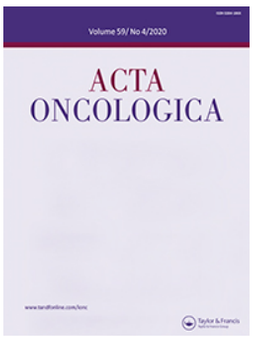

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ORIGINAL ARTICLE

Practice variation on hospital level in the systemic treatment of metastatic colorectal cancer in The Netherlands: a population-based study

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ABSTRACT

Introduction: Population-based data on the implementation of guidelines for cancer patients in daily practice are scarce, while practice variation may influence patient outcomes. Therefore, we evaluated treatment patterns and associated variables in the systemic treatment of metastatic colorectal cancer (mCRC) in the Netherlands.

Material and methods: We selected a random sample of adult mCRC patients diagnosed from 2008 to 2015 from the National Cancer Registry in 20 (4 academic, 8 teaching and 8 regional) Dutch hospitals. We examined the influence of patient, demographic and tumour characteristics on the odds of being treated with systemic therapy according to the current guideline and assessed its association with survival.

Results: Our study population consisted of 2222 mCRC patients of whom 1307 patients received systemic therapy for mCRC. Practice variation was most obvious in the use of bevacizumab and anti-EGFR therapy in patients with *(K)RAS* wild-type tumours. Administration rates did not differ between hospital types but fluctuated between individual hospitals for bevacizumab (8–92%; $p < .0001$) and anti-EGFR therapy (10–75%; $p = .05$). Bevacizumab administration was inversely correlated to higher age (OR:0.2; 95%CI: 0.1–0.3) comorbidity (OR:0.6; 95%CI: 0.5–0.8) and the presence of metachronous metastases (OR:0.5; 95%CI: 0.3–0.7), but patient characteristics did not differ between hospitals with low or high bevacizumab administration rates. The hazard ratios for exposure to bevacizumab and anti-EGFR therapy were 0.8 (95%CI: 0.7–0.9) and 0.6 (95%CI: 0.5–0.8), respectively.

Discussion: We identified significant inter-hospital variation in targeted therapy administration for mCRC patients, which may affect outcome. Age and comorbidity were inversely correlated with non-administration of bevacizumab but did not explain inter-hospital practice variation. Our data suggest that practice variation is based on individual strategy of hospitals rather than guideline recommendations or patient-driven decisions. Individual hospital strategies are an additional factor that may explain the observed differences between real-life data and results obtained from clinical trials.

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Introduction

Clinical guidelines are generated to facilitate the delivery of high-quality and evidence-based care, but population-based data on the implementation of guidelines in daily practice are scarce. Obviously, guidelines should leave room for personalisation of treatment to individual patients, but patient-independent practice variation is undesired since this may result in over- or undertreatment and thereby influence both patients' quality of life and survival. Recent Dutch colorectal cancer guidelines (2008 and 2014) [1] provide clear recommendations for the systemic treatment of patients with metastatic colorectal cancer (mCRC), but the adherence to these recommendations in daily practice has not been studied.

Improvements in median overall survival of mCRC patients have been achieved by the availability of more effective (targeted) drugs and more frequent use of resection of (mostly liver) metastases [2]. The 2014 Dutch guideline recommendations for mCRC included the use of fluoropyrimidines (5-fluorouracil, capecitabine), oxaliplatin and irinotecan as cytotoxic drugs, and bevacizumab and cetuximab/panitumumab as targeted drugs [1]. Data from retrospective analyses as well as prospective randomised trials suggest that the outcome of patients improves when all effective cytotoxic drugs are made available during the course of disease [3–6]. Retrospective data suggest that the same principle applies for targeted drugs [2].

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Supplemental data for this article can be accessed here.

However, especially the use of targeted drugs is accompanied with high costs for healthcare, which may affect prescription rates of these drugs [7,8]. In a recent Dutch multicentre study in first-line mCRC, in which the incidence of hand-foot syndrome was compared between two oral fluoropyrimidines, the use of bevacizumab was left to the discretion of the local physician [9]. Approximately 40% of patients did not receive bevacizumab, which cannot fully be explained by medical contraindications. Furthermore, the use of salvage treatment with anti-EGFR therapy in this and another Dutch mCRC study [10] was also much lower than expected. A regional study focussing on patients with metachronous metastases found suboptimal use of bevacizumab [11]. Other international studies reported a wide range of chemotherapy and targeted therapy administration rates, but did not focus on patient outcomes [12–17]. Population-based studies that examine practice variation in the systemic treatment of mCRC patients on hospital level, including co-variables that might influence therapy administration and the association of practice variation with survival, are lacking.

Therefore, the aim of our population-based study is to evaluate practice variation in the systemic treatment of mCRC between 2008 and 2015 in the Netherlands, to identify variables that are associated with practice variation and examine practice variation and its influence on overall survival.

Material and methods

Study design and population

We conducted a retrospective cohort study including mCRC patients diagnosed between 2008 and 2015 as registered in the Dutch National Cancer Registry (NCR). The Dutch NCR has nationwide coverage and includes all patients diagnosed with colorectal cancer and therefore guarantees a reliable reflection of the population. Our source population consisted of 106.998 stage I-IV CRC patients. The following data-items are routinely registered in the Dutch NCR up to February 2015: hospital, hospital type, period of diagnosis of metastases, gender, age, primary tumour localisation, metastatic sites at diagnosis, pathologic features (tumour stage, morphology and differentiation grade) and first-course treatment information including start and stop dates (surgery of the primary tumour, local treatment of metastases and first-line systemic treatment regimens). Since February 2015, additional variables including subsequent lines of systemic therapy are routinely collected.

In our study, we were interested in both first and subsequent lines of systemic therapy in the period between 2008 and 2015. For this purpose, an independent collaborator selected a representative random sample of approximately 4000 adult stage II-IV CRC patients from our source population (106.998 patients) specified for hospital type (4 academic, 8 teaching, 8 regional, randomly selected), tumour stage at diagnosis (II/III versus IV; ratio 1:1), histology (adenocarcinoma or adenocarcinoma-like tumours) and year of diagnosis.

Thereafter, we collected the following additional variables from patients' electronic health records: comorbidity score (based on comorbid conditions in the following categories: pulmonary disease, cardiovascular disease, digestive disease, genitourinary disease, systemic and rheumatoid disease, neurologic disease, metabolic disease, coagulation disorders and infectious disease), molecular test results (*BRAF*, *(K)RAS* and mismatch repair status), registration of subsequent lines of systemic treatment including start and stop dates and treatment information in case of metachronous metastases. The indication for anti-EGFR therapy changed from *KRAS* wild-type tumours to *RAS* wild-type tumours during our study [18,19]. The Dutch National Cancer Registry does not differentiate between *KRAS* and *NRAS* mutated tumours.

Cohort classification

Our mCRC patient cohort consisted of patients with synchronous (stage IV) and metachronous metastases (extracted from patients with stage II/III disease). Metachronous metastases were defined as occurring $\geq$ 6 months after resection of the primary tumour. We divided our mCRC patient cohort into three subgroups: patients who received upfront systemic treatment (Cohort A), upfront local treatment of metastases (Cohort B), or best supportive care (Cohort C; Figure 1). Upfront local treatment of metastases consisted of surgical resection, HIPEC, radiofrequency ablation (RFA), microwave ablation (MWA) or (stereotactic) radiotherapy, either alone or in combination.

Definition of systemic treatment regimens

We defined lines of systemic treatment based on start and stop dates of individual chemotherapeutic and/or targeted agents and calculated the duration of each treatment regimen. In case a new agent was added to a regimen prior to the first radiological evaluation of response (usually after 8–9 weeks of treatment), we considered this agent as part of this treatment line. We considered an agent as reintroduction of therapy if it was administered after an interval of at least 3 months after previous administration. If this interval was less than 3 months, it was considered as continuation of an existing line of therapy. If reintroduction of an agent was preceded by a different line of treatment, reintroduction was considered as a new line of treatment. We defined maintenance treatment as continuation with a less intensive regimen upon achievement of at least stable disease (usually after 6 or 8 cycles of initial treatment). The duration of different treatment lines was determined by start and stop dates of treatment and was calculated based on the duration of initial treatment, maintenance treatment and reintroduction of therapies.

Guidelines recommendations

The most recent Dutch colorectal cancer guidelines [1] (versions 2008 and 2014) recommend a fluoropyrimidine-containing schedule (monotherapy or combined with irinotecan or oxaliplatin) in combination with bevacizumab as standard of care in first-line treatment in both versions. Bevacizumab is not recommended in subsequent lines of systemic therapy. The 2014 version differentiates between patients with permanently unresectable and potentially resectable metastases. In case of the latter, first-line combination chemotherapy

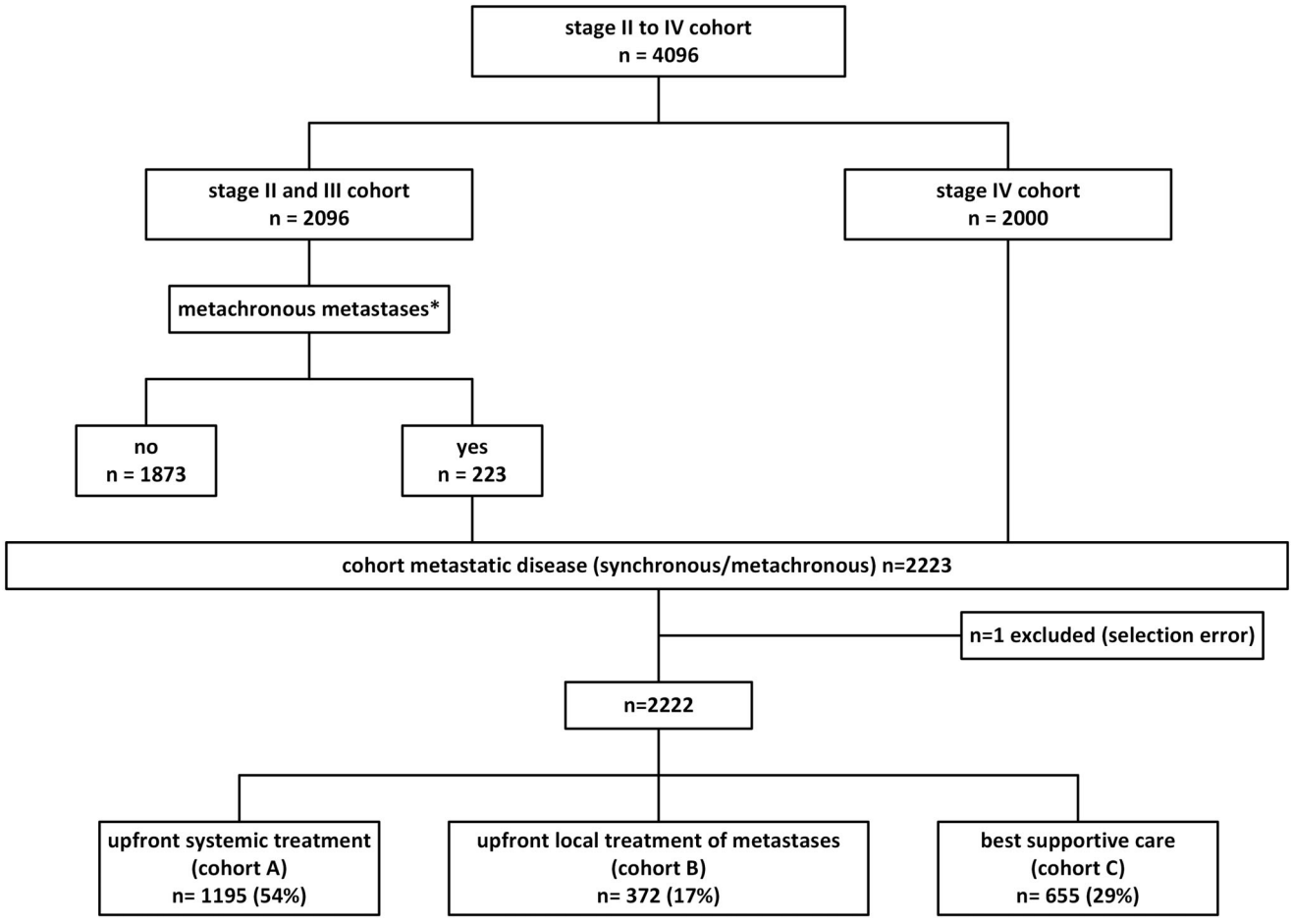

Figure 1. Flowchart of study population. *Metachronous metastases were defined as occurring $\geq$ 6 months after resection of the primary tumour.

with bevacizumab is recommended in patients with *(K)RAS* mutant tumours. For patients with *(K)RAS* wild-type tumours, both bevacizumab and anti-EGFR antibodies are options in combination with chemotherapy. For patients with permanently unresectable metastases and *(K)RAS* wild-type tumours, anti-EGFR treatment is recommended as salvage treatment, either alone or in combination with chemotherapy. The Dutch guideline recommendations concerning systemic therapies were largely in line with other international mCRC guidelines at that time [20,21].

Outcomes

The primary outcomes are the frequencies and variety of systemic treatment regimens that are used for mCRC patients. We studied practice variation patterns among individual hospitals and between different types of hospitals and compared treatments with prevailing guideline recommendations (2008 until March 2014: 2008 guideline; as of April 2014: 2014 guideline). Secondary outcomes are the associations of demographic, clinical and tumour characteristics with (non)-administration of systemic treatment and overall survival.

Statistical analysis

Descriptive statistics using frequency tables and percentages were generated for all study variables and are presented for cohort A, B and C separately. Variation in the administration of targeted therapies was assessed by $\chi 2$ tests or Fisher's exact tests if applicable. Univariable logistic regression analysis was performed to determine the unadjusted association between demographic, clinical and tumour characteristics on the odds of being treated with bevacizumab and anti-EGFR therapy. Subsequently, we tested for multicollinearity between variables and the same variables were examined in multivariable logistic analyses to explore which variables were independently associated with targeted therapy treatment. Patients with known *(K)RAS* mutated tumours or with unknown *(K)RAS* mutation status were excluded from analyses that concerned anti-EGFR therapy. Overall survival (OS) was defined as the interval between date of diagnosis until date of death. Patients who were alive at the end of follow-up (1 February 2017) were censored. Crude survival rates were calculated with a Kaplan Meier method. We presented median OS in months with corresponding 95% confidence intervals (CI's) and used a log-rank test to assess differences in survival curves between patient groups who were exposed versus not exposed to different systemic agents. A Cox proportional hazard ratio analysis was performed to study the influence of included co-variables on the risk of death. A co-variable was included in the analyses if we expected an association between the co-variable and practice variation and/or overall survival. All statistical analyses were performed using SAS, version 9.4. A *p*-value below .05 was considered as statistically significant.

Results

Study population

Our initial cohort consisted of 4096 patients (stage II/III: $n = 2096$; stage IV: 2000). In total, 223 stage II and stage III patients developed metastases during the follow-up of our study, resulting in a mCRC cohort of 2223 patients (Figure 1). The low number of patients with metachronous metastases is due to a high percentage of included patients since 2015 with a relatively short follow-up time and because metachronous metastases of patients who do not receive treatment are not registered. One patient was excluded due to a selection error (squamous cell carcinoma instead of adenocarcinoma), resulting in a cohort of 2222 patients. The characteristics of included patients are presented in Table 1.

Table 1. Baseline characteristics of study population (cohort A, B and C).

	Total cohort $n = 2222$ (100%) *n* (%)	Upfront systemic treatment (cohort A) $n = 1195$ (54%) *n* (%)	Upfront local treatment of metastases (cohort B) $n = 372$ (17%) *n* (%)	Best supportive care (cohort C) $n = 655$ (29%) *n* (%)	*p*-Value
Hospital type					
Academic	457 (21)	240 (20)	108 (29)	109 (17)	
Teaching	924 (42)	485 (41)	142 (38)	297 (45)	
Regional	841 (38)[a]	470 (39)	122 (33)	249 (38)	**<.0001***
Period of diagnosis (metastases)					
2008–2010	539 (24)	269 (23)	95 (26)	175 (27)	
2011–2013	591 (27)	306 (26)	92 (25)	193 (29)	
2014–2017	1092 (49)	620 (52)[a]	185 (50)[a]	287 (44)	**.02***
Gender					
Male	1245 (56)	678 (57)	217 (58)	350 (53)	
Female	977 (44)	517 (43)	155 (42)	305 (47)	.24
Age					
<60	479 (22)	324 (27)	96 (26)	59 (9)	
60–69	689 (31)	419 (35)	138 (37)	132 (20)	
70–79	711 (32)	367 (31)	104 (28)	240 (37)	
>79	343 (15)	85 (7)	34 (9)	224 (34)	**<.0001***
Number of comorbid conditions					
0	728 (33)	441 (37)	142 (38)	145 (22)	
1	667 (30)	355 (30)	109 (29)	203 (31)	
≥ 2	800 (36)	393 (33)	119 (32)	288 (44)	
Unknown	27 (1)	6 (1)[a]	2 (1)	19 (3)	**<.0001***
Primary tumour localisation					
Colon	1673 (75)	876 (73)	298 (80)	499 (76)	
Rectosigmoid	44 (2)	27 (2)	6 (2)	11 (2)	
Rectum	505 (23)	292 (24)[b]	68 (18)	145 (22)	.10
Tumour sidedness					
Right	808 (36)	430 (36)	136 (37)	242 (37)	
Left	1342 (60)	731 (61)	231 (62)	380 (58)	
Unknown	72 (3)[b]	34 (3)	5 (1)	33 (5)	**.02***
Differentiation grade					
Grade I–II	1166 (52)	616 (52)	275 (74)	275 (42)	
Grade III–IV	349 (16)	161 (13)	48 (13)	140 (21)	
Unknown	707 (32)	418 (35)	49 (13)	240 (37)	**<.0001***
Number of organs affected with metastases at diagnosis					
1	1315 (59)	678 (57)	277 (74)	360 (55)	
2	606 (27)	350 (29)	54 (15)	202 (31)	
≥ 3	301 (14)	167 (14)	41 (11)	93 (14)	**<.0001***
Microsatellite status					
MSI low	211 (10)	132 (11)	52 (14)	27 (4)	
MSI high	21 (1)	9 (1)	6 (2)	6 (1)	
Unknown	1990 (90)[a]	1054 (88)	314 (84)	622 (95)	**<.0001***
BRAF mutation status					
Wild-type	328 (15)	277 (23)	41 (11)	10 (2)	
Mutated	64 (3)	50 (4)	10 (3)	4 (1)	
Unknown	1830 (82)	868 (73)	321 (86)	641 (98)[a]	**<.0001***
(K)RAS mutation status					
Wild-type	322 (14)	274 (23)	41 (11)	7 (1)	
Mutated	332 (15)	275 (23)	46 (12)	11 (2)	
Unknown	1568 (71)	646 (54)	285 (77)	637 (97)	**<.0001***
Synchronous versus metachronous metastases					
Synchronous	1999 (90)	1127 (94)	287 (77)	585 (89)	
Metachronous	223 (10)	68 (6)	85 (23)	70 (11)	**<.0001***

[a]Column percentages of variable add up to 101% due to rounding inaccuracies.
[b]Column percentages of variable add up to 99% due to rounding inaccuracies.
*Statistically significant differences.

Overview and sequence of systemic therapy in different patient cohorts

In total, 1307 out of 2222 mCRC patients (59%) from cohort A and cohort B, including patients with synchronous and metachronous metastases, were treated with systemic treatment for metastatic disease at some time point during the course of disease. The majority of Cohort A ($n = 1195$; upfront systemic treatment) received systemic treatment only ($n = 999$) without local treatment of metastases. The exposure to the different cytotoxic and targeted therapy agents of these 999 patients and an overview of the sequence of different lines of systemic therapy (including the number of patients who received maintenance treatment and/or reintroduction of treatment regimens) are presented in Supplementary Figures 1 and 2. The median duration of first-line treatment was 112 days, with CAPOX-B (capecitabine, oxaliplatin and bevacizumab; 37%), CAPOX (24%), capecitabine monotherapy (20%) and CAP-B (7%) as most commonly administered regimens (Figure 2). In total, 387 patients (39%) received salvage systemic treatment, consisting in second-line most often of irinotecan monotherapy (56%), anti-EGFR therapy (10%) or 5-FU plus irinotecan (FOLFIRI; 10%; Figure 2 and Supplementary Figure 2). A minority of patients received third ($n = 131$; 13%), fourth ($n = 21$; 2%) and fifth ($n = 1$; <1%) line systemic treatment. Anti-EGFR therapy was predominantly prescribed in third and fourth line (52% and 33%, respectively; Figure 2).

A minority of Cohort A patients ($n = 196$; 16%) underwent subsequent local treatment of metastases after upfront systemic treatment. These patients were predominantly treated with CAPOX ($n = 84$; 43%) and CAPOX-bevacizumab ($n = 81$; 41%) in first line before local treatment of metastases (Supplementary Figure 3). Three patients were treated with anti-EGFR therapy in first line.

A minority of Cohort B patients (112 out of 372 patients (30%)) received systemic therapy targeting metastases later in the course of disease after local treatment of metastases. An overview of systemic therapy lines is presented in Supplementary Figure 3.

Practice variation in targeted therapy administration

In total, 796 of 1307 patients (61%) who received systemic therapy, were exposed to targeted drugs. Tumours of 47% of patients ($n = 610$) were tested for *(K)RAS* mutations (*(K)RAS* wild-type: 301 (49%); *(K)RAS* mutant: 309 (51%)). Of systemically treated patients ($n = 1307$), 55% ($n = 720$) received bevacizumab and 13% of patients ($n = 164$) received anti-EGFR therapy during the course of disease. Specified for first-line regimens, 615 out of 1307 patients (47%) received bevacizumab and 10 out of 1307 patients (1%) received anti-EGFR

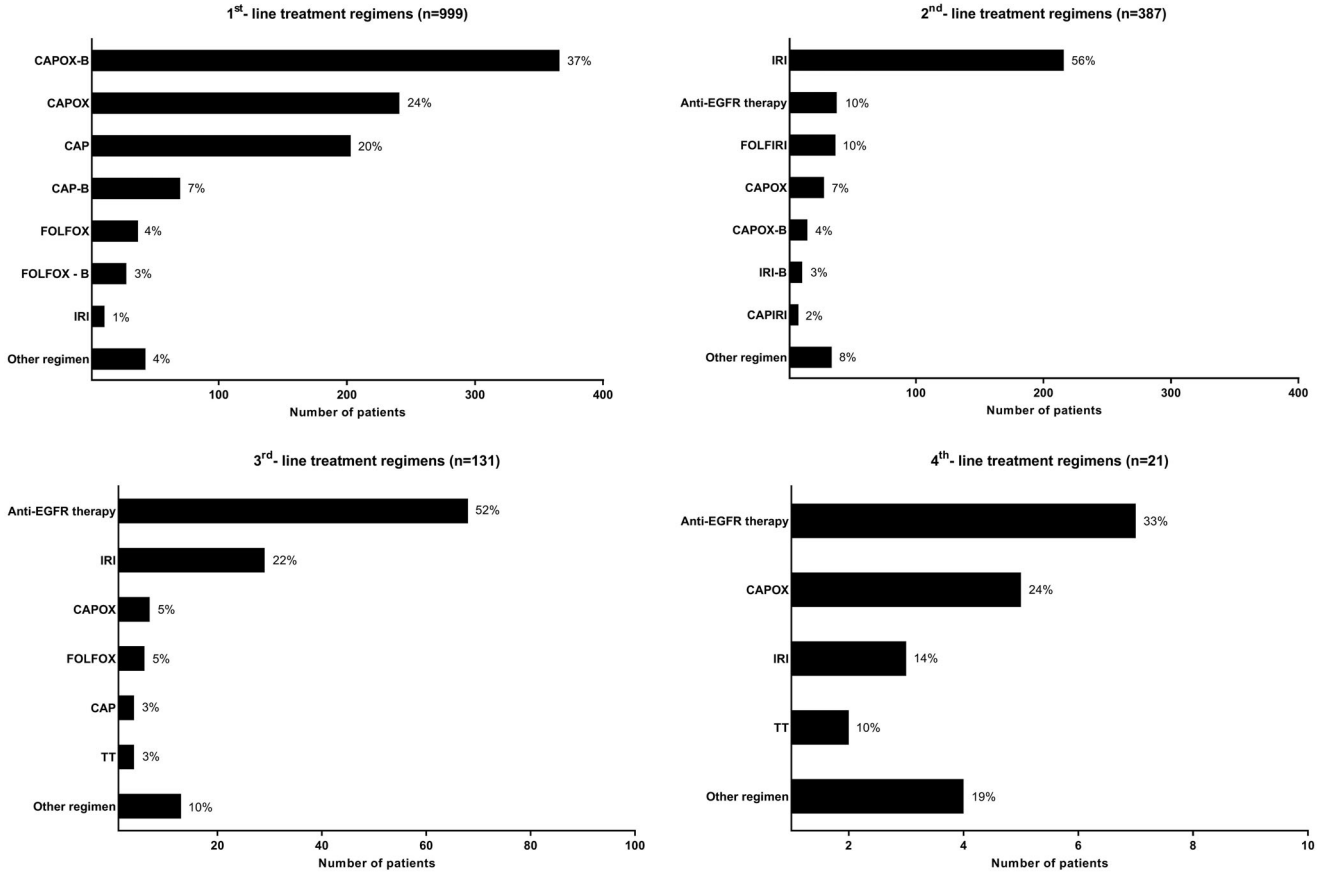

Figure 2. Overview of first and subsequent lines of systemic treatment. Analysis is restricted to patients treated with systemic therapy only ($n = 999$). CAPOX: capecitabine & oxaliplatin; B: bevacizumab; CAP: capecitabine; FOLFOX: 5-fluorouracil & oxaliplatin; IRI: irinotecan; FOLFIRI: 5-fluorouracil & irinotecan; TT: Trifluridine tipiracil; Anti-EGFR therapy: cetuximab or panitumumab.

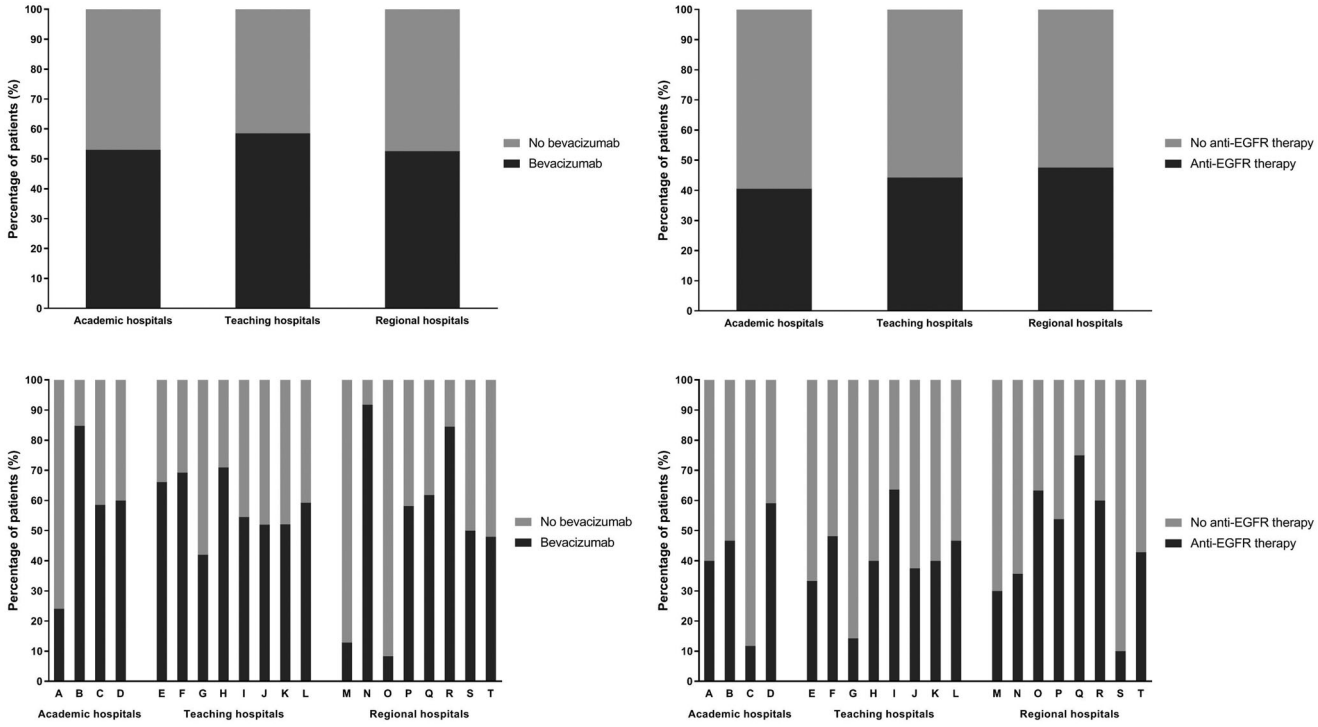

Figure 3. Practice variation in bevacizumab and anti-EGFR therapy administration during the treatment of metastatic colorectal cancer. $n = 1307$. Analysis concerning anti-EGFR therapy is restricted to *(K)RAS* wild-type patients; $n = 301$.

therapy in first line. Bevacizumab administration did not differ between *(K)RAS* wild-type ($n = 175$) and *(K)RAS* mutant ($n = 188$) patients ($p = .50$). Of patients receiving anti-EGFR therapy, 134 patients (82%) were *(K)RAS* wild-type, 3 patients (2%) were *(K)RAS* mutant and 27 patients (16%) had an unknown *(K)RAS* status. If specified for proven *(K)RAS* wild-type patients ($n = 301$), 45% of patients ($n = 134$) received anti-EGFR therapy. Overall, 72 *(K)RAS* wild-type patients (24%) received treatment with subsequent bevacizumab and anti-EGFR therapy.

There was significant variation in the use of bevacizumab ($p < .0001$) and anti-EGFR therapy ($p = .05$) between individual hospitals, but not between different types of hospital (bevacizumab: $p = .12$; anti-EGFR therapy: $p = .64$). Bevacizumab administration between hospitals ranged from 8% to 92% (median: 58%; IQR: 49–68%) and anti-EGFR administration (in *K(RAS)* wild-type patients) from 10% to 75% (median: 41%; IQR: 34–58%; Figure 3).

More recent period of diagnosis (of metastases; 2011–2013 and 2014–2017 compared to 2008–2010), a higher age (>79 years compared to <60 years), comorbidity (≥ 2 versus no comorbidity) and metachronous metastases were associated with non-administration of bevacizumab (Table 2). All variables remained significantly associated with non-administration of bevacizumab after adjusting for all covariables as listed in Table 2: period of diagnosis (OR: 0.5; 95% CI: 0.4–0.7 and OR: 0.7; 95% CI: 0.5–0.9), higher age (OR: 0.2; 95% CI: 0.1–0.3), comorbidity (OR: 0.6; 95% CI: 0.5–0.8) and metachronous metastases (OR 0.5; 95% CI: 0.3–0.7). Patients who received bevacizumab were significantly younger (mean = 63.9 (95% CI: 63.1–64.6); sd = 9.8) compared to patients who did not received bevacizumab (mean = 66.6 (95% CI: 65.7–67.5); sd = 11.0; $p < .0001$), but patients in hospitals with lower bevacizumab use were not significantly older. Patients not treated with bevacizumab were more likely to have hypertension ($p < .0001$), heart disease ($p = .02$), vascular disease ($p = .05$) thrombotic disease ($p = .002$) and/or renal disease ($p = .01$). However, we did not observe significantly higher incidence rates of these comorbidities in hospitals with lower bevacizumab use. Comorbidity rates were similar for *(K)RAS* wild-type patients who did or did not receive anti-EGFR therapy. There were 195 patients (15%) and 59 patients (20% in *(K)RAS* wild-type cohort) without comorbidities who were not exposed to bevacizumab and anti-EGFR therapy, respectively. There were no variables associated with the administration of anti-EGFR therapy in both univariable and multivariable analyses (Table 2).

Survival analysis

The median overall survival (OS) of our mCRC cohort ($n = 2222$) was 14.3 months (95% CI: 13.4–15.0 months) with a 1-year survival rate of 56%. The median overall survival (OS) of Cohort C patients (best supportive care; $n = 655$) was 3.6 months (95% CI: 3.2–4.5 months). Patients in cohort A (upfront systemic therapy) who were subsequently treated with local treatment of metastases had a median survival of 36.1 months (95% CI: 30.8–39.7 months) compared to 14.0 months (95% CI: 13.1–14.8 months) for patients treated with systemic therapy only ($p < .0001$). Patients who were treated with systemic therapy only and were exposed to bevacizumab had a median OS of 15.9 months (95% CI: 14.6–17.0 months) compared to 12.2 months (95% CI: 10.9–13.1 months) for patients not exposed to bevacizumab

Table 2. Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) on bevacizumab and anti-EGFR therapy administration.

	Bevacizumab administration		Anti-EGFR therapy administration	
	$n = 1307$		$n = 301$[a]	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Hospital type				
Academic	Reference	Reference	Reference	Reference
Teaching	1.3 (0.9–1.7)	1.3 (1.0–1.8)	1.2 (0.7–2.1)	1.3 (0.7–2.3)
Regional	1.0 (0.7–1.3)	1.0 (0.7–1.4)	1.3 (0.7–2.4)	1.4 (0.7–2.6)
Period of diagnosis (metastases)				
2008–2010	Reference	Reference	Reference	Reference
2011–2013	**0.5 (0.3–0.6)***	**0.5 (0.4–0.7)***	0.9 (0.5–1.8)	1.0 (0.5–2.0)
2014–2017	**0.7 (0.5–0.9)***	**0.7 (0.5–0.9)***	0.6 (0.3–1.2)	0.7 (0.4–1.3)
Gender				
Male	Reference	Reference	Reference	Reference
Female	0.9 (0.7–1.1)	0.8 (0.6–1.0)	0.9 (0.5–1.4)	0.9 (0.5–1.4)
Age (years)				
<60	Reference	Reference	Reference	Reference
60–69	0.9 (0.7–1.2)	1.1 (0.8–1.4)	0.8 (0.4–1.3)	0.8 (0.4–1.4)
70–79	0.8 (0.6–1.0)	0.9 (0.6–1.2)	1.2 (0.7–2.1)	1.2 (0.6–2.4)
>79	**0.2 (0.1–0.3)***	**0.2 (0.1–0.3)***	0.4 (0.1–1.8)	0.3 (0.0–1.7)
Number of comorbid conditions				
0	Reference	Reference	Reference	Reference
1	0.9 (0.7–1.2)	1.0 (0.7–1.3)	1.0 (0.6–1.8)	1.1 (0.6–2.0)
≥ 2	**0.6 (0.4–0.7)***	**0.6 (0.5–0.8)***	0.9 (0.5–1.5)	0.9 (0.5–1.6)
Tumour sidedness				
Right	Reference	Reference	Reference	Reference
Left	1.1 (0.9–1.4)	1.0 (0.8–1.3)	1.3 (0.8–2.2)	1.2 (0.7–2.1)
Unknown	1.4 (0.7–2.9)	1.2 (0.6–2.5)	0.7 (0.1–3.0)	0.6 (0.1–2.6)
Differentiation grade				
Grade I–II	Reference	Reference	Reference	Reference
Grade III–IV	0.8 (0.6–1.2)	0.9 (0.6–1.2)	0.7 (0.4–1.4)	0.7 (0.3–1.5)
Unknown	1.0 (0.8–1.2)	0.9 (0.7–1.2)	1.2 (0.7–2.0)	1.2 (0.7–2.1)
Number of organs affected with metastases at diagnosis				
1	Reference	Reference	Reference	Reference
2	1.0 (0.8–1.3)	1.1 (0.8–1.4)	0.8 (0.5–1.4)	0.9 (0.5–1.5)
≥ 3	0.9 (0.6–1.2)	1.0 (0.7–1.4)	0.9 (0.4–1.8)	0.8 (0.4–1.9)
Synchronous versus metachronous metastases				
Synchronous	Reference	Reference	Reference	Reference
Metachronous	**0.5 (0.3–0.7)***	**0.5 (0.3–0.7)***	1.4 (0.6–3.5)	1.6 (0.6–4.5)

[a]Analysis restricted to patients with a *(K)RAS* wild-type status ($n = 301$).
*Statistically significant differences.

($p = .002$). Patients with a *(K)RAS* wild-type status ($n = 238$) treated with anti-EGFR therapy had a median OS of 23.8 months (95% CI: 20.0–27.2 months) compared to 14.9 months (95% CI: 13.1–16.5 months) for patients not treated with anti-EGFR therapy ($p < .0001$). Exposure to bevacizumab (HR: 0.8; 95% CI: 0.7–0.9) and exposure to anti-EGFR therapy (HR: 0.6; 95% CI: 0.5–0.8) remained associated with better survival after adjusting for all co-variables (Supplementary Table 1). A multivariable analysis on the effect of anti-EGFR therapy administration in patients with *(K)RAS* wild-type tumours ($n = 238$) confirmed this finding (HR: 0.6; 95% CI: 0.4–0.8).

Discussion

The results of our population-based longitudinal cohort study demonstrate substantial inter-hospital practice variation in the systemic treatment of mCRC patients between 2008 and 2015 in the Netherlands. The majority of mCRC patients (59%) received systemic treatment. Of systemically treated patients, 61% received targeted drugs during the course of their disease, which concerned bevacizumab in 55% of patients and anti-EGFR therapy in 45% of patients with *K(RAS)* wild-type tumours.

We observed significant inter-hospital variation in the use of targeted drugs, irrespective of hospital type. Absolute contraindications for anti-EGFR and bevacizumab treatment are rare, and for bevacizumab are limited to unhealed surgical wounds, major bleedings, recent haemoptysis, gastrointestinal perforation, uncontrolled hypertension and arterial thromboembolism [22]. We found that patients who were not exposed to bevacizumab more often had a diagnosis of hypertension, heart disease, thrombotic disease or renal disease. However, the incidence of these comorbidities did not differ between patients from hospitals with low versus high bevacizumab use. Therefore, the large inter-hospital variation for targeted drugs administration in our study (range bevacizumab: 8% to 92% and anti-EGFR therapy: 10% to 75%) is not explained by the medical condition of patients. Unawareness of guideline recommendations is unlikely, given the laborious and adversarial procedure of the establishment of oncological guidelines. The significant and wide inter-

hospital variation in the use of targeted drugs rather suggests a difference in hospital policy towards the use of expensive drugs in palliative setting, leading to guideline nonadherence and undesired practice variation. Although the use of bevacizumab and anti-EGFR antibodies in mCRC patients is covered by health insurance, their reimbursement in the Netherlands is part of a lump sum agreement between third party payers and hospitals. This allows hospitals to make individual strategic choices in the spending of their budget. However, these choices are usually not made public.

The survival rates of patients who were treated with systemic therapy in our study are lower compared to data from clinical trials. This is most likely attributable to the population-based design of our study compared to clinical trials, which concern selected patient populations under strict follow-up [23,24]. The median OS of patients treated with bevacizumab in our study is slightly lower compared to data from other observational studies in mCRC [25–27]. This may be explained by differences in patient characteristics, since other studies restricted the inclusion to patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, a life expectancy of at least 3 months, and adequate organ function [26], or (mostly) to patients who received combination chemotherapy in first line [25,27]. Our results reflect unselected real-life data of clinical practice.

The survival benefit that we observed for patients receiving bevacizumab and anti-EGFR therapy should be interpreted with caution, because of the influence of confounding by indication due to the observational design of our study. However, the effect of the addition of targeted therapy remained significant after adjusting for all co-variables listed with a reduced hazard of death if patients were exposed to bevacizumab or anti-EGFR therapy. Therefore, our data support the survival benefit of targeted therapies in patients with mCRC as demonstrated in earlier studies.

We observed a significant association of period of diagnosis (2011–2013 and 2014–2017 compared to 2008–2009), higher age (>79 years compared to <60), comorbidity (≥2 versus 0) and the presence of metachronous metastases with non-administration of bevacizumab. The decrease in bevacizumab use over the years is remarkable, in which the 2008 publication of the less favourable results of the NO16966 study [28] compared to the initial study by Hurwitz et al. of 2004 [29] may have played a role. However, these data did not change the recommendation of bevacizumab as part of first-line treatment in the 2014 Dutch guideline. Our finding that bevacizumab administration rates are inversely correlated to higher age and comorbidity cannot be fully explained by evidence-based considerations about the applicability of this agent under such circumstances, since the use of bevacizumab in combination with chemotherapy has been shown safe and effective in elderly patients [30,31].

In conclusion, our results demonstrate undesired practice variation of guideline-recommended systemic treatment of mCRC patients in the Netherlands, which appears to affect clinical outcome of patients. Our data warrant continuous monitoring in daily practice of the implementation of up-to-date guideline recommendations, with documentation of reason(s) for guideline non-adherence, including possible financial barriers on the use of expensive drugs. This will provide valuable and currently unavailable information on the quality of oncological care, which will be highly relevant for the implementation in clinical practice of the increasing number of novel and often expensive cancer drugs. Observational population-based studies, such as currently ongoing in the Netherlands [32], are highly suitable for this purpose. Lastly, our data show that the implementation of approved and guideline-recommended drugs into daily practice is not self-evident, and that strategies of individual hospitals add to the observed differences between real-life data and results obtained from clinical trials.

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