Journal of Cancer Research and Clinical Oncology (2020) 146:493–501
https://doi.org/10.1007/s00432-019-03077-w

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Clinical impact of first-line bevacizumab plus chemotherapy in metastatic colorectal cancer of mucinous histology: a multicenter, retrospective analysis on 685 patients

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Received: 22 July 2019 / Accepted: 2 November 2019 / Published online: 6 November 2019

Abstract

Purpose In metastatic colorectal cancer (MCRC), mucinous histology has been associated with poor response rate and prognosis. We investigated whether bevacizumab combined with different chemotherapy regimens may have an impact on clinical outcomes of MCRC patients with mucinous histology.

Methods 685 MCRC patients were classified in mucinous adenocarcinoma (MC) and non-mucinous adenocarcinoma (NMC) and were treated with first-line bevacizumab plus fluoropyrimidine (FP)-based, oxaliplatin (OXA)-based, irinotecan (IRI)-based, or FOLFOXIRI.

Results Ninety-four (13.7%) patients had MC. With a median follow-up of 50 months, MC patients had a median overall survival (OS) of 28.2 months compared with 27.7 months for the NMC group [hazard ratio (HR) = 0.92; 95% confidence interval (CI) 0.70–1.19, $P = 0.530$]. The overall response rates for MC and NMC were 41.5% (95% CI 31.5–51.4) and 62.4% (95% CI 58.4–66.3), respectively (Chi-square test, $P < 0.003$). After correcting for significant prognostic factors by multivariate Cox regression analysis, age, resection of the primary tumour, and number of metastatic sites were found to be associated with poorer OS, but not mucinous histology.

Conclusion Compared with NMC, MCRC patients with mucinous histology treated with bevacizumab plus chemotherapy had comparable OS despite lower overall response rate.

Keywords Metastatic colorectal cancer · Mucinous histology · Chemotherapy · Bevacizumab

Data presented in part at the Italian Association of Medical Oncology Annual Meeting 2017, Rome, Italy (abstract #A2).

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Introduction

Colorectal cancer with mucinous histology is the second largest subtype next to colorectal adenocarcinoma, accounting for 10–15% of all colorectal cases (Hamilton et al. 2010). Mucinous tumours are defined as being composed of more than 50% extracellular mucin produced by tumour acinar cells. In the pools of mucus, malignant epithelium can be found in clumps of cells or as single cells (Hamilton et al. 2010). Compared with NMC, MC is more commonly found in younger patients, in the proximal colon and at higher stage at presentation (Hyngstrom et al. 2012; Hugen et al. 2016). Specific molecular features are associated with mucinous differentiation. Decreased expression of MUC-2 is generally found in patients with colorectal cancer (Weiss et al. 1996), while overexpression of MUC2 is a common finding in MC. Compared with NMC, MC is associated with increased microsatellite instability (MSI), CpG island methylation phenotype high (CIMP-H) and aberrations in the RAF/RAF/MAPK (BRAF and RAS) and PI3K/AKT (PIK3CA) pathways (Hugen et al. 2014).

The prognostic significance of mucinous histology for colorectal cancer is still controversial. Some Authors have shown a worse survival in MC (Green et al. 1993; Kanemitsu et al. 2003), while others did not find any adverse prognostic effect (Consorti et al. 2000; Kang et al. 2005). A recent meta-analysis of 44 articles showed a 2–8% significantly increased hazard of death of MC compared with NMC in the colorectum, which persisted after correction for stage (Verhulst et al. 2012). On the other hand, an analysis from the US National Cancer Data Base demonstrated MC is independently associated with poorer outcomes for rectal, but not for colon cancer patients (Hyngstrom et al. 2012).

In the metastatic setting, patients with MC have generally a worse prognosis than that of patients with NMC. Mucinous histology was associated with poorer response rates (Negri et al. 2005; Catalano et al. 2009; Mekenkamp et al. 2012) to first-line chemotherapy and reduced OS (Negri et al. 2005; Catalano et al. 2009; Mekenkamp et al. 2012; Maisano et al. 2012) compared with NMC colorectal cancer. Chemotherapy consisted of FP-based (Negri et al. 2005), OXA-based (Catalano et al. 2009; Mekenkamp et al. 2012; Maisano et al. 2012), and/or IRI-based (Catalano et al. 2009; Mekenkamp et al. 2012).

Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is indicated combined with 5-fluorouracil (5FU)-based chemotherapy for the first-/second-line chemotherapy of patients with MCRC. VEGF inhibitors impair tumour neoangiogenesis by impacting the proliferation and survival of endothelial cells present in the tumour-associated stroma, thereby indirectly dampening tumour outgrowth (Ferrara et al. 2004).

Mekenkamp et al. (2012) explored also the role of biologic agents in a pooled analysis on patients receiving bevacizumab ± cetuximab, so that we have no data on the role of mucinous histology over the treatment efficacy when bevacizumab alone is associated with first-line chemotherapy. The aim of this retrospective analysis was to assess whether bevacizumab combined with different chemotherapy regimens may impact on clinical outcomes of MCRC patients with mucinous histology.

Materials and methods

The study population included 685 consecutive MCRC patients that were enrolled from October 2007 to February 2016 in five Italian oncology centres.

They were enrolled in the study if had histologically confirmed diagnosis of metastatic colorectal adenocarcinoma, unidimensional measurable disease, received first-line bevacizumab plus chemotherapy (FP-based: capecitabine/deGramont; OXA-based: FOLFOX/CAPOX; IRI-based: FOLFIRI/CAPIRI; FOLFOXIRI), normal hematologic values, and adequate hepatic, renal, and cardiac functions. Patients were excluded from the analysis if they had received prior chemotherapy, adjuvant/neoadjuvant treatment completed less than 6 months previously, previous neoplastic disease in the last 5 years (except for basal cell skin cancer or in situ carcinoma of the cervix), familiarity of adenomatous polyposis or hereditary non-polyposis colorectal and high penetrant genetic colorectal cancer predisposition.

Patients were classified according to the histology in MC if mucin constituted > 50% of tumour volume and NMC if < 50% of mucinous component was present (Hamilton et al. 2010). The classification was performed by pathologists from the five participating hospitals. In order to avoid evaluator variability in the patients, all the pathologists were not aware of the clinical results. Patients with signet ring cells and undifferentiated carcinoma were not included in the data analysis.

Data collected included: sex, age, primary tumour location defined as right-sided (caecum, ascending colon, hepatic flexure, and transverse colon) or left-sided colon (splenic flexure, descending colon, sigmoid colon, and rectum), histology type, RAS and BRAF status, previous surgery, adjuvant therapy (chemotherapy and/or radiotherapy), number and sites of metastatic disease, type of chemotherapy regimen used as first-line treatment, tumour response, survival.

Treatment protocols and evaluation of response

The following first-line regimens were used to treat this population: (i) capecitabine 1250 mg/m^2 b.i.d. day 1–14, every 3 weeks; (ii) deGramont schedule—leucovorin 200 mg/

m^2 day 1–2, bolus 5FU 400 mg/m^2 day 1–2, 22 h continuous infusion 5FU 600 mg/m^2 day 1–2, every 2 weeks; (iii) FOLFOX—OXA 85 mg/m^2 day 1 plus deGramont schedule, every 2 weeks; (iv) CAPOX—capecitabine 1000 mg/m^2 b.i.d. day 1–14, OXA 100–130 mg/m^2 day 1, every 3 weeks; (v) FOLFIRI— IRI 180 mg/m^2 day 1 plus deGramont schedule, every 2 weeks; (vi) CAPIRI—capecitabine 1000 mg/m^2 b.i.d. day 1–14, IRI 250 mg/m^2 i.v. day 1, every 3 weeks; (vii) FOLFOXIRI—IRI 165 mg/m^2 followed by OXA 85 mg/m^2, leucovorin 200 mg/m^2 and 5FU 3200 mg/m^2 administered as a 48-h continuous infusion, every 2 weeks. Bevacizumab was administered on day 1 at a dose of 5 mg/kg for cycles every 2 weeks or at a dose of 7.5 mg/kg for cycles every 3 weeks.

Assessment of response was performed every 8–12 weeks. Response Evaluation Criteria in Solid Tumours (RECIST) guidelines were used to define all responses (Eisenhauer et al. 2009). All radiology studies were reviewed for confirming the treatment outcomes.

Statistical analysis

The two groups of patients were compared using 2 × 2 tables for binary factors using the χ^2 test, or the Fisher's exact test where appropriate. OS was calculated from the starting date of first-line chemotherapy until death of any cause, or censored at last follow-up visit. Progression-free survival (PFS) was calculated from the starting date of first-line chemotherapy to the date of progression (per investigator assessment), or death from any cause. Survival data were analysed using the Kaplan–Meier product-limit method. Comparison of survival curves were performed using log-rank test. HRs and 95% CIs for multivariate analyses were computed using the Cox proportional hazards regression models. All tests of significance were two-tailed; differences at P values of < 0.05 were considered to be significant. Analyses were carried out using IBM SPSS ver. 23.0.

Results

The clinical pathological characteristics of patients are shown in Table 1, 591 of them (86.3%) had histologically confirmed diagnosis of NMC colorectal cancer and 94 (13.7%) had mucinous histology. Median age was 64 years for both groups and females/males ratio did not differ in NMC patients (40.9%/59.1%, respectively) and MC patients (44.7%/55.3%, respectively). Mucinous tumours were more frequently located into the right colon (43.6% compared to 31.8% for NMC tumours, $P = 0.0282$). More patients in the MC group had one metastatic site than NMC patients (60.6% and 52.6%, respectively; $P = 0.0309$). As concerning the site of metastases, liver and lungs were the most common sites in

Table 1 Baseline characteristics of the patients

	Non-mucinous ($n = 591$)		Mucinous ($n = 94$)		P value
	n	%	n	%	
Number of patients	591	86.3	94	13.7	
Age, median (range)	64	25–86	64	38–84	0.0624
Sex					
Females	242	40.9	42	44.7	0.5689
Males	349	59.1	52	55.3	
Tumour site					
Right colon	188	31.8	41	43.6	0.0282
Left colon	398	67.3	53	56.4	
Multiple	5	0.9	0	0	
Mutation status					
RASmut	326	62.2	52	61.9	0.9568
RASwt	198	37.8	32	38.1	
BRAFmut	21	4.7	6	9.7	0.1760
BRAFwt	429	95.3	56	90.3	
Metastases at diagnosis					
Yes	425	71.9	65	69.1	0.6684
No	166	28.1	29	30.9	
Metastatic sites involved					
1	311	52.6	57	60.6	0.0309
2	180	30.5	31	33.0	
> 2	100	16.9	6	6.4	
Site of metastasis					
Liver	450	76.1	51	54.2	< 0.0001
Lungs	191	32.3	13	13.8	0.0004
Lymph nodes	158	26.7	19	20.2	0.2244
Peritoneum	106	17.9	34	36.2	0.0001
Bone	23	3.9	2	2.1	0.5816
Abdomen/pelvis	12	2.0	7	7.4	0.0085
Others	44	7.4	11	11.7	0.2276
Previous surgery					
Yes	396	67.0	70	74.5	0.1498
No	195	33.0	24	25.5	
Previous adjuvant chemotherapy					
Yes	138	23.4	29	30.9	0.1488
No	453	76.6	65	69.1	
Previous radiotherapy	16	2.7	3	3.2	0.9422
Chemotherapy regimens					
deGramont/capecitabine-Bev	39	6.6	4	4.3	0.1470
FOLFOX/CAPOX-Bev	159	26.9	18	19.1	
FOLFIRI/CAPIRI-Bev	263	44.5	43	45.7	
FOLFOXIRI-Bev	130	22.0	29	30.9	

Bev bevacizumab, *CAPIRI* capecitabine and irinotecan, *CAPOX* capecitabine and oxaliplatin

NMC patients, whereas peritoneum and abdominal or pelvic metastases were more frequent in MC patients. There was no difference of regimen type distribution between NMC and MC groups (Table 1). The most frequent regimen was IRI-based plus bevacizumab (NMC, $n=263$; MC, $n=43$), followed by OXA-based plus bevacizumab (NMC, $n=159$; MC, $n=18$) and FOLFOXIRI plus bevacizumab (NMC, $n=130$; MC, $n=29$), whereas FP-based plus bevacizumab (NMC, $n=39$; MC, $n=4$) was used in a small percentage of patients.

RAS and BRAF assessments were available for 608 (88.7%) and 512 (74.7%) patients, respectively. RAS mutations were comparable between NMC and MC patients, while there was a trend to higher incidence of BRAF mutations in MC tumours (9.7% versus 4.7%, respectively, $P=0.176$).

With a median follow-up of 50 months, the median OS for MC was 28.2 months not significantly different from that for NMC with 27.7 months [HR = 0.92 (95% CI 0.70–1.19), $P=0.530$] (Fig. 1). When considering the different regimens of chemotherapy, median OS was comparable between NMC and MC patients treated with FP-based/bevacizumab [16.1 months versus 12.7 months, respectively; HR = 1.31 (95% CI 0.39–4.39), $P=0.6836$], IRI-based/bevacizumab [29.9 months versus 32.7 months, respectively; HR = 1.06 (95% CI 0.74–1.54), $P=0.7309$], or FOLFOXIRI/bevacizumab [28.4 months versus 32.7 months, respectively; HR = 0.86 (95% CI 0.52–1.44), $P=0.5490$], but not when patients received OXA-based/bevacizumab regimens [26.1 months versus 15.9 months, respectively; HR = 1.95 (95% CI 1.10–3.44), $P=0.0157$] (Fig. 2).

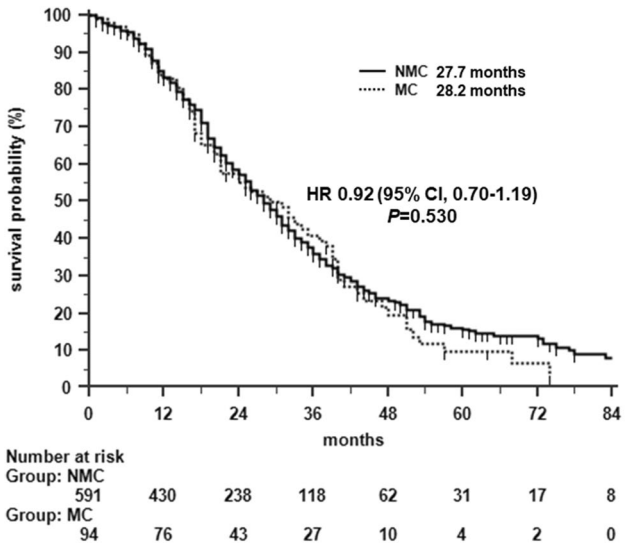

Fig. 1 Kaplan–Meier curves for overall survival according to histology. *NMC* non-mucinous adenocarcinoma, *MC* mucinous adenocarcinoma

Right-sided colorectal cancers were associated with a not significant lower OS compared with left-sided colorectal cancers [25.9 months versus 29.4 months, respectively; HR = 1.15 (95% CI 0.94–1.41), $P=0.1610$]. When considering the mucinous histology and the primary tumour location, median OS of the right-sided NMC group was 25.9 months compared with 29.4 months for the left-sided NMC, 31.7 months for the right-sided MC and 28.2 months for the left-sided MC [HR = 0.98 (95% CI 0.88–1.11), $P=0.8258$].

No difference in median OS was found according to RAS status, with 30.3 months for RAS wild-type group and 27.3 months for RAS-mutant patients, respectively [HR = 0.86 (95% CI 0.71–1.06), $P=0.1593$]. By contrast, as expected, patients whose tumours were BRAF wild-type had a better median OS compared to patients with BRAF-mutant tumours [28.5 months and 20.1 months, respectively; HR = 0.49 (95 CI 0.22–1.10), $P=0.0127$].

After correcting for significant prognostic factors by multivariate Cox regression analysis (Table 2), age [HR = 1.02 (95% CI 1.01–1.03), $P<0.0001$], resection of the primary tumour [HR = 1.55 (95% CI 1.23–1.95), $P<0.0001$]), and number of metastatic sites [HR = 1.41 (95% CI 1.15–1.73), $P=0.001$] were found to be associated with poorer OS. The multivariate analysis confirmed that mucinous histology was not a prognostic factor of poor outcome ($P=0.366$).

PFS according to histology did not show any difference between the two groups, in particular NMC had 11.7 months of PFS and MC 11.2 months [HR = 0.99 (95% CI 0.7–1.25), $P=0.9811$] (Fig. 3). When considering the different regimens of chemotherapy (Fig. 4), MC patients who were treated with OXA-based or FP-based plus bevacizumab had lower PFS compared to those of NMC patients, however these differences were not statistically significant.

Tumour response data are reported in Table 3. MC patients had a lower overall response rate (41.5%; 95% CI 31.5–51.4) compared with that of NMC patients (60.6%; 95% CI 56.6–64.5) and this difference among the two groups was statistically significant ($P=0.003$). Disease control rate (complete response + partial response + stable disease) was observed in 83.0% of the patients in the MC group and 87.3% of NMC patients ($P=0.3244$). No difference of duration of response was found between NMC and MC patients (14.0 months versus 15.2 months; $P=0.6005$), nor in terms of duration of disease control (complete response + partial response + stable disease) which was 13.1 months for both groups ($P=0.6718$).

When considering the different regimens of chemotherapy (Table 4), NMC patients had a significantly higher number of responders to chemotherapy with FOLFOXIRI/bevacizumab (75.4% versus 48.3% for MC patients, $P=0.0076$) and OXA-based/bevacizumab (62.3% versus 33.3% for MC patients, $P=0.0344$). Patients receiving IRI-based plus

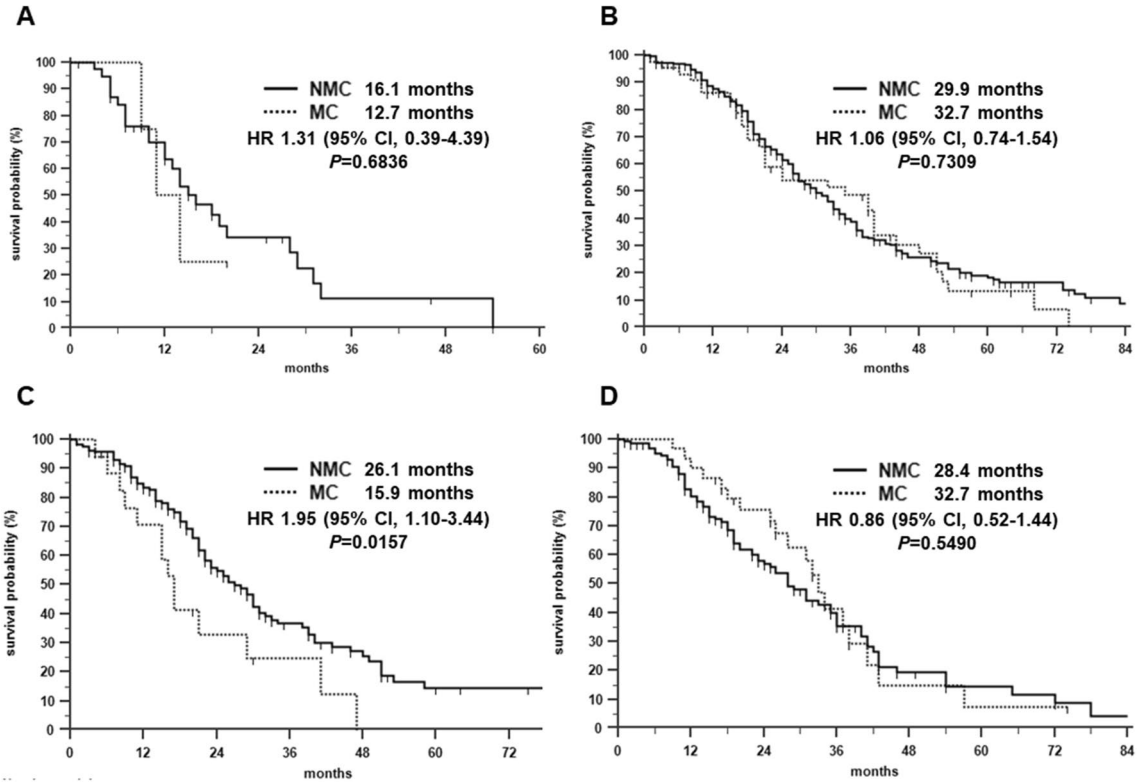

Fig. 2 Kaplan–Meier curves for overall survival according to histology stratified by treatment group. **a** Fluoropyrimidine (FP)-based plus bevacizumab group (NMC, $n=39$; MC, $n=4$); **b** irinotecan/FP-based plus bevacizumab group (NMC, $n=263$; MC, $n=43$); **c** oxaliplatin/FP-based plus bevacizumab group (NMC, $n=159$; MC, $n=18$); **d** FOLFOXIRI plus bevacizumab group (NMC, $n=130$; MC, $n=29$). *NMC* non-mucinous adenocarcinoma, *MC* mucinous adenocarcinoma

Table 2 Multivariate analysis: Cox proportional hazards regression modelling

Variables	HR	95% CI	*P* value
Sex	1.155	0.948–1.407	0.1520
Age	1.023	1.013–1.032	0.0001
Resection of primary tumour	1.553	1.237–1.950	0.0001
Site of primary tumour	0.888	0.725–1.090	0.2590
Synchronous metastasis	0.938	0.711–1.238	0.6530
Histology	1.132	0.865–1.483	0.3660
Adjuvant chemotherapy	1.028	0.780–1.356	0.8430
Number of metastatic sites	1.412	1.150–1.735	0.0010
Hepatic metastasis	1.022	0.796–1.313	0.8630
Peritoneal carcinomatosis	0.855	0.578–1.156	0.3700

CI confidence interval; *HR* hazard ratio

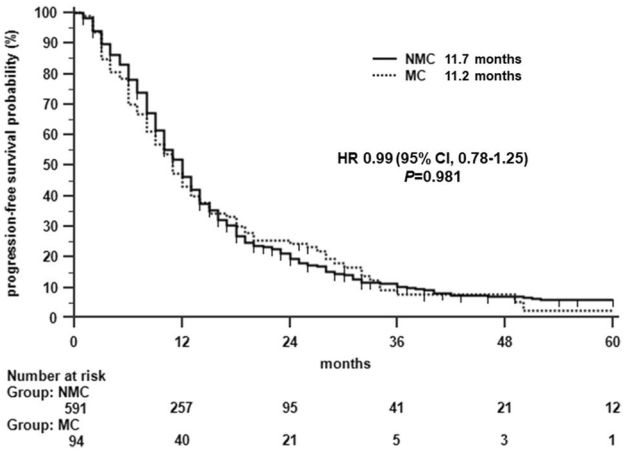

Fig. 3 Kaplan–Meier curves for progression-free survival according to histology. *NMC* non-mucinous adenocarcinoma, *MC* mucinous adenocarcinoma

bevacizumab regimens showed no significant difference of response rate.

Second-line chemotherapy was given to 367 (62.1%) NMC patients and 70 (74.5%) MC patients ($P=0.0205$), while third-line treatment was started for 179 (30.2%) and 29 (30.8%) patients ($P=0.3122$). Resection of the primary tumour was performed in 36/195 (37.9%) of NMC patients and in 4/24 (16.7%) of MC patients ($P=0.8303$), while resection of metastases was achieved by 76 (12.9%) NMC patients and 11 (11.7%) MC patients ($P=0.7544$).

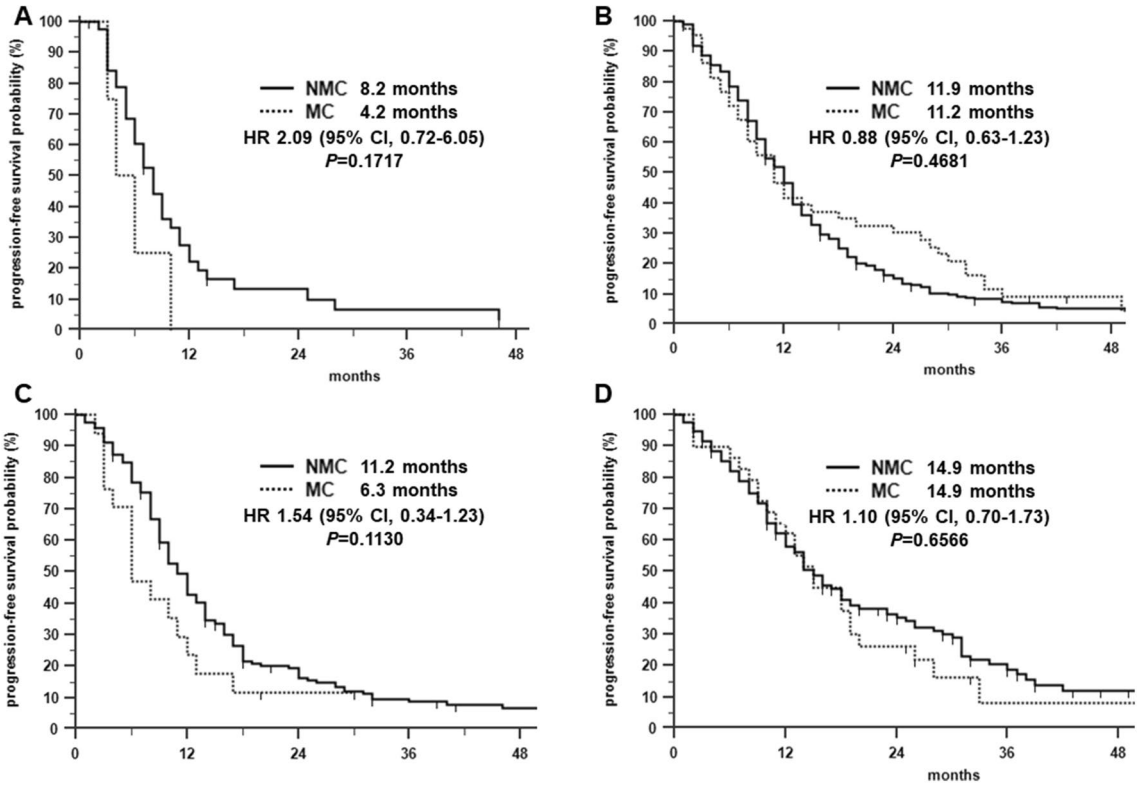

Fig. 4 Kaplan–Meier curves for progression-free survival according to histology stratified by treatment group. **a** Fluoropyrimidine (FP)-based plus bevacizumab group (NMC, $n=39$; MC, $n=4$); **b** irinotecan/FP-based plus bevacizumab group (NMC, $n=263$; MC, $n=43$); **c** oxaliplatin/FP-based plus bevacizumab group (NMC, $n=159$; MC, $n=18$); **d** FOLFOXIRI plus bevacizumab group (NMC, $n=130$; MC, $n=29$). *NMC* non-mucinous adenocarcinoma, *MC* mucinous adenocarcinoma

Table 3 Response to chemotherapy

	Non-mucinous ($n=591$)		Mucinous ($n=94$)		*P* value
Complete response	20	3.4	4	4.3	
Partial response	338	57.2	35	37.2	
ORR (95% CI)	60.6	56.6–64.5	41.5	31.5–51.4	0.003
Stable disease	158	26.7	39	41.5	
Progressive disease	70	11.8	15	16.0	
Not assessable	5	0.8	1	1.1	

CI confidence interval, *ORR* overall response rate

Discussion

The optimal systemic therapy for treating MCRC patients with mucinous histology is still a matter of debate. In several retrospective studies, mucinous histology was associated with unfavourable clinical outcomes and poor prognosis. In 2005, Negri et al. (2005) highlighted poor responsiveness and survival to 5FU-based chemotherapy in mucinous MCRC. Similar results were also confirmed in subsets of patients receiving FOLFOX Maisano (2012) and OXA-based or IRI-based or FOLFOXIRI regimens (Catalano et al.

Table 4 Responders according to histology and regimens of chemotherapy

	n	Non-mucinous ($n=591$)		*n*	Mucinous ($n=94$)		*P* value
		ORR	%		ORR	%	
deGramont/CAP-Bev	39	18	46.2	4	1	25.0	0.6175
FOLFOX/CAPOX-Bev	159	99	62.3	18	6	33.3	0.0344
FOLFIRI/CAPIRI-Bev	263	143	54.4	43	18	41.9	0.1743
FOLFOXIRI-Bev	130	98	75.4	29	14	48.3	0.0076

Bev bevacizumab, *CAP* capecitabine, *CAPIRI* capecitabine and irinotecan, *CAPOX* capecitabine and oxaliplatin, *ORR* overall response rate

2009). Mekenkamp et al. (2012) found a worse outcome in patients with MC compared to patients with NMC focusing on two different phase III randomized trials, the CAIRO (Koopman et al. 2007) and CAIRO2 (Tol et al. 2009) subset analyses. Data derived from the CAIRO2 study were analysed considering patients receiving bevacizumab ± cetuximab as a whole. Therefore, to the best of our knowledge, the present analysis is the first report which evaluates the role of bevacizumab as the only target agent in addition to chemotherapy in patients with mucinous MCRC.

The main finding of the present study is that mucinous histology does not negatively impact on prognosis when first-line chemotherapy is coupled with the anti-angiogenic agent bevacizumab. Results from analyses of genetic/molecular landscapes in colorectal cancer may contribute to explain these findings. Recently, it has been postulated the presence of four groups called consensus molecular subtypes (CMS) in colorectal carcinomas: CMS1 includes MSI-immune tumours; CMS2 shows epithelial and canonical colorectal carcinogenesis; CMS3 is described as epithelial with dysregulated metabolism; CMS4 is characterized by a mesenchymal phenotype (Guinney et al. 2015). The CMS classification is a prognostic factor which is independent of cancer stage, with CMS4 tumours showing the worse prognosis. In retrospective analyses, the CMS classification showed predictive value. Kahn et al. (2018) analysed CMS in colorectal carcinomas of mucinous histology and they found CMS1 cases in about one-third of the study population, and CMS2–4 in the remaining two-thirds of patients. According to recent translational investigations, intermediate-to-high chromosomal instability (CIN) levels mostly occurring in CMS2/4 categories have been correlated with improved response to bevacizumab (Smeets et al. 2018). Again, Mooi et al. (2018) suggested a significant improvement in CMS2 and CMS3 tumours especially when first-line capecitabine-based regimens were associated to bevacizumab. As far chemotherapy is concerned, Sadanandam et al. (2013) described an association between sensitivity to IRI and colorectal carcinomas with CMS3–4 features. More recently, Okita et al. found in CMS4 tumours that IRI-based chemotherapy significantly improved PFS and OS compared to OXA-based chemotherapy (Okita et al. 2018).

Under a mechanistic perspective, it should be considered that mucinous tumours have large amounts of mucin surrounding cancer cells, thus creating a barrier that reduces the availability of anticancer drugs. This barrier may have a role in cancer progression, survival and may protect cancer cells from the host immune response (Komatsu et al. 2001). Vessel compression exerted by the surrounding abundant mucin has the potential to minimize blood flow and may decrease the availability of anticancer drugs into the tumour (Stylianopoulos and Jain 2013). In this regard, bevacizumab may increase drug availability to the tumour (Willett et al. 2004). So that, the use of bevacizumab in mucinous colorectal cancer could be effective due to the vascular normalization and this effect may improve tumour perfusion and drug delivery, thus potentially increase treatment efficacy (Stylianopoulos and Jain 2013).

The results of the analysis of tumour response seem to diverge. MC patients had significantly lower overall response rate than NMC patients. As far as the response assessment in mucinous MCRC is concerned, it may be affected by the presence of large volume of mucus. The tumour cells of MC could respond to systemic chemotherapy, but given the presence of large amounts of mucin which are unresponsive to therapy, the tumour volume would not change substantially and this would lead to false negative conclusions (Hugen et al. 2016). Notably, the disease control rate (complete response + partial response + stable disease) was comparable between MC and NMC patients, thus confirming observations remarked by Mekenkamp et al. (2012). It is likely that the RECIST criteria may not be the optimal way to assess tumour response in MC (Hugen et al. 2016), but this topic needs to be further evaluated.

An intriguing additional finding in the present study is the significantly different overall survival outcomes between patients treated with OXA-based and IRI-based regimens. Actually, these results should be looked at with caution since the small number of patients treated with OXA-based chemotherapy. In fact, the lack of statistical power may also explain the lower, but not-significant PFS of MC patients treated with OXA-based or FP-based plus bevacizumab compared to NMC patients.

The aforementioned role of molecular subtypes on chemosensitivity with putative differences in activity between OXA-based and IRI-based regimens seems to be confirmed in additional studies. Del Rio et al. (2017) found higher response rate and longer OS in patients with MCRC treated with FOLFIRI regimen than FOLFOX regimen when the tumour classifier was enriched with Wnt signalling upregulation. Notably, Wnt signalling upregulation characterizes initiation of mucinous colorectal carcinomas (Jung et al. 2018). In a pharmacogenetic perspective, Glasgow et al. (2005) found that thymidylate synthase and glutathione S-transferase-pi (GSTP1), which are markers of resistance to 5FU and OXA, were overexpressed in MC tumours compared to NMC and normal mucosa samples. At the same time, CRC with mucinous histology may display UGT1A enzymes downregulation (responsible for SN38 glucuronidation), therefore leading to increased responsiveness to IRI (Marisa et al. 2013).

In conclusion, mucinous histology represents a very complex entity with peculiar pathogenesis and molecular pathways which may negatively affect prognosis. The present study addressed the question of the role of an anti-VEGF antibody in addition to first-line chemotherapy in

patients with mucinous MCRC. Notably, a negative interaction between mucinous histology and treatment benefit from bevacizumab plus chemotherapy was not found. Given the retrospective nature of the study, our analysis may present biases correlated to imbalances in the two observed groups. Accordingly, firm conclusions need to be confirmed in additional large studies. Also, the question whether or not the chemotherapy backbones matter in this setting should be investigated in additional investigations. If confirmed, mucinous histology may represent a surrogate marker for adopting IRI-based regimens and bevacizumab in metastatic MC patients. In fact, a simple histology analysis in place of sophisticated and costly molecular profiling may guide the choice of first-line systemic therapy in these patients.

Author contributions All named authors have participated in the study to a sufficient extent to be named as authors. The authors of the manuscript have seen and approved its final version. The article is original, it has not been previously published or has not been submitted for publication elsewhere while under consideration.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the provisions of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards and in accordance with international standards of Good Clinical Practice.

Informed consent Informed consent was waived due to the retrospective nature of this study. Conduct of the investigation was approved by the review board of the Ethics Committee of the "Azienda Ospedaliera Ospedali Riuniti Marche Nord", Pesaro, Italy.

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