CIs: 0.7–2.5; $P = 0.404$). The median survival time was 330 days (95% CI: 270–396) (Figure S2). The estimate of median survival for K-ras wild-type CRCs was 322 days (95% CI: 240–425) and for K-ras mutated CRCs was 340 days (95% CI: 270–455). There was no evidence that patients with K-ras wild-type CRC survived longer than those with K-ras mutant CRC (RR, 0.92; 95% CI: 0.5–1.6; $P = 0.762$) (Figure S3). Median survival time was 384 days for patients treated with biological therapy (95% CI: 322–575) and 240 days (95% CI: 120–365) for those not treated with biological therapy. Patients treated with biological therapy had a lower risk of death, and thus survived longer than patients not treated with biological therapy (RR, 0.5; 95% CI:0.3–0.9; $P = 0.020$).

4. Discussion

SEMSs have been widely used in the management of malignant inoperable colorectal obstruction; however, although associated with a good clinical success rate, SEMS placement carries a relatively high complication rate, which tends to increase over time. Indeed, long-term complication rates vary widely according to published studies, ranging from 20% to 25% to more than 50% [8], [21] and [22]. Therefore, the long-term efficacy of SEMS for palliation of obstructing CRC has been questioned, and the identification of risk factors for SEMS-related complications has been a major task in recent years.

The relationship between anti-tumour treatments and SEMS-related complication rates remains poorly defined. In the study of van Hooft et al., 4 out of 7 stented patients, who were treated with chemotherapy, had a bowel perforation [23]. In the retrospective study of Fernandez-Esparrach et al., 8 out of 9 patients with stent migration and 2 out of 3 patients with perforations had been treated with chemotherapy [8]. Conversely, two large retrospective studies (one single centre study and a multicentre study) did not find any correlation between chemotherapy and risk of SEMS-related complications [5] and [24].

In our study, we did not find any significant association between chemotherapy and SEMS-related complications. Furthermore, we investigated the role of K-ras mutation status and cetuximab-based regimens on long-term SEMS-related complication rates. Cetuximab-based treatments have been approved by the Food and Drug Administration for the treatment of metastatic CRC and are actually used in first and second-line treatments, as well as in refractory disease. The prognosis of patients with K-ras wild-type CRCs can be improved by the additional administration of

EGFR inhibitors (cetuximab and panitumumab), thus theoretically increasing the risk of long-term complications. Based on our results, we did not find any difference in terms of complication rates according to both K-ras mutation status and cetuximab treatments.

Bevacizumab is a recombinant humanised monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) [25]. Disruption of the VEGF signalling is a major focus of new cancer therapeutics, and bevacizumab was the first angiogenesis inhibitor approved by the US Food and Drug Administration and the European Medicines Agency as first and second-line treatment for metastatic CRC [26], [27] and [28]. It is well known that the use of bevacizumab is associated with potentially life-threatening gastrointestinal perforations, with rates up to 1.5–1.7% as compared to controls [18] and [29]. It has been suggested that the pressure exerted by the radial force of the SEMS against the neoplastic tissue, weakened by bevacizumab treatment, could further increase the risk of perforation [30] and [31]. The single-institution study of Small et al. reported that bevacizumab treatment was associated with higher perforation rates than those in patients not treated with bevacizumab, but the difference did not reach statistical significance (15.4% vs. 6.8%; $P = 0.06$) [24]. Conversely, in a multicentre study, Manes et al. reported a significantly increased risk of colonic perforation in patients treated with bevacizumab compared to untreated patients, or patients who received standard chemotherapy (50% vs. 2.5%; OR 19.6; 95% CI: 5.9–64.5) [5]. In our study, although patients treated with bevacizumab tended to have an increased risk of perforation compared with untreated patients (11.8% vs. 7%), there was no statistically significant difference between the two groups. Although our findings need to be confirmed by larger studies, they may have important clinical implications, since they highlight the relationship among the biological characteristics of CRC, the anti-tumour treatments, and the risk of complications due to SEMS. Colonic perforation represents the most serious and potentially life-threatening SEMS-related complication, which can compromise the long-term outcome of patients. In contrast to other complications (i.e., migration and occlusion) that can be endoscopically managed simply placing other SEMSs, perforation can rarely be managed conservatively, and surgery represents the only curative treatment [19]. Our data show that the colorectal SEMS-related risk of perforation is lower than that previously reported [5] and [24]. Therefore, SEMS can be placed safely in patients with obstructive CRC without precluding them from the beneficial effects of bevacizumab-based treatments.

The long-term clinical success rate reported in our study is slightly higher than that reported in other studies [6], [8] and [24]. Indeed, the cumulative probabilities of clinical success at 12 and 24 months after stent placement were 70.7% and 42.2%, respectively. More importantly, at the time of death, SEMS remained a clinical success in 43 out of 55 non-survivors (78%), fulfilling its palliative purpose in these patients. The difference between our results and those of other studies can partly be explained by the following factors: different study populations, since we excluded patients with extrinsic compression due to cancer other than CRC; different techniques, because balloon dilation of the strictures was never attempted in any centre participating in our study; different types of chemotherapy and biological regimens, since anti-tumour treatments have been modified in order to provide more targeted regimens, according to the prognostic factors.

This study presents several limitations. Although 10 tertiary referral centres were involved, only 91 patients were included, and two centres provided the majority of cases (58 out of 91 patients, 64%); the main reason for this limited accrual is the strict selection criteria. Indeed, most of the patients were excluded because SEMSs were placed as bridge-to-surgery, K-ras mutation status was unknown, or follow-up was incomplete. We cannot exclude that the lack of a relationship between anti-tumour treatments and the risk of SEMS-related complications could be due to the small sample size of our series. Therefore, the results of our study need to be confirmed in the setting of prospective studies with a larger cohort of patients. This is a retrospective study and, although all the centres routinely complete a database of consecutively stented patients reporting the complications observed during follow-up, the interpretation of the results should be considered with caution, since biases cannot be excluded. The multicentre design introduces heterogeneity in the data, since differences in terms of patients' selection, endoscopic techniques, and type of SEMSs used are unavoidable. However, the main goal of our study was to evaluate the influence of K-ras mutation status and anti-tumour treatments on colorectal SEMS-related complication rates, and the two groups of patients (K-ras wild-type and mutants) were homogenous, since they did not differ according to all demographic and clinical variables.

To our knowledge, this is the first study investigating the influence of both K-ras mutation status of CRC and anti-tumour therapies on the outcomes of SEMS placed for palliation of obstructive stage IV CRC. Indeed, while previous studies mainly focused on risk factors determined both by technical aspects of colorectal SEMS insertion and clinical characteristics of the patients, the aim of our study was to point out possible relationships between SEMS-related adverse events and both biological features of CRC and anti-tumour therapies administered to patients after colorectal stenting. According to our data, SEMSs are a valid alternative to surgery, have a good long-term clinical success, independently from the K-ras mutation status of CRC, and do not jeopardise the results of anti-tumour therapies. A long-term predicted survival of patients with obstructive stage IV CRC does not represent a contraindication to SEMS insertion; in fact, in our series, approximately 50% of SEMS were patent 2 years after their placement, and a strict follow-up of the patients allowed prompt intervention (endoscopy vs. surgery) to solve possible adverse events due to late SEMS malfunctioning.

In conclusion, the results of our study suggest that K-ras mutation status, chemotherapy, and biological treatments of advanced CRC do not influence SEMS-related complication rates; in addition, they support the strategy of SEMS insertion to palliate patients with obstructive stage IV CRC. These results need to be confirmed by larger and possibly prospective studies.
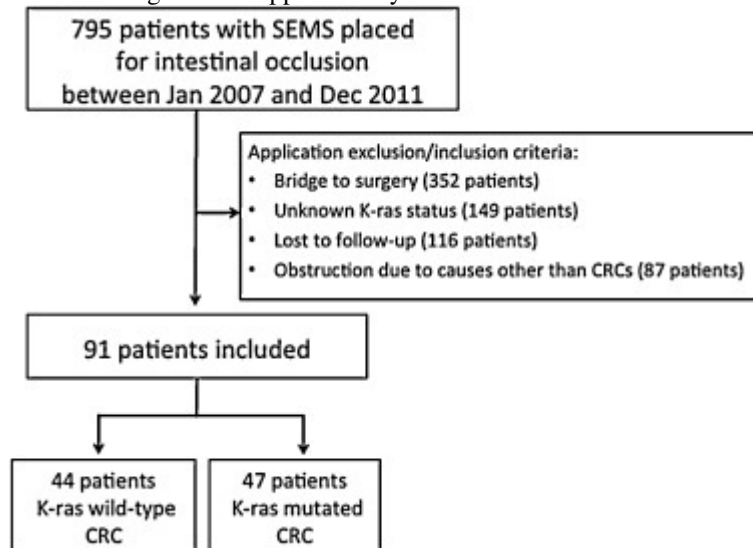
Conflict of interest

None declared.

Appendix A.

KRASTENT Study Group:
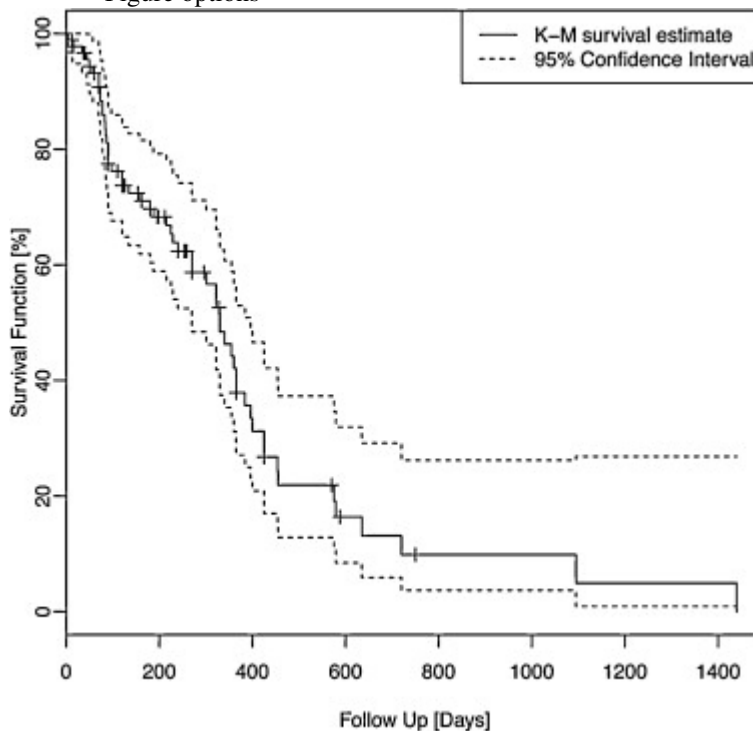
Appendix B. Supplementary data

The following are the supplementary data to this article:
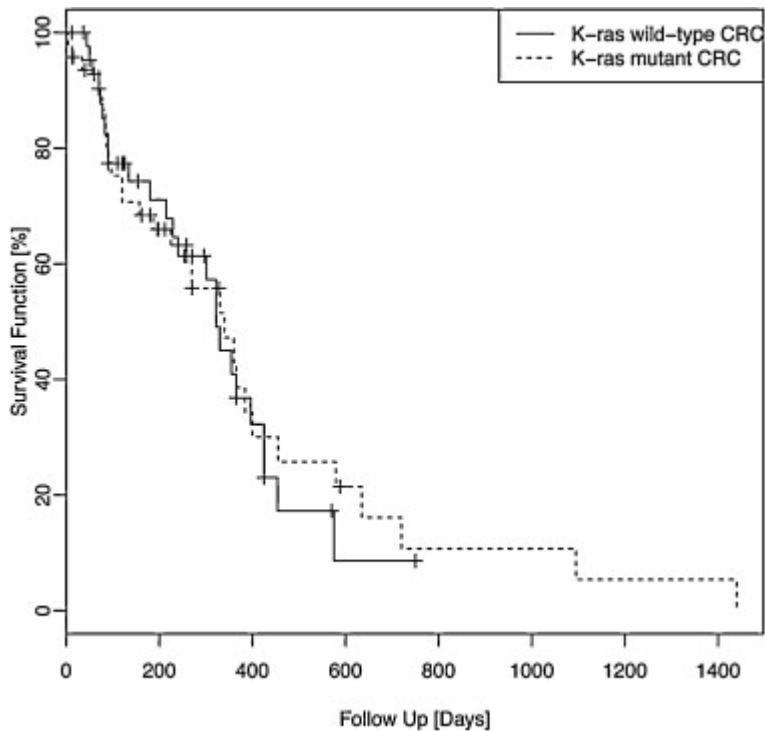

Supplementary Fig. I.
Study flow-chart.
Figure options

Supplementary Fig. II.
Kaplan–Meier estimates of survival time for the entire cohort. The median survival time was 330 days (95% CI: 270–396.
Figure options

Supplementary Fig. III.

Kaplan–Meier survival curves for K-ras wild-type mutant colorectal cancers. There was no evidence that patients with K-ras wild-type tumours survived longer than those with K-ras mutated colorectal cancers (RR, 0.92; 95% CI: 0.5–1.6; *P* = 0.762).

References

- [1]
- R. Siegel, C. DeSantis, K. Virgo *et al.*
- Cancer treatment and survivorship statistics, 2012
- CA: A Cancer Journal For Clinicians, 62 (2012), pp. 220–241
- [2]
- R. Siegel, D. Naishadham, A. Jemal
- Cancer statistics, 2012
- CA: A Cancer Journal For Clinicians, 62 (2012), pp. 10–29
- [3]
- L. Smothers, L. Hynan, J. Fleming *et al.*
- Emergency surgery for colon carcinoma
- Diseases of the Colon & Rectum, 46 (2003), pp. 24–30
- [4]
- G.T. Deans, Z.H. Krukowski, S.T. Irwin
- Malignant obstruction of the left colon
- British Journal of Surgery, 81 (1994), pp. 1270–1276
- [5]
- G. Manes, M. de Bellis, L. Fuccio *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
- Archives of Surgery, 146 (2011), pp. 1157–1162
- [6]
- A. Repici, G. De Caro, C. Luigiano *et al.*
- WallFlex colonic stent placement for management of malignant colonic obstruction: a prospective study at two centers
- Gastrointestinal Endoscopy, 67 (2008), pp. 77–84

- [7]
- A.J. Small, T.H. Baron
- Comparison of Wallstent and Ultraflex stents for palliation of malignant left-sided colon obstruction: a retrospective, case-matched analysis
- [8]
- G. Fernandez-Esparrach, J.M. Bordas, M.D. Giraldez *et al.*
- Severe complications limit long-term clinical success of self-expanding metal stents in patients with obstructive colorectal cancer
- American Journal of Gastroenterology, 105 (2010), pp. 1087–1093
- [9]
- L. Best, P. Simmonds, C. Baughan *et al.*
- Palliative chemotherapy for advanced or metastatic colorectal cancer. Colorectal Meta-analysis Collaboration
- Cochrane Database of Systematic Reviews (2008), p. CD001545
- [10]
- J.L. Bos, E.R. Fearon, S.R. Hamilton *et al.*
- Prevalence of ras gene mutations in human colorectal cancers
- Nature, 327 (1987), pp. 293–297
- [11]
- C.S. Karapetis, S. Khambata-Ford, D.J. Jonker *et al.*
- K-ras mutations and benefit from cetuximab in advanced colorectal cancer
- New England Journal of Medicine, 359 (2008), pp. 1757–1765
- [12]
- R.G. Amado, M. Wolf, M. Peeters *et al.*
- Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer
- Journal of Clinical Oncology, 26 (2008), pp. 1626–1634
- [13]
- W. De Roock, H. Piessevaux, J. De Schutter *et al.*
- KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab
- Annals of Oncology, 19 (2008), pp. 508–515
- [14]
- F. Di Fiore, F. Blanchard, F. Charbonnier *et al.*
- Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by cetuximab plus chemotherapy
- British Journal of Cancer, 96 (2007), pp. 1166–1169
- [15]
- H.J. Andreyev, P.J. Ross, D. Cunningham *et al.*
- Antisense treatment directed against mutated Ki-ras in human colorectal adenocarcinoma
- Gut, 48 (2001), pp. 230–237
- [16]
- H.J. Andreyev, A.R. Norman, D. Cunningham *et al.*
- Kirsten ras mutations in patients with colorectal cancer: the multicenter "RASCAL" study
- Journal of the National Cancer Institute, 90 (1998), pp. 675–684
- [17]
- L. Barault, N. Veyrie, V. Jooste *et al.*
- Mutations in the RAS-MAPK, PI(3)K (phosphatidylinositol-3-OH kinase) signaling network correlate with poor survival in a population-based series of colon cancers
- International Journal of Cancer, 122 (2008), pp. 2255–2259
- [18]
- S. Hapani, D. Chu, S. Wu
- Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis
- Lancet Oncology, 10 (2009), pp. 559–568
- [19]
- T.H. Baron, L.M. Wong Kee Song, A. Repici
- Role of self-expandable stents for patients with colon cancer (with videos)
- Gastrointestinal Endoscopy, 75 (2012), pp. 653–662

- [20]
- C.J. Allegra, J.M. Jessup, M.R. Somerfield *et al.*
- American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy
- Journal of Clinical Oncology, 27 (2009), pp. 2091–2096

- [21]
- L. Gianotti, N. Tamini, L. Nespoli *et al.*
- A prospective evaluation of short-term and long-term results from colonic stenting for palliation or as a bridge to elective operation versus immediate surgery for large-bowel obstruction
- Surgical Endoscopy, 27 (2012), pp. 832–842
- [22]
- J.Y. Kim, S.G. Kim, J.P. Im *et al.*
- Comparison of treatment outcomes of endoscopic stenting for colonic and extracolonic malignant obstruction
- Surgical Endoscopy, 27 (2013), pp. 272–277
- [23]
- J.E. van Hooft, P. Fockens, A.W. Marinelli *et al.*
- Early closure of a multicenter randomized clinical trial of endoscopic stenting versus surgery for stage IV left-sided colorectal cancer
- Endoscopy, 40 (2008), pp. 184–191
- [24]
- A.J. Small, N. Coelho-Prabhu, T.H. Baron
- Endoscopic placement of self-expandable metal stents for malignant colonic obstruction: long-term outcomes and complication factors
- Gastrointestinal Endoscopy, 71 (2010), pp. 560–572
- [25]
- J. Folkman
- Role of angiogenesis in tumor growth and metastasis
- Seminars in Oncology, 29 (2002), pp. 15–18
- [26]
- H. Hurwitz, L. Fehrenbacher, W. Novotny *et al.*
- bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer
- New England Journal of Medicine, 350 (2004), pp. 2335–2342
- [27]
- F. Kabbinavar, H.I. Hurwitz, L. Fehrenbacher *et al.*
- Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer
- [28]
- H.J. Schmoll, E. Van Cutsem, A. Stein *et al.*
- ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making
- Annals of Oncology, 23 (2012), pp. 2479–2516
- [29]
- M.W. Saif, A. Elfiky, R.R. Salem
- Gastrointestinal perforation due to bevacizumab in colorectal cancer
- Annals of Surgical Oncology, 14 (2007), pp. 1860–1869
- [30]
- V. Cennamo, L. Fuccio, V. Mutri *et al.*
- Does stent placement for advanced colon cancer increase the risk of perforation during bevacizumab-based therapy?
- Clinical Gastroenterology and Hepatology, 7 (2009), pp. 1174–1176
- [31]
- L. Fuccio, V. Cennamo
- Bevacizumab-based therapy and complication risk after colonic stent placement: is it time for a warning?
- Gastrointestinal Endoscopy, 72 (2010), p. 1330 [author reply 1330–2]