Role of Primary Tumour Resection and Addition of Bevacizumab to Chemotherapy in the Management of Advanced Colorectal Cancer with Inoperable Metastasis: A Retrospective Analysis

Javier Garde Noguera[1,*], Elena Evgenyeva[2], Mireia Gil Raga[3], Asunción Juárez Marroquí[4], Juan Manuel Gasent Blesa[5], Juan Laforga[2], Laia Bernet[6], Mónica Clemente Císcar[7], Carlos Camps Herrero[8] and Antonio Llombart Cussac[1]

[1]*Servicio Oncología Médica, Hospital Arnau de Vilanova de Valencia, Spain*

[2]*Servicio de Anatomía Patológica, Hospital Marinasalud de Denia, Spain*

[3]*Servicio Oncología Médica, Hospital de Sagunto, Spain*

[4]*Servicio Oncología Médica, Hospital de Elda, Spain*

[5]*Servicio Oncología Médica, Hospital Marinasalud de Denia Spain*

[6]*Servicio de Anatomía Patológica y Oncología Diagnóstica, Hospital Lluís Alcanyís, Xativa, Spain*

[7]*Centro de Gestión de la Calidad y el Cambio, Universitat Politécnica de Valencia, Spain*

[8]*Servicio de Oncología Médica, Consorcio Hospital General Universitario de Valencia, Spain*

Abstract: *Purpose*: To analyze the impact of primary tumour resection on treatment outcomes in patients with advanced colorectal cancer (CRC) and inoperable metastases at diagnosis in combination with optimal systemic therapy.

Methods: A retrospective study was carried out in four hospitals in Valencia (Spain) including all consecutive patients diagnosed between 1/2009 and 12/2010 of advanced CRC with inoperable metastasis and treated with a fluoropyrimidine and oxaliplatin combination chemotherapy regimens with or without bevacizumab (B). Treatment outcomes were compared between patients undergoing or not primary tumour resection.

Results: A total of 112 patients met inclusion criteria: 62 patients underwent resection of the primary tumour (Group 1) and 50 were treated with exclusive chemotherapy (Group 2). Globally, patients in group 2 presented more disfavorable characteristics. Forty-five (72%) and 31 (62%) patients received chemotherapy with bevacizumab respectively. Overall response rate (ORR) were 67% in Group 1 and 56% in Group 2. There were no statistically significant differences between the two groups in progression free survival (PFS) (12 vs. 10 months; p =0.11) and overall survival (OS) (27 vs. 22 months; p 0.1). B regimens increased ORR (73% vs. 42%; p = 0.003) and PFS (12 vs. 11 months; p = 0.019) but not OS. Complications were higher in the group of patients without primary tumour resection, particularly when associated to B regimens.

Conclusions: Primary tumour resection offers no survival gain for patients with advanced CRC and inoperable metastases. Benefits of adding Bevacizumab to standard chemotherapy were similar in both groups, but it increases the risk of complications in non-resected patients.

Keywords: Primary Tumour Resection, Advanced Colorectal Cancer, Metastases, Survival, Bevacizumab.

INTRODUCTION

In Western countries, approximately 20% of patients with colorectal cancer (CRC) present advanced disease stage at diagnosis [1-3]. The standard approach for advanced CRC with inoperable metastasis has been systemic treatment with chemotherapy for over 40 years. Initially 5-fluorouracil (5-FU) which provided response rates of 10-20% as a single agent [4], followed by combinations with oxaliplatin that increased both response rates and overall survival (OS) [5], and finally with the addition of Bevacizumab (Avastin®), a humanized monoclonal antibody that inhibits vascular endothelial growth factor, a key mediator of angiogenesis [6-8], that has shown in several randomized clinical trials benefit when it is used in combination with various standard chemotherapy regimens [9-12]. The combined use of XELOX-bevacizumab provides a median progression free survival (PFS) of 9.4 months and a median OS of 21.3 months [12], and this combination is currently the most commonly used first-line treatment regimens in patients with advanced CRC.

Despite new advances in chemotherapy, surgery remains an important treatment option for advanced CRC, especially since it offers a curative option for select groups: patients with metastatic disease confined to a single organ, patients with a local

*Address correspondence to this author at the Servicio Oncología Médica, Hospital Arnau de Vilanova de Valencia, Spain; Tel: 699307265; Fax: 963987700; E-mail: javiergardenoguera1@gmail.com

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recurrence only or patients with limited intra-abdominal disease. In such cases, an aggressive and multimodal management integrating both surgical resection and systemic chemotherapy treatment allows achieving long-term surviving rates of 50% [13]. Furthermore, surgical resection is the palliative treatment of choice for patients with symptomatic primary tumours that result in bowel obstruction or severe gastrointestinal bleeding, even in patients who are not candidates for metastatic resection.

The most controversial indication for surgery arises in those cases in which the patient has unresectable metastatic disease and an asymptomatic primary tumour. In such cases, the risk-benefit ratio of the primary tumour resection must be evaluated carefully. The role of surgery in these cases is controversial, some authors have noted that the initial resection of the primary tumour may slow the progression of the disease and have a favourable impact on patients´ survival [14-17], whereas other studies involving patients treated with modern chemotherapy combinations found no differences in OS rates between patients with primary tumour resection and without surgery [18-20]. There is concern about the increased risk of tumour complications in non operated patients such as bowel obstruction, perforation or haemorrhages, specially with addition of bevacizumab. Results of a phase II study conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP C-10) involving 86 patients with advanced CRC without primary tumour resection and treated with FOLFOX and bevacizumab [21], has shown a morbidity rate higher than 16% in this patients, with 12% of patients requiring surgery during the treatment (8 for bowel obstruction, 1 for perforation, and 1 for pain), and yielding a median survival time of 19.9 months.

The main objective of our study was to retrospectively analyze the impact of primary tumour resection on the overall survival of advanced CRC patients with inoperable metastases treated with fluoropyrimidine and oxaliplatin combination chemotherapy regimens (with or without bevacizumab). As secondary objectives, we intended to analyze the safety of the chemotherapy schedules; the rate of major complications resulting from resection and the rate of complications related the primary tumour in those patients who were not operated.

MATERIALS AND METHODS

This was a multicenter and retrospective study of patients with advanced CRC at diagnosis and treated with fluoropyrimidine and oxaliplatin combination chemotherapy regimens (with or without bevacizumab), at four different hospitals in Valencia (Spain).

Patient Characteristics

The medical records of patients diagnosed with advanced CRC were reviewed. Patients presented pathology-confirmed colorectal adenocarcinoma and were treated between January 2009 and December 2012 with a first-line chemotherapy regimen involving FOLFOX or XELOX in combination (or not) with bevacizumab.

Treatment and Follow-Up

All enrolled patients were treated with fluoropyrimidine and oxaliplatin combination chemotherapy regimens (with or without bevacizumab). A complete review of the medical history and baseline measures of the tumour before the treatment beginning were performed to evaluate the patients. The diagnosis and treatment evaluation was carried out with computed axial tomography. Analytical data was also collected before the treatment beginning, including hematologic cell counts, lactate dehydrogenase (LDH) and carcinoembryonic antigen (CEA) levels.

Treatment toxicity was assessed according to the criteria published by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. Tumour response was evaluated according to RECIST criteria. OS was calculated as the time elapsed from diagnosis to the date of death, and PFS as the time elapsed from the start of treatment to the documented date of disease progression.

Major primary tumour complications were considered those requiring new surgical intervention, discontinuation of chemotherapy or those that resulted in the patient's death.

Statistical Methods

All statistical analyses were performed using the SPSS statistical package version 8.2. A descriptive statistics analysis, including measures of central tendencies and dispersions of quantitative variables, as well as absolute and relative frequencies for categorical variables, was also carried out. T-test was used to compare two independent samples of continuous variables. The chi-square test was used to compare two or more independent groups of subjects with respect to a given categorical variable. Survival curves

were estimated using the Kaplan-Meier method, and then compared using the log rank test.

RESULTS

Patient Characteristics

We found 112 patients with advanced CRC at diagnosis and treated with fluoropyrimidine and oxaliplatin combination chemotherapy regimens (XELOX or FOLFOX) with or without bevacizumab in our medical records. Sixty-two patients (55.3%) underwent resection of the primary tumour prior to chemotherapy treatment (Group 1). The remaining 50 (44.7%) patients did not undergo surgery and received only chemotherapy as first-line treatment of the advanced disease (Group 2).

Patient's characteristics are summarized in Table **1**. The median age of the total population was 68 years (67.5 in Group 1 vs. 69.5 in Group 2). The rate of patients over 70 years in Groups 1 and 2 was 33% vs. 50%, respectively (p= 0.063). Differences were also observed between groups with regard the proportion of women enrolled (33% vs. 55%, p= 0.025), of patients with weight loss higher than 10% (3% vs. 34%, p= 0.019) and of patients with high CEA levels at diagnosis (71% vs. 90%, p= 0.018).

Treatment

In Group 1, 45 out of 62 patients (72.5%) received chemotherapy in combination with bevacizumab (14 with FOFLOX-B and 33 with XELOX-B), the remaining (17 patients) received chemotherapy without bevacizumab (3 with FOLFOX and 14 with XELOX). In Group 2, 31 (62%) patients received chemotherapy with bevacizumab (13 with XELOX-B and 18 with FOLFOX-B), and 19 patients (38%) received chemotherapy without bevacizumab (7 with FOLFOX and 12 with XELOX).

In the total population, 101 patients were evaluated for response: 58 in Group 1 and 43 in Group 2. The

Table 1: Demographic and Clinical Data at Baseline in the Study Population

	Primary tumour resection (n=62)	No primary tumour resection (n= 50)	p value
Age (years), median	67.5	69.5	
Age >70 years	21/62 (33%)	25/50 (50%)	0.063
Gender, (Male vs Female)	31/62 (50%) vs 31/62 (50%)	35/50 (70%) vs 15/50 (30%)	0.025*
PS 0-1	52/61 (85.2%)	35/48 (72%)	0.089
HT at diagnosis	25/55 (45%)	18/43 (41%)	0.44
Weight loss >10%	7/51 (13%)	14/41 (34%)	0.019*
Rectal bleeding	17/51 (33%)	18/42 (42%)	0.23
Occlusive Symptoms	8/51 (15%)	2/41 (4.8%)	0.09
Metastatic Sites >1	37/62 (59.6%)	23/50 (46%)	0.1
High CEA levels	37/52 (71%)	38/42 (90%)	0.018*
Anaemia	23/44 (52%)	23/41 (56%)	0.44
High LDH levels	13/34 (38.2%)	19/31 (61%)	0.054
Chemotherapy with BEVACIZUMAB	44/62 (70.9%)	31/50 (62%)	0.21
KRAS mutation	24/36 (66%)	11/20 (55%)	0.3

Table 2: Treatment Response According to the Primary Tumor Resection and Bevacizumab Use

Response	Primary tumour resection (n=58)	No primary tumour resection (n= 43)	Chemotherapy + bevacizumab (n=66)	Chemotherapy - bevacizumab (n=35)
Complete Response	2 (3.4%)	1 (2.3%)	3 (4.5%)	0 (0%)
Partial Response	37 (63%)	23 (46%)	45 (68.1%)	15 (42.8%)
Stable Disease	13 (22.4%)	10 (23.2%)	13 (19.6%)	10 (28.5%)
Progressive Disease	6 (10%)	9 (20%)	5 (7.5%)	10 (28.5%)
p value	0.16		0.003	

response rate in Group 1 was 67.4% [2 Complete Response (CR), 37 Partial Response (PR), 13 Stable Disease (SD), 6 Progressive Disease (PD)], compared with 55.8% Group 2 (1 CR, 23 PR, 10 SD and 9 PD), the differences were not statistically significant (p= 0.16) (Table **2**).

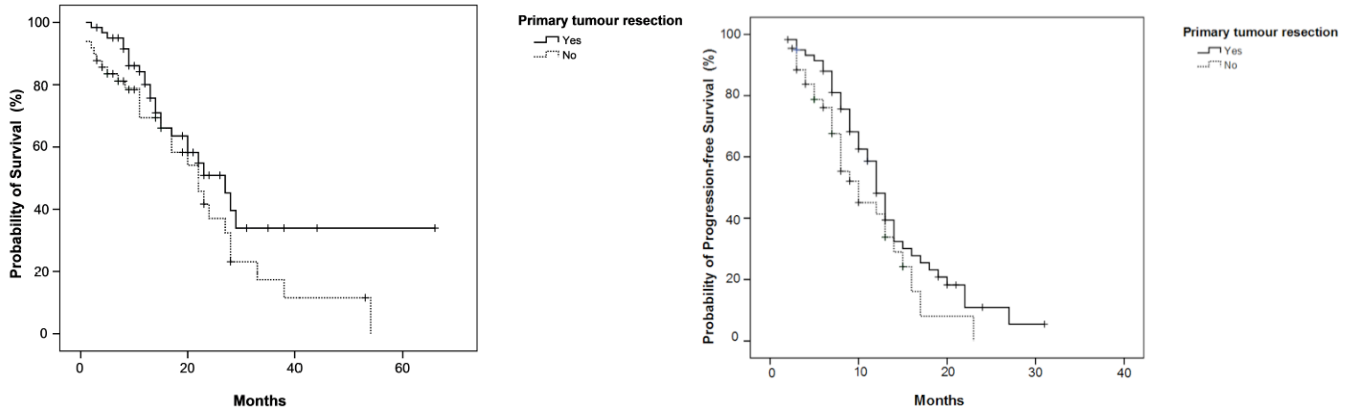
Of the 101 patients who were evaluated for response, 66 received chemotherapy with bevacizumab and 35 received chemotherapy without bevacizumab. The response rate in the bevacizumab group was 72.7% (3 CR, 45 PR, 13 SD and 5 PD), compared to 42.8% in the group without bevacizumab (0 CR, 15 PR, 10 SD and 10 PD, P= 0.003) (Table **2**).

Overall Survival and Disease Progression-Free Survival

Median OS in Group 1 was 27 months, and 22 months in Group 2 (p= 0.1). The PFS was also higher in Group 1, although the difference was not statistical significant either (12 vs. 10 months, p= 0.11) (Figure **1**).

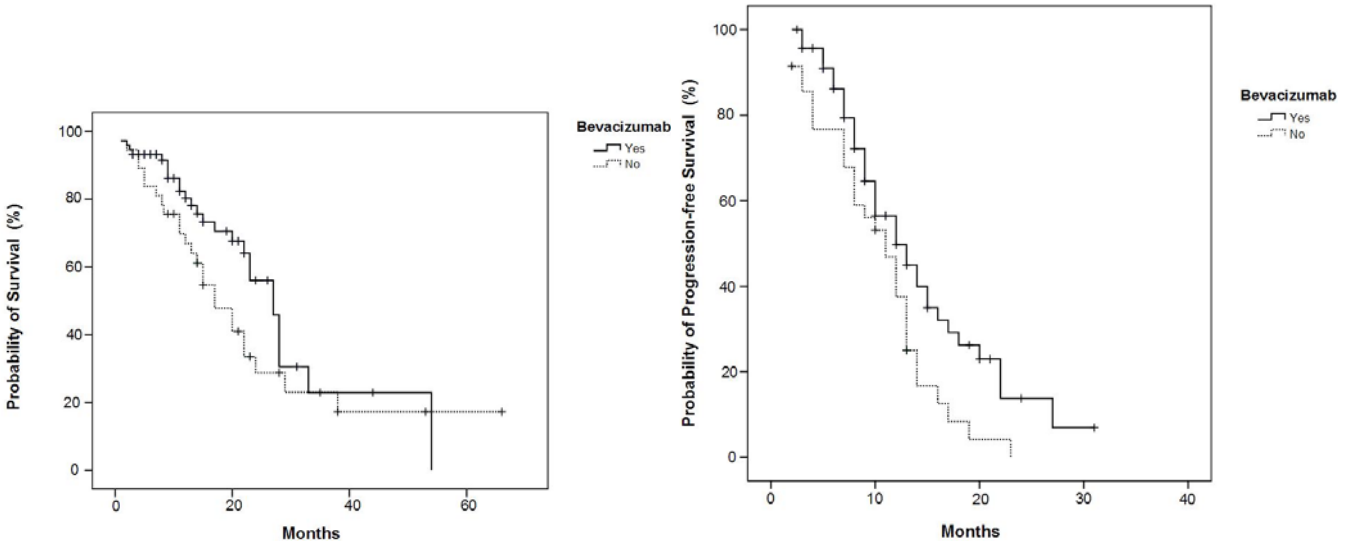
Median OS in patients treated with chemotherapy and bevacizumab was 27 months compared with 17 months in patients treated with chemotherapy without bevacizumab (p= 0.108). PFS was significantly higher in patients treated with bevacizumab (12 vs. 11 months, p= 0.019) (Figure **2**).

In Group 1, patients treated with chemotherapy in combination with bevacizumab achieved a median OS of 27 months, compared with 15 months in patients treated with chemotherapy without bevacizumab. Similarly, in Group 2, patients treated with chemotherapy with bevacizumab achieved a higher median OS than patients treated with chemotherapy without bevacizumab, but differences were not statistically significant (27 vs. 20 months, p= 0.11) (Figure **3**).



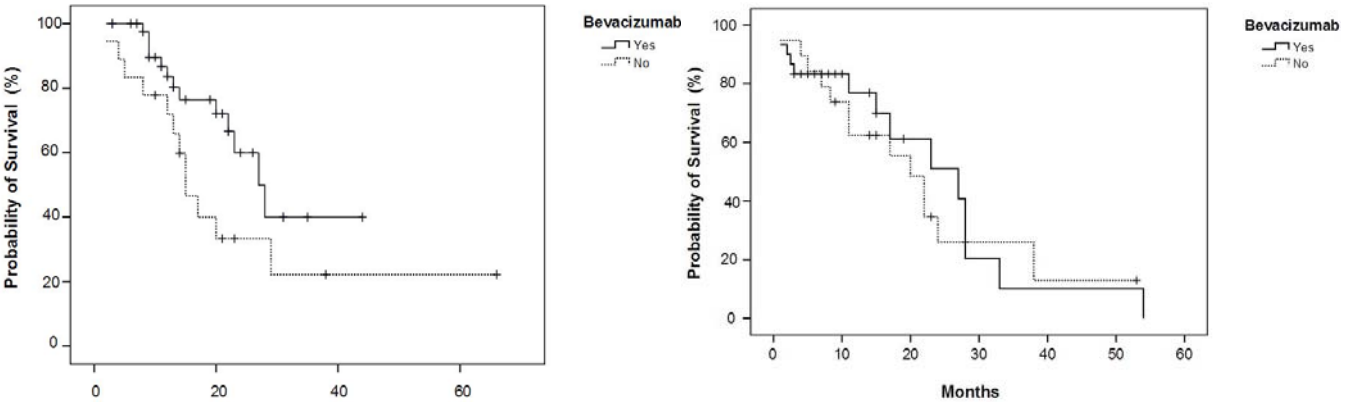
(**A**) (**B**)

Figure 1: Overall survival (**A**) and progression-free survival (**B**) according to primary tumour resection.



(**A**) (**B**)

Figure 2: Overall survival (**A**) and progression-free survival (**B**) according to the use of bevacizumab.



(**A**) (**B**)

Figure 3: Overall Survival according to bevacizumab use in patients with primary tumour resection (**A**) and without primary tumour resection (**B**).

Complications Related to the Primary Tumour or Postoperative

Nine patients suffered major complications resulting from the primary tumour or after the surgery. Eight of these patients belonged to Group 2: 2 patients died from an abdominal perforation, 2 from a bowel obstruction, 4 experienced severe bleeding (resulting in death in 3 of the 4 patient). One patient in Group 1 died 8 weeks after the surgery due to an abdominal sepsis and after receiving the first cycle of chemotherapy. The major complication rate was 16% (8/50) in Group 2 vs. 1.6% (1/62) in Group 1 (p= 0.007).

Of the 8 patients in Group 2 with a major complication resulting from the primary tumour, 6 were received bevacizumab. The rate of major complications in Group 2 treated with bevacizumab was 19.3% (6/31), compared to 0% in Group 1 (p= 0.004). No differences in the major complication rate was observed between patients of Group 1 and Group 2 who did not receive chemotherapy with bevacizumab: 5.5 vs. 10.5%, respectively (p= 0.521).

Toxicity and Adverse Effects of Chemotherapy

Toxicity after chemotherapy is summarized in Table **3**. In the total population, the rate of patients who required a delay in chemotherapy treatment was 38.4%, while the dose was reduced due to toxicity in 32% of patients. The most common toxicity was neuropathy, presented in 34.8% of patients (G3-4 8.9%), and followed by gastrointestinal toxicity presented in 26.3% of patients (3.6% G3-4). Two

Table 3: Toxicity After Chemotherapy

	Total		Primary tumour resection				Bevacizumab			
			Yes		NO		Yes		NO	
	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4
Anaemia	9%	1%	7.8%	1.9%	10.5%	0%	12%	1.7%	9.6%	0%
Neutropenia	7.2%	5.4%	3.9%	3.9%	15.7%	10.5%[a]	8.6%	5.1%	9.6%	9.6%
Thrombocytopenia	3.6%	2.7%	1.9%	1.9%	7.8%	5.2%	1.7%	3.4%	9.6%	3.2%
Febrile neutropenia		1.8%		3.9%		0%		3.4%		0%
Neuropathy	25.9%	8.9%	40.3%	15.3%	20.5%	5.1%[b]	31.6%	13.3%	32.2%	6.4%
Gastrointestinal	22.7%	3.6%	29.4%	5.8%	28.9%	2.6%	34.4%	5.1%	19.3%	3.2%
Vomiting	6.3%	2.7%	11.7%	5.8%	5.4%	0%	12.2%	3.5%	0%	3.2%
Renal	1.8%	0%	3.9%	0%	0%	0%	0%	0%	6.4%	0%

Treatment toxicity assessed according to the criteria published by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0: Grade 0: none; Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: life-threatening.
[a]p=0.043, [b]p=0.003.

patients were hospitalized due to febrile neutropenia (1.8%). The frequency of other G3-4 toxicities was: neutropenia 5.4%, vomiting 2.7%, and thrombocytopenia 2.7%. Patients in Group 2 suffered a significantly higher incidence of G3-4 neutropenia compared with Group 1 (10.5 vs. 3.9%, p= 0.043), whereas patients in Group 1 presented a higher rate of neuropathy G3-4 (15.3 vs. 5.1%, p= 0.003). No significant difference in the incidence of toxicity was observed in patients with chemotherapy in combination with bevacizumab compared to patients with chemotherapy without bevacizumab.

Nine patients discontinued treatment with bevacizumab due to side effects related to the drug: 3 patients developed deep vein thrombosis in the lower limbs, 2 pulmonary embolisms, 2 uncontrollable hypertension with conventional antihypertensive drugs, 1 rectal bleeding and another had adverse reaction during drug infusion. The rate of complications requiring bevacizumab discontinuation was 12% (9/75).

DISCUSSION

This retrospective study was designed to assess the impact of primary tumour resection in survival and tumour related events among patients presenting the novo metastatic colorectal carcinoma (CRC) with no indication for a curative approach but receiving optimal palliative chemotherapy. Our study did not found significant differences in terms of response rate, PFS, or OS according to the resection of the primary tumour.

Our study, as the studies published to date that explore the benefit of primary tumour surgery, has a retrospective nature and provides conflicting results. Cook *et al*. published data from a retrospective study involving over 26,000 advanced CRC patients treated between 1988 and 2000, 66% of them with primary tumour surgery. Patients who underwent surgery were younger (median, 67 vs. 70.3 years), with lower rate of peritoneal carcinomatosis and rectal carcinomas. Such patients had higher median OS and one-year survival rate (46 vs. 11%). However, no information is provided on the existing symptoms prior to surgery, or types of chemotherapy administered or number of metastatic sites involved [15]. Likewise, Karoui *et al*. published a multicentre study involving 208 asymptomatic patients with advanced CRC treated in France between 1998 and 2007. Eighty-five patients with surgery presented a median OS higher than the non-surgery group (31 vs. 22 months) [17]. More recently, Venderbosch *et al*. have reported the results of a retrospective analysis of 847 patients included in the phase III CAIRO and CAIRO2 studies with 547 patients with primary tumour resection. The authors found an increase in both PFS and OS in patients who underwent surgery [22]. Finally, in the 2012 meeting of the American Society of Clinical Oncology (ASCO), Faron *et al*. presented data of 810 patients (478 with surgery and 332 without surgery), and the preliminary results were consistent with previous studies that observed higher survival rates in patients with surgery of the primary tumour [23].

As expected, patients undergoing tumour resection presented slightly better characteristics, with a lower median age, better performance status, less weight loss, lower proportion of patients with high CEA level, and higher exposition to bevacizumab. Our study, like

other retrospective series can not rule out this. A favourable trend was found in patients who underwent resection of the primary tumour in these three variables (rates of response 67.4 vs. 55.8%, PFS 12 vs. 10 months, and OS 27 vs. 22 months). These differences suggest the existence of different patient profiles that may influence the primary tumour surgery indication.

On the other hand, Poultsides *et al*. reported the results of a study involving 233 consecutive advanced CRC patients enrolled between 2000 and 2006 with combined chemotherapy regimen with 5-FU with either irinotecan or oxaliplatin in combination or not with bevacizumab, and without primary tumour resection. Only 7% of the patients needed emergency surgery for complications related to the primary tumour, another 4% required local intervention (radiation or a stent placement), while the remaining 89% did not need any type of intervention. The authors concluded that for advanced asymptomatic CRC patients the palliative surgery of the primary tumour could be avoided if patients are treated with modern combination chemotherapy regimens [24]. Similarly, McCachill *et al*. published the results of a prospective phase II clinical trial that investigated the combined use of FOFLOX-bevacizumab in advanced CRC patients without surgery. They found that the 86 patients included in the trial had a median survival time of 19.9 months, with a rate of major complications related to the primary tumour requiring surgery of 14%, and with a mortality rate of 2.3% [21]. Finally, a Cochrane review of 7 recently published randomized studies including a total of 1086 patients, concluded that the primary tumour resection is not consistently associated with an improvement in OS nor significantly reduces the risk of complications such as bowel obstructions, intestinal perforations or gastrointestinal bleeding [25]. Since none of these studies assessed the potential effects of chemotherapy on disease evolution or controlled all of the possible likely confounding variables, we should wait for the results of future randomized clinical trials to obtain a better understanding of the real benefits that primary tumour resection offers to such patients.

As a secondary objective of our study, we found a 16% of complications resulting from the primary tumour. It is noteworthy that the incidence of complications among bevacizumab-treated patients was significantly higher in patients without surgery (19.3% vs 0%). The fact that among patients treated only with chemotherapy no differences were observed in the rate of complication between patients with and without surgery suggests that bevacizumab may be an important risk factor for patients treated without primary tumour resection. The complication rate in our study is comparable to those previously published: Scheer *et al*. reported an intestinal occlusion rate of 13.9% and a bleeding rate of 3% in non-surgery patients [26]; Scoogins *et al*. reported an bowel obstruction rate of 9% [18]; Pultsides *et al*. found a 11% of cases with a type of obstruction or perforation requiring some type of local treatment [24]; and finally in the study by McCachill *et al*., which included both patients with surgery and with chemotherapy regimen with bevacizumab, the rate of complications related to the primary tumour was very similar, 14% [21], although the mortality rate was 2.3%, much lower than in our study. Differences in the clinical characteristics of patients (younger, with better PS and lower rates of comorbidities) and the fact that patients were participating in a clinical trial that encouraged more aggressive salvage surgical interventions could explain the differences between the results. Moreover, the risk of post-operative complications associated with the set of antiangiogenics drugs such as bevacizumab is known and has been previously described in surgical interventions for CRCs [27].

Only one patient with primary tumour resection suffered a surgery major complication (onset of abdominal sepsis after the first cycle of chemotherapy) representing 1.6% of the patient population. These data are below of the previously published rates of morbidity and mortality, which ranged approximately 20-30% and 1-6%, respectively [14, 18 and 28]. However, it is difficult to assess the real rate of surgical morbidity and mortality in our study because our eligibility criteria focused our analysis strictly on patients who had received chemotherapy, and it is possible that other patients that initially underwent surgery might have had complications that would have barred them from receiving a chemotherapy regimen and, therefore, excluding them from our analysis.

Chemotherapy with bevacizumab was significantly associated with higher rates of response and PFS, and although differences in OS did not reach statistical significance we also observed a positive trend in favour of this combined treatment strategy. The benefit of adding bevacizumab was evident in both groups, which is consistent with previously published data [12, 21 and 24], and toxicity results in our study are also consistent with other studies. No significant differences were observed between groups or according to bevacizumab use.

CONCLUSIONS

In conclusion, data from our study suggest that the resection of the primary tumour offers no benefits for patients with advanced CRC and inoperable metastases. Moreover, we observed that the benefits associated with the addition of bevacizumab to chemotherapy with fluoropyrimidines and oxaliplatin were no different between patients with and without resection. In patients without resection, we detected a significantly increased risk of complications. Therefore, caution must be exercised in the use of these drugs and patients should be carefully evaluated prior to the administration of such treatment. All the data currently available come form retrospective studies with important selection criteria biases that hamper to determine the real impact of the primary tumour resection on the evolution of patients with advanced CRC and inoperable metastases. Thus, the results of ongoing randomized and prospective studies are needed to clarify this issue.

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CONFLICT OF INTEREST

Financial support for this research was provided by Roche. The authors declare that they have no conflict of interest.

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