

## Colon or Rectal Stent Positioning for Advanced Cancer Influences Quality of Life: A Critical Point of View

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**Abstract.** *Background/Aim:* Endoluminal self-expanding metallic stents (SEMS) may overcome the risk of mortality and morbidity of acute intestinal obstruction because of stage IV colon (CC) or rectal (RC) cancer. We evaluated the QoL in these groups of patients. *Patients and Methods:* Forty-eight patients were enrolled in a prospective longitudinal cohort single-center trial to undergo SEMS positioning. Twenty-five patients had a CC and 23 RC. Karnofsky performance scale, Visual Analogue Scale and the EQ-5D- 5L™ questionnaire were administered before treatment and at 1, 3 and 6 months. *Results:* Harmonized to the Italian population, the index values showed a statistically significant deterioration of the QoL in patients with RC when compared to those with CC at 1-, 3- and 6-months (1 month:  $p=0.001$ ; 3- month:  $p=0.001$ ; 6-month:  $p=0.045$ ). Similarly, Visual Analogue Scale showed variations at 1- ( $p=0.008$ ), 3- ( $p=0.001$ ) and 6-months ( $p=0.020$ ). Rectal stent deployment was the only independent predictor for a worse QoL in all domains ( $p<0.017$ ;  $OR=0.196$ ;  $95\%CI=0.51-0.749$ ). *Conclusion:* Patients affected with stage IV CC had a better QoL after SEMS placement when compared to those affected with RC. The persistency of the primary tumor at the rectal level, even if irradiated, might negatively affect QoL.

When the tumor is located at or distal to the splenic flexure, acute intestinal obstruction is the presentation of colorectal cancer in 7-30% of cases (1). The risk of impending bowel

necrosis and colonic perforation caused by acute intestinal obstruction requires a prompt surgical bowel decompression. The therapeutic options include tumor resection with primary anastomosis or a two- or three-stage procedures (2). After an emergent surgery the mortality and major complications reach 15% to 20%, and 50%, respectively, whereas the mortality ranges between 0 and 9%, and major complications between 5 and 20% when patients undergo elective surgery (3). Endoluminal self-expanding metallic stents (SEMS) positioning in the treatment of malignant gastrointestinal obstruction may overcome the risk of mortality and morbidity because it is an effective and safe option to open surgery (4).

Theoretically, SEMS placement might be the preferred treatment for patients affected with unresectable stage IV colorectal cancer presenting with acute and subacute obstruction symptoms (3). SEMS is able to relieve the obstruction and offers many advantages, such as converting an emergent operation to an elective operation (5). The appropriateness of the different therapeutic options in patients affected with an advanced colorectal cancer should be measured with the quality of life (QoL). We recently demonstrated that during follow-up SEMS placement has a bimodal fluctuation pattern in terms of QoL. Stent positioning seems, in fact, to have better results at 1-month whereas at 6-months significantly worsened when compared to patients undergoing surgical resection (6). This study included patients affected with a stage IV colorectal cancer, but it was unable to elucidate the eventual differences in QoL related to SEMS positioning in the colon or rectal tract. We are well aware that QoL of patients affected with advanced rectal cancer may be negatively influenced by the persistency of symptoms after stent positioning: this treatment modality is able to solve tumor obstruction, but it is unable to relief symptoms from nerve compression or invasion. In association with radiation therapy may reduce this symptomatology (7, 8).

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*Key Words:* Advanced colorectal cancer, endoscopic stent positioning, surgical resection, quality of life (QoL).

In the present study we aimed to evaluate, in a prospective longitudinal cohort single-center trial, the QoL of advanced colon cancer patients treated with SEMS placement compared to those with advanced rectal cancer.

## Patients and Methods

All patients presenting with stage IV colon or rectal cancer at our Institution from February 2013 to January 2020 were enrolled into this prospective longitudinal cohort trial. All patient' data were handled according to the principles of the Declaration of Helsinki and a formal ethic approval from our Institutional Research Committee was obtained. The protocol was properly registered at a public trial registry, [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (Trial identifier NCT03451643). A written informed consent for the treatment and the analysis of data for scientific purposes was obtained from all patients. All patients were acknowledged of their terminal disease with the assistance of a psychologist.

A computerized database was then created to prospectively collect all clinical, pathological, intra- and post-operative outcomes, Karnofsky performance status scale (9), Visual Analogue Scale (10), quality of life (EQ-5D™) (11) and long-term survival.

Inclusion criteria were: age less than 85 years, pre-treatment histological diagnosis of colon or rectal adenocarcinoma, computed tomography (CT), adjuvant-neoadjuvant radio-chemotherapy regimen, symptoms of subacute large bowel obstruction (defined as continued passage of flatus and/or feces beyond 6-12 h after the onset of symptoms namely colicky abdominal pain, vomiting and abdominal distension relieving with conservative treatment), lumen reduction ranging between 70% and 99% at colonoscopy.

Criteria for exclusion were a white blood cell count less than 4,000/l, platelet count less than 70,000/l, patients with renal failure (*i.e.* albumin to creatinine ratio >30 mg/mmol and estimated glomerular filtration rate <30-44 ml/min/1.73 m<sup>2</sup>), patients with major alterations of liver function tests (*i.e.* total bilirubin >25.6 μmol/l, AST >5 U/l, ALT >5 U/l, PT-INR >1.5).

Out of 61 patients presenting with Stage IV colon or rectal cancer and symptoms of subacute large bowel obstruction, 48 were enrolled in the present trial. The remaining 13 patients were excluded from the study because of serum bilirubin levels above 25.6 μmol/l (5 patients), low platelet and white blood cell count (6 patients), and renal insufficiency (2 patients). In 4 patients there were more than one of the above-mentioned reasons to be excluded from the study and 3 of them also refused to have surgery. Twenty-five (52%) patients who were affected by advanced stage IV colon cancer formed the colon cancer group (CC) and 23 (48%) with advanced stage IV rectal cancer formed the rectal cancer group (RC).

*Endoscopic procedure.* Briefly, our endoscopic procedure has been previously described (6). All patients had one stent placed but in 2 patients two stents were required.

*Karnofsky performance scale and Quality of life (QoL) assessment.* Briefly, the functional status before SEMS positioning and reclassification after its deployment was analyzed with the Karnofsky performance scale (9). The EQ-5D-5L™ questionnaire (©EuroQol Group, Rotterdam, The Netherlands) (11) was administered before SEMS positioning and thereafter at 1-, 3- and 6-months according to our previously described methods (6) and the results adapted to the general population in Italy matched for age

(11). Furthermore, to help patients say properly respond to questions regarding their health state, a visual analog scale (EQ-VAS™) (10) was administered.

*Follow-up evaluation.* Patients were followed-up on outpatient basis every month. Hematochemical tests, abdominal CT scan and chest X-ray were performed every three months for the first year, and thereafter every year.

*Statistical analysis.* Our data were analyzed using the SPSS Ver. 25.0.0.2 software (SPSS Chicago, IL, USA) for MacOS High Sierra ver. 10.13.4 (Apple Inc. 1983-2018 Cupertino, CA, USA). Due to sample sizes, non-parametric tests were applied. The Mann-Whitney *U*-test was used to analyze the continuous variables whereas the Chi-square test or the Fisher's exact test explored the categorical variables. Due to the heterogeneity of the sample, data were expressed as mean±standard deviation, median, interquartile range (IQR) and mode (12). Actuarial survival rate was assessed by the Kaplan-Meier method at 1-year. Standard error (SE) of survival rate was estimated for each censored case. Actuarial survival was limited at 1-year because analysis of longer time period was statistically inappropriate for the small number of patients and the consequent high standard deviations. Logistic regression (forward stepwise method) analysis was used to identify factors affecting the areas of QoL investigation and was computed at the end of the study (6-month). Separate logistic regression model was used for the EQ-5D-5L™ questionnaire and the visual analog scale. The following variables were used for logistic regression analysis: age, gender, marital status (married, divorced widowed), social situation (upper, upper-middle, middle, working and lower social classes), level of education, clinical data, neoadjuvant and adjuvant radio-chemoradiation therapy, SEMS deployment in the colon or rectum, and postoperative complications. The 5 areas of investigation were dichotomized with a cut-off value of 15; specifically, 3 was the cut-off value for each domain. The visual analog scale was dichotomized with a cut-off value of 51. Differences with  $\alpha$ -level of <0.05 were considered statistically significant.

## Results

*Demographics and clinical findings.* Thirty-one (65%) patients were males and 17 (35%) females and our population had a mean age at presentation of 76±9 years (min. 44-max. 89; median 77; IQR=6; mode 80). Table I summarizes the demographic and clinical data of our series. There were no significant differences among the two groups. Marital and social status were similar among the groups. Specifically, 35 (73%) were married, 7 (15%) divorced and 6 (12%) widowed and no differences among the groups were recorded. Two (4%) patients defined their social status as appertaining to the upper, 4 (8%) to the upper-middle, 20 (42%) to the middle, 19 (40%) to the working and 3 (6%) to the lower classes. The level of education was similar, and, specifically the majority of them (29-60%) had a basic education (primary, intermediate and secondary) whereas 19 (40%) had college or master education.

*Early results.* There were no postoperative mortality and major complications within 30 days. There was a significantly

Table I. Demographics and clinical data.

	CC	RC	Significance
Number	25	23	<i>p</i> -Value
Mean age (SD; IQR; Median; Mode)	76 (9; 7; 77; 80)	76 (9; 6; 77; 80)	0.943
Gender (M/F)	17/8	14/9	0.764
Total bilirubin (µmol/l)	22 (3)	21 (4)	0.563
AST (U/l)	4 (0.3)	4 (0.2)	0.748
ALT (U/l)	5 (0.2)	4 (0.3)	0.427
PT-INR	0.8 (0.2)	1.0 (0.2)	0.612
Ascites	2	2	0.875
Liver metastasis			0.773
Less than 3	5	4	
More than 3	8	7	
Pulmonary metastases (presence or absence)	8	11	0.263

Between brackets standard deviation; SD: Standard deviation; IQR: interquartile range; AST: aspartate aminotransferase; ALT: alanine transaminase; PT-INR: prothrombin time-international normalized ratio.

higher incidence of minor complications in RC as compared to CC ( $p=0.046$ ); 4 (17%) patients had, in fact, rectal bleeding for 1-2 days, which resolved spontaneously.

Overall mean length of stay was  $2\pm 1$  days (min. 1 - max. 5; mode 1, IQR=2) and there were no statistical differences among the two Groups ( $p=0.869$ ; 95%CI=-0.753-0.638).

**Long-term results.** No patients were lost to follow-up (mean  $9\pm 3$  months; min. 4-max. 18; median 9; mode 9, IQR=4). There were no major or life-threatening complications related to chemotherapy but 3 (6%) patients (2 patients in CC and 1 in RC) stopped chemotherapy because of a significant deterioration of their liver function after the first cycle. Symptoms, potentially related to chemotherapy (fatigue, partial hair loss, decreasing liver function) were common (32-67% patients), and equally distributed in the two groups (18 in CC and 14 RC).

One-year actuarial survival rate of CC was 22% (SE=0.10; 95%CI=6.162-11.838) whereas in RC was 42% (SE=0.15; 95%CI=9.278-14.722).

**Karnofsky performance scale and Quality of Life (QoL).** Preoperative Karnofsky performance scale classified patients' functional impairment showing no significant differences among the two groups ( $73\pm 14$  and  $73\pm 13$ , respectively, for CC and RC;  $p=0.951$ ; 95%CI=-8.17405-7.68709). Similarly, the Karnofsky performance scale at 1-, 3- and 6-month showed no statistical differences between CC and RC (1-month:  $60\pm 11$  and  $62\pm 12$ , respectively, for CC and RC,  $p=0.451$ ; 95%CI=-9.39395-4.24612; 3-month:  $60\pm 9$  and  $59\pm 7$ , respectively, for CC and RC,  $p=0.581$ ; 95%CI=-3.41311-6.02181; 6-month:  $55\pm 8$  and  $58\pm 7$ , respectively for CC and RC,  $p=0.255$ ; 95%CI=-7.50301-2.04847). Harmonized to the Italian population, the preoperative index values were similar among

the groups ( $0.35\pm 0.08$  and  $0.34\pm 0.11$ , respectively for CC and RC,  $p=0.823$ ; 95%CI=-0.051892-0.064887). Conversely, at 1-, 3- and 6-month, index values showed a statistically significant deterioration of the QoL in patients of RC when compared to those of CC (1 month:  $0.33\pm 0.08$  and  $0.10\pm 0.11$ , respectively, for CC and 2,  $p=0.001$ ; 95%CI=0.162891-0.286386; 3- month:  $0.26\pm 0.09$  and  $0.10\pm 0.10$ , respectively, for CC and RC,  $p=0.001$ ; 95%CI=0.98630-0.206024; 6-month:  $0.51\pm 0.18$  and  $0.39\pm 0.20$ , respectively, for CC and RC;  $p=0.045$ ; 95%CI=0.003138-0.235979). Preoperative visual analog scale was similar among CC and RC ( $74\pm 13$  and  $74\pm 12$ , respectively for CC and RC;  $p=0.933$ ; 95%CI=-7.75168-7.12560). Conversely, significant variations among the two groups of patients in the postoperative period at 1- ( $65\pm 11$  and  $56\pm 9$ , respectively for CC and RC;  $p=0.008$ ; 95%CI=2.27223-14.24951), 3- ( $60\pm 9$  and  $52\pm 7$ , respectively for CC and RC;  $p=0.001$ ; 95%CI=3.25368-12.76372) and 6-month ( $55\pm 8$  and  $49\pm 6$ , respectively, for CC and RC,  $p=0.020$ ; 95%CI=0.91955-10.17136) were observed.

**Factors influencing QoL.** In the EQ-5D-5L™ questionnaire, the independent predictor of a worse QoL in all domains was location of SEMS deployment. Specifically, patients who had a rectal stent deployment experienced a worse QoL with respect to those who had a colon stent deployment ( $p<0.017$ ; OR=0.196; 95%CI=0.51-0.749). Conversely, none of the variables inserted into the model identified independent factors influencing QoL on the visual analog scale.

## Discussion

In patients with limited life-expectancy due to unresectable colon or rectal tumors associated with metastatic disease, SEMS deployment seems to be effective in relieving

obstructive symptoms and preventing the need for general anesthesia or emergency surgery (13-15), whereas the discomfort of this procedure is minimal (6). Furthermore, we recently observed that the QoL of advanced colorectal cancer patients improves significantly because it permits a better relationship with their relatives and allows a regular social life compared to palliative diverting surgery (14, 15). Disappointingly, the QoL had a bimodal fluctuation pattern at 1-month it was better in patients treated with stent but at 6-months it was significantly better in patients who underwent surgical resection (6). These figures are very interesting, and intriguing, but it was hard to find a proper explanation for this difference. However, in our previous study (6) we included patients affected with unresectable stage IV colon or rectal cancer with symptoms of obstruction without any distinction regarding the location of the primary tumor.

The present study was undertaken to answer the question whether the location of the stent might have a role in the worst QoL of patients at a mid-term follow-up and, therefore, we first compared the QoL of patients who had SEMS placement at the colon or rectal level.

The present data showed a significant worse QoL of patients who underwent SEMS positioning for rectal tumor when compared to those who had a colon stent deployment at 1-, 3- and 6-month follow-up. Multivariate analysis confirmed that the only independent predictor of a poor QoL in all domains of the questionnaire was the location of SEMS deployment.

These data necessitate a deep reflection and probably a change in the approach of patients affected with an advanced rectal tumor. Three important aspects should be highlighted: firstly, rectal nerve anatomy, which follows a completely different pathway of innervation compared to the colon, consists of a large network of fibers that can be compressed and cause per se more symptoms (7, 8) (tenesmus, abdominal and rectal pain during and after evacuation, genito-urinary related symptoms such as urinary urgency or pollakiuria) than the colon segment, and this occurrence is clearly independent from the stent deployment and it might be even worsened by the insertion of the stent. Therefore, the differences in the nerve network between these two anatomical regions might explain the divergencies in QoL among the two groups of patients. Secondly, in our series radiotherapy apparently had a marginal role in improving the QoL of patients with advanced rectal cancer (16-18). Thirdly, since the improvement of the QoL drives our strategy for treatment, these results might suggest that, whenever it is possible, a surgical approach may be preferable to a stent positioning in advanced rectal cancer.

Interestingly, although colon or rectal SEMS positioning might be risky because of the eventual serious complications, including perforation, we only recorded some minor complications (3, 5). We recommend stent positioning to be

performed by experienced staff personnel with a proper preoperative preparation (nasogastric tube and fasting with correction of the fluid and electrolytes imbalance with the intent to reduce the caliber mismatch from above and below the tumor stricture) and selection of the patients amenable of this procedure excluding patients with residual gross colonic dilatation, in whom there is a persistent significant risk of perforation and/or ischemia, and can undergo conventional surgery (3, 5, 13, 19-29).

We are well aware that our study has several limitations. The enrollment of patients was limited by the fact that this was a single-center study, thus having a significant heterogeneity in the presentation of stage IV colorectal cancer. Furthermore, we did not compare any of the two groups with a matched group of patients undergoing a primary tumor surgical resection. Conversely, our study has some strengths *i.e.* no patients were lost at follow-up, and all questionnaires with formally validated scales were completed by all patients.

In conclusion, patients affected with stage IV colon cancer have better QoL after SEMS placement when compared to those who undergo SEMS positioning for stage IV rectal cancer. We hypothesized that the persistency of the primary tumor at the rectal level even if irradiated might negatively affect the QoL if SEMS is positioned.

## Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

## Authors' Contributions

Enrico Fiori: Conception, design and data analysis; Daniele Crocetti: Conception, design and writing the manuscript; Paolo Sapienza: Conception, design and writing the manuscript; Antonietta Lamazza: Analysis and interpretation of data; Michelangelo Miccini: Data analysis; Roberto Cirocchi: Conception; Antonio V. Sterpetti: Conception and design; Francesca De Felice: Conception and writing the manuscript; Silvano Costi: Data analysis; Gioia Brachini: Collection of data; Andrea Mingoli: Interpretation of data; Giorgio De Toma: Conception and design.

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