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ORIGINAL ARTICLE

Complications from the primary tumour are not related with survival in patients with synchronous stage IV colorectal cancer receiving chemotherapy without primary tumour resection

Javier Suárez[1] · **Gabriel Marín**[1] · **Ruth Vera**[2] · **Begoña Oronoz**[1] · **Fabiola Oteiza**[1] · **Elena Mata**[2]

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Abstract
Background The aim of this study was to evaluate the rate of complications from the primary tumour (CPT) requiring surgical or endoscopic intervention during chemotherapy treatment in patients with incurable synchronous stage IV colorectal cancer, the possibility of predicting such complications and their influence on survival.
Methods One hundred and twenty-five patients were initially treated with chemotherapy. Patients were grouped on the basis of appearance or not of CPT. We assessed the relation between age, gender, carcinoembryonic antigen (CEA) level, primary tumour location, alkaline phosphatase level, unilobar or bilobar liver involvement, presence of peritoneal carcinomatosis, the number of sites of metastatic disease, the addition of target therapies to chemotherapy, the ability to traverse the tumour with an endoscope and the appearance of complications due to the primary tumour and overall survival.
Results Mean age was 64.9 years, and 89 patients were men. Over a mean of 234 days, 25 patients (20 %) developed a CPT. Eighteen patients required surgery, and seven were treated exclusively by an endoscopic procedure. Mean survival was 15.8 months. We found a statistically relevant correlation between the inability to traverse the tumour with an endoscope and the occurrence of a CPT. There was no statistical differences in survival between both groups, but patients receiving target therapies had better survival.
Conclusion Twenty percent of patients will suffer a CPT during chemotherapy treatment. The inability to pass the tumour with an endoscope can predict the CPT. Survival was only related to the addition of target therapies to chemotherapy.

Keywords Colorectal cancer · Metastatic colorectal cancer · Synchronous metastatic colorectal cancer · Upfront chemotherapy · Self-expanding metallic stent

For the table of contents Approximately 20 % of patients with synchronous stage IV colorectal cancer receiving chemotherapy without primary tumour resection will develop complications from the primary tumour. Intestinal obstruction will be the most frequent complication and is related to non-endoscopically passable tumours. These complications have not been related to the survival.

✉ Javier Suárez
fj.suarez.alecha@cfnavarra.es

[1] Department of General Surgery, Coloproctology Unit, Complejo Hospitalario de Navarra, c/ Irunlarrea 3, 31008 Pamplona, Spain

[2] Department of Medical Oncology, Complejo Hospitalario de Navarra, Pamplona, Spain

Approximately 25 % of patients with colorectal cancer present with metastases at initial diagnosis [1]. Surgical resection of the primary and metastatic tumours is feasible in a limited number of patients, and palliative management is the treatment of choice for the remaining patients. The primary goals of palliative treatment are to prolong survival and to improve quality of life. Resection of the primary colorectal tumour is a feasible option in cases of obstruction, perforation or haemorrhage.

Nevertheless, prophylactic resection of the primary tumour is controversial in patients with stage IV colorectal cancer who present with minimal symptoms resulting from the primary tumour. Surgery might avoid future complications, although this should be weighed against the morbidity [2] and mortality [3] associated with surgery in stage-IV patients. In addition, forgoing surgery avoids delays in starting chemotherapy and, if the primary tumour regresses after chemotherapy, symptoms might not be developed [4].

Previous studies report a 17 % complication rate due to the primary tumour in patients with synchronous stage IV

colorectal cancer who were treated with systemic chemotherapy, being the intestinal obstruction the most common complication [5]. A recent study suggests that the need for later intervention is not associated with decreased survival [6].

The aim of this study was to evaluate the rate of complications due to the primary tumour that required surgical or endoscopic intervention in patients who were undergoing non-operative management of synchronous stage IV colorectal cancer and presented with minimal symptoms resulting from the primary tumour. This study also assessed the influence of such complications on patient survival and the factors related to such complications.

Material and methods

The study was approved by the Research Ethics Committee of the Complejo Hospitalario de Navarra, Pamplona. Patients were identified from the data set of the Colorectal Cancer Multidisciplinary Meeting of our institution. From February 2003 to December 2012, 125 patients were assessed; these patients were diagnosed with synchronous stage IV colorectal cancer, presented with minimal or no symptoms from the primary tumour, and were initially treated with chemotherapy. Abdomen and thorax contrast-enhanced computed tomography was routinely performed for staging. PET scans were selectively performed to rule out the possibility of surgically removing the metastatic tumours. Incurability was assessed in the Multidisciplinary Meeting of our institution. Patients who underwent surgery to remove the primary lesion at the time of diagnosis or underwent surgery to remove metastatic tumours after a positive response to chemotherapy treatment were excluded. The remaining patients were stratified into two groups: on the one hand, those patients requiring surgery or endoscopic treatment owing to a complication from their primary tumour (complication group), and on the other hand, those ones who did not require treatment of the primary tumour (non-complication group).

Patient data, including age, gender, pretreatment carcinoembryonic antigen (CEA) level, primary tumour location, pretreatment alkaline phosphatase level (AP), unilobar or bilobar liver involvement, number of sites of metastatic disease, peritoneal involvement, addition of biological agents to chemotherapy (anti-EGFR therapy or angiogenesis inhibitors) and the ability to go through the tumour with an endoscope, were recorded and compared between the complication and the non-complication groups. Tumours located proximal to the splenic flexure were classified as proximal tumours; tumours located between the splenic flexure and the canal anal were classified as distal tumours. In the complication group, we analysed the type of complication and the procedure required for treatment.

Laboratory variables were dichotomized according to its normal or elevated value. The patients were divided by age 75 on the basis of previous studies [7].

The categorical variables are described in absolute numbers and in percentages. We assessed whether there was a correlation between the recorded variables and the development of late complications using a univariate and multivariate Cox-model regression. The log-rank test was used to evaluate means and medians of the variables in relation to the survival. The association between variables and groups and survival was evaluated using a univariate and multivariate Cox-model regression. Significant or near significant variables ($p<0.1$) were included in multivariate analysis. The IBM SPSS Statistics 20 system for Windows was used for statistical calculations.

Results

This study included 99 men and 26 women, with a mean age of 65 (33–84) years. At the time of diagnosis, no patient had radiological or clinical evidence of bowel obstruction, perforation or active haemorrhage. Patient characteristics are shown in Table 1. Table 2 shows the first line chemotherapy

Table 1 Baseline characteristics

Age	<75	99 (79.2 %)
	>75	26 (20.8 %)
Gender	Male	89 (71.2 %)
	Female	36 (28.8 %)
CEA	Normal	21 (16.8 %)
	Raised	103 (82.4 %)
	Unknown	1 (0.8 %)
Alkaline phosphatase	Normal	63 (50.4 %)
	Raised	54 (43.2 %)
	Unknown	8 (6.4 %)
Tumour location	Proximal tumours	41 (32.8 %)
	Distal tumours	84 (67.2 %)
Metastatic disease	One organ	81 (64.8 %)
	Two or more	44 (35.2 %)
Liver involvement	Unilobar	8 (7.5 %)
	Bilobar	98 (92.4 %)
Colonoscopic traversability	Yes	68 (62.4 %)
	No	41 (32.8 %)
	Unknown	16 (12.8 %)
Carcinomatosis	Yes	20 (16 %)
	No	105 (84 %)
Biological agents	Yes	63 (50.4 %)
	No	62 (49.6 %)
Primary tumour complication	Yes	25 (20 %)
	No	100 (80 %)

Table 2 First line chemotherapy (ChT) regime and rate of biological agents administration

First line ChT regime	*n* (%)
Irinotecan based ChT	19 (15.2)
Oxaliplatin based ChT	62 (49.6)
Capecitabine	9 (7.2)
Irinotecan plus anti-EGFR	2 (1.6)
Oxaliplatin plus anti-EGFR	21 (16.8)
Oxaliplatin plus Bevacizumab	12 (9.6)
Overall biological agents administration *n* (%)	63 (50.4)
First-line biological agents administration *n* (%)	35 (28)

treatments. In half of the patients, therapy target to EGFR, VEGF or both was added to chemotherapy.

Complications rate and management

Over a mean of 234 (41–944) days, 25 patients (20 %) developed a complication related to the primary tumour. Twenty complications (80 %) occurred in the first year. Most patients with complications had an intestinal obstruction (23 patients), whereas a perforation was found in two cases (none of them had previously received angiogenesis inhibitors). In 22 cases, complicated tumours were located distally to the splenic flexure. Two patients with perforation and 11 patients after obstruction underwent surgery. Twelve patients were managed after obstruction by an endoscopic stent insertion, but five patients later needed a surgical procedure due to absence of relief of symptoms, immediate complications or a new delayed intestinal obstruction. Ultimately, seven patients (28 %) were treated exclusively by an endoscopic procedure.

Factors related with the appearance of complications

In 109 patients, the ability to go through the tumour with an endoscope was reported. The endoscope could not pass through the tumour in 41 cases. On 10 of the patients in whom the tumour could be passed through by an endoscope, and in 15 patients in whom the tumour could not be passed, primary tumour complications requiring surgical or endoscopic relief were developed (14.7 vs 36.5 %; $p=0.005$). The patients with distal tumours had a higher rate of complications; this difference was near statistically significant in univariate analysis (26.1 vs 7.3 %; $p=0.060$). In the multivariate analysis, the impossibility to pass through the tumour with an endoscope was significantly related to the appearance of complications (HR 3.313; 95 %CI 1.478–7.424; $p=0.004$). Age, gender, CEA level, primary tumour location, AP level, unilobar or bilobar liver involvement, number of sites of metastatic disease, addition of biological agents to chemotherapy and peritoneal involvement were not related with the appearance of primary tumour complications (Table 3).

Influence of the primary tumour complications on survival

Median and mean survival was 13 and 15.6 months, respectively, for all cases (range 2 to 52 months). Patients with an elevated CEA level (15.2 vs 21.4 months; $p=0.048$) and proximal tumours (12.8 vs 17.8 months; $p=0.031$) had significant correlation to a poor outcome in the univariate analysis but not in the multivariate analysis. Addition of biological agents to chemotherapy was the only factor related with survival in multivariate analysis (10.5 vs 21.6 months; HR 2.688; 95 %CI 1.800–4.014). There was no relation between age, gender, PA level, unilobar or bilobar liver involvement, number of sites of metastatic disease, peritoneal involvement or ability to pass through the tumour with an endoscope to the overall survival. There were no statistical differences in survival between the complication and non-complication groups (16.1 vs. 16.2 months for the non-complication and complication group, respectively; $p=0.980$) (Table 4).

Discussion

Primary tumour resection in stage IV colorectal cancer is a subject of debate. Since the goal of treatment in these patients is to prolong survival and improve the quality of life by diminishing the symptoms of the disease, in the subgroup of patient asymptomatic primary tumours, the need for surgery is difficult to justify. Surgery in this case would only be justified to avoid late complications. Several studies demonstrated a lack of clear benefit from primary tumour resection in these patients and proposed chemotherapy as the treatment of choice. Tebbutt reported a benefit with respect to the median survival time (14 months for patients initially treated with surgery and 8.2 months for patients initially treated with chemotherapy), but this benefit was not detected in a multivariate analysis [8]. Similarly, Ruo et al. reported a benefit in median and 2-year survival times for patients initially treated with surgery, but in the multivariate analysis, only the volume of liver replacement was a significant predictor of survival [9]. A recent review by Cirocchi et al. shows that the resection of the primary tumour in asymptomatic patients who are managed with chemo/radiotherapy is not associated with an improvement in overall survival or with a significant reduction of complication risks from the primary tumour [10]. Howbeit, a meta-analysis of eight retrospective comparative studies reported an improvement in the survival among patients with primary tumour palliative resection [11]. A major draw-back of these studies was that patients with better prognosis at the moment of diagnosis were more likely to undergo surgery. An

Table 3 Univariate and multivariate analysis of risk factors for primary tumour complication

	N	Complicated	HR (95 % CI) Univariate	*p*	HR Multivariate	*p*
Age						
<75	99	23 (23.2 %)	3.145 (0.739–13.378)	0.121		
>75	26	2 (7.6 %)	1.00			
Gender						
Male	90	21 (23.3 %)	1.492 (0.874–2.547)	0.143		
Female	35	4 (11.4 %)	1.00			
Tumour location						
Distal	84	22 (26.1 %)	3.192 (0.953–10.690)	0.060	2456	0.146
Proximal	41	3 (7.3 %)	1.00			
CEA						
<5 ng/ml	21	7 (33.3 %)	1.660 (0.692–3.797)	0.256		
>5 ng/ml	103	18 (17.4 %)	1.00			
Unknown	1					
Alkaline phosphatase						
>108 U/l	63	15 (23.8 %)	1.382 (0.585–3.264)	0.461		
<108 U/l	54	8 (14.8 %)	1.00			
Unknown	8					
Metastatic disease						
Two or more	44	10 (22.7 %)	1.394 (0.603–3.021)	0.466		
One organ	81	15 (18.5 %)	1.00			
Liver involvement						
Bilobar	98	20 (20.4 %)	2.110 (0.283–15.759)	0.467		
Unilobar	8	1 (12.5 %)		1.00		
No	19					
Colonoscopic traversability						
No	41	15 (36.5 %)	3.138 (1.405–7.013)	0.005	3313	0.004
Yes	68	10 (14.7 %)	1.00			
Unknown	16					
Peritoneal carcinomatosis						
Yes	20	6 (30 %)	1.774 (0.707–4.453)	0.222		
No	105	19 (18 %)	1.00			
Biological agents						
Yes	63	12 (19 %)	0.692 (0.092–5.194)	0.721		
No	62	13 (20.9 %)	1.00			

analysis of patients from CAIRO and CAIRO2 studies showed a benefit in overall survival and progression-free survival for patients in which the primary tumour resection was performed [12]. These data can be influenced by the criteria used for selecting patients and depend on the extent of the metastatic disease and the condition of the patients. CAIRO 4 trial and NCT01978249 trial from Yonsei might be able to shed light on this question [13, 14].

In patients with in situ primary tumours who are treated with chemotherapy, some complications, including obstructions, haemorrhage, peritonitis and fistula, can occur. In previous reports, the rate of complications due to the primary tumour ranged between 8.5 and 30 % [12, 15, 16]. The most frequent complication was obstruction followed by haemorrhage. Muratore [15] and Ruo [9] reported a rate of intestinal obstruction of 5.6 and 29 %, respectively. Haemorrhage was found in 3.7 % of patients in a study by Tebbutt, which reported peritonitis or fistula at a rate of 6 % [8]. In a phase II trial, McCahill et al. reported a complication rate of 16.3 % in patients with an intact primary tumour receiving treatment by FOLFOX and Bevacizumab [16]. In our experience, an intestinal obstruction was developed in 23 patients (18.4 %) and a perforation in two patients (1.6 %). In total, 25 patients (20 %) suffered a complication from the primary tumour with this strategy of treatment. In concordance with NSABP trial C-10, most complications (80 %) appeared in the first year

Table 4 Univariate and multivariate analysis of risk factors for overall survival

	Mean (months)	Median (months)	HR (95 % CI) Univariate	*p*	HR Multivariate	*p*
Age						
<75	16.5	13	0.811 (0.517–1.271)	0.361		
>75	14.6	13	1.00			
Gender						
Male	16.3	13	0.978 (0.802–1.194)	0.830		
Female	15.8	13	1.00			
Tumour location						
Distal	17.8	14	1.525 (1.039–2.238)	0.031	1.286	0.206
Proximal	12.8	11	1.00			
CEA						
>5 ng/ml	15.2	13	1.706 (1.004–2.897)	0.048	1.420	0.201
<5 ng/ml	21.4	19	1.00			
FA						
<108 U/l	17.2	14	0.833 (0.572–1.214)	0.341		
>108 U/l	14.6	9	1.00			
Metastatic disease						
One organ	17.4	14	0.744 (0.511–1.085)	0.124		
Two or more	13.9	13	1.00			
Liver involvement						
Unilobar	16.8	15	0.762 (0.352–1.649)	0.490		
Bilobar	14.5	12	1.00			
Colonoscopic traversability						
No	14.9	12	1.260 (0.843–1.884)	0.260		
Yes	17.7	15	1.00			
Primary tumour complication						
Yes	16.1	13	0.994 (0.629–1.572)	0.980		
No	16.2	12	1.00			
Peritoneal carcinomatosis						
Yes	15.4	10	0.993 (0.599–1.647)	0.993		
No	16.2	13	1.00			
Monoclonal antibody						
Yes	21.6	18	2.920 (1.968–4.332)	0.000	2.688	0.000
No	10.5	8	1.00			

after the diagnosis; McCahill et al. found 83.3 % of complications within the first year [16].

In a recent meta-analysis, Scheer et al. reported a mortality rate of 2.7 % and a major morbidity rate of 11.8 % after resection of the primary tumour in patients with metastatic colorectal cancer [11]. Because obstructions are the most frequent complication, non-invasive procedures such a stent placement could be advisable in some cases to avoid the risks of surgery. Seven of 22 patients with an obstruction were successfully treated by an endoscopic procedure.

Previous data demonstrate that left side tumours develop symptoms more frequently than proximal tumours [2]. We found a non-significant lower rate of complications in proximal tumours in multivariate analysis (7.3 vs. 26.1 %; p=0.060). Moreover, the inability to pass through the tumour with an endoscope correlated with the appearance of complications from the primary tumour. In our study, patients with non-traversable tumours developed complications significantly more frequent than traversable tumours in multivariate analysis (36.5 vs 14.7 %; p=0.005). These data are concordant with a recent report from Japan. They found that non-traversable lesions had higher 2-year rates of symptom-directed surgery than those with colonoscope-traversable lesions (64.3 vs 9.9 %). Moreover, the median time until symptom-directed surgery was significantly lower in colonoscopic non-traversable tumours (2.1 vs 15.5 months; p=0.01) [17]. Miyamoto et al. found that patients with circumferential tumours were likely to suffer an obstruction

during chemotherapy treatment [18]. Whether a prophylactic surgery should be considered, instead of carefully vigilance to avoid an emergent surgical or endoscopic procedure, is yet unclear.

For patients with metastatic tumours who are undergoing chemotherapy as primary treatment, previously reported data showed a mean survival ranging between 8.2 and 22 months [8, 19]. We found a mean survival of 15.6 months for cases in our study.

Stelzner et al. reported previously relation between low CEA level and better prognosis [7]. Bajwa et al. showed that proximal tumours were associated with poor outcome [20]. In the univariate analysis, a raised CEA level (15.2 vs 21.4 months; $p=0.048$) and proximal tumours (12.8 vs 17.8 months; $p=0.031$) were significantly related to poor overall survival. Both variables did not maintain its significance in multivariate analysis. Actually, the benefit of targeted therapies in survival of metastatic colorectal cancer patients with metastatic colorectal cancer is clearly defined [21, 22]. Half of the patients received biological agents in combination with chemotherapy, 28 % in the first line treatment. This relatively low rate of treatment with biological agents is related with the patients of the first period of the study. In the present study, only the addition of targeted therapies to chemotherapy was the only factor related to survival in multivariate analysis (10.5 vs 21.6 months; $p=0.000$).

Other prognostic factor previously described such age [7], PA level, peritoneal involvement [8], unilobar liver metastases [23] or liver involvement minor than 25 % [9] were not related to overall survival in our experience. Concern arises over long-term survival being or not compromised when primary tumour complications require endoscopic or surgical intervention. Although this specific issue has been poorly studied, we have found no differences in survival between the complication and the non-complication groups (16.1 vs 16.2 months; $p=0.980$), in concordance with Poultsides et al. [6].

The present study holds two limitations. Firstly, it is a retrospective study that lacks criteria for inclusion based on the definition of an asymptomatic patient with regard to the primary tumour at the time of the diagnosis. Secondly, it is difficult to evaluate possible complications due to primary tumours that did not need surgical or endoscopic intervention although they could have been implied on the treatment of the patient. Finally, it is useful to evaluate the total percentage of patients that suffered a complication due to the primary tumour and needed a surgical or endoscopic procedure and to evaluate the role of such complications in the long-term survival of patients.

In conclusion, after upfront chemotherapy in asymptomatic patients with synchronous stage IV colorectal cancer, approximately 20 % of these patients will suffer complications due to the primary tumour, with intestinal obstructions being the most frequent issue. The inability to traverse the tumour with an endoscope can predict the late appearance of complications. The appearance of such primary tumour complications did not have influence on overall survival.

Conflict of Interest The authors declare that they have no competing interests.

Author contributions Conception and design was done by J. Suárez, R. Vera and G. Marín. Data collection was conducted by E. Mata. Data analysis and interpretation were performed by all authors. Manuscript writing was done by J. Suárez. The final manuscript was approved by all authors.

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