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Resection or Stenting in the Treatment of Symptomatic Advanced Metastatic Rectal Cancer: A Dilemma

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Abstract. *Background/Aim: Patients affected with Stage IV colorectal cancer and unresectable metastases represent a heterogeneous group. Resection of the primary tumor or stent positioning followed by chemotherapy and/or targeted therapies still represent a difficult choice for surgeons. Patients and Methods: From February 2013 to September 2019, 46 patients were enrolled into a prospective randomized open label parallel trial presenting with Stage IVA and IVB rectal cancer, unresectable metastases and symptoms of subacute large bowel obstruction. Our population was divided into two groups: Group 1 included 20 patients who underwent placement of a self-expandable metal stent and Group 2 included 26 patients in whom primary tumor resection was performed. Results: One-year actuarial survival rate of Group 1 was significantly lower compared to Group 2. Overall 17 patients had survival longer than 1-year (3 in Group 1 and 14 in Group 2). Cox regression analysis showed that endoscopic stent positioning and the suspension of the chemotherapy because of deterioration of liver function tests were the two most important factors negatively influencing survival. Conclusion: Patients affected with stage IVA and IVB rectal cancer and symptoms of bowel obstruction had a significant longer survival rate when submitted to surgical rectal resection followed by chemotherapy.*

Colorectal cancer is a commonly diagnosed cancer. More than 25% of the patients have an initial diagnosis at a Stage IV, with a 5-year overall survival ranging from 10 to 18% (1). Simultaneous resection of the primary tumor and of all metastases can be conceptually curative; however, more than 80% of the patients present with unresectable colorectal metastases (1-4), and signs and symptoms of chronic intestinal obstruction in up to 85% of cases (5). Primary tumor resection is an accepted therapeutic option in patients with major symptoms related to a Stage IV colorectal cancer, with unresectable metastases. However, complications for surgery of large bowel obstruction are relatively frequent, with reported mortality rates ranging from 8.8% to 27% (6-10). Rectal stenting has been recently suggested as an alternative to surgery, allowing relief from obstruction and eventual stoma formation with low mortality rates and with technical and clinical success in 92% and 88% of cases, respectively (10). Despite these results, there is a potential risk for complications including perforation, stent obstruction or dislocation (11-13).

Median overall survival managed with best supportive care alone is about 5 to 6 months (14). Conversely, systemic therapy provides meaningful improvements in median survival and progression-free survival. Overall, with the judicious use of novel cytotoxic and biologic agents (15-18), the median overall survival has been extended to approximately 2 years (19-21). Standard therapy after the resolution of chronic intestinal occlusion includes the new chemotherapeutic agents such as oxaliplatin, bevacizumab, capecitabine, and regorafenib. These new drugs, alone or in combination with fluorouracil and leucovorin, have opened new therapeutic horizons and perspectives (22-24). Epidemiological analyses have demonstrated that simultaneously to the introduction of these new chemotherapeutic agents there has been reduced number of operations (25). Patients with Stage IV colorectal cancer and unresectable metastases represent a significantly heterogeneous group. In selected patients, combination of resection of the primary tumor with chemotherapy with bevacizumab, could improve the clinical outcome, giving a special significance and importance to primary resection in the multidisciplinary treatment planning.

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Key Words: Rectal cancer, targeted therapy, stent positioning.

In our open prospective randomized trial, we compared the long-term survival rates of patients affected with symptoms of chronic intestinal obstruction and metastatic Stage IVA and IVB rectal cancer (26) treated by endoscopic placement of a self-expandable metal stent or palliative tumor resection, followed by chemotherapy based on a combination of bevacizumab, cetuximab when indicated and fluorouracil.

Patients and Methods

All patients presenting with stage IVA and IVB, according to the American Joint Committee of Cancer (26, 27), rectal cancer and unresectable metastases at our Institution from February 2013 to September 2019 were enrolled into this prospective randomized open label parallel trial. The protocol was properly registered at a public trial registry, www.clinicaltrials.gov (Trial identifier NCT03451643).

All patient' data were carried out according to the principles of the Declaration of Helsinki and a formal ethics approval from our Institutional Research Committee was obtained. A written informed consent for the treatment and the analysis of data for scientific purpose was obtained from all patients. All patients were acknowledged of their terminal disease with the assistance of a psychologist.

Inclusion criteria were: age less than 90 years, pre-treatment histological diagnosis of rectal adenocarcinoma, computed tomographic (CT) scan showing unresectable metastases, symptoms of subacute large bowel obstruction (defined as continued passage of flatus and/or fecis beyond 6-12 hours 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, a Karnofsky Performance Scale Index (28) greater than 60%.

Criteria for exclusion were a white blood cells count less than 4,000/l, a 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^2), 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 55 patients presenting with Stage IVA and IVB rectal cancer, unresectable metastases and symptoms of subacute large bowel obstruction, 46 were enrolled in the present trial. Sixteen patients were excluded from the study because of a poor Karnofsky Performance Scale Index (4 patients), serum bilirubin levels above 25.6 μmol/l (2 patients), low platelet and white blood cell count (2 patients), and renal insufficiency (1 patients). In 4 patients there were more than one of the above-mentioned reasons to be excluded from the study. The enrolled patients were randomly assigned into two treatment groups: Group 1 included 20 patients who underwent placement of a self-expandable metal stent and Group 2 included 26 patients in whom primary tumor resection was performed. Localization of the tumor was defined as lower (0 to 6 cm), middle (7 to 11 cm) and upper (12 to 15 cm) according to the anatomical division of the rectum (29).

Endoscopic stenting. Bowel preparation consisted of 1 liter of water with PLENVU® (Norgine Italia S.r.l., Milan, Italy) (polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride for oral solution) powder administered according to the manufacturer's instructions. Few hours before the endoscopy a low-pressure water enema was performed. The procedure was performed under light sedation with benzodiazepine at a dosage depending on his/her body weight.

Briefly, we adopted a modification of previously described technique, a pediatric nasogastroscope (4.8 mm in diameter) was used to pass the obstruction (30, 31). Under direct vision, the guidewire was passed through the nasogostrocope above the obstructed bowel segment (32). Fluoroscopy was also used to follow the course of the guidewire and the deployment of the stent. The time during which fluoroscopy was used was much shorter than the time required with the standard technique. This has made the procedure much simpler, faster, and theoretically with reduced risk of perforation or bleeding. The self-expandable metallic stent (SEMS) apparatus (Precision Stent System Microvasive, Boston Scientific Corporation, Boston, MA, USA) was placed at the level of the obstruction through the guidewire previously inserted, and finally deployed under fluoroscopic guidance. The length of the stent ranged from 9 to 12 cm. We used uncovered stents: initially Ultraflex OTS stent, and lately Wallflex TTS stents (Boston Scientific, Boston, USA). The majority of the patients had one stent placed. In 1 patient two stents were required.

Surgery. Open surgery was performed in 20 patients, and laparoscopic surgery in 6 patients, after colonic preparation (as described above). Primary tumors were always completely resected but in 4 cases a terminal colostomy and in 8 an ileostomy was performed because the bowel reconstruction was felt at risk of leakage since the patients were operated on for symptoms of chronic intestinal obstruction.

Chemotherapy. Patients received adjuvant chemotherapy based on standard FOLFOX scheme [Oxaliplatin 85 mg/m^2 intravenous (IV), day 1, leucovorin 400 mg/m^2 IV day 1, 5-fluorouracil (5-FU) 400 mg/m^2 bolus on day 1, then 1200 mg/m^2 day for 2 days (total 2400 mg/m^2 over 46-48 hours) continuous infusion] or FOLFOXIRI regimen [irinotecan 165 mg/m^2 day 1, oxaliplatin 85 mg/m^2 day 1, leucovorin 200 mg/m^2 day 1, 5-FU 2400 mg/m^2 48-h continuous infusion plus cetuximab (400 mg/m^2 first infusion, 250 mg/m^2 thereafter) or panitumumab (6 mg/kg) or bevacizumab (5 mg/kg) based on wild-type (cetuximab/panitumemab) or mutated (bevacizumab) Ras-BRAF status.

Follow-up. Patients were followed-up on an out-patient basis. Blood chemistry, abdominal CT scan and Chest X ray were performed every 4-months for the first year, and thereafter every 6-months.

Statistical analysis. We analyzed our data with a computer software program (SPSS Ver. 25.0.0.1; 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 continuous variables. The Chi-square test or the Fisher's exact test were used for categorical variables. Due to the heterogeneity of the sample, data were expressed as mean±standard deviation, median, interquartile range (IQR) and mode. Actuarial survival rate was assessed by the Kaplan–Meier method at 1-year. Standard error (SE) of survival rate was estimated at 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. Cox regression analysis was applied to assess the influence of demographics, clinical

Table I. *Demographics and clinical data.*

	Group 1	Group 2	*p*-Value
Number	20	26	
Mean age (SD; IQR; Median; Mode)	76 (9.9; 6; 77; 77)	71 (6.4; 8; 72; 72)	0.106
Gender (M/F)	12/8	19/7	0.267
Pretreatment Karnofsky Performance Scale (SD)	73 (14)	68 (11)	0.206
Total bilirubin (μmol/l)	25 (1)	23 (2)	0.655
AST (U/l)	4 (0.1)	5 (0.3)	0.784
ALT (U/l)	4 (0.2)	4 (0.3)	0.575
PT-INR	1.0 (0.1)	0.9 (0.2)	0.418
Rectal tumor location			0.916
High (%)	9 (45)	13 (50)	
Medium (%)	8 (40)	10 (38)	
Low (%)	3 (15)	3 (12)	
Ascites (%)	1 (5)	1 (38)	0.686
Liver metastasis			0.207
Less than 3 (%)	11 (55)	10 (38)	
More than 3 (%)	9 (45)	16 (62)	
Pulmonary metastases (%)	7 (35)	6 (23)	0.287
Peritoneal involvement (%)	-	3 (11%)	0.236

SD: Standard deviation; IQR: interquartile range; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

data and hematochemical parameters on survival rates. Variables that significantly differed at a level of significance <0.05 (type of treatment and less or more than 3 unresectable liver metastases) were entered into the model, whose goodness of fit was assessed by the Hosmer-Lemeshow test. Differences with α-level of <0.05 were considered statistically significant.

Results

Demographics and clinical findings. There were 31 males and 15 females. Mean age at presentation was 73±8 years (min. 44 - max. 89 years; median=74.5 years; IQR=9; mode 76). Demographic and clinical data of the two groups are summarized in Table I. No significant differences among the two groups were noted. There were 38 (83%) patients classified as Stage IVA and 8 (17%) as Stage IVB. The simultaneous presence of metastasis in the liver and lung was observed in 5 (10%) patients whereas 3 (6%) patients had peritoneal involvement. Tumor grading ranged between G2 and G4 (G2=10; G3=26; G4=10). No differences were observed among the two groups (p=0.984).

Early results. Eight (31%) protective ileostomies and 4 (15%) terminal colostomies were performed in Group 2. There were no postoperative mortality and major complications within 30 days. Overall, we recorded 5 minor complications; 2 superficial wound infections, 1 pulmonary pneumonia (treated with specific antibiotics), 1 urinary tract infection (treated with specific antibiotics), in Group 2, and 1 rectal bleeding for 2 days which spontaneously resolved after medical therapy (whole blood and fresh plasma transfusions with correction of the coagulation assay) in Group 1. Oral feeding was resumed significantly earlier in Group 1 (1±0.3 days) patients compared to Group 2 (3±0.6 days) patients (p=0.001; CI=–1.961 - –1.378).

Table II. *Multivariate analysis. Cox regression analysis to determine negative predictors of overall 5-year survival rates.*

	Odds ratio	95%CI	*p*-Value
Stent positioning	0.284	0.131-0.616	0.001
Presence of more than 3 liver metastases	2.369	1.214-4.622	0.011

Model fit after Hosmer Lemeshow test df=8, p=0.42. CI: Confidence interval.

Overall length of stay was 8±3 days (min. 2 - max. 15; median=8 days, IQR=6). Hospitalization was significantly shorter in Group 1 (mean=4±1.7 days; min. 2 - max. 8) when compared to Group 2 (mean=10±1.8 days; min. 8 - max. 15) (p=0.001; CI=–6.878 - –4.737).

One-year results. No patients were lost to follow-up (mean 11±5 months; min. 4 - max. 24; median=8; IQR=7). There were no major or life-threatening complications related to chemotherapy but 4 (9%) patients stopped chemotherapy because of a significant deterioration of the liver function after the second cycle. Patients who stopped chemotherapy died within 5 months (1 in Group 1 and 3 in Group 2). Symptoms, potentially related to chemotherapy (fatigue,

partial hair loss, decreasing liver function) were common (61%-28 patients), and equally distributed in the two groups (12 Group 1 and 16 Group 2).

One-year actuarial survival rate of Group 1 (40%-SE=0.11) was significantly lower compared to Group 2 (54%-SE=0.10) (p=0.015; 95%CI=6.784-11.216). Overall 17 patients had survival longer than 1-year (3 in Group 1 and 14 in Group 2) (p=0.013; 95%CI=1.552-28.169). The simultaneous presence of multiple metastasis in different organs or the peritoneal involvement had no influence in overall survival (Stage IVA 1-year survival 37%; 95%CI=7.738-12.262; Stage IVB 1-year survival 37%; 95%CI=5.228-10.772; p=0.461).

Factors influencing survival. Cox regression analysis is presented in Table II and showed that endoscopic stent positioning (p=0.001; 95%CI=0.131–0.616) and the presence of more than 3 liver metastases (p=0.011; 95%CI=1.214–4.622) were the two most important factors negatively influencing survival.

Discussion

Despite the increasing public attention to screening and significant awareness of the importance of an early diagnosis, the majority of the patients with Stage IVA and IVB colorectal cancer have not resectable metastases with an advanced local tumor (1, 2). Survival rates of these patients are discouraging (33). Current treatment of advanced rectal cancer presents a controversy: the role of the surgical resection of the primary tumor without a curative intent; but it also has a certainty: the adjuvant systemic chemotherapy based on 5-FU or oxaliplatin associated with leucovorin. However, new approaches to this clinical picture, improvements in sequencing multimodality treatment methods, and novel and effective systemic therapies have been proposed to improve the outcome of these patients. In the recent years, emerging systemic therapies with targeted and nontargeted agents as well as immunotherapy became, in fact, available. Several trials have shown a significant role for bevacizumab and cetuximab, alone or in combination with fluorouracil and leucovorin, in prolonging survival and in reducing the advent of major complications (15-17, 34, 35). Several reports have shown a significant role for primary tumor resection in patients with Stage IV colorectal cancer and unresectable metastases (36, 37). All these studies were retrospective in nature, and inevitably the possibility of biases in selection exists. Some retrospective studies have used a propensity matching score in analyzing the clinical outcomes of patients who had primary tumor resection *versus* those who had only chemotherapy, with conflicting results (38, 39). A propensity matching score compares retrospectively patients with the same clinical characteristics, avoiding, often only in part, the inevitable selection biases associated with a retrospective study. The matter became more complicated by analyzing the results of three trials, recently published (40-42). Bevacizumab had no positive effect, in patients with Stage III colorectal cancer who had primary tumor resection.

The principal finding of our study was that rectal resection (43, 44), without a curative intent, permits better survival rates than endoscopic stent positioning both associated with postoperative chemo- and immunotherapies. None of our patients had neoadjuvant therapies because they were admitted for signs and symptoms of chronic intestinal obstruction and needed a rapid resolution of their clinical status.

Our previous study (27) comparing the quality of life (QoL) after endoscopic placement of a self-expandable metal stent *versus* primary tumor resection, in patients with stage IV colorectal cancer, has demonstrated at 1-month after treatment a statistically significant deterioration of the QoL in patients who underwent surgery compared to those who had the stent positioning. However, at 6-months patients submitted to a resection of the primary tumor had better QoL. This result may be related to the presence of a specific symptomatology due to the metal stent positioning *i.e.* tenesmus, incomplete evacuation and small rectal bleeding. This finding corroborates our hypothesis that the removal of the primary tumor brings several theoretical advantages. Tumoral cells produce high quantities of vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF), which can also be found in the blood circulation (45). These growth factors could have a stimulatory action on the liver metastases, neutralizing the action of the biological chemotherapy. The high levels of growth factors in the primary tumor could neutralize the majority of the targeted therapy, which will result in an inability to act on liver metastases. Liver metastases can differentiate from the primary tumor, with higher possibility of being sensitive to the biological drugs.

To these theoretical advantages, we should add the negative effect on the immune system of surgery *per se*. Furthermore, there is the possibility of significant side-effects of targeted therapy with reduced quality of life and life-expectancy; we registered 4 complications with these therapeutic regimens, which required the interruption of the therapies and these patients died within 5 months. Therefore, the results of our study showed the importance of a careful attention to the general conditions of patients in order to correctly select the optimal treatment. Patients with Stage IVA and IVB rectal cancer and unresectable metastases represent a significantly heterogenous group and the therapeutic approach should be personalized according to the specific clinical scenario, the biological characteristics of the primary tumor, the general conditions of the patients, and their liver involvement. The needs and expectations of the patient, based on an honest and sincere discussion, should represent the guidelines in deciding the most appropriate therapeutic approach (27).

Better survival rates were observed in patients who had rectal resection combined with targeted therapy, which was significantly related to the presence of less than 3 liver metastases.

This study has several limitations. Firstly, this is a single center study with a small number of patients, with significant heterogeneity on the presentation of stage IVA and IVB rectal cancer. Secondly, life expectancy in patients with stage IVA and IVB rectal cancer and altered liver function are significantly reduced and an aggressive either surgical or endoscopic and chemotherapeutic approach may negatively influence, at least theoretically, the survival rates.

In conclusion, our study demonstrated that patients affected with stage IVA and IVB rectal cancer and symptoms of bowel obstruction had a significant longer survival rate when submitted to surgical rectal resection followed by chemotherapy and the presence of less than 3 liver metastases was the other factor positively influencing survival.

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), Antonietta Lamazza (Conception and Collection of data), Francesca De Felice (Writing the manuscript), Mariarita Tarallo (Collection), Antonio V. Sterpetti (Conception and design), Andrea Mingoli (Conception and design), Paolo Sapienza (Conception, design and writing the manuscript), Giorgio De Toma (Conception and design).

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