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Original Research

Evaluating sex as a predictive marker for response to bevacizumab in metastatic colorectal carcinoma: Pooled analysis of 3,369 patients in the ARCAD database

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KEYWORDS
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Abstract ***Background:*** Previous studies suggest a possible sex-specific response to bevacizumab in metastatic colorectal carcinoma (mCRC), showing a benefit in males, while the effect in females is less significant.
Methods: Data from 3369 patients with mCRC enrolled on four first-line randomised trials testing chemotherapy with or without bevacizumab (2000–2007) were pooled. Association between sex and progression-free survival and overall survival (OS) was evaluated by stratified Cox regression model, adjusted for potential confounders. Predictive value was evaluated by interaction effect between sex and treatment. In a pre-planned secondary analysis, analyses were stratified using an age cut point of 60 years to evaluate the possible role of menopausal-related effects.
Results: Bevacizumab was associated with an improved median OS in males and females, with a 2.3- and 0.6-months benefit, respectively. Stratified by age, bevacizumab resulted in improved OS in males at both age categories. In females at or above the age of 60 (n = 731), bevacizumab resulted in improved OS. However, in females below the age of 60 (n = 634), OS benefit did not reach statistical significance (adjusted hazard ratio = 0.94, 95% confidence interval 0.74–1.20).
Conclusions: Our results confirmed the OS benefit from the addition of bevacizumab to first-line chemotherapy in mCRC in both sexes. Among females, the benefit was less than 1 month. For females under the age of 60, there was no survival benefit. These findings could be used to relieve financial toxicity or be redistributed within healthcare systems for other health-related purposes.

1. Introduction

Bevacizumab is a humanised monoclonal antibody that binds to vascular endothelial growth factor-A (VEGF-A), a member of the VEGF receptor-activating ligands family. In a pivotal early trial, the addition of bevacizumab to first-line chemotherapy improved median overall survival (OS) by 4.7 months in metastatic colorectal carcinoma (mCRC) [1]. Since then, bevacizumab is used for first-line therapy in mCRC with a variety of chemotherapy backbones. However, in following studies, the magnitude of the effect of bevacizumab on median OS was only around 2 months [2].

Review of previously published literature suggests a possible sex-specific response to bevacizumab in mCRC. In the TML (ML18147) study, continuing bevacizumab beyond progression on a first-line bevacizumab-containing regimen improved median OS by 1.4 months. However, the hazard ratio (HR) for OS benefit in males and females was 0.73 (95% confidence interval [CI] = 0.60–0.88) and 0.99 (95% CI = 0.77–1.28), respectively [3]. In the AVF2192g study, the addition of bevacizumab to first-line chemotherapy improved median progression-free survival (PFS) by 3.7 months. However, the HR for PFS benefit in males and females was 0.37 (95% CI = 0.22–0.62) and 0.72 (95% CI = 0.43–1.20), respectively [4]. In the Italian Trial in Advanced Colorectal Cancer (ITACa) study, although PFS was not improved by the addition of bevacizumab to first-line chemotherapy, HRs for males and females were 0.83 (95% CI = 0.63–1.09) and 1.00 (95% CI = 0.71–1.40), respectively, suggesting a sex-specific effect [5]. Similarly, in non-small cell lung carcinoma, the Eastern Cooperative Oncology Group (ECOG) 4599 study showed improved OS with the addition of bevacizumab to first-line chemotherapy, but the benefit was shown only for males and not for females [6].

Preclinical data from breast and uterine human cell lines and animal models suggest that female hormones are involved in VEGF upregulation [7–12]. Additionally, ERbeta is expressed in colon cancer [13–15], thereby suggesting a possible role for female hormones in response to bevacizumab.

In this study, we aimed to assess the benefit of bevacizumab addition to first-line chemotherapy in mCRC, according to sex and age below or above 60 years as a surrogate for menopausal status (as appears in National Comprehensive Cancer Network (NCCN) Guidelines for Breast Cancer), using individual patient data from four randomised clinical trials.

2. Materials and methods

We included individual patient data from prospective controlled, randomised trials collected in the ARCAD database evaluating first-line chemotherapy ± bevacizumab in patients with metastatic colorectal cancer. The studies included are listed in Supplementary Table 1. Patients were excluded if the sex was unknown. Individual trials were approved through countries' mechanisms at the time trials were done. All patients provided written, informed consent at enrolment in the respective trials. The ARCAD database collaboration research protocol was approved by Mayo Clinic Institution Review Board. Individual patient data of all trials were collected and the analyses were performed at an

independent statistical centre at Mayo Clinic, Rochester, MN, USA. The cut-off date for this analysis was 22nd July 2021. The study followed the relevant requirements of the Strengthening the Reporting of Observational studies in Epidemiology statement.

The primary outcome was OS defined as time from randomisation to death due to any cause. PFS, defined as the time from randomisation to first documented progression or death due to any cause, whichever occurred first, was analysed as a secondary end-point. We used the log-rank test, stratified by studies, to compare OS and PFS in patients randomised to chemotherapy plus bevacizumab versus chemotherapy alone within females and males separately, following intention-to-treat principle. We assessed the interaction term between sex and treatment, as well as the effect of menopausal status on treatment, by using pre-planned subgroups based on age, $<$ or $\geq$ the age of 60 years (according to NCCN Breast Cancer Guidelines [16]). We estimated the distribution of survival outcomes by Kaplan–Meier curves. We used stratified multivariable Cox models to assess the prognostic associations of sex with outcomes, adjusting for other key clinical-pathological factors (age, ECOG performance score, primary tumour location [colon versus rectum], involvement of lung, liver and peritoneal sites and number of metastatic sites). Forest plots were used to illustrate the HR for bevacizumab use by trial. Analyses were done with SAS (version 9.4; SAS Institute, Cary, NC, USA). Two-sided p values of less than 0.05 were considered to be significant and were not adjusted for multiple comparisons.

3. Results

Data from 3369 patients with metastatic colorectal cancer enrolled in four first-line randomised trials testing the effect of bevacizumab addition to a chemotherapy backbone were pooled (AVF2107g, N016966, AVF2192g, AGITG MAX) [1,4,17,18]. Overall, the baseline patient characteristics were balanced between treatment groups (Table 1). There were 1365 (40.5%) females and 2004 males (59.5%). The median follow-up time was 13.6 years (interquartile range 9.9–17.6).

Median OS was not statistically different between males and females in the entire study population (18.8 versus 17.6 months, respectively; adjusted HR = 0.92, 95% CI = 0.84–1.02, p = 0.11; Fig. 1).

Bevacizumab was associated with an improved median OS of 1.8 months in the entire study population (Fig. 2A), and with a 2.3- and 0.6-months benefit in males and females, respectively (Fig. 2B). OS was significantly improved in males and females (Table 2), HR = 0.77 (95% CI 0.67–0.89) and HR = 0.81 (95% CI 0.69–0.95). There was no statistically significant interaction effect between sex and treatment, p = 0.61 (Table 2).

Further stratified by age, in males under the age of 60, bevacizumab had a 3.1-months benefit, HR = 0.72 (95% CI 0.57–0.91) (Fig. 3A and Table 3A; per trial analysis is shown in Supplementary Fig. 1A). The effect of bevacizumab on OS in females under the age of 60 did not reach statistical significance, with a 1.1 months reduction of median OS, HR = 0.94 (95% CI 0.74–1.20) (Fig. 3B and Table 3A; per trial analysis is shown in Supplementary Fig. 1B). Both males and females at or over the age of 60 derived a benefit of 1.6 and 3.4 months in median OS, HR = 0.81 (95% CI 0.68–0.96) and HR = 0.74 (95% CI 0.60–0.92), respectively (Fig. 3C and D; Table 3B; per trial analysis is shown in Supplementary Figs. 1C and 1D). There was no statistically significant interaction effect between sex and treatment among individuals under the age of 60 (p = 0.13) (Table 3A), but there was such an interaction among individuals at or over the age of 60 (p = 0.02) (Table 3B).

Bevacizumab was associated with an improved median PFS of 2.0- and 1.9-months in males and females, HR = 0.69 (95% CI 0.63–0.77) and HR = 0.75 (95% CI 0.66–0.84), respectively (Table 2). There was no statistically significant interaction effect between sex and treatment, p = 0.22 (Table 2).

Further stratified by age, both males and females under the age of 60 who received bevacizumab derived a benefit of 2.6 and 1.5 months in median PFS, HR = 0.65 (95% CI 0.55–0.77) and HR = 0.81 (95% CI 0.68–0.98), respectively (Table 3A). Both males and females at or over the age of 60 derived improved median PFS from the addition of bevacizumab, 1.8 and 2.2 months, HR = 0.73 (95% CI 0.64–0.83) and HR = 0.69 (95% CI 0.59–0.82) (Table 3B). There was a statistically significant interaction effect between sex and treatment among individuals under the age of 60 (p = 0.04) (Table 3A), as well as among individuals at or above the age of 60 (p = 0.045) (Table 3B).

Notably, the baseline characteristics of females under the age of 60 or at or above the age of 60 were similar, except for ECOG performance status, which was better in females under the age of 60 (Supplementary Table 2).

4. Discussion

The importance of sex and gender as modifiers of health and disease is increasingly recognised in different disciplines of medicine [19]. However, the field of oncology was largely sex- and gender-blind in the last decades. In view of increasing evidence for a sexual dimorphism in drug response and cancer biology, the European Society for Medical Oncology recently addressed the topic [20]. In this context, using the ARCAD database, our study analysed systematically sex differences in 3369 patients enrolled in four first-line randomised trials testing chemotherapy ± bevacizumab in mCRC. Median OS was improved in males by 2.3 months in the entire study population; this effect was regardless of age. Median OS

Table 1
Patient characteristics.

	Chemotherapy regimen includes bevacizumab?		
	No (N = 2007)	Yes (N = 1362)	Total (N = 3369)
Age at enrolment			
Mean (SD)	60.7 (11.49)	61.1 (11.49)	60.8 (11.49)
Median (IQR)	61.0 (53–69)	62.0 (54–70)	62.0 (53–69)
Gender, n (%)			
Female	818 (40.8%)	547 (40.2%)	1365 (40.5%)
Male	1189 (59.2%)	815 (59.8%)	2004 (59.5%)
Performance score, n (%)			
0	1087 (54.2%)	760 (55.8%)	1847 (54.9%)
1-2	918 (45.7%)	597 (43.8%)	1515 (45.1%)
Missing	2	5	7
BMI			
N	1996	1353	3349
Mean (SD)	26.1 (4.98)	26.5 (5.23)	26.3 (5.08)
Median	25.6	25.8	25.7
Range	13.2–52.0	15.0–59.7	13.2–59.7
Primary site, n (%)			
Colon	1399 (69.7%)	980 (72.0%)	2379 (70.6%)
Rectum	503 (25.1%)	320 (23.5%)	823 (24.4%)
Both	102 (5.1%)	61 (4.5%)	163 (4.8%)
Missing	3	1	4
Number of metastatic sites, n (%)			
0	2 (0.1%)	1 (0.1%)	3 (0.1%)
1	766 (38.2%)	511 (37.5%)	1277 (37.9%)
≥2	1239 (61.7%)	850 (62.4%)	2089 (62.0%)
Lung metastasis, n (%)			
No involvement	1164 (58.1%)	789 (58.0%)	1953 (58.1%)
Lung involvement only	100 (5.0%)	71 (5.2%)	171 (5.1%)
Lung and ≥1 non-lung involvement	738 (36.9%)	500 (36.8%)	1238 (36.8%)
Missing	5	2	7
Liver metastasis, n (%)			
No involvement	473 (23.6%)	312 (22.9%)	785 (23.3%)
Liver involvement only	540 (26.9%)	374 (27.5%)	914 (27.2%)
Liver and ≥1 non-liver involvement	991 (49.5%)	676 (49.6%)	1667 (49.5%)
Missing	3	0	3
Peritoneal metastasis, n (%)			
No involvement	1245 (86.0%)	729 (87.5%)	1974 (86.5%)
Peritoneal involvement only	26 (1.8%)	9 (1.1%)	35 (1.5%)
Peritoneal and ≥ 1 non-peritoneal involvement	177 (12.2%)	95 (11.4%)	272 (11.9%)
Missing	559	529	1088

benefit for females in the entire population was less than 1 month. Stratified by age, females at or over the age of 60 had a 3.4 months benefit in median OS from addition of bevacizumab, while for females under the age of 60, the effect of bevacizumab on OS was not statistically significant. Importantly, there was a statistically significant interaction effect between sex and treatment among individuals at or over the age of 60 in terms of both OS and PFS, and in individuals under the age of 60 in terms of PFS, but not in terms of OS.

Previous studies in mCRC evaluating bevacizumab have shown an improved PFS without a matching OS benefit [4,17,18]. A similar discrepancy was also shown in other tumour types, including head and neck [21], ovarian [22,23], small cell lung cancer [24] and glioblastoma [25,26].

Although bevacizumab is usually well-tolerated, it has also been noted to cause serious adverse events. The United States Food and Drug Administration (FDA) Boxed Warnings on bevacizumab include gastrointestinal fistula or perforation (2% in CRC), wound healing and surgical complications (2%) and severe haemorrhage (including intracranial haemorrhage, haemoptysis, rectal haemorrhage and tumour-associated haemorrhage) [27,28]. In a single study evaluating bevacizumab safety in Japanese patients, sex was not a risk factor for perforation and tumour-associated haemorrhage [29].

The clinical decision to use bevacizumab in mCRC must take into account risk–benefit calculations. The most critical end-points to patients are OS and quality of life, followed by symptom relief. In this regard, in breast cancer, the FDA initially approved bevacizumab for this indication based on improved PFS. However, this approval was later withdrawn due to safety concerns and lack of OS benefit [30,31], which in the opinion of the FDA's commissioner, outweighed the

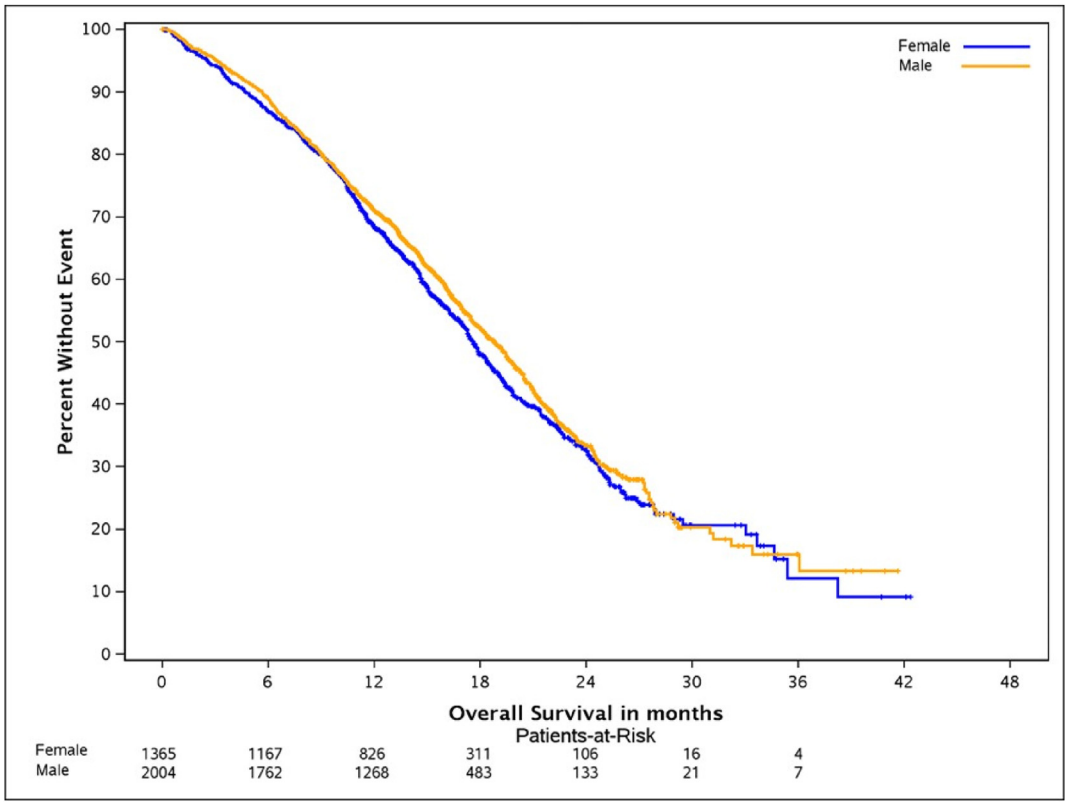


Fig. 1. OS by sex in the entire study population. OS, overall survival.

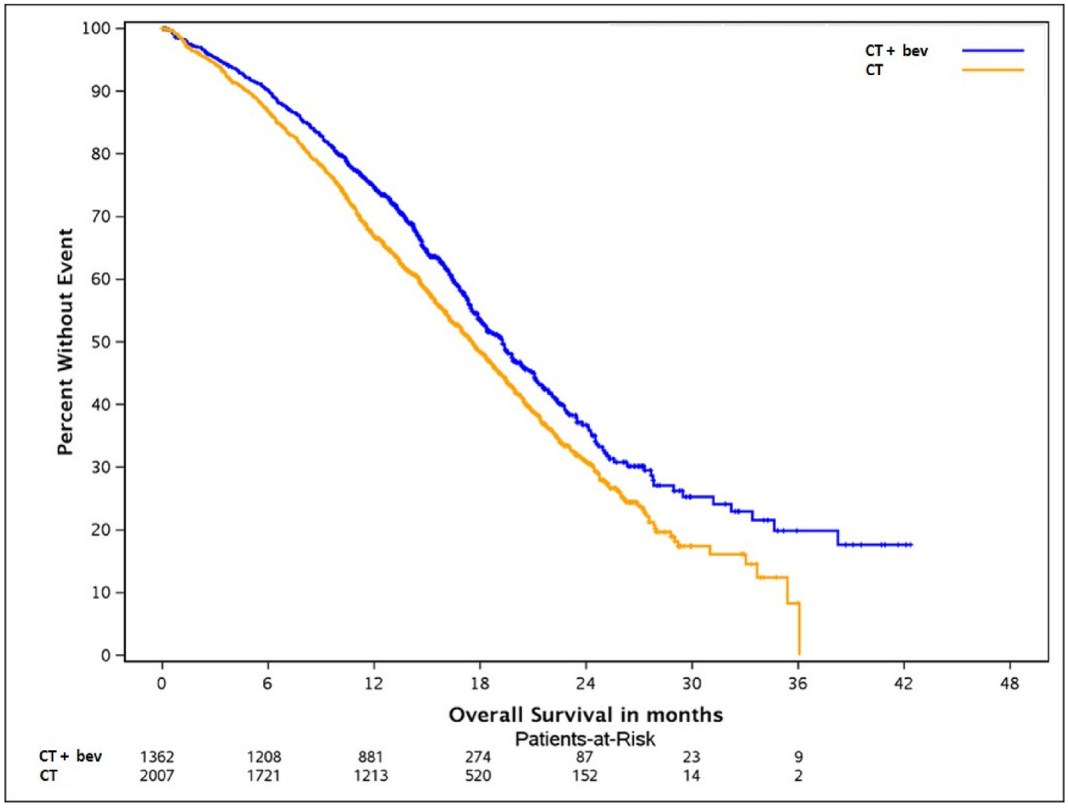


Fig. 2. A: OS by bevacizumab in the entire study population OS, overall survival. B: OS by sex and bevacizumab in the entire study population. OS, overall survival.

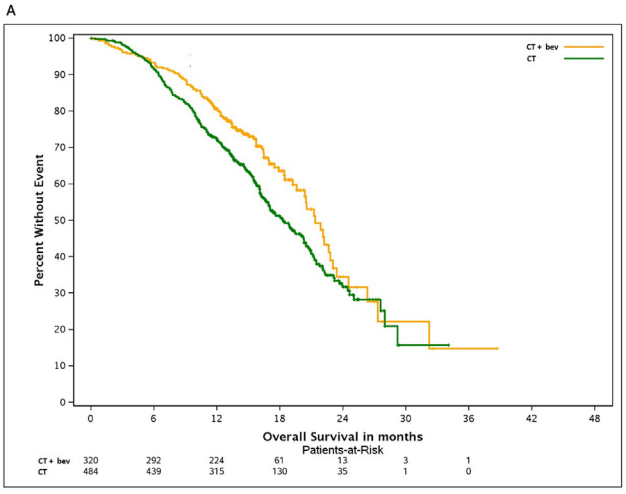
Table 2
PFS and OS in females and males by bevacizumab in the entire study population.

Sex	Bev	Median PFS (months)	HR_{adj} (95% CI)	*p* Inter.	Median OS (months)	HR_{adj} (95% CI)	*p* Inter.
Females	N	6.9	Ref.	0.22	17.3	Ref.	0.61
	Y	8.8	0.75 (0.66–0.84)		17.9	0.81 (0.69–0.96)	
Males	N	7.4	Ref.		17.7	Ref.	
	Y	9.4	0.69 (0.63–0.77)		20.0	0.77 (0.67–0.89)	

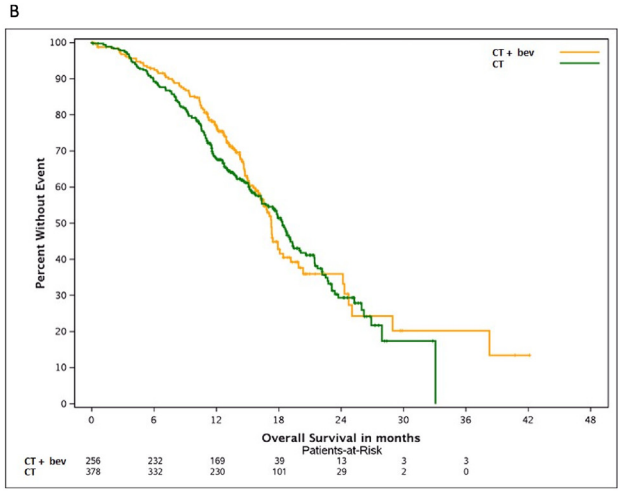
PFS benefit [32,33]. Whereas bevacizumab improved PFS across all sexes and age groups, the less than 1-month benefit in median OS noted in our study for females receiving bevacizumab further highlights the dilemma of whether or not to use this drug, taking into account the possible risks involved.

Clinical studies in oncology in general, and in colon cancer in particular, are hampered by inadequate representation of female patients. Likewise, females were underrepresented in the current study, comprising only 40.8% of the study population. The overrepresentation of males cannot be attributed solely to the minor difference in colon cancer incidence between the sexes, i.e. 52,590 versus 51,680 new cases in males and females, respectively, in 2021 in the United States [34]. Similarly, in two other large studies, namely, the IDEA and CALGB 80405, conducted in the adjuvant and metastatic setting of colon cancer, the percentage of females was only 43.6% and 38.7%, respectively [35,36].

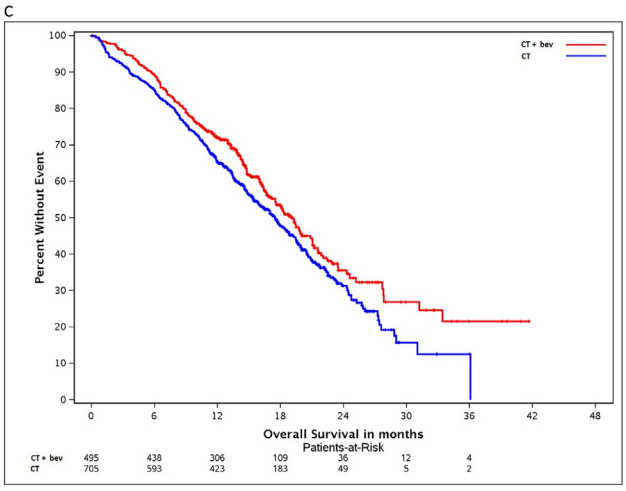
Sex is known to impact various aspects of colon cancer treatment and outcome. Female patients eliminate fluorouracil more slowly than males, and therefore



CT, chemotherapy; bev, bevacizumab.



CT, chemotherapy; bev, bevacizumab.



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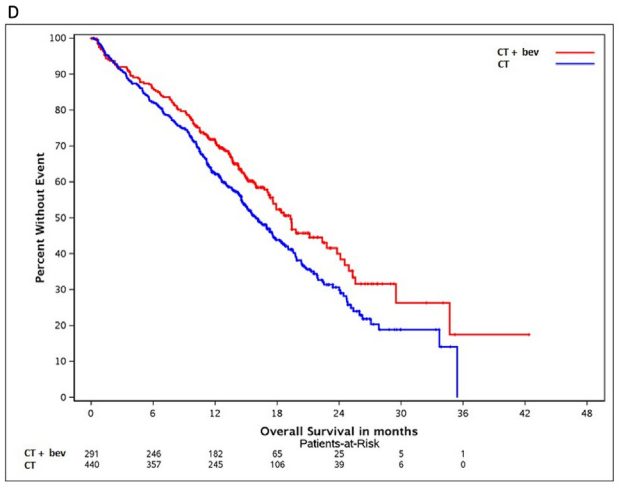

CT, chemotherapy; bev, bevacizumab.

Fig. 3. A: OS in males under the age of 60 by bevacizumab OS, overall survival. B: OS in females under the age of 60 by bevacizumab OS, overall survival. **C:** OS in males at or over the age of 60 by bevacizumab OS, overall survival. D: OS in females at or over the age of 60 by bevacizumab. OS, overall survival.

Table 3A
PFS and OS in females and males under the age of 60 by bevacizumab.

Sex	Bev	Median PFS (months)	HR_{adj} (95% CI)	*p* Inter.	MedianOS (months)	HR_{adj} (95% CI)	*p* Inter.
Females	N	7.3	Ref.	0.04	18.3	Ref.	0.13
	Y	8.8	0.81 (0.68–0.98)		17.2	0.94 (0.74–1.20)	
Males	N	7.7	Ref.		18.3	Ref.	
	Y	10.3	0.65 (0.55–0.77)		21.4	0.72 (0.57–0.91)	

Table
4 PFS and OS in females and males at or over the age of 60 by bevacizumab.

Sex	Bev	Median PFS (months)	HR_{adj} (95% CI)	*p* Inter.	Median OS (months)	HR_{adj} (95% CI)	*p* Inter.
Females	N	6.6	Ref.	0.045	15.9	Ref.	0.02
	Y	8.8	0.69 (0.59–0.82)		19.3	0.74 (0.60–0.92)	
Males	N	7.2	Ref.		17.4	Ref.	
	Y	9.0	0.73 (0.64–0.83)		19.0	0.81 (0.68–0.96)	

have higher levels of the drug for a longer duration [37,38]. This difference appears even more pronounced in the elderly [39]. Accordingly, a higher fluorouracil-related toxicity has been reported in female patients with colorectal cancer [40–42]. Likewise, female sex has also been identified as a risk factor for irinotecan-induced neutropenia [43]. In terms of efficacy, a recent study showed that females benefit more than males from first-line irinotecan in metastatic colorectal cancer [44]. To the best of our knowledge, our report is the first to show a sex-dependent benefit for bevacizumab in patients with colon cancer.

Limited preclinical data using human cell lines and animal models suggest that female hormones are involved in VEGF regulation. Oestradiol and oestrogen receptor upregulate VEGF expression in breast [7,8] and uterus [9,11,12], also through an oestrogen response element found in the VEGF gene promoter region [7,10]. These preclinical data raise the hypothesis that in younger premenopausal females, the higher levels of VEGF confer resistance to bevacizumab treatment.

It would be worthwhile to consider the economic implications of this study, if bevacizumab were not to be used in women under the age of 60, where it appears to lack efficacy. The annual global revenue for originator bevacizumab (Avastin) is $2.4 billion [45]. This revenue has been decreasing significantly in recent years due to the arrival of biosimilar bevacizumab, which must be considered in any economic estimation. To understand the financial relevance, one must firstly subtract the sales related to non-colorectal cancer. Then one would subtract sales for men with colorectal cancer, and subsequently women over age 60 with colorectal cancer. As a result, if women under the age of 60 were no longer treated with bevacizumab, one could expect health-care payers around the world to save many millions of dollars. This could be used to relieve financial toxicity or be redistributed within healthcare systems for other health-related purposes.

The main strength of this study is using the ARCAD database, pooling four randomised-controlled studies, comprising a total of 3369 patients. Of note, in all pooled studies, bevacizumab was tested in the first-line setting. This database enables adjusting for several important confounders, including performance status score, BMI and involvement of specific metastatic sites. This study had several important limitations. First, no data on RAS and BRAF status were available for this analysis. Second, the chemotherapy backbone differed between studies (i.e. IFL, FOLFOX/XELOX, 5FU or capecitabine in the studies used for the analysis). Third, primary tumour location within the colon was not stratified by side. Finally, p-interaction between age, gender and treatment did not reach statistical significance in all analyses. This result may be due to the fact that the effect of bevacizumab on median PFS and median OS in our analysis did not exceed 3.5 months.

In conclusion, our results confirmed the median OS benefit from the addition of bevacizumab to first-line chemotherapy in mCRC in both males and females. Among females, the benefit was less than 1 month. For females under the age of 60, there was no OS benefit from the addition of bevacizumab. This study emphasises the need for sex- and age-specific reporting in future clinical trials testing bevacizumab [46–49], as well as retrospective analyses of previously completed studies.

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Data availability

The data sharing of individual patient data from each participating trial will be subject to the policy and procedures of the institutions and groups who conducted the original study.

Author contributions

Conceptualization: OM, QS and HJL. Methodology: OM and QS. Software: WSH, MMV, CO and QS. Validation: WSH, MMV, CO and QS. Formal analysis: OM, WSH, MMV, CO and QS. Investigation: OM, WSH, MMV, CO and QS. Resources: AdG, QS and HJL. Data curation: WSH, MMV, CO and QS. Writing – original draft: OM, WSH, ESS, MMV, BB, ADW, RC, CO, LBS, RAA, BC, JZ, AdG, QS, HJL. Writing – review and editing: OM, WSH, ESS, MMV, BB, ADW, RC, CO, LBS, HH, NCT, FFK, RAA, BC, AdG, TY, JZ, AG, QS, HJL. Visualization: OM, WSH, MMV, CO. Supervision: AdG, QS and HJL. Project administration: AdG, QS and HJL Funding acquisition: AdG.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: OM reports research funding from Checkmate Pharmaceuticals and Bristol-Myers Squibb; consultancy fees from Rhenium/Oncotest; personal fees from Roche/Genentech and Merck Serono. LBS reports consultancy fees for Genor Biopharma Ltd. RAA reports speaker fees and conference fees from Amgen and Servier; consultancy fees from Bayer. TY reports honoraria from Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Merck Biopharma, Bayer Yakuhin, Ono Pharmaceutical and MSD; research funding from Ono Pharmaceutical, Sanofi, Daiichi Sankyo, PAREXEL International, Pfizer Japan, Taiho Pharmaceutical, MSD, Amgen, Genomedia, Sysmex, Chugai Pharmaceutical and Nippon Boehringer Ingelheim. JZ reports stock and other ownership interests from Biomarin, Opthea, Amarin Corporation, Concert Pharmaceuticals, Frequency Therapeutics, Gilead Sciences, Madrigal Pharmaceuticals, UniQure, Zogenix, Orphazyme, Moderna Therapeutics, Twist Bioscience and Novavax (to myself); honoraria from Specialised Therapeutics, Merck Serono, Targovax, Halozyme, Gilead Sciences and Deciphera (to myself); consulting or advisory role from Merck serono, Targovax, Merck Sharp & Dohme, Halozyme, Lipotek, Specialised Therapeutics, Center for Emerging & Neglected Diseases, Deciphera, Revolution Medicine, FivePHusion, Genor Biopharma, 1Globe Health Institute, Novotech (to myself); research funding from Merck Serono, Bristol-Myers Squibb, AstraZeneca, Pfizer, IQvia, Mylan, Ipsen, Eisai, Medtronic and MSD Oncology (to institution); travel, accommodations and expenses from Merck Serono, AstraZeneca, Merck Sharp & Dohme, Deciphera and Sanofi (to myself). QS reports consulting/advisory role from Yiviva Inc, Boehringer Ingelheim Pharmaceuticals, Inc, Regeneron Pharmaceuticals, Inc, Hoosier Cancer Research Network (to myself); honorarium/speaker role from Chugai Pharmaceutical Co, Ltd; stock from Johnson & Johnson, Amgen, and Merck & Co (to myself); research funds from Celgene/BMS, Roche/Genentech, Janssen, Novartis (to institution). All remaining authors have declared no relevant conflicts of interest.

Appendix A. Supplementary data

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