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SHORT REPORT

Deprived social status is associated with decreased use of oral chemotherapy in patients with metastatic colorectal cancer: A retrospective cohort study on administrative databases in a French University Hospital

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Abstract

Factors associated with the choice of oral versus intravenous CT are not clearly established. Our purpose was to evaluate the influence of social status and home distance to hospital on the use of oral CT in patients with metastatic colorectal cancer (mCRC). This retrospective single-center study included mCRC patients between 2011 and 2017. Patient social status was assessed by European Deprivation Index (EDI) and home distance to the hospital was calculated. Univariable and multivariable logistic regression analyses were performed. One hundred and seventy-five mCRC patients were included, with 71 receiving oral CT. Most deprived patients received less oral CT (OR 0.5 [0.26, 0.96], $p = .039$). No association was found for road distance. Previous use of adjuvant oral CT was associated with oral CT in mCRC (OR 2.65 [1.06, 6.66], $p = .038$). Our results suggest that deprived social status is a factor associated with decreased use of oral CT in patients with mCRC.

Clinical trial registration: no registration.

KEYWORDS
colorectal cancer, deprivation, oral chemotherapy, patient care

1 | INTRODUCTION

Over the past decade, cancer treatments with oral chemotherapy (CT) have been developed and are widely used in most developed countries including France.[1] In metastatic colorectal cancer (mCRC), available oral CT drugs include Capecitabine, Regorafenib, and most recently Trifluridine/Tipiracil.[2–6] It has been widely used in the first or second line of treatment, alone or in combination with other CT molecules, and/or targeted therapies. A preference of patients for the oral route has been reported, attributed to ease of use, decreased need for hospitalization, and reduced impact on professional activity.[7–9] In addition, studies have suggested

Abbreviations: CCI, Charlson comorbidity index; CRC, colorectal cancer; CT, chemotherapy; EDI, European Deprivation Index; mCRC, metastatic colorectal cancer; mCRC, metastatic colorectal cancer.

that oral CT could be associated with a decrease in treatment costs.[10–12]

However, oral CT has also been shown to be associated with several side effects such as diarrhea or hand-foot syndrome (for Capecitabine).[13] Adherence to planned treatment is required to limit side effects. Nonadherence is more frequent in patients of older age, lower level of education, or lower income and may increase with the distance between home and cancer care facilities.[14] Patient education may be proposed to improve adherence to treatment[15,16] but is not available in all areas.[17,18] In cases where both oral and intravenous treatment are feasible, 71% of practitioners reported a preference for oral CT in a palliative situation.[19] To date, factors associated with the oncologist's choice of oral versus intravenous route are not clearly established in mCRC.

In this context, our objective was to assess the influence of patient deprivation and distance to cancer care centers on the use of oral CT in patients with mCRC. For this purpose, we used administrative databases of our hospital to perform a retrospective survey comparing patients receiving oral CT and patients receiving IV CT for mMRC to assess if social status and distance from patient home to hospital were independent risk factors of receiving oral CT instead of IV CT.

2 | MATERIALS AND METHODS

Patients treated by intravenous or oral CT for a nonresectable mCRC between January 1, 2011 and December 31, 2017 at Rouen University Hospital were eligible for the study. In France, a multidisciplinary consultation meeting is mandatory before the decision on cancer treatment. For mCRC, this includes a review of staging (including the judgment on the nonresectable nature of metastasis) by an oncologist, a digestive surgeon, and a radiologist. Diagnosis coding of hospitalizations relies on the result of multidisciplinary consultation meeting assessment. We selected all patients with at least one hospitalization during the study period with an ICD-10 diagnosis code of colorectal cancer (C18, C19, C20, or C21) and an ICD-10 diagnosis code of metastasis (C78 or C79).

To ensure that all patients with metastatic colon cancer were identified, we also manually reviewed medical records with an ICD-10 diagnosis code of colorectal cancer without metastasis or hospitalization with an ICD-10 diagnosis code of metastasis without primary location. Electronic medical records were reviewed, and only cases with a theoretical indication for oral or intravenous 5FU (alone or in combination) according to French Guidelines were included in the analysis.

We collected sex, age at metastasis diagnosis, marital status (single or couple), having children, professional activity in four categories (still in work/on sick leave, unemployment, retirement, or adult disability living allowance), home address, year of metastasis diagnosis, stage at diagnosis (adjuvant or metastatic), tumor location (colon or rectum), previous history of oral CT in adjuvant stage, and Charlson comorbidity index (CCI). Data concerning follow-up and treatment sequence were also collected. In addition, we recorded the number of years of practice of the attending physician.

Home address was allocated by the MapInMed platform to IRIS (Ilots Regroupés pour l'Information Statistique), which is a geographical unit defined by INSEE, the French national statistics agency.[20] An IRIS represents the smallest geographical census unit available in France. Each IRIS includes approximately 2000 individuals with homogenous social characteristics.[20] For each IRIS, an aggregate deprivation score, the European Deprivation Index (EDI), is available.[21] EDI is an ecologic score available for each European country. It is a weighted combination of census-aggregated variables at the IRIS level highly correlated with individual deprivation scores. In France, EDI includes the following components: rates of overcrowded housing, no access to a system of central or electric heating, household nonowners, unemployment, persons of foreign nationality, no access to a car, unskilled worker–farm worker, household with ≥persons, low level of education, and of single-parent household.[21] Home address was also used by the MapInMed platform to calculate the road distance between patient's home and the hospital.

2.1 | Statistical analysis

2.1.1 | Main outcome

We performed a multilevel logistic regression. The dependent variable was the use of oral CT. First, in the model with no explanatory variable, we used the test of random intercept to check the inter-IRIS heterogeneity. The nonsignificant test ($p = .43$) allowed us to use "simple" regression. After checking multicollinearity issues, we used a multivariate logistic regression, including all variables with a p value of ≤.20 in univariate analyses.

EDI score was separated into national quintiles (Q1 represents the most affluent patients and Q5 the most deprived). The first three quintiles were grouped together and compared with the last two as proposed in previous studies.[22] The road distance between a patient's home and the university hospital was transformed into quartile of distribution: <8 km, [8–33], [33–54], ≥54 km. Attending physicians were divided into two groups according to the number of years of practice (<10 or ≥10). Years of metastasis diagnosis were divided into four groups according to the date of publication guidelines: 2008/2009/2010, 2011/2012/2013, 2014/2015, and 2016/2017.

For the purpose of the study, CCI includes 19 medical conditions weighted from 1 to 6 according to the risk of death, creating a total score from 0 to 37. No points were awarded for metastatic cancer. CCI was divided into two classes: 0, 1 and more.

TABLE 1 Characteristics of patients

	Nonresectable metastatic colorectal cancer treated by IV chemotherapy *N* = 104 patients *n* (%)	Nonresectable metastatic colorectal cancer treated by oral chemotherapy *N* = 71 patients *n* (%)
EDI (European Deprivation Index) quintiles		
1, 2, 3	40 (38.5)	39 (54.9)
4, 5	64 (61.5)	32 (45.1)
Distance to hospital (km)		
<8	31 (29.8)	15 (21.1)
[8–33]	23 (22.1)	20 (28.2)
[33–54]	25 (24)	17 (23.9)
>54	25 (24)	19 (26.8)
Sex		
Male	59 (56.7)	38 (53.6)
Female	45 (43.3)	33 (46.4)
Age at metastasis diagnosis (years)		
<60	25 (24)	25 (35.2)
60–70	38 (36.5)	19 (26.8)
70–80	27 (26)	18 (25.3)
>80	14 (13.5)	9 (12.7)
Marital status (missing data *n* = 3)		
Married	68 (65.3)	52 (73.2)
Single	33 (31.7)	19 (26.8)
Having children (missing data *n* = 47)		
No	67 (64.4)	47 (66.2)
Yes	11 (10.6)	8 (11.3)
Professional activity (missing data *n* = 2)		
Retirement	78 (75)	49 (69)
Still in work/on sick leave/ unemployment	25 (24)	21 (29.6)
Charlson's comorbidity index		
0	64 (61.5)	32 (45)
≥1	40 (38.5)	39 (55)
Year of metastasis diagnosis		
2008/2009/2010	20 (19.2)	16 (22.5)
2011/2012/2013	45 (43.3)	37 (52.1)
2014/2015	30 (28.9)	11 (15.5)
2016/2017	9 (8.7)	7 (9.9)
Stage at diagnosis		
Metastatic	59 (56.8)	47 (66.2)
Nonmetastatic	45 (43.3)	24 (33.8)
Previous history of oral chemotherapy		
No	91 (87.5)	48 (67.6)
Yes	13 (12.5)	23 (32.4)
Tumor location		
Colic	75 (72.1)	44 (62)
Rectal	29 (27.9)	27 (38)
Numbers of years of practice of attending physician (years)		
<10	61 (58.7)	30 (42.3)
≥10	43 (41.3)	41 (57.7)
CT Chemotherapy		

(Continues)

2.1.2 | Missing data

Three variables have missing values (marital status, having children, and professional activity). For "having children," missing values were considered as "missing at random" (i.e., dependent on other factors of the model). Consequently, missing data were imputed by using a multiple imputation model by chained equations, including all covariates except the outcome variable. Conclusions were similar to those of complete case analysis. The two other variables were considered as "missing completely at random" (i.e., the probability of missing data is the same for all observations) and treated by complete case analysis.

R software (3.5.1 version, R Foundation for Statistical Computing) was used to perform analysis.

3 | RESULTS

Between 2011 and 2017, 388 patients with nonresectable mCRC were hospitalized in our French University Hospital. There were 283 patients treated by CT, including 175 (62%) with a possible indication for either IV or oral CT. Among them, 71 (41%) patients received oral CT. More than half (55%) of the patients were from EDI quintiles 4 or 5 (Table 1).

In univariate analysis (Table 2), the odds of receiving oral CT were lower for patients with an EDI quintile of 4 or 5 (OR 0.51 [0.3, 0.9]) compared to patients with an EDI quintile of 1, 2, or 3. The use of oral CT was more frequent in patients with a previous history of oral CT (OR 3.35 [1.6, 7.2], $p = .002$), in patients with CCI ≥1 (OR 1.9 [1.1, 3.6], $p = .032$), and in patients who had an attending physician with more than 10 years of practice (OR 1.9 [1.05, 3.6], $p = .034$). No association was found between the use of oral CT and the distance from patient's home to hospital, therefore, the factor "distance to hospital" was not included in multivariate analysis. No association was found between patient characteristics and deprivation or between patient characteristics and the road distance between patient's home and hospital.

In the final multivariate analysis model (Table 3), two factors were significantly associated with the use of oral CT: an EDI quintile of 4 or 5 (OR 0.5 [0.26, 0.96], $p = .039$) and the previous history of

TABLE 2 Factors affecting prescription of oral chemotherapy in univariate logistic regression model

	OR [IC 95%]	*p*
EDI (European Deprivation Index)		
1, 2, 3	**Ref.**	**.032**
4, 5	**0.51 [0.3, 0.9]**	
Distance to hospital (km)		
<8	Ref.	.58
[8–33]	1.8 [0.8, 4.2]	
[33–54]	1.4 [0.4, 3.4]	
>54	1.6 [0.7, 3.7]	
Sex		
Male	Ref.	.67
Female	1.14 [0.6, 2.1]	
Age at metastasis diagnosis (years)		
<60	Ref.	.38
60–70	0.50 [0.2, 1.1]	
70–80	0.67 [0.3, 1.5]	
>80	0.64 [0.2, 1.8]	
Marital status (missing data $n = 3$)[b]		
Married	Ref.	.41
Single	0.75 [0.4, 1.5]	
Having children (missing data $n = 47$)[a]		
No	Ref.	.80[c]
Yes	0.85 [0.3, 2.9]	
Professional activities (missing data $n = 2$)[b]		
Retirement	Ref.	.40
Still in work/on sick leave/ Unemployment	1.34 [0.7, 2.6]	
Charlson's comorbidity index		
0	**Ref.**	**.032**
≥1	**1.9 [1.1, 3.6]**	
Year of metastasis diagnosis		
2008/2009/2010	Ref.	.22
2011/2012/2013	1.03 [0.5, 2.3]	
2014/2015	0.46 [0.2, 1.2]	
2016/2017	0.97 [0.3, 3.2]	
Stage at diagnosis		
Metastatic	**Ref.**	**.032**
Non-metastatic	**2.57 [1.4, 4.8]**	
Previous history of oral chemotherapy		
No	**Ref.**	**.002**
Yes	**3.35 [1.6, 7.2]**	
Tumor location		
Colic	Ref.	.16
Rectal	0.63 [0.3, 1.2]	
Number of years of practice of attending physician (years)		
<10	**Ref.**	**.034**
≥10	**1.9 [1.05, 3.6]**	

Abbreviation: aOR, adjusted odds ratio.

p values < .05 are in bold characters.

[a]Multiple imputation technique.

[b]Complete case analysis.

[c]Result of complete case analysis (OR 0.94 [0.4, 2.5] 0.9).

TABLE 3 Factors affecting prescription of oral chemotherapy in multivariate logistic regression

	OR [1.95]	*p*
EDI (European Deprivation Index)		
1, 2, 3	**Ref.**	**.039**
4, 5	**0.5 [0.26, 0.96]**	
Charlson's comorbidity index		
0	Ref.	.05
≥1	1.92 [1, 3.69]	
Numbers of years of practice of attending physician (years)		
<10	Ref.	.109
≥10	1.72 [0.9, 3.3]	
Stage at diagnosis		
Metastatic	Ref.	.152
Nonmetastatic	1.71 [0.8, 3.6]	
Previous history of oral chemotherapy		
No	**Ref.**	**.038**
Yes	**2.65 [1.06, 6.66]**	
Tumor location		
Colic	Ref.	.99
Rectal	1 [0.47, 2.11]	
CT: chemotherapy	1 (4.8)	

p values < .05 are in bold characters.

oral CT (OR 2.65 [1.06, 6.66], $p = .038$). Presence of comorbidities tended to be associated with oral CT (1.92 [1, 3.69], $p = .05$).

4 | CONCLUSION

The results of this study support the hypothesis that socioeconomic status may influence the decision to perform oral CT in patients with mCRC. Socioeconomic status is a complex notion that affects physician–patient relationships and perceptions. To our knowledge, no study has previously investigated the influence of social disparities on the use of oral CT. One explanation is that lower social status may be considered by oncologists as a major limitation for the prescription of oral CT because of the risk of noncompliance and toxicity management in this subgroup of cancer patients. This finding is in line with previous studies which showed that patients with low education levels need more time and support to understand medical information.[23] Moreover, it has also been pointed out that physicians spend less time with patients with lower education levels and deliver less information.[24,25]

From the physician's perspective, patients with low socioeconomic status are more often considered as of a low education level and, although this is not really established, noncompliant, less rational, and with a poor social network,[24,26] leading to limited use of oral medication in this population.[27,28] A previous qualitative survey in primary care showed that this perception may influence clinical

decisions.[26] However, in a French study performed in 2007,[27] physicians stated that they indeed selected patients suited for oral CT but did not report social status as a selection criterion.

In this context, our findings suggest that the most deprived patients are less prone to receive oral CT in mCRC than patients with similar cancer, age, and comorbidities but with a more favorable social status.

Several studies have suggested an association between distance to care centers and cancer management. Campbell et al., in Scotland, demonstrated that radiotherapy for colorectal cancer (CRC) was less likely when the distance to care center increased[29] but did not observe the same trend for CT. In contrast, Dejardin et al., in a study conducted in 2066 patients in two geographic areas found that patients with advanced CRC living far from a care center were less likely to receive CT.[30] In our study, distance to care center was not associated with receiving oral CT or not. A study including a larger geographic area as well as several other cancer centers could be of interest to better evaluate the impact of home–hospital distance on being treated with oral CT.

In our work, the previous history of oral CT use was also independently associated with oral CT treatment in the metastatic setting. We hypothesize that use of oral CT was easier, for both physicians and patients, when the drug had already been used previously. Regnier Denois et al., in a French qualitative survey of 42 patients and 10 oncologists, also showed that a patient's previous experience was one of the main criteria to decide or not a novel oral CT exposure.[27] Last, Twelves et al. showed in patients with mCRC that the knowledge of previous oral administration is also a predominant factor that reinforces the choice for this type of drug.[9]

In our survey, more experienced physicians were more likely to prescribe oral CT. Several studies have suggested an influence of physician clinical experience on clinical management.[31,32] Some physicians seem less inclined to oral CT use because it modifies their organization and their relationship with the patient.[27] More experienced physicians may have a better time organization and increased confidence in patient–physician relationship that could facilitate their decision for oral CT.

In contrast to Cavalli-Björkman et al., who showed that a patient's social support may influence an oncologist's treatment decision, we did not find an association between the patient's family structure (having a spouse, having children) and use of oral chemotherapy.[28,33] A large number of missing data in our study regarding this topic precludes any definite conclusion.

There were some limitations to our study. First, this was a retrospective single-center study with a relatively limited sample of patients. We believe that this point probably limited the analysis of several factors related to patients such as the distance between home and hospital, social environment/network, the complete description of treatment toxicities, as well as factors related to physicians such as their perception of patient characteristics.

Second, we chose to study colorectal cancer, cancer whose incidence is not influenced by socioeconomic status in France.[34] A different result could be observed for other cancers. Third, since we chose to include only patients with mCRC, for who neither oral nor intravenous was preferred by French guidelines, we were only able to include a limited number of patients.

Our study also presents some strengths. EDI is a pragmatic, widely used and reliable ecologic score to be used as a proxy for measuring individual socioeconomic status. Its validity as a very good approximation of individual social status has been demonstrated[21,34,35] and it has the advantage of being available for all inpatients since the patient's address is systematically collected in the medical records.

Second, we performed a thorough search through hospital databases in order to identify our target population. Therefore, we were able to generate a nonbiased exhaustive list of homogeneous patients.

In conclusion, deprivation may be a factor associated with the decreased use of oral CT in patients with mCRC. A multicenter study including several cancer locations will allow us to assess whether these results are consistent in other settings and for other cancer locations.

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DISCLOSURE

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTIONS

Gwendoline Gautier contributed to data collection, data analysis and interpretation, and manuscript drafting. Mélodie Lucas contributed to the study design, data interpretation, and manuscript reviewing. Thomas Vermeulin and Frederic Di Fiore contributed to the study design, data analysis, and manuscript reviewing. Véronique Merle contributed to the study design, data interpretation, and manuscript reviewing. All authors have seen and approved the final version of the article.

ETHICAL APPROVAL STATEMENT

The Rouen University Hospital institutional review board approved the present study protocol.

PATIENT CONSENT STATEMENT

According to French law, no patient consent statement was required for this survey.

DATA AVAILABILITY STATEMENT

Data are available on request.

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