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Phase II randomized trial of capecitabine with bevacizumab and external beam radiation therapy as preoperative treatment for patients with resectable locally advanced rectal adenocarcinoma: long term results

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Abstract

Background: Preoperative chemoradiotherapy with capecitabine is considered as a standard of care for locally advanced rectal cancer. The "Tratamiento de Tumores Digestivos" group (TTD) previously reported in a randomized Ph II study that the addition of Bevacizumab to capecitabine-RT conferred no differences in the pre-defined efficacy endpoint (pathological complete response).
We present the follow-up results of progression-free survival, distant relapse-free survival, and overall survival data at 3 and 5 years.

Methods: Patients (pts) were randomized to receive 5 weeks of radiotherapy (45 Gy/25 fractions) with concurrent Capecitabine 825 mg/m2 twice daily, 5 days per week with (arm A) or without (arm b) bevacizumab (5 mg/kg once every 2 weeks).

Results: In our study, the addition of bevacizumab to capecitabine and radiotherapy in the neoadjuvant setting shows no differences in pathological complete response (15.9% vs 10.9%), distant relapse-free survival (81.0 vs 80.4 and 76.2% vs 78.2% at 3 and 5 years respectively), disease-free survival (75% vs 71.7 and 68.1% vs 69.57% at 3 and 5 years respectively) nor overall survival at 5-years of follow-up (81.8% vs 86.9%).

(Continued on next page)

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(Continued from previous page)
Conclusions: the addition of bevacizumab to capecitabine plus radiotherapy does not confer statistically significant advantages neither in distant relapse-free survival nor in disease-free survival nor in Overall Survival in the short or long term.

Trial registration: EudraCT number: 2009–010192-24.
Clinicaltrials.gov number: NCT01043484.

Keywords: Locally-advanced rectal cancer, Bevacizumab, Neoadjuvant, Chemoradiotherapy

Background

Significant progress in the management of locally advanced rectal cancer (LARC) has been achieved during the last two decades. This includes the use of postoperative Radiotherapy [1]; postoperative chemoradiotherapy (CRT) [2]; and the widespread implementation of total mesorectal excision and autonomic nerve preservation [3]. The German Rectal Cancer Study Group established that there was a significant improvement in local control, toxicity profile and sphincter preservation in patients with LARC treated with preoperative versus postoperative CRT [4]. Currently perioperative CRT is worldwide accepted as standard treatment in patients with locally advanced (T3-T4) rectal cancer because it improves local control and survival. This strategy provides early exposure to systemic therapy, maximizes downstaging, and increases the options of sphincter-sparing surgery.

Although local recurrences with this approach have dropped from 20 to 40% [5] to less than 10% with CRT [6], the impact of 5FU added to radiotherapy in survival has been questioned as systemic treatment following the results of Bujko et al [7]. Probably a fluoropyrimidine-alone chemotherapy regimen is unlikely to be adequate as systemic treatment because its modest single-agent activity in colorectal cancer might be compromised by the reduced dosing necessary for safe concurrent administration with radiotherapy.

Capecitabine is a drug designed to improve the convenience of 5FU and has largely replaced it in metastatic and localized disease along with radiotherapy [8].

In the metastatic setting, bevacizumab (BVZ) increases the activity of polychemotherapy [9] and fluoropyrimidine monotherapy [10, 11] although its activity in combination with FOLFOX in the first-line setting has been questioned [12]. The advantage conferred by the treatment with BVZ plus chemotherapy in the treatment of CRC cancer patients could be due to increased tumour cell sensitivity to the action of the chemotherapy, or the better distribution of chemotherapy into the tumour. It is an attractive drug to be used in combination with fluoropyrimidines and radiation therapy given its good tolerance, especially in a population whose average age is over 65 years. Therefore, we published a randomized phase II study in 2015 [13] and we present here its long term results in survival outcomes.

Methods

Trial design

This study was a national, multicenter, open-label randomized phase II trial performed by the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD Group). The study was performed following the Declaration of Helsinki and Good Clinical Practice Guidelines, and written informed consent was obtained from all patients before taking part in the study. The Reference Ethics Committee was Comité Ético de Investigación Clínica del Hospital Universitario 12 de Octubre, Avda de Córdoba, s/n, 28,041 Madrid. The protocol was locally approved in all the participating centers by the institutional review boards. This study adhered to CONSORT guidelines and has strictly followed CONSORT recommendations.

The main objective of the study was the complete pathological response (ypCR) rate, defined as ypT0 and ypN0 in the surgical specimen and was previously reported as well as the possible molecular dynamic and predictive factors of response in tissue of the diagnostic tumoral biopsy and the angiogenic profile. Other secondary objectives were: Disease-free survival (DFS) and distant relapse-free survival (DRFS) at 3 and 5 years, and overall survival (OS).

Disease-free survival (DFS) was defined as the time elapsed between the randomization and the time of the first local relapse; distant relapse-free survival (DRFS) was defined as the time from randomization until the moment of first distant relapse. OS was defined as the time elapsed between randomization and date of death.

Once it was corroborated that patients had signed the informed consent and fulfilled selection criteria, they were randomly assigned in a 1:1 ratio to CRT treatment with or without BVZ. Randomization was performed centrally, by PIVOTAL Contract Research Organization.

Patient selection

Eligibility criteria included patients with clinical stages II and III LARC within < 15 cm from the anal verge (T and N defined by pelvic magnetic resonance

imaging (MRI) and categorized according to the AJC on Cancer Staging Manual 6th Edition), candidates to surgical resection, with adequate organ and bone marrow function, ECOG performance status 0 or 1, age ≥ 18 years and chemotherapy and radiation therapy naïve. Other patient's selection criteria previously described [13].

Treatment schedule

Patients were randomly assigned to radiotherapy (45 Gy delivered in 25 daily fractions over 5 weeks) with capecitabine or capecitabine plus BVZ and stratified by center and tumour location in upper, middle and lower rectum. Arm A consisted of BVZ (5 mg/kg) on day 1 of weeks 1, 3, and 5 plus capecitabine and patients included in arm B received only capecitabine as previously described [13]. Patients underwent surgery 6–8 weeks after the completion of CRT as part of clinical practice. The type of postoperative chemotherapy was not defined, nor if it should be used.

Capecitabine dose-modification criteria were established but for bevacizumab no dose-reductions were contemplated.

Evaluations during the study

A complete colonoscopy with biopsy, pelvic MRI, thoracoabdominal computed tomography (or abdominal

Table 1 Post operatory toxicities

	ARM A		ARM B	
	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)
Abdominal abscess	2 (4.55)	–	–	–
Peritonitis	2(4.55)	–	–	–
Bacteremia	1(2.27)	–	–	–
Perineal abscess	–	–	1(2.17)	–
Septic shock	–	1(2.27)	–	–
Tracheobronchitis	1(2.27)	–	–	–
Urinary tract infection	1(2.27)	–	–	–
Wound infection	1(2.27)	–	–	–
Pelvic abscess	–	–	1(2.17)	–
Post-operatory wound infection	–	–	1(2.17)	–
Intestinal obstruction	2(4.55)	–	–	–
Proctitis	1(2.27)	–	–	–
Enterovesical fistula	–	–	–	1(2.17)
Intestinal ischemia	–	–	1(2.17)	–
Paralytic ileus	–	–	1(2.17)	–
Anastomotic failure	–	1(2.27)	–	1(2.17)
Complication of a gastrointestinal stoma	1(2.27)	–	–	..
Wound dehiscence	.	1(2.27)	–	–
Coagulopathy	1 (2.27)	–	–	–
Anemia	–	–	1(2.17)	–
Iron deficiency anemia	–	–	1(2.17)	–
Auricular fibrillation	1 (2.27)	–	–	–
Cardiorespiratory arrest	.	1(2.27)	–	–
Acute renal injury	1 (2.27)	–	–	–
Renal failure	–	–	1(2.17)	–
Vaginal fistula	–	–	1(2.17)	–
Hepatic insufficiency	1 (2.27)	–	–	–
Chest pain	1 (2.27)	–	–	–
Blood calcium	1 (2.27)	–	–	–
Fistula	–	1(2.27)	–	–
Hypertension	–	–	1(2.17)	–

computed plus tomography thoracic x-ray), and electrocardiogram were performed prior to the beginning of the study. Laboratory studies (haematology, chemistry, coagulation profile, urinalysis, carcinoembryonic antigen) were repeated before the start of each treatment cycle. Histologic assessment (ypT, ypN) and grading of regression (according to Mandard scale) were assessed after surgery. A follow-up of up to five years was planned after surgery.

Sample size calculation and statistical analysis

The sample size and the decision rule were based on the Simon, Wittes, and Ellenberg (SWE) method for randomized phase II trials. Forty-one patients were needed per arm assuming an ypCR proportion of 15% in one of the arms, a difference between arms of 10%, and accepting a probability of making a correct selection of 87%. This number was increased by 10% until 90 considering the possible loss of evaluable patients. All statistical tests were two-sided. Additional data have been previously published [13].

All eligible and consenting patients (the full analysis population) were included in the analyses of OS, DRFS, and DFS and the cumulative incidence rates of local and distant recurrences, according to the intention-to-treat principle.

Univariate analyses of survival were carried out by the Kaplan–Meier method, and the evaluation of differences was performed with the log-rank test.

Results

We previously published the baseline characteristics of the patients participating in this study [13]; here we present the long-term follow-up results at 3 and 5 years of DFS, DRFS, and OS.

Ninety patients were included from December 2009 until March 2011 in 12 hospitals in Spain; 44 were randomly assigned to arm A and 46 to arm B.

Patients received a median of 3 (range 2–3) BVZ cycles, one dose delay of BVZ, there were no cases of BVZ dose reductions or discontinuations. For both arms, the median number of capecitabine received cycles was

Table 2 Tumoral regression among 89 resected patients

		A (BVZ + CAPE + RT) (*N* = 44)	B (CAPE + RT) (*N* = 46)	Total (*N* = 90)	*P* Value Test
Pathologic response per tumoral regression (TRG)*					
TRG 1(Complete pathologic response)	*N*(%)	8 (18.18)	5 (10.87)	13 (14.44)	Fisher: 0.1458
TRG 2	*N*(%)	8 (18.18)	15 (32.61)	23 (25.56)	
TRG 3	*N*(%)	14 (31.82)	19 (41.30)	33 (36.67)	
TRG 4	*N*(%)	12 (27.27)	6 (13.04)	18 (20.00)	
TRG 5(Disease progression)	*N*(%)	0 (0.00)	1 (2.17)	1 (1.11)	
ND	*N*(%)	1 (2.27)	0 (0.00)	1 (1.11)	
Missing	*N*(%)	1 (2.27)	0 (0.00)	1 (1.11)	
ypT improvement					
Better	*N*(%)	26 (59.09)	18 (39.13)	44 (48.89)	**Fisher: 0.0429**
Remained the same	*N*(%)	16 (36.36)	28 (60.87)	44 (48.89)	
Worse	*N*(%)	1 (2.27)	0 (0.00)	1 (1.11)	
Missing	*N*(%)	1 (2.27)	0 (0.00)	1 (1.11)	
ypN improvement					
Better	*N*(%)	24 (54.55)	35 (76.09)	59 (65.56)	Fisher: 0.0865
Remained the same	*N*(%)	15 (34.09)	8 (17.39)	23 (25.56)	
Worse	*N*(%)	4 (9.09)	2 (4.35)	6 (6.67)	
No evaluable*	*N*(%)	0 (0.00)	1 (2.17)	1 (1.11)	
Missing	*N*(%)	1 (2.27)	0 (0.00)	1 (1.11)	
ypT and ypN improvement					
Improvement in both	*N*(%)	18 (40.91)	16 (34.78)	34 (37.78)	Fisher: 0.5612
Improvement in one	*N*(%)	14 (31.82)	20 (43.48)	34 (37.78)	
No improvement	*N*(%)	11 (25.00)	9 (19.57)	20 (22.22)	
Non-evaluable*	*N*(%)	0 (0.00)	1 (2.17)	1 (1.11)	
Missing	*N*(%)	1 (2.27)	0 (0.00)	1 (1.11)	

* A patient was reported as NX

Table 3 Adjuvant treatment after surgery

		A (BVZ + CAPE + RT) (*N* = 44)	B (CAPE + RT) (*N* = 46)	Total (*N* = 90)
Patients receiving adjuvant chemotherapy				
No	*n* (%)	10 (22.73)	5 (10.87)	15 (16.67)
Yes	*n* (%)	34 (77.27)	41 (89.13)	75 (83.33)
Adjuvant schedule				
capecitabine	*n* (%)	18 (40.9)	21 (45.65)	39 (43.33)
XELOX	*n* (%)	10 (22.73)	15 (32.61)	25 (27.78
FOLFOX	*n* (%)	6 (13.64)	8 (17.39)	14 (15.56)
Oxaliplatin + Raltitrexed	*n* (%)	1 (2.27)	1 (2.17	2 (2.22)
5-Fu	*n* (%)	–	2 (4.34)	2 (2.22)

3 (range 1–3). There were not any statistically significant differences regarding the number of patients with delayed capecitabine cycles, occurring in 66.67% cycles in arm A and 77.78 in arm B. Only 5 patients had early treatment discontinuation (2 in arm A, 3 in arm B); 1 patient required a capecitabine dose reduction.

Overall, the median dose intensity was equivalent to 85% of expected, observing similar values across both groups.

Safety, treatment-related toxicity and surgical outcomes

Treatment was well tolerated. Eighty patients (88.89%) reported treatment-emergent adverse events. *There were no differences in grade 3–4 treatment-related toxicity.* No grade 3 or greater haematological toxicity *was reported*. Two patients in arm A presented hypertension. One patient in the study received only 2 cycles of BVZ due to capecitabine-related toxicity.

Surgery was delayed more than 9 weeks after the end of treatment in 4 patients in arm A, and 5 in arm B. There were no differences in the surgical technique performed nor in the frequency of anal sphincter preservation. Nineteen patients (43%) and 18 (39%) patients in arm A and B experienced at least one postoperative complication, respectively. 10 patients (7 in arm A (16.3%) and 3 in arm B (6.5%)) required repeat surgery, due to suture failures (Table 1). There were no perioperative deaths. There were no differences for hospitalization time among arms: 11 vs 10 days for arm A and b respectively.

Eighty-three percent of the patients (34 patients in arm A and 41 patients in arm B) received adjuvant

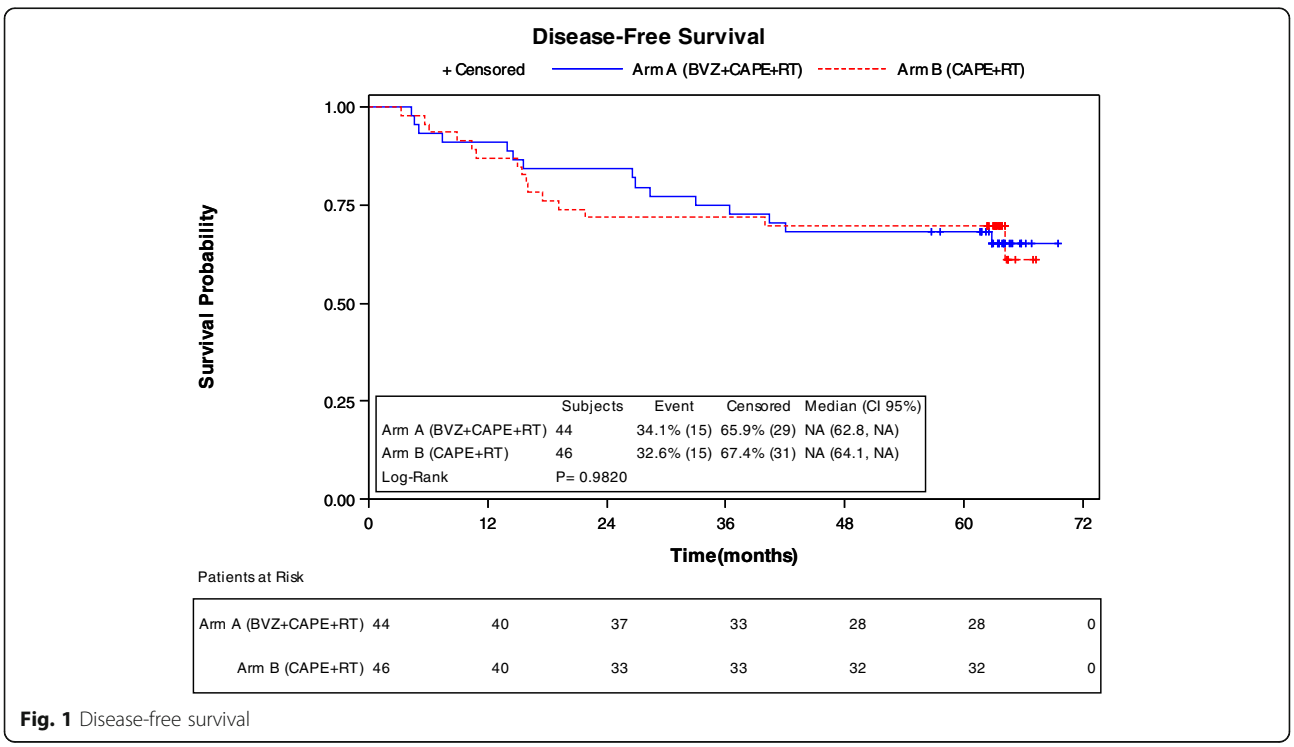

Fig. 1 Disease-free survival

treatment, and 20% (8 patients in arm A and 10 in arm B) received further systemic treatment for metastatic disease.

Response to treatment

Pathological complete response was achieved in 15.9% (95% CI 7–31%) and 10.9% (95% CI 4–24%) in arms A and B, respectively. Although there were no differences in histologic tumoral regression, a statistic trend was found in primary tumour pathological downstaging (Table 2).

Treatment after surgery

Thirty-four patients in arm A and 41 in arm B received adjuvant treatment. Seventeen cases from arm A received combination with oxaliplatin compared with 24 in arm B (Table 3).

Disease-free survival (DFS), distant-relapse free survival (DRFS) and overall survival (OS)

DFS at 3 years in arm A (Fig. 1) was of 75% (CI 95% 59.42, 85.30); and 71.7% (CI95% 56.3, 82.50) in arm B. At 5 years the DFS probability was of 68.18 (CI95% 52.27, 79.76) and 69.57% (CI95% 54.09, 80.71) for arms A and B, respectively. DRFS probability at 3 and 5 years was of 81.05% (65.65, 90.04) and 76.2% (60.27, 86.43) for arm A, and 80.43% (65.77, 89.30) and 78.26% (63.36, 87.66) for Arm B (Table 4). Eleven patients (25%) of arm A and 10 patients (21.7%) of arm B had a distant relapse, (Fig. 2).

In an exploratory analysis, we observed a benefit in DFS for those patients receiving BVZ that achieved a T-downstaging ($p = 0.012$), as well as for those receiving BVZ obtaining an N-downstaging ($p = 0.005$). supplementary Figs. 1 and 2.

Seventeen patients died during the study. In arm A, one patient died from advanced dementia, another from

Table 4 Distant relapse-free survival and progression free survival

	Arm A (BVZ + CAPE + RT)	Arm B (CAPE + RT)
Distant relapse-free survival	**44 patients**	**46 patients**
No of patients with event	11 (25.00%)	10 (21.74%)
No of censored patients	33 (75.00%)	36 (78.26%)
Percent Survival (%, 95 CI)		
36 Time (months)	81.05 (65.65, 90.04)	80.43 (65.77, 89.30)
60 Time (months)	76.20 (60.27, 86.43)	78.26 (63.36, 87.66)
Kaplan-Meier model		
P-value (Log-rank)		0.6923
Cox Model	**Hazard ratio (95% CI)**	**Cox Model *P*-value**
Arm A (BVZ + CAPE+RT) vs Arm B (CAPE+RT)	1.1887 (0.5047, 2.8000)	0.6924
Disease free survival		
No of patients with event	15 (34.09%)	15 (32.61%)
Earliest contributing event:		
Distant metastases	11	10
Second tumor	1	4
Death	3	1
No of censored patients	29 (65.91%)	31 (67.39%)
Lab		
Median (95% CI)	NA (62.76, NA)	NA (64.13, NA)
25th–75th percentile	34.67 - NA	19.22 - NA
Percent Survival (%, 95 CI)		
36 months	75.00 (59.42, 85.30)	71.74 (56.36, 82.50)
60 months	68.18 (52.27, 79.76)	69.57 (54.09, 80.71)
Kaplan-Meier model		
P-value (Log-rank)		0.9820
Cox Model	**Hazard ratio (95% CI)**	**Cox Model *P*-value**
Arm A (BVZ + CAPE+RT) vs Arm B (CAPE+RT)	1.0083 (0.4927, 2.0635)	0.9820

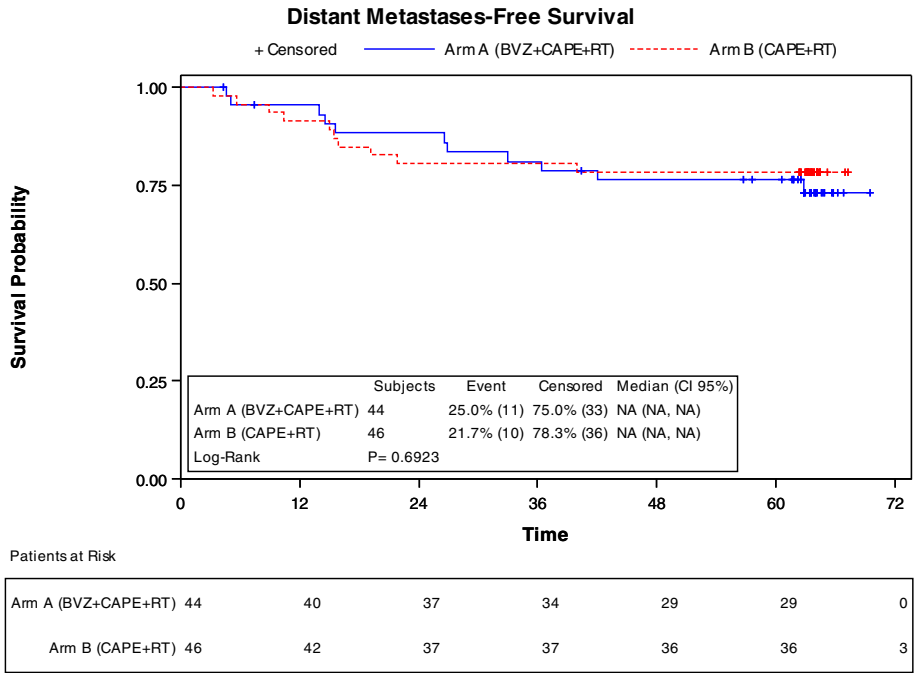

Fig. 2 Distant relapse-free survival

complications of chronic obstructive pulmonary disease, and 8 from disease progression. In arm B, 2 (38.6%) patients died from unknown causes, 1 (14.3%) form respiratory insufficiency, and 4 (57.4%) from disease progression.

OS probability at 3 and 5 years was of 88.6% (CI 95% 74.83, 95.11) and 81.82 (CI95% 66.92, 90.46) for arm A, and 95.65% (CI95% 83.71, 98.89) and 86.96 (CI95% 73.25, 93.92) for Arm B (Table 5). There were no OS statistically significant differences among both treatment arms ($p = 0.33$ Fig. 3).

Discussion

At present, LARC treatment has reached an elevated percentage of local control with optimization of surgery and neoadjuvant radiotherapy or chemoradiotherapy; the current efforts are aimed at improving quality of life in low-risk cases, and both increasing local control and reducing distant metastases that are the leading cause of neoplastic death in these patients [14].

In the last decade, most drugs tested concomitantly with radiotherapy plus fluoropyrimidines in the pre-operative setting have not succeeded to become new treatment standards despite having previously shown efficacy in the metastatic colorectal cancer setting. These included oxaliplatin [15], irinotecan [16] and monoclonal antibodies (MoAb) such as BVZ and Cetuximab [17]. The most promising exploratory combinations involved oxaliplatin, that has been intensively studied in phase II trials, with increased ypCR rate up to 21–37% [18, 19] but no benefit in long term survival outcomes [20–24].

Due to the discouraging results of irinotecan in the adjuvant colon cancer setting, this drug has not been extensively studied as neoadjuvant treatment. The ypCR rate communicated for Wang et al is in the rage of those reported with oxaliplatin combinations, although long term results have not been reported [16].

The main objective of our study, ypCR (T and N), did not show differences between treatment arms and it is in the range of other studies (8–27%) [25–27], and although we found an statistical trend to yPT downstaging with capecitabine plus bevacizumab this was an unplanned exploratory finding. This is in line with other phases I and II trials of BVZ in combination with RT and fluoropyrimidines alone (5-Fluorouracil [28] or capecitabine [29]) or in combination with oxaliplatin [18, 30–33] with response rates not better than with chemotherapy alone (13–18%). Now we report the results of long term DFS, DRFS, and OS, where we have found no significant differences between treatment arms. Interestingly 5-year DFS and OS results observed in our study were somewhat inferior to others, which probably relates to the randomized design and less restricted selection criteria in our study. Toxicities observed in this study were not different between arms; nevertheless, more patients required surgery due to suture failures. This might be related to BVZ despite the long time elapsed between bevacizumab's last dose and surgery.

Table 5 Overall survival

	Arm A (BVZ + CAPE + RT)	Arm B (CAPE + RT)
Summary of events		
No of patients	44	46
No of patients with event	10 (22.73%)	7 (15.22%)
No of censored patients	34 (77.27%)	39 (84.78%)
Lab		
Median (95% CI)	NA (NA, NA)	NA (NA, NA)
25th–75th percentile	NA - NA	NA - NA
Percent Survival (%, 95 CI)		
36 months	88.64 (74.83, 95.11)	95.65 (83.71, 98.89)
60 months	81.82 (66.92, 90.46)	86.96 (73.25, 93.92)
Kaplan-Meier model		
P-value (Log-rank)		0.3350
Cox Model	**Hazard ratio (95% CI)**	**Cox Model *P*-value**
Arm A (BVZ + CAPE+RT) vs Arm B (CAPE+RT)	1.6013 (0.6091, 4.2097)	0.3397

Some differences in the number of patients that received postoperative chemotherapy and regimens used were observed. Oxaliplatin was used in 41 patients based on the results of adjuvant colon cancer clinical trials [34, 35]. This drug has been studied in rectal cancer in association with 5FU in several randomized trials in rectal cancer showing no improvement in survival [36–38] except for the ADORE trial in which patients were randomized after surgery [39]. In this study, the addition of OXL to adjuvant 5FU in patients with positive lymph nodes after surgery improved OS. However, the role of adjuvant chemotherapy for patients with rectal cancer remains controversial, and two Pooled analyses have shown conflicting results [40, 41]. Furthermore, recommendations of complementary treatment of rectal cancer patients are mostly based on the results of old trials (before pre-operative treatment was standard) [2, 42, 43]. We therefore assume that differences in the adjuvant treatment have not affected substantially the

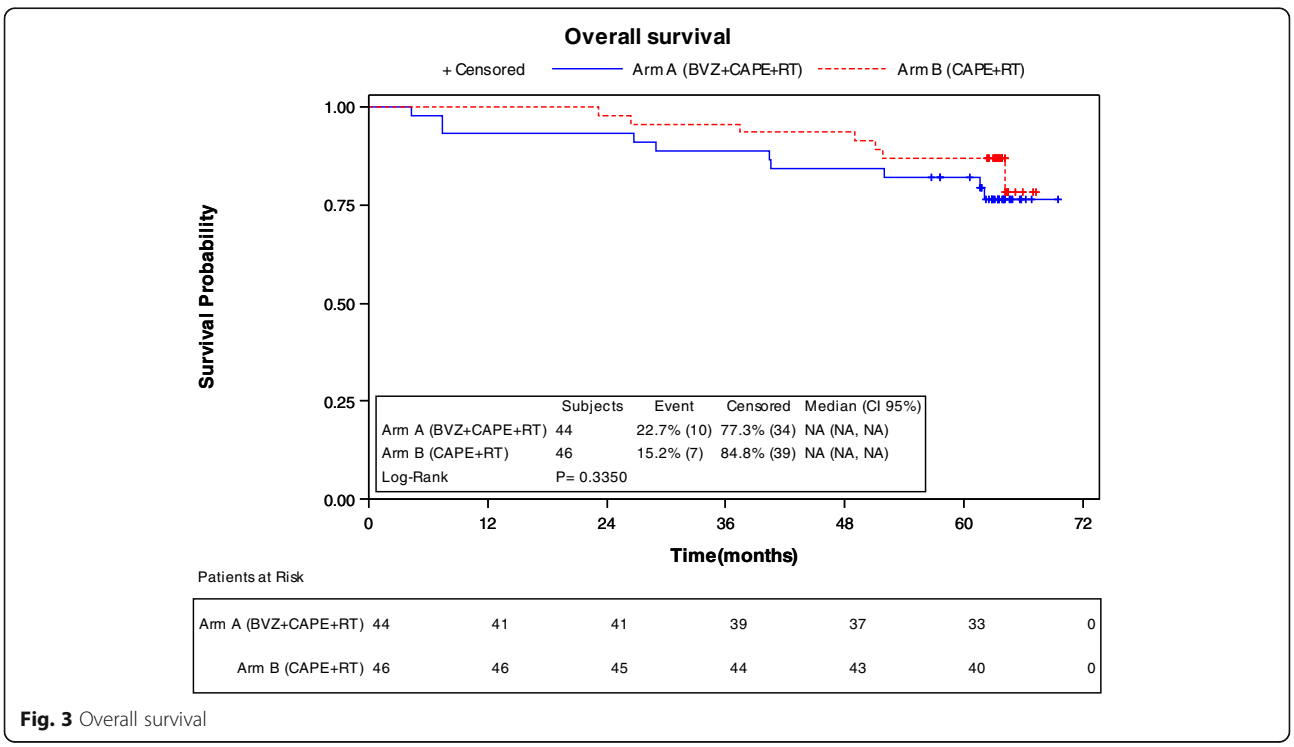

Fig. 3 Overall survival

long-term results of our study. OS survival and DFS results from our study are consistent with other randomized studies recently reported [19, 20, 32, 38, 44].

Conclusion

No differences in OS, DFS, or DRFS were obtained with the inclusion of bevacizumab in the preoperative setting of rectal cancer. These results are in line with those of the main endpoint of the study and other reports that have shown that the addition of bevacizumab does not improve yPCR. At this time treatment with fluoropyrimidines plus radiotherapy should continue to be considered the standard neoadjuvant treatment in rectal cancer.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-020-07661-z.

Additional file 1: Supplementary Figure 1. DFS – T-downstaging and treatment arm

Additional file 2: Supplementary Figure 2. DFS. N-downstaging and treatment arm.

Abbreviations

AJC: American Joint Committee; CRT: Chemoradiotherapy; ypCR: Complete pathologic response; DFS: Disease-free survival; DRFS: Distant relapse-free survival; EBRT: External Beam Radiation Therapy; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organization for Research and Treatment of Cancer; 5-FU: 5-Fluorouracil; BVZ: Bevacizumab; LARC: Locally advanced rectal carcinoma; MoAb: Monoclonal antibodies; MRI: Magnetic resonance imaging; NCI-CTC: National Cancer Institute Common Toxicity Criteria; OS: Overall Survival; RT: Radiotherapy; SWE: Simon, Wittes, and Ellenberg; TRG1: Primary tumor regression; TME: Total mesorectal excision; TTD: Treatment of Digestive Tumors; VEGF: Vascular endothelial growth factor

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Conception or design of the study: Cristina Grávalos, Ramón Salazar, Amalia Palacios, Sebastiano Biondo. Data collection: All Authors. Data analysis and interpretation: Cristina Grávalos, Ramón Salazar. Drafting the article: Cristina Grávalos, Ramón Salazar. Critical revision of the article: Cristina Grávalos, Ramón Salazar. Final approval of the version to be published: All Authors.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was performed following the Declaration of Helsinki and Good Clinical Practice Guidelines, and written informed consent was obtained from all patients before taking part in the study.
The protocol was approved by the institutional review boards of all participating centers: Instituto Catalán de Oncología, Hospital 12 de Octubre, Hospital Universitario Reina Sofía, Hospital Universitari Vall D'Hebrón, Hospital U. German Trias I Pujol, Complejo Sanitario Parc Taulí, Hospital U. Marqués de Valdecilla, Hospital G. de L'Hospitalet, Hospital General U. de Valencia, Hospital Universitario Miguel Servet, Hospital Clínico U. Lozano Blesa, Hospital General U. de Elche, Hospital C. U. San Carlos.
Reference ethics committee: Comité Ético de Investigación Clínica del Hospital Universitario 12 de Octubre, Avda de Córdoba, s/n, 28,041 Madrid

Consent for publication

This manuscript does not contain any details, images or videos relating to individual persons.

Competing interests

E.Aranda has received honoraria for advisory role from Amgen, Bayer, Celgene, Merck, Roche, Sanofi. Beatriz García Paredes has received honoraria from Roche. Carlos López has received honoraria from advisory role, research funding and other honoraria from Roche. The other authors have stated they have no conflicts of interest.

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