Anticancer drugs and cardiovascular-related hospitalization in metastatic colorectal cancer: Insights from the AVOCETTE population-based study

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Running head: Cardiovascular events, colorectal cancer

ABSTRACT

We aimed to investigate the association between anticancer drugs and cardiovascular-related hospitalization (CVRH) in metastatic colorectal cancer (mCRC) patients. A cohort study was conducted using the French county Calvados registry of digestive tumors. Incident mCRC cases between 2008 and 2014 were included. The follow-up end date was December 2016. Data from the county hospital center pharmacy and medical information departments were matched with the registry data. A competing risk approach was used. Statistical tests were two-sided. A total of 1,116 mCRC patients were included; they were administered 12,374 rounds of treatment; fluorouracil, oxaliplatin, irinotecan and bevacizumab were most common. A total of 208 CVRH events occurred in 145 patients (13.0%). The International Cancer Survival Standards type 1 standardized incidence was 84.0 CVRH per 1,000 person-years (95% confidence interval: 72.6-95.5). Anticancer drugs were not associated with a higher incidence of CVRH. Men, elderly patients, patients with a prior history of CVRH and patients with a higher Charlson comorbidity index were associated with a higher incidence of CVRH. CVRH was significantly associated with a higher all-cause mortality (multivariable hazard ratio for death 1.58, 95%CI 1.28-1.95). Anticancer drugs were not associated with a higher incidence of CVRH in mCRC patients.

KEY WORDS: metastatic colorectal cancer; anticancer drugs; cardiovascular events; all-cause mortality; population based-registry

ABBREVIATIONS:

CCI: Charlson Comorbidity Index

CI: confidence interval

mCRC: metastatic ColoRectal Cancer

CVAE: CardioVascular Adverse Event

CVRH: CardioVascular-Related Hospitalization

EGFR: Epidermal Growth Factor Receptor

HR: Hazard Ratio

VEGF: Vascular Endothelial Growth Factor

Colorectal cancer is one of the top 3 most incident cancers in France and the second cause of cancer-related death, with a world standardized incidence of 34.0 cases per 100,000 person-years in men and 23.9 cases per 100,000 person-years in women and mortality of 11.5 and 6.9 per 100,000 person-years in 2018, respectively.[1] The incidence of colorectal cancer is steadily increasing after the age of 50, with a peak incidence of 503.8 and 320.3 per 100,000 person-years in men and women in the 85-89 year-class; the median age of diagnosis is 71 in men and 73 in women.[1] Novel anticancer therapies such as vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) inhibitors led to substantial improvements in progression-free and overall survival of metastatic colorectal cancer (mCRC).[2–4] With the improvement in life expectancy of these patients and the use of new pharmacological classes (i.e., targeted drugs as opposed to cytotoxic agents), cardiovascular adverse events (CVAEs) progressively appeared to be a critical concern.[5] Drug labels indicate that ischaemic heart disease, coronary spasm and arrhythmia can occur with antipyrimidique antimetabolites (fluorouracil and capecitabine) in clinical trials. VEGF inhibitors (aflibercept, bevacizumab) which bind VEGF and prevent vascular endothelial growth and endothelial cell proliferation, may induce hypertension, stroke, venous thromboembolism and ischaemic heart disease, whereas EGFR inhibitors (panitumumab) could cause hypertension and venous thromboembolism. High rates of cardiovascular risk factors and diseases can be found in cancer patients, partly due to the aging population, but also to cancer treatments themselves.[6,7] Californian 4- to 14-year-old survivors of colorectal cancer had significantly higher rates of hypertension (61.9%), tobacco use (58.1%), diabetes (20.3%) and obesity (24.1%) compared to a general population sample in similar age ranges.[7]

CVAEs with severe clinical presentation may require a cardiovascular-related hospitalization (CVRH). A monocentric study in patients with colorectal neoplasms showed that both physical and function well-beings of patients were negatively and significantly associated with the number of monthly hospitalisations.[8] The patient quality of life has taken growing importance in the management of cancer survivors and it is also an independent predictor of all-cause mortality among colorectal cancer long-term survivors.[9] Whether anticancer drug-induced CVAEs require dedicated cardiovascular-related hospitalization (CVRH) as well as the incidence of CVRH in the real-life setting in mCRC patients are unknown.

Therefore, we evaluated the association between anticancer drugs exposure and CVRH in mCRC patients in a county-level registry using a competing risk approach.

METHODS

The Strengthening the Reporting of Observational studies in Epidemiology statement was used to report the present cohort study.[10] The study protocol was prospectively registered on ClinicalTrials.gov, NCT03923036.

Data sources

Data sources belong to three categories. 1) The Calvados registry of digestive tumors has been exhaustively registering all cases of incident digestive tumors diagnosed within the county since 1978. It includes demographic parameters (age, sex), the Charlson comorbidity index (CCI),[11] the presence of a prior history of cancer, tumor data (date of diagnosis, date and type of progression, the tumor type with International Classification of Diseases Oncology 3rd codes), the treatment type (surgery including resection and surgical derivation, radiotherapy,

chemotherapy) and outcome. A continuous follow-up is performed to collect treatment and outcome information, and the vital status is updated for all patients every 1-2 years (last update in June 2018) with a query to the French national death registry (*Répertoire national d'identification des personnes physiques*). 2) The county hospital pharmacy departments and 3) the county medical information departments (details in Web Appendix 1).

Study design

We conducted a retrospective registry-based cohort study in Calvados County of incident cases of synchronous or metachronous mCRC from January 1st, 2008, (inclusion period start date) until December 31, 2014 (inclusion period end date). Synchronous mCRC referred to patients with distant metastasis occurring within 6 months of the primary diagnosis of CRC, whereas metachronous mCRC referred to patients with diagnosis of distant metastasis beyond this date. All patients had stage IV disease during follow-up. The medical information departments' databases were matched with the registry to identify CVRH in mCRC patients. CVRH and vital status were recorded until December 31, 2016 (follow-up end date). The pharmacy department databases were matched with the registry to identify the anticancer drugs delivered to the mCRC patients (details in Web Appendix 1). There was no attempt to collect CVRH or anticancer drug data outside of Calvados County. We mapped the geographical repartition of CVRH and anticancer drug delivery in the county to explore potential data leaks.

Exposure variables

Anticancer drug exposure was collected from the hospital center pharmacy departments. The mCRC anticancer drug list was based on the French society of digestive cancers and disease

guidelines for the management of metastatic colon cancer and rectal cancer (*Thésaurus national de cancérologie* digestive) during the study period.[12] Any anticancer drug recommended in monotherapy or as part of a chemotherapy protocol in these guidelines was retained. The drug names, doses in milligrams and dates of administration were collected for alkylating agents (mitomycin C, oxaliplatin), antimetabolites (capecitabine, fluorouracile, raltitrexed), EGFR inhibitors (cetuximab, panitumumab), rapidly accelerated fibrosarcoma inhibitors (regorafenib), thymidine phosphorylase inhibitors (trifluridine/tipiracil), topoisomerase inhibitors (irinotecan) and VEGF inhibitors (aflibercept, bevacizumab). Anticancer drug exposure was modelled as a time-dependent variable. Demographic parameters (age, sex), prior history of cancer (but not the presence of additional non-colorectal synchronous primaries), CCI and other mCRC treatments (surgery and radiotherapy recorded as dichotomous variables) were collected from the registry. The CCI is a numerical score based on the patient's age and comorbidities. The CCI has been shown to be a predictor of long-term mortality in colorectal cancer patients.[13,14] To assess the impact of comorbidities independently of patient age, we calculated a modified CCI by subtracting the age subscore (mCCI). An mCCI of 0 indicated the absence of comorbidities. Prior CVRH was defined as a dichotomous variable from the PMSI data when the patient had a hospital admission with a primary diagnosis related to a cardiovascular disease ("I" type International Classification of Diseases, 10th revision codes) prior to the mCRC incidence date.

Outcome variables

CVRHs were defined using the PMSI data as any hospital admission with a primary diagnosis related to a cardiovascular disease ("I" type International Classification of Diseases, 10th revision code) occurring after the incidence date of the mCRC. Patients admitted several times for CVRH

were censored at the date of the first CVRH in the model. Nevertheless, all CVRH admissions were counted in the calculation of the standardized incidence. Subgroups of CVRH were based on the International Classification of Diseases, 10th revision classification of cardiovascular diseases (Web Appendix 1) to identify the pattern of cardiovascular diseases (e.g., heart failure, ischemic heart disease).

Outcomes

The primary outcome was the association between anticancer drugs exposure and CVRH in mCRC patients. Secondary outcomes were the incidence of CVRH, the influence of the cumulative dose of anticancer drugs on CVRH, the association between anticancer drugs exposure and disease-specific hospitalization (arrhythmia, ischemic heart disease, heart failure and venous thromboembolism) and the association between CVRH and mortality.

Study size

CVRH in mCRC patients was not directly assessed previously. A study based on healthcare databases showed that fluorouracile and capecitabine were associated with a reduced risk of claims for heart failure and cardiovascular diseases (Hazard ratios 0.43 to 0.98). The CVAE relative risk of bevacizumab ranged from 1.37 for arterial and venous events to 6.67 for cerebral ischemia in a randomized controlled trial meta-analysis.[15] The potential risk of the other mCRC anticancer drugs was not assessed in the real-life setting. Given the unprecedented nature of our study and the possibility of a low to moderate influence of anticancer drugs on CVRH, we chose to include the highest number of mCRC patients with available data on CVRH and anticancer

drug intakes. Thus, all mCRC patients in the registry were included during the inclusion period of our study.

Statistical analysis

The median and interquartile range were used to describe quantitative variables, except the mCCI, which was used as a non-transformed continuous variable and expressed in categories; frequencies and percentages were used for qualitative variables. Analyses were conducted with a competing risk approach: CVRH and fatality were both censoring events. CVRH incidence was standardized on type 1 International Cancer Survival Standards (ICSS1) for the comparison between cancer patient studies.[16] Disease-specific hospitalization standardized incidences were compared between mCRC patients and the French national standardized incidences for heart failure, ischemic heart disease, venous thromboembolism and cerebrovascular disease.[17] For this latter comparison, the 2010 European population was used for standardization.[17,18] A Cox hazard regression model and a Fine and Gray model were used to explore the etiologic and prognostic aspects of CVRH .[19,20] Exposure variables were included in the model without procedural statistical selection. Cause-specific hazard ratios (HRs) and sub-distribution HRs were computed with their 95% confidence interval (CI) and a Wald test was used to generate *P*-values for exposure variables with at least 10 events. The cumulative CVRH event curve according to exposure variables was computed using the Fine and Gray model. To prevent the immortal time bias, time-dependent variables were used for anticancer drug exposure, radiotherapy and surgery.[21] Thus, patients receiving an anticancer drug were appropriately not considered exposed to this drug in the time window period before their first drug intake. Because we expected that CVRH and death could occur shortly after anticancer drug intakes, there was no latency window

period in our study. The proportional hazard assumption was visually assessed with Schoenfeld residual plots and outliers were assessed by dfbeta plots. There was no attempt to impute missing data; a complete case analysis was performed. Statistical tests were two-sided. A *P*-value<0.05 was deemed significant. The statistical analysis was performed with R v3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) using the "survival" package.[22]

Models

For the primary outcome, CVRH and fatality were treated as competing risks, and anticancer drug exposures were considered dichotomous time-dependent covariates. In a secondary analysis, the risk of anticancer drug cumulative dose-induced CVRH was assessed using cumulative time-dependent covariates. CVRH and fatality were also competing risks for this second model. The cumulative time-dependent covariates were expressed in number of rounds and in absolute dose in milligrams (Drug doses were not adjusted on body surface area). A third, non-competitive, Cox model was used to assess the association of CVRH and mortality.

Ethics statement

The study protocol was approved by the local ethics committee.

RESULTS

Description of mCRC patients

Of 5,982 incident digestive cancers in Calvados County between 2008 and 2014; 3,028 were colorectal cancers. A total of 1,116 patients had at least one incident mCRC between 2008 and 2014, of whom 796 (71.3%) were synchronous and 320 (28.7%) metachronous. Figure 1 shows the flow chart of the patient selection. Baseline characteristics of mCRC patients are displayed in

Table 1 and Web Table 1. The main histological type was adenocarcinoma (1017, 91.1%) and the cancers were localized in the colon in 700 patients (62.7%), in the rectum in 330 patients (29.6%) and in the rectosigmoid junction in 86 patients (7.7%). The median age was 72 years (IQR 62-81), and 609 (54.7%) patients were males. The mCCI score was 0 (absence of comorbidity) in 562 (50.4%) patients. Anticancer drugs were delivered to 705 (63.2%) patients, for a total of 12,374 rounds of treatment (mean number of anticancer drugs per round: 2.0, mean number of rounds per patient: 17.5). Elder patients and women were significantly less likely to receive anticancer drugs. Details of anticancer drugs delivered to mCRC patients are shown in Web Table 2. The patients who were not treated with anticancer drugs received surgery (257, 62.5%), radiotherapy (47, 11.4%) or no cancer treatment (135, 32.9%). Missing data were limited to anticancer drug dosage (Web Table 2) and were observed in 47 patients (4.2%). Details on anticancer drugs are shown in Table 1 and Web Figure 1. The median follow-up time was 16 months, and the total follow-up was 2,212 person-years.

Primary outcome: anticancer drugs and CVRH risk

CVRH occurred in 145 patients (13.0%), and 43 patients had 2 or more CVRH (Table 2 and Web Figure 2). The most frequent primary diagnoses were ischemic heart disease (29.3%), venous thromboembolism (23.7%) and heart failure (14.0%) (Table 2 and Web Table 3). We observed 908 (81.3%) deaths of which 769 were competing events with CVRH and therefore were accounted in the primary analysis. Anticancer drugs were not associated with a higher incidence of CVRH. Multivariate HR for VEGF inhibitors aflibercept and bevacizumab were 2.48 (95%CI 0.57, 10.82) and 0.77 (0.42, 1.41) in the Cox model and 2.30 (0.53, 9.89) and 0.87 (0.48, 1.57) in the Fine and Gray model, respectively; for EGFR inhibitors cetuximab and

panitumumab were 0.78 (0.36, 1.7) and 1.11 (0.39, 3.12) in the Cox model and 0.62 (0.28, 1.38) and 0.89 (0.32, 2.49) in the Fine and Gray model, respectively; for antimetabolites capecitabine and fluorouracile were 0.58 (0.18, 1.83) and 0.68 (0.37, 1.26) in the Cox model and 0.70 (0.22, 2.20) and 0.81 (0.44, 1.50) in the Fine and Gray model, respectively (Table 3 and 4, Web Figure 2). In the Cox model, men, elderly patients, the mCCI and patients with a prior history of CVRH were significantly associated with a higher incidence of CVRH in bivariate analysis and the associations remained significant after adjustment on age, sex, prior history of CVRH, mCCI and anticancer drugs. In the Fine and Gray model, males, patients with a prior history of CVRH and higher mCCI were associated with a higher cumulated incidence of CVRH in bivariate and multivariate analyses. Elder patients were associated with a higher cumulative risk of CVRH in multivariate analysis.

Incidence of CVRH

The crude CVRH incidence was 85.9 per 1,000 person-years. The International Cancer Survival Standards standardized CVRH incidence was 84.0 per 1,000 person-years (95%CI: 72.6, 95.5). After standardization to the European population, the CVRH incidence in mCRC patients was 36.3 per 1,000 person-years, and the incidence of ischemic heart disease hospitalizations was 9.7 per 1,000 person-years (95%CI: 7.1, 12.2). The incidence of heart failure hospitalizations was 4.3 per 1,000 person-years (95%CI: 2.7, 5.8), the incidence of venous thromboembolism hospitalizations was 8.1 per 1,000 person-years (95%CI: 5.8, 10.4), and the incidence of cerebrovascular disease hospitalizations was 3.4 per 1,000 person-years (95%CI: 1.3, 5.5).

Association between the cumulative dose of anticancer drugs and CVRH

To investigate a potential effect of the cumulative dose of anticancer drugs, we analyzed anticancer drug exposure as cumulative time-dependent covariates (Web Table 4). Higher cumulative doses of aflibercept were associated with a higher incidence of CVRH.

Specific CVRH risk of anticancer drugs

Disease-specific hospitalization analyses are shown in Web Table 5. There was an increased incidence of venous thromboembolism hospitalization for aflibercept, irinotecan and panitumumab (EGFR inhibitor). Higher doses of aflibercept and bevacizumab yielded a higher incidence of venous thromboembolism hospitalization. A higher cumulative dose of aflibercept was associated with a higher incidence of ischemic heart disease. Heart failure hospitalization was less likely to occur in chemotherapy-treated patients. Anticancer drugs did not alter the incidence of arrhythmia hospitalization.

Association of CVRH and mortality

A non-competitive Cox model was used to evaluate the association between CVRH and mortality. CVRH was associated with a higher mortality in the bivariate (HR 1.64, 95%CI 1.34, 2.01) and multivariate analyses (HR 1.58, 95%CI 1.28, 1.95) adjusted for age, sex, cancer treatments and mCCI (Table 5). A prior history of CVRH was associated with a higher mortality in the bivariate analysis but not in the multivariate analysis.

DISCUSSION

In this registry-based cohort study of mCRC patients, anticancer drugs were not associated with an increased CVRH incidence. CVRH were more likely to occur in men, elderly patients,

patients with a prior history of CVRH and patients with higher mCCI scores. In secondary analyses, higher cumulative doses of aflibercept were also associated with more CVRH. Finally, CVRH was significantly associated with a worsened prognosis of mCRC patients.

To the best of our knowledge, this is the first study to specifically investigate the factors influencing CVRH in mCRC patients in a real-life setting. Although cardiotoxicity is well established for some mCRC anticancer drugs, they were not associated with an increased CVRH incidence in our study. Several hypotheses can be formulated to explain this finding. First, patients receiving intravenous anticancer drugs are usually hospitalized and cardiotoxicity usually occur during anticancer drug infusion. Thus, in the absence of a particular severity, CVAEs occurring during the hospital stay might be managed without the need for dedicated hospitalization and therefore may not appear as primary diagnosis. For example, fluorouracil-related CVAEs mainly occur shortly after or during the perfusion.[5] Second, chemotherapy protocols are divided into several rounds separated by only a few weeks. A patient experiencing a non-threatening CVAE between the rounds might wait the following scheduled hospitalization to inform the medical team and receive the appropriate care.[23] Third, a significant proportion of CVAEs may be of low to moderate severity and have minimal impact on the patient quality of life and can be manage without any hospitalization. In cohort studies with high cardiotoxicity rates (approximately 30%), the cardiotoxicity definition could include asymptomatic electrocardiogram abnormalities or troponin increases, most CVAEs were judged of low to moderate severity.[23,24] For clinical practice, it is important to note that the absence of hospitalization might limit the impact of CVAEs on the patient's quality of life.

Our study showed that patients with cardiovascular risk factors such as age, male sex, or a prior history of cardiovascular disease were more likely to experience CVRH. This finding is

consistent with previous studies in cancer survivors where cardiovascular risk factors and comorbidities were associated with higher rates of cardiovascular events in cancer patients (6- to 19-fold increased risk of cardiovascular diseases in patients with hypertension).[6,25] Surgery might reflect a subset of patients at lower risk of mortality, as it was associated with a lower all-cause mortality. The CVRH incidence was very high in our study, with 13% of the mCRC patients being hospitalized at least once for a cardiovascular disease and 3.8% experiencing more than one CVRH. This is a new finding, as published literature did not focus on CVRH.[23,24,26,27] The mCRC patients had a 2.7-fold higher ischemic heart disease incidence compared to the general French population (9.7 versus 3.5 per 1,000 person-years, respectively), a 1.8-fold higher heart failure incidence (2.4 versus 4.3 per 1,000 person-years and a 4-fold higher venous thromboembolism incidence (8.1 versus 2.0 per 1,000 person-years). Furthermore, CVRH was associated with a worsened prognosis in mCRC patients. This emphasizes the need for close cardiovascular monitoring in these patients, in whom cardiovascular therapeutics are too often restricted when thinking that their cancer will prevail in their prognosis. Although the increased incidence of venous thromboembolism is a well-known cardiovascular issue in mCRC patients, the higher incidence of ischemic heart disease and heart failure merits attention from physicians in clinical practice. A close collaboration between cardiologists and oncologists is needed for the optimal management of cardiovascular risk factors and diseases in mCRC patients.[6]

Study limitations

Our study has some limitations that must be acknowledged. First, the retrospective design cannot prove the causality between anticancer drug delivery and CVRH. CVRH were sought in the

county hospitals but not outside the county borders. County-border-living patients may have been referred to another hospital and would have been lost to follow-up for CVRH but not for death. However, the geographical repartition of both anticancer drug delivery and CVRH was focused on the capital city of Caen (Web Figures 1), which happens to be centrally located in the county, thus making data leaking at the county border marginal.

We did not access cardiovascular risk factors (except age and sex), comorbidities or cardiovascular treatments of the included patients and prior CVRH as a surrogate to cardiovascular risk for patients diagnosed with colorectal cancer in 2008 were assessed in a remote period shorter than 1 year. Furthermore, physicians might have had established risk stratification strategies and pretreatment screenings in place for routine care during the study period, which could exclude patients at highest cardiovascular risk from potentially cardiotoxic treatment. CVRH as a composite outcome can lead to bias since the severity of cardiovascular diseases leading to hospitalization may be heterogeneous and more severe outcomes can cause worse effects. Our study was likely underpowered to estimate non-composite outcomes in the secondary analyses. Schoenfeld residuals for sex in multivariate analyses might not have met the assumptions of the model, thus caution is required to interpret its HR. Cardiovascular diseases that occur during a hospital stay are not recorded as the primary diagnosis unless the patient is transferred to another care unit during the stay. Therefore, it is likely that we underestimated the true CVRH incidence. However, we chose to not take into account hospital admission-associated or related diagnoses since we expected substantial heterogeneity for the recording of these diagnoses. Oral anticancer drugs are mostly not delivered by the hospital pharmacy department, and our study was underpowered to assess their effect.

In a real-life registry-based cohort study, anticancer drugs were not associated with a higher incidence of CVRH in mCRC patients. Cardiovascular risk factors and a prior history of CVRH increased the incidence of CVRH. CVRH was significantly associated with a higher all-cause mortality in mCRC patients.

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Members of a study group

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Disclaimer

Not applicable

Disclaimer

Not applicable

DATA SHARING AND ACCESSIBILITY

The datasets generated and/or analyzed during the current study are not publicly available due to the risk of individual privacy violation but are available from the corresponding author on reasonable request.

PATIENT CONSENT

According to the approval of the French Data Protection Authority (*Commission Nationale Informatique et Liberté*) under the decision number DR-2018-291 issued on November 9th, 2018, adequate medias including posters in hospital care departments and website delivered information on the study protocol throughout the Calvados county. Individual consent was not sought as most of the accrued patients died before the conception of this study.

ETHICAL APPROVAL

The study protocol was approved by the local ethics committee and by the French Data Protection Authority (*Commission Nationale Informatique et Liberté*) under the decision number DR-2018-291 issued on November 9th, 2018.

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TABLES

Table 1. Baseline Characteristics of Incident Metastatic Colorectal Cancer Patients in the French County Calvados Between 2008 and 2014.

Characteristic	No. (total number of patients: 1,116)	%
Age, years[a]	72 (62-81)	
Follow-up, months[a]	16 (6-39)	
Sex, female	507	45.4
Prior CVRH	119	10.7
Modified Charlson comorbidity index[b]		
0	562	54.0
1	257	24.6
2	135	12.9
3 or more	89	8.5
Cancer treatment		
Surgery	794	71.1
Radiotherapy	200	17.9
Chemotherapy	705	63.2
Alkylating agents		
Mitomycin C	7	0.6
Oxaliplatin	593	53.1
Antimetabolites		
Capecitabine	42	3.8
Fluorouracil	614	55
Raltitrexed	2	0.2
EGFR inhibitors		
Cetuximab	124	11.1
Panitumumab	71	6.4

RAF inhibitors		
Regorafenib	6	0.5
Thymidine phosphorylase inhibitors		
Trifluridine/Tipiracil	0	0
Topoisomerase inhibitors		
Irinotecan	417	37.4
VEGF inhibitors		
Aflibercept	21	1.9
Bevacizumab	336	30.1

Abbreviations**:** CVRH: cardiovascular-related hospitalization, EGFR: endothelial growth factor receptor, RAF: rapidly accelerated fibrosarcoma, VEGF: vascular endothelial growth factor.

[a]Values are expressed as median (interquartile range).

[b]Available in 1043

Table 2. Cardiovascular-Related Hospitalizations in Incident Metastatic Colorectal Cancer Patients in the French County Calvados Between 2008 and 2014 and Followed up to 2016.

Hospitalization features	**No. (total number of hospitalizations: 208)**	**%**
Patients	**145**	
Length of stay, days[a]	4 (2-8)	
Patients with a single admission	102	
Patients with more than one admission	43	
Cardiovascular diseases during admission	**215**	
Arrhythmias	26	12.1
Cardiac arrest	2	0.9
Cerebrovascular diseases	14	6.5
Chronic rheumatic heart diseases	1	0.5
Conductive disorders	4	1.9
Heart failure	30	14
Hypertensive diseases	2	0.9
Ischemic heart diseases	63	29.3
Other and unspecified disorders of the circulatory system	6	2.8
Pericardial diseases	3	1.4
Peripheral arterial diseases	12	5.6
Venous thromboembolism	51	23.7

Abbreviations: HC: hospital center.

[a]Values are expressed as median (interquartile range).

Table 3. Cox Regression Model analyses for Cardiovascular-Related Hospitalization in Incident Metastatic Colorectal Cancer Patients in the French County Calvados Between 2008 and 2014 and Followed up to 2016.[a]

Characteristics		**Bivariate models**			**Multivariate model[b]**		
Exposure variable	**n**	**cs-HR**	**95% CI**	**P-value**	**cs-HR**	**95% CI**	**P-value**
Sex, female	507	0.67	0.47, 0.94	0.02	0.65	0.46, 0.93	0.019
Age (+10 years)		1.36	1.18, 1.57	<0.001	1.36	1.16, 1.61	<0.001
Prior CVRH	119	2.69	1.78, 4.07	<0.001	1.87	1.2, 2.91	0.0054
mCCI (+1 point)[c]		1.24	1.12, 1.37	<0.001	1.19	1.06, 1.34	0.0024
Prior history of cancer	133	1.13	0.68, 1.88	0.63	0.72	0.42, 1.23	0.23
Surgery	794	0.68	0.46, 1.01	0.057			
Radiotherapy	200	1.00	0.65, 1.55	1.00			
Chemotherapy (any)	705	0.81	0.56, 1.17	0.26			
Alkylating agents							
Oxaliplatin	593	0.83	0.58, 1.20	0.33	1.32	0.75, 2.33	0.34
Antimetabolites							
Capecitabine	42	0.50	0.16, 1.58	0.24	0.57	0.18, 1.83	0.35
Fluorouracil	614	0.75	0.52, 1.07	0.12	0.68	0.37, 1.26	0.22
EGFR inhibitors							
Cetuximab	124	0.84	0.41, 1.74	0.64	0.78	0.36, 1.70	0.54
Panitumumab	71	1.02	0.38, 2.78	0.96	1.12	0.4, 3.14	0.83
Topoisomerase inhibitors							
Irinotecan	417	1.07	0.71, 1.60	0.75	1.84	0.98, 3.45	0.058
VEGF inhibitors							
Aflibercept	21	2.48	0.59, 10.37	0.21	2.47	0.57, 10.80	0.23
Bevacizumab	336	0.90	0.58, 1.41	0.65	0.77	0.42, 1.41	0.4

Abbreviations: CI: confidence interval, CVRH: cardiovascular related-hospitalization, cs-HR: cause-specific hazard ratio, EGFR: endothelial growth factor receptor, mCCI: modified Charlson comorbidity index, VEGF: vascular endothelial growth factor.

[a]Statistical tests were two-sided.

[b]Adjustment variables: sex, age, prior CVRH, mCCI, aflibercept, bevacizumab, capecitabine, cetuximab, fluorouracil, irinotecan, oxaliplatin, panitumumab.

[c]Range, 0-9

Table 4. Fine and Gray Model (Competing Risk Model) Analyses for Cardiovascular-Related Hospitalization in Incident Metastatic Colorectal Cancer Patients in the French County Calvados Between 2008 and 2014 and Followed up to 2016.[a]

		Bivariate models			Multivariate models[b]		
Exposure variable	**n**	**sd-HR**	**95% CI**	***P*-value**	**sd-HR**	**95% CI**	***P*-value**
Sex, female	507	0.62	0.44, 0.88	0.007	0.64	0.44, 0.91	0.013
Age (+10 years)		1.11	0.97, 1.26	0.13	1.19	1.01, 1.39	0.038
Prior CVRH	119	2.15	1.42, 3.25	<0.001	1.66	1.06, 2.60	0.026
mCCI (+1 point)[c]		1.18	1.06, 1.3	0.0015	1.14	1.02, 1.27	0.025
Prior history of cancer	133	0.97	0.59, 1.61	0.91	0.74	0.43, 1.27	0.27
Surgery	794	1.31	0.91, 1.88	0.14			
Radiotherapy	200	1.36	0.88, 2.10	0.16			
Chemotherapy (any)	705	1.30	0.91, 1.86	0.15			
Alkylating agents							
Oxaliplatin	593	1.32	0.92, 1.88	0.13	1.66	0.95, 2.89	0.075
Antimetabolites							
Capecitabine	42	0.73	0.23, 2.30	0.59	0.77	0.24, 2.43	0.65
Fluorouracil	614	1.16	0.81, 1.65	0.42	0.82	0.45, 1.50	0.51
EGFR inhibitors							
Cetuximab	124	0.92	0.45, 1.90	0.83	0.65	0.3, 1.42	0.28
Panitumumab	71	0.95	0.35, 2.57	0.91	0.80	0.29, 2.24	0.68
Topoisomerase inhibitors							
Irinotecan	417	1.27	0.85, 1.91	0.24	1.80	0.97, 3.36	0.063
VEGF inhibitors							
Aflibercept	21	2.96	0.72, 12.18	0.13	2.38	0.55, 10.24	0.24
Bevacizumab	336	1.16	0.74, 1.81	0.51	0.86	0.48, 1.57	0.63

Abbreviations: CI: confidence interval, CVRH: Cardiovascular-Related Hospitalization, EGFR: endothelial growth factor receptor, mCCI: modified Charlson comorbidity index, sd-HR: sub-distribution hazard ratio, VEGF: vascular endothelial growth factor.

[a]Statistical tests were two-sided.

[b]Adjustment variables: sex, age, prior CVRH, mCCI, aflibercept, bevacizumab, capecitabine, cetuximab, fluorouracil, irinotecan, oxaliplatin, panitumumab.

[c]Range, 0-9

Table 5. Cox Model to Evaluate the Factors Associated With Mortality in Incident Metastatic Colorectal Cancer Patients in the French County Calvados Between 2008 and 2014 and Followed up to 2016 (no Competing Risk).[a]

	Bivariate models			Multivariate model[b]		
Exposure variable	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Sex, female	1.11	0.97, 1.26	0.12	1.08	0.94, 1.24	0.27
Age (+10 years)	1.42	1.34, 1.51	<0.001	1.45	1.36, 1.55	<0.001
Prior CVRH	1.32	1.07, 1.62	0.0081	1.03	0.82, 1.28	0.83
mCCI (+1 point)[c]	1.09	1.04, 1.15	<0.001	1.03	0.97, 1.08	0.36
CVRH	1.64	1.34, 2.01	<0.001	1.58	1.28, 1.95	<0.001
Surgery	0.43	0.37, 0.50	<0.001	0.42	0.36, 0.50	<0.001
Radiotherapy	0.82	0.68, 0.97	0.023	0.84	0.70, 1.01	0.059
Chemotherapy (any)	0.83	0.72, 0.96	0.011	1.19	1.01, 1.40	0.041

Abbreviations: CI: confidence interval, CVRH: cardiovascular-related hospitalization, mCCI: modified Charlson comorbidity index, HR: hazard ratio.

[a]Statistical tests were two-sided.

[b]Adjustment variables: sex, age, mCCI, prior CVRH, surgery, radiotherapy, chemotherapy.

[c]Range, 0-9

FIGURE LEGENDS

Figure 1. Flow chart of the study population in the French county Calvados between 2008 and 2014.

Abbreviations: mCRC: metastatic colorectal cancer.