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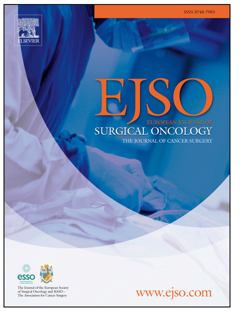

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PII: S0748-7983(18)31078-3

DOI: 10.1016/j.ejso.2018.05.024

Reference: YEJSO 4974

To appear in: *European Journal of Surgical Oncology*

Received Date: 18 February 2018

Revised Date: 2 May 2018

Accepted Date: 17 May 2018

Please cite this article as: Vallance AE, vanderMeulena J, Kuryba A, Braun M, Jayne DG, Hill J, Cameron IC, Walker K, Socioeconomic differences in selection for liver resection in metastatic colorectal cancer and the impact on survival, *European Journal of Surgical Oncology* (2018), doi: 10.1016/j.ejso.2018.05.024.

Socioeconomic differences in selection for liver resection in metastatic colorectal cancer and the impact on survival

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Submitted as original article

No funding was received for this manuscript

Abstract

Background Socioeconomic inequalities in colorectal cancer (CRC) survival are well recognised. The aim of this study was to describe the impact of socioeconomic deprivation on survival in patients with synchronous CRC liver-limited metastases, and to investigate if any survival inequalities are explained by differences in liver resection rates.

Methods Patients in the National Bowel Cancer Audit diagnosed with CRC between 2010 and 2016 in the English National Health Service were included. Linked Hospital Episode Statistics data were used to identify the presence of liver metastases and whether a liver resection had been performed. Multivariable random-effects logistic regression was used to estimate the odds ratio (OR) of liver resection by Index of Multiple Deprivation (IMD) quintile. Cox-proportional hazards model was used to compare 3-year survival.

Results 13,656 patients were included, of whom 2,213 (16.2%) underwent liver resection. Patients in the least deprived IMD quintile were more likely to undergo liver resection than those in the most deprived quintile (adjusted OR 1.42, 95% confidence interval (CI) 1.18-1.70). Patients in the least deprived quintile had better 3-year survival (least deprived vs. most deprived quintile, 22.3% vs. 17.4%; adjusted hazard ratio (HR) 1.20, 1.11-1.30). Adjusting for liver resection attenuated, but did not remove, this effect. There was no difference in survival between IMD quintile when restricted to patients who underwent liver resection (adjusted HR 0.97, 0.76-1.23).

Conclusions Deprived CRC patients with synchronous liver-limited metastases have worse survival than more affluent patients. Lower rates of liver resection in more deprived patients is a contributory factor.

Key words:

Colorectal cancer; liver metastases; socioeconomic deprivation

1. Introduction

Socioeconomic inequalities in survival have been reported for most adult cancers worldwide [1-3]. Even in the United Kingdom (UK) where there is a universal entitlement to healthcare within the National Health Service (NHS), the health inequalities between the most deprived and least deprived areas of the country are showing little sign of reducing [4]. The improved cancer survival that has occurred over the last two decades in the United Kingdom has been reflected more in patients living in affluent areas than for those living in deprived areas [5]. It is estimated that 11 per cent of deaths from common cancers would be avoided if survival for all patients was as high as in the most affluent group [5].

Colorectal cancer (CRC) is one of the most common malignancies in the Western world and the fourth most common cancer in the United Kingdom (UK) [6]. There are over 40,000 new cases of CRC diagnosed per annum and CRC is the second most common cause of cancer-related deaths in the UK. Poorer cancer-specific and overall survival in CRC patients in lower socioeconomic groups has been reported in United States [7], European [8, 9] and UK [9-11] populations. The origins of these disparities in survival are not fully understood. Although late stage at presentation is a commonly cited cause of the lower survival amongst more deprived patients [12], studies which correct for stage have reported that this difference remains [13]. Evidence now also points to both differential access to treatment and differential disease management within the healthcare system [14] . Access to specialist care is known to favour the affluent [15] and differences in rates of primary CRC resection [16-18] and receipt of chemotherapy [7, 19-21] according to socioeconomic status have been demonstrated.

Synchronous liver metastases are present in around 20 per cent of patients diagnosed with CRC [22]. Liver resection in suitable patients is the only curative treatment modality with 5-year survival rates from 44 to 74 per cent reported following resection [23-25]. Relatively little is known about the impact of socioeconomic status on liver resection rates, with studies reporting conflicting findings. A study of selection for liver resection in an English CRC population diagnosed from 1998-2004 demonstrated higher socioeconomic status to independently predict liver resection [24]. Similarly, Wiggans and co-authors. (2015), reported that affluent patients were over-represented amongst a regional English cohort of patients undergoing liver resection when compared to the demographics of the local population [26]. In contrast, a population-based study of patients with synchronous liver-limited metastases in Sweden did not find either income or education to be independently associated with liver resection [27]. No previous study has examined socioeconomic status as an independent predictor of mortality in this cohort. In this paper we describe the association between socioeconomic deprivation and the rate of liver resection and survival in patients with synchronous CRC liver metastases. We also investigate if any survival inequalities related to deprivation within this cohort are explained by differences in rates of liver resection.

2. Methods

2.1 Study population

Data from patients included in the National Bowel Cancer Audit (NBOCA) [28] were linked to Hospital Episode Statistics (HES) data. NBOCA data is prospectively collected and submission of patient data for those with a new diagnosis of CRC is mandatory for NHS trusts in England. In this study we included all patients recorded in the NBOCA dataset with a diagnosis of primary CRC from 1st January 2011 to 31st December 2015 with synchronous liver-limited metastases.

2.2 Study variables

Diagnostic information is captured in HES according to ICD-10 [29]. Synchronous liver metastases and extra-hepatic metastases were defined as an ICD-10 code for secondary cancer within the liver (C787) or secondary cancer elsewhere (C780-784, C786, C790-96) recorded up to one year before and 30-days after diagnosis of CRC. A year before CRC diagnosis was chosen to include patients who are found to have metastases before determining the site of the primary CRC.

Admission type (elective or emergency) was obtained from the linked HES records. The Royal College of Surgeons Charlson co-morbidity score [30] was used to identify co-morbid conditions in the HES records in the preceding year.

Socioeconomic status was calculated by the English Indices of Deprivation according to the patient's postcode [31]. This is the official measure of relative deprivation for neighbourhoods in England. The Index of Multiple Deprivation (IMD) ranks every small area in England from 1 (most deprived area) to 32,844 (least deprived area). Every such neighbourhood covers an average population of around 1500 people or 400 households. This measure is based on 37 indicators organised across 7 distinct domains of deprivation. These are combined to calculate the Index of Multiple Deprivation (IMD). The 7 domains of deprivation relate to 1) income, 2) employment, 3) education, 4) health and disability, 5) crime, 6) barriers to housing and services and 7) living environment. Quintiles are calculated by ranking the 32,844 small areas in England from most deprived to least deprived and dividing them into five equal groups.

Liver metastases were identified in HES data because the NBOCA records only the presence, but not the site, of metastatic disease. Of all patients with CRC identified in the NBOCA database as having metastatic disease at diagnosis, 60 per cent had a metastases code recorded in HES data. Despite the potential under-reporting of liver metastases in HES, odds ratios still represent a valid measure of the relationship between patient characteristics and the liver resection rate, in the same way that an odds ratio provides a valid measure of relative risk in case–control studies. This is valid as long as under-recording is not dependent on the risk factor under investigation (socioeconomic status). The use of patients with recorded liver metastases in HES as a representative sample of all patients with liver metastases has been previously validated by comparing the characteristics of patients with metastases, irrespective of their site, identified in the NBOCA database and corresponding patients in the HES database [32].

Procedure information is captured in HES according to OPCS-4 [33]. All HES records in the year following the date of CRC diagnosis were searched for codes indicating a liver resection: right hemihepatectomy (J021), left hemihepatectomy (J022), resection of segment of liver (J023), wedge excision of liver (J024), extended right hemihepatectomy (J026), extended left hemihepatectomy

(J027), partial excision of liver (J028/9), excision of lesion of liver (J031) and extirpation of lesion of liver (J038/9).

2.3 Study endpoints

The primary endpoints were receipt of liver resection within one year of date of CRC diagnosis and three-year all cause survival from date of CRC diagnosis. These two outcomes as well as demographic and tumour characteristics were compared between IMD quintiles to highlight any differences between groups of decreasing deprivation.

2.4 Statistical analysis

The statistical significance of differences in patient characteristics according to IMD quintile were assessed using the χ^2 test. Multivariable random-effects logistic regression was used to estimate the odds ratio of liver resection by IMD quintile, firstly adjusted for the following risk factors: gender, age, Charlson co-morbidity score, primary cancer site within the colon and rectum, admission type, T-stage and N-stage. A further model was fitted additionally adjusting for the presence of hepatobiliary surgical services on-site. A random intercept was modelled for each hospital trust to reflect the possible clustering of results within trusts. Missing values for the risk factors were imputed with multiple imputation using chained equations, creating ten data sets and using Rubin's rules to combine the estimated odd ratios across the data sets. Survival curves were estimated using the Kaplan–Meier method. Difference in 3-year survival in the first three years after diagnosis between IMD quintiles was tested with the log rank test. Comparisons were made adjusting for other risk factors using a multivariable Cox proportional hazards model with a shared frailty factor, again to reflect the possible clustering of results within hospitals. STATA® version 14.1 (StataCorp, College Station, Texas, USA) was used for all analyses.

3. Results

3.1 Study population

There were 18,899 patients out of the 130,554 patients diagnosed with primary CRC from 1st January 2011 to 31st December 2015 with synchronous liver metastases (14.5 per cent) identified from NBOCA linked HES data. Of these, 5,243 patients were excluded due to recorded extra-hepatic metastases, resulting in a final cohort of 13,656 CRC patients with synchronous liver-limited metastases. This group formed the study population and their demographic data, divided into quintiles of deprivation, are summarized in Table 1. Patients in the lower socioeconomic quintiles tended to be younger, have more comorbidities, have rectal cancer, and more commonly had an emergency presentation leading to CRC diagnosis

3.2 Liver resection

Overall 2,213 out of 13,656 patients with synchronous liver-limited CRC metastases had a liver resection (16.2 per cent). Liver resection was performed more frequently in patients in the least deprived IMD quintile when compared to those in the most deprived quintile (18.7 per cent vs. 13.3 per cent, $p<0.001$).

With adjustment for differences in patient and institutional characteristics, patients in the least deprived quintile remained more likely to undergo liver resection than patients in the most deprived quintile, with a trend of increasing chance of liver resection with decreased quintile of deprivation (least deprived vs. most deprived IMD quintile OR 1.42, 95 per cent confidence interval (C.I.) 1.18 to 1.70) (Table 2).

3.3 Survival

Median follow up was 45 months. There was a significant difference in all-patient survival, regardless of whether of liver resection was undertaken, according to IMD quintile. Three-year survival for patients in the most deprived quintile was 17.4 per cent compared to 22.3 per cent for patients in the least deprived quintile ($p<0.001$) (Table 3). There remained significant difference when risk adjusted for patient and institutional characteristics (least deprived vs. most deprived IMD quintile, hazard ratio (HR) 1.20, 95 per cent C.I. 1.11 to 1.30) (Table 4). Adding liver resection as a covariate in the multivariable model attenuated, but did not remove, this effect (least deprived vs. most deprived IMD quintile HR 1.15, 95% C.I. 1.06 to 1.24).

When survival analysis was restricted to patients undergoing a liver resection, there was no significant difference in unadjusted (Table 3) or adjusted (Table 4) survival according to IMD quintile. In patients not undergoing liver resection, patients in the least deprived group had better 3-year survival then those in the most deprived group (7.3 per cent vs. 9.3 per cent; P<0.001). This difference remained after adjusting for differences in patient characteristics.

4. Discussion

4.1 Principal findings

Reducing health inequities in England has been a longstanding priority of the government with more than £20 billion spent between 1997 and 2007 on a dedicated strategy to target this [34]. Moving forwards, the Cancer Research Taskforce for England which is working to develop a cancer survival improvement strategy on behalf of NHS England, has recommended that the tackling of socioeconomic variation is a top priority over the next five years [35]. The relationship between cancer and socioeconomic status has been studied extensively, and it has been found that social factors strongly influence treatment and survival [5, 7-11]. In this study we demonstrate socioeconomic deprivation to be associated with lower rates of liver resection and poorer 3-year survival amongst CRC patients with synchronous liver-limited metastases. This was irrespective of differences in demographic, tumour related and institutional factors. Socioeconomic deprivation was no longer associated with poorer outcomes when only patients undergoing liver resection were considered.

4.2 Interpretation of results and comparison with other studies

The findings in this study show that socioeconomic differences in survival in patients with CRC liver metastases can be explained in part by inequalities in treatment. These findings, which mirror those reported in non-metastatic CRC [36], ovarian cancer [37] and lung cancer [38] suggest equal treatment yields equal outcomes, regardless of deprivation. For patients who did not undergo liver resection, socioeconomic deprivation continued to be associated with poorer survival after controlling for differences in patient and tumour characteristics. For this palliative cohort survival outcomes may relate to use of chemotherapy [7, 19-21], or enrolment in clinical trials [39], both reportedly lower in more deprived patients. Data regarding these variables were not available and therefore not included in the multivariable model.

There are a number of obstacles to overcome for a patient with CRC liver metastases to undergo a liver resection. In patients undergoing the traditional bowel-first approach for resection of liver metastases, they must survive the resection of their primary tumour, they must recover sufficiently from this operation to potentially undergo further surgery, they must be referred to a hepatobiliary multidisciplinary team (MDT) for consideration of surgical resection and finally their metastases must be deemed operable. A patient’s socioeconomic status may influence how they negotiate this complex pathway. Within a publicly-funded health system it is an uncomfortable notion that socioeconomic status can influence treatment, and thus survival, for patients with CRC liver metastases. There are several mechanisms by way of which a patient’s socioeconomic status may influence rates of liver resection, including uptake of bowel cancer screening, stage of disease at presentation, presence of comorbidities, access to local services, clinical decision making and health-seeking behaviour.

Although clinical and pathological characteristics in CRC patients are associated with both socioeconomic status and likelihood of liver resection, controlling for such differences did not account for the differences in liver resection rates. The presence of comorbidity, more prevalent in patients in lower socioeconomic groups in this study cohort, can impact upon a patient’s fitness for liver resection. After adjusting for differences however in Charlson comorbidity score, the association between less deprivation and increased likelihood of liver resection remained. Patients with higher levels of deprivation are also more likely to suffer post-operative complications and mortality related to primary CRC resection that render them unfit for liver resection [11]. However, when patients who died within 90 days of major CRC resection were excluded in a sensitivity analysis, the difference in rates of liver resection remained. More advanced disease stage at diagnosis is often cited as a main cause of inequality in cancer related treatment and outcomes according to social status [40]. However this was not a factor in this study cohort, where there was no statistically significant difference in stage according to level of deprivation.

Differences in liver resection rates according to socioeconomic status in this cohort may also relate to access to specialist care. This is particularly pertinent when considering services, such as hepatobiliary surgery, that exist in a centralised system. Several studies have now demonstrated that the presence of specialist hepatobiliary services on-site at the hospital trust of treatment increases liver resection rates amongst patients with CRC liver metastases [27, 41]. Deprived patients were more commonly diagnosed at a hospital trust with no hepatobiliary services on site. Ability to travel for healthcare may be lower amongst more deprived patients and therefore the necessity to travel to access hepatobiliary services may preferentially disadvantage those of a lower socioeconomic status [42]. However controlling for the on-site presence of specialist services in the study cohort did not reduce the effect of deprivation on likelihood of liver resection. In addition, there was no evidence of a different effect of deprivation in hospital trusts with and without on-site specialist services (results not shown), suggesting this is not the explanation for the finding.

A patient's socioeconomic status may also modify the behaviour of the treating clinicians and cause inequalities in access to specialist care. There is an element of discretion by clinician practitioners in many stages of the patient pathway prior to surgery for CRC liver metastases. Although few surgeons would admit to altering their management of patients due to deprivation, clinicians may consider more deprived patients to have a lack of social support [43], or be less able to travel to specialist services [42] and therefore be less likely to refer these patients to a hepatobiliary MDT for consideration of liver resection. Finally, factors relating to a patient's health seeking behaviour may partly explain differences in rates of liver resection. Low health literacy is associated with both poorer health outcomes and use of health care services [44]. As a result, more deprived patients may be less likely to themselves seek referral to a hepatobiliary unit than more affluent patients [26].

4.3 Implications for policy

Inequalities in receipt of liver resection amongst patients with CRC liver metastases appear to account in part for differences in patient survival. Future focus should therefore be on ensuring that more deprived patients have access to liver resection. The National Institute of Health and Clinical Excellence recommends for the management of metastatic CRC that if the secondary tumour is considered 'resectable' the patient should be considered for surgery [45]. However, clinical guidelines for colorectal MDTs are often unclear about what should be considered 'resectable' disease, leaving referral practices to local policy and a clinician's own judgement. Inequalities in tertiary referral related to deprivation, are reportedly more likely to occur in the absence of explicit clinical guidance [46], suggesting that the development of clearer referral guidelines for colorectal MDTs would help to reduce these differences.

4.4 Strengths and Weaknesses

This study benefits from the use of a national clinical audit, with mandatory data submission. NBOCA reports a colorectal cancer case ascertainment of 93.0 per cent [28]. However, we recognise the limitations of this work. HES data does not contain information regarding the distribution or size of liver metastases, an important factor in determining the operability of liver metastases. We were therefore unable to ascertain whether differences in liver resection rates reflected clinically appropriate decision making or inequity. In addition, around 20 per cent of T-stage and N-stage data is missing from NBOCA data. Importantly, there was no difference in proportion of missing data according to IMD quintile. Missing values were imputed using multiple imputation to minimise the bias associated with excluding patients with missing values. As chemotherapy is usually administered on an outpatient basis, the HES dataset does not contain details regarding its provision. Adjuvant chemotherapy is less frequently used in more deprived patients and differences in its use may account in part for the reported variation in rates of liver resection and survival inequality in patients who did not undergo liver resection [7, 19-21]. A further limitation of HES is the under-reporting of liver metastases. Some 15 per cent of patients with CRC were found to have a HES code recorded for liver metastases at the time of diagnosis, whereas other population-based studies have reported corresponding percentages of up to 20 per cent. However, as explained in section 2.2, the odds ratio can be used as a valid measure of the impact of socioeconomic status on resection rates as socioeconomic status does not affect the recording of metastases in HES [32].

This study only includes patients undergoing liver resection in a NHS hospital. The inclusion of private patients, the majority of whom will be in the most affluent quintile, would likely make the liver resection rate, and therefore the survival differences between IMD quintiles, more pronounced. More details regarding the structure of hepatobiliary services in England may further explain the disparity observed. Liver resection rates amongst more deprived patients may be higher at sites which do not have hepatobiliary surgical services on-site but do conduct hepatobiliary outreach clinics, therefore reducing the travel burden for patients.

5. *Conclusions*

This study has demonstrated that more deprived CRC patients with synchronous liver metastases have worse survival than more affluent patients in England. Lower rates of liver resection in poorer CRC patients is likely to be a major contributory factor. As both the patient and tumour characteristics and institutional variables included in the multivariable model in this study did not account for the differences in liver resection rates according to socioeconomic status, this suggests that is it is differences in the availability of services or in decision making by socioeconomic status that account for the differences observed. Targeted efforts should be made by healthcare providers to ensure equitable access to specialist care for this cohort.

Table 1 Characteristics of patients according to IMD quintile for 13,656 patients diagnosed with colorectal cancer and synchronous liver-limited metastases colorectal cancer from 2010 to 2016

		IMD quintile					
		1 (most deprived) N=2,233 (%)	**2 N=2,628 (%)**	**3 N=2,886 (%)**	**4 N=3,009 (%)**	**5 (least deprived) N=2,890 (%)**	**P-value**
Sex	Male	1,398 (62.6)	1,561 (59.4)	1,764 (61.1)	1,810 (60.2)	1,711 (59.2)	0.089
	Female	835 (37.4)	1,067 (40.6)	1,222 (38.9)	1,199 (39.9)	1,179 (40.8)	
Age	<65	830 (37.2)	889 (33.8)	1,004 (34.8)	888 (29.5)	934 (32.3)	**<0.001**
	65-74	671 (30.1)	752 (28.6)	846 (29.3)	915 (30.4)	829 (28.7)	
	>74	732 (32.8)	987 (37.6)	1,036 (35.9)	1,206 (40.1)	1,127 (39.0)	
Site	Right	762 (34.1)	871 (33.1)	1,015 (35.2)	1,130 (37.6)	1,074 (37.2)	**0.002**
	Left	886 (39.7)	1,100 (41.9)	1,196 (41.4)	1,190 (40.0)	1,110 (38.4)	
	Rectum	585 (26.2)	657 (25.0)	675 (23.4)	689 (22.9)	706 (24.4)	
Charlson comorbidity score	0	1,130 (55.4)	1,364 (56.5)	1,695 (63.5)	1,777 (64.1)	1,711 (65.3)	**<0.001**
	1	604 (29.6)	743 (30.8)	671 (25.1)	717 (25.9)	676 (25.8)	
	2	306 (15.0)	308 (12.8)	305 (11.4)	279 (10.1)	233 (8.9)	
	Missing	193	213	215	236	270	
T-stage	0-2	104 (6.1)	133 (6.6)	135 (6.0)	161 (6.9)	186 (7.9)	0.17
	3	880 (51.7)	1,043 (51.7)	1,164 (51.9)	1,203 (51.5)	1,262 (53.8)	
	4	719 (42.2)	842 (41.7)	943 (42.1)	970 (41.6)	898 (38.3)	
	Missing	530	610	644	675	544	
N-stage	0	340 (19.8)	461 (22.7)	473 (20.9)	501 (21.4)	502 (21.4)	0.495
	1	710 (41.4)	820 (40.3)	887 (39.1)	936 (39.9)	943 (40.1)	
	2	665 (38.8)	754 (37.1)	906 (40.0)	908 (38.7)	905 (38.5)	
	Missing	518	593	620	664	540	
Emergency admission	No	1,257 (61.7)	1,539 (63.8)	1,752 (65.5)	1,835 (66.2)	1,880 (71.3)	**<0.001**
	Yes	782 (38.4)	875 (36.3)	921 (34.5)	936 (33.8)	757 (28.7)	
	Missing	194	214	213	238	253	
Hepatobiliary services on-site	No	593 (26.6)	482 (18.3)	507 (17.6)	506 (16.8)	590 (20.4)	**<0.001**
	Yes	1,640 (73.4)	2,146 (81.7)	2,379 (82.4)	2,503 (83.2)	2,300 (79.6)	
Liver resection	No	1,937 (86.7)	2,217 (84.4)	2,411 (83.5)	2,517 (83.7)	2,351 (81.4)	**<0.001**
	Yes	296 (13.3)	411 (15.6)	475 (16.5)	492 (16.4)	539 (18.7)	

Table 2 Odds ratio of undergoing liver resection adjusted for patient, tumour and hospital characteristics

		Odds ratio (95% confidence interval)	**P-value**	**Odds ratio (95% confidence interval) adjusted for patient and tumour characteristics**	**P-value**	**Odds ratio (95% confidence interval) adjusted for patient, tumour and hospital characteristics**	**P-value**
IMD quintile	1 (most deprived)	1	**<0.001**	1	**0.005**	1	**0.003**
	2	1.21 (1.02-1.42)		1.22 (1.02-1.46)		1.24 (1.03 to 1.48)	
	3	1.29 (1.10-1.52)		1.30 (1.09-1.56)		1.32 (1.1 to 1.58)	
	4	1.30 (1.11-1.53)		1.29 (1.08-1.54)		1.30 (1.09 to 1.56)	
	5 (least deprived)	1.47 (1.25-1.73)		1.41 (1.18-1.68)		1.42 (1.18 to 1.70)	
Gender	Male	-	-	1	0.18	1	0.187
	Female	-	-	1.07 (0.97-1.20)		1.07 (0.97 to 1.20)	
Age	<65	-	-	1	**<0.001**	1	**<0.001**
	65-74	-	-	0.66 (0.59-0.74)		0.66 (0.59 to 0.74)	
	75-84	-	-	0.32 (0.27-0.36)		0.31 (0.27 to 0.36)	
	>=85	-	-	0.07 (0.05-0.11)		0.07 (0.05 to 0.11)	
Emergency admission	No	-	-	1	**<0.001**	1	**<0.001**
	Yes	-	-	0.44 (0.38-0.50)		0.44 (0.38 to 0.5)	
Charlson comorbidity score	0	-	-	1	0.469	1	0.454
	1	-	-	0.99 (0.88-1.12)		0.99 (0.87 to 1.12)	
	2	-	-	0.89 (0.73-1.07)		0.88 (0.73 to 1.07)	
Cancer site	Right	-	-	1	**<0.001**	1	**<0.001**
	Left	-	-	1.21 (1.08-1.38)		1.22 (1.07 to 1.38)	
	Rectum	-	-	0.96 (0.83-1.10)		0.96 (0.83 to 1.1)	
T-stage	0-2	-	-	1	**<0.001**	1	**<0.001**
	3	-	-	1.11 (0.91-1.36)		1.1 (0.9 to 1.35)	
	4	-	-	0.84 (0.68-1.04)		0.84 (0.68 to 1.04)	
N-stage	0	-	-	1	**<0.001**	1	**<0.001**
	1	-	-	0.62 (0.54-0.70)		0.62 (0.54 to 0.7)	
	2	-	-	0.41 (0.36-0.48)		0.42 (0.36 to 0.48)	
Hepatobiliary services on-site	No	-	-	-	-	1	**0.003**
	Yes	-	-	-		1.38 (1.12 to 1.7)	

Table 3 Unadjusted 3-year survival from date of colorectal cancer diagnosis according to IMD quintile for all patients (P<0.001) and restricted to patients undergoing liver resection (P=0.742) and those not undergoing liver resection (P<0.001)

IMD quintile	**All patients**	**Patients undergoing liver resection**	**Patients not undergoing liver resection**
	3-year survival % (95% CI)		
1 (most deprived)	17.4 (15.7-19.1)	65.5 (59.7-70.1)	7.3 (6.0-8.8)
2	19.0 (17.4-20.7)	71.3 (66.7-75.4)	6.8 (5.6-8.0)
3	19.0 (17.4-20.5)	67.7 (63.2-71.8)	7.2 (6.1-8.4)
4	19.5 (18.0-21.1)	69.0 (54.6-72.9)	7.8 (6.5-8.9)
5 (least deprived)	22.3 (20.7-24.0)	69.3 (65.1-73.2)	9.3 (8.0-10.7)

Table 4 Hazard ratio of 3-year survival after colorectal cancer diagnosis adjusted for demographic, tumour and intuitional factors, for all patients and restricted to patients undergoing liver resection

		All patients (95% CI)	P-value	Liver resection patients (95% CI)	P-value	No liver resection patients (95% CI)	P-value
IMD quintile	**1 (most deprived)**	**1**	**<0.001**	**1**	**0.568**	**1**	**<0.001**
	2	**1.05 (0.97 to 1.14)**		**1.02 (0.79 to 1.32)**		**0.98 (0.91 to 1.06)**	
	3	**1.08 (0.99 to 1.15)**		**0.89 (0.7 to 1.14)**		**1.02 (0.93 to 1.1)**	
	4	**1.14 (1.05 to 1.23)**		**0.93 (0.74 to 1.19)**		**1.1 (1.01 to 1.19)**	
	5 (least deprived)	**1.20 (1.11 to 1.30)**		**0.97 (0.76 to 1.23)**		**1.16 (1.08 to 1.27)**	
Gender	Male	1	0.22	1	0.572	1	0.142
	Female	0.97 (0.93 to 1.02)		0.93 (0.8 to 1.06)		0.96 (0.92 to 1.01)	
Age	<65	1	**<0.001**	1	**<0.001**	1	**<0.001**
	65-74	0.78 (0.74 to 0.82)		0.89 (0.76 to 1.05)		0.85 (0.8 to 0.91)	
	75-84	0.5 (0.47 to 0.53)		0.65 (0.53 to 0.79)		0.62 (0.58 to 0.66)	
	>=85	0.31 (0.47 to 0.53)		0.3 (0.17 to 0.52)		0.45 (0.49 to 0.49)	
Emergency admission	No	1	**<0.001**	1	**<0.001**	1	**<0.001**
	Yes	0.56 (0.53 to 0.59)		0.69 (0.57 to 0.83)		0.63 (0.6 to 0.66)	
Charlson comorbidity score	0	1	**<0.001**	1	0.484	1	**<0.001**
	1	0.95 (0.9 to 1)		0.93 (0.78 to 1.1)		0.93 (0.88 to 0.99)	
	2	0.85 (0.79 to 0.91)		0.79 (0.61 to 1.04)		0.85 (0.79 to 0.92)	
Cancer site	Right	1	**<0.001**	1	**0.003**	1	**<0.001**
	Left	1.22 (1.16 to 1.28)		1.32 (1.11 to 1.56)		1.15 (1.09 to 1.22)	
	Rectum	1.10 (1.04 to 1.18)		0.99 (0.81 to 1.2)		1.14 (1.06 to 1.2)	
T-stage	0-2	1	**<0.001**	1	**0.022**	1	**0.012**
	3	1.05 (0.95 to 1.16)		0.71 (0.51 to 0.98)		1.06 (0.96 to 1.18)	
	4	0.91 (0.83 to 1.01)		0.57 (0.41 to 0.81)		0.99 (0.88 to 1.1)	
N-stage	0	1	**<0.001**	1	**<0.001**	1	**<0.001**
	1	0.69 (0.65 to 0.74)		0.64 (0.53 to 0.78)		0.79 (0.74 to 0.85)	
	2	0.56 (0.52 to 0.6)		0.49 (0.4 to 0.6)		0.69 (0.65 to 0.75)	
Hepatobiliary services on-site	No	1	**0.04**	1	0.411	1	0.215
	Yes	1.10 (1.00 to 1.20)		0.92 (0.77 to 1.09)		1.06 (0.97 to 1.15)	

References

1. Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. Ann Oncol. 2006;17(1):5-19.
2. Coleman MP, Rachet B, Woods LM, Mitry E, Riga M, Cooper N, et al. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. Br J Cancer. 2004;90(7):1367-73.
3. Kogevinas M, Porta M. Socioeconomic differences in cancer survival: a review of the evidence. IARC Sci Publ. 1997;138:177-206.
4. Newton JN, Briggs ADM, Murray CJL, Dicker D, Foreman KJ, Wang H, et al. Changes in health in England, with analysis by English regions and areas of deprivation, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet (London, England). 2015;386(10010):2257-74.
5. Ellis L, Coleman MP, Rachet B. How many deaths would be avoidable if socioeconomic inequalities in cancer survival in England were eliminated? A national population-based study, 1996-2006. Eur J Cancer. 2012;48(2):270-8.
6. Cancer Research UK. Bowel Cancer incidence statistics 2017 13/03/2017. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-Zero.
7. Aarts MJ, Lemmens VEPP, Louwman MWJ, Kunst AE, Coebergh JWW. Socioeconomic status and changing inequalities in colorectal cancer? A review of the associations with risk, treatment and outcome. European Journal of Cancer. 2010;46(15):2681-95.
8. Eloranta S, Lambert P, Cavalli-Bjorkman N, Andersson T-L, Glimelius B, Dickman P. Does socioeconomic status influence the prospect of cure from colon cancer–a population-based study in Sweden 1965–2000. European Journal of Cancer. 2010;46(16):2965-72.
9. Dejardin O, Jones AP, Rachet B, Morris E, Bouvier V, Jooste V, et al. The influence of geographical access to health care and material deprivation on colorectal cancer survival: Evidence from France and England. Health & Place. 2014;30:36-44.
10. Jeffreys M, Rachet B, McDowell S, Habib AG, Lepage C, Coleman MP. Survival from rectal and anal cancers in England and Wales, 1986–2001. European Journal of Cancer. 2006;42(10):1434-40.
11. Møller H, Sandin F, Robinson D, Bray F, Klint Å, Linklater KM, et al. Colorectal cancer survival in socioeconomic groups in England: variation is mainly in the short term after diagnosis. European Journal of Cancer. 2012;48(1):46-53.
12. Wrigley H, Roderick P, George S, Smith J, Mullee M, Goddard J. Inequalities in survival from colorectal cancer: a comparison of the impact of deprivation, treatment, and host factors on observed and cause specific survival. Journal of Epidemiology and Community Health. 2003;57(4):301-9.
13. Hole DJ, McArdle CS. Impact of socioeconomic deprivation on outcome after surgery for colorectal cancer. The British journal of surgery. 2002;89(5):586-90.
14. Lejeune C, Sassi F, Ellis L, Godward S, Mak V, Day M, et al. Socio-economic disparities in access to treatment and their impact on colorectal cancer survival. Int J Epidemiol. 2010;39(3):710-7.
15. Dixon A, Grand JL, Henderson J, Murray R, Poteliakhoff E. Is the British National Health Service equitable? The evidence on socioeconomic differences in utilization. Journal of Health Services Research & Policy. 2007;12(2):104-9.
16. Tilney H, Lovegrove RE, Smith JJ, Thompson MR, Tekkis PP. The National Bowel Cancer Project: social deprivation is an independent predictor of nonrestorative rectal cancer surgery. Dis Colon Rectum. 2009;52(6):1046-53.
17. Pollock AM, Vickers N. Deprivation and emergency admissions for cancers of colorectum, lung, and breast in south east England: ecological study. BMJ. 1998;317(7153):245-52.

18. Raine R, Wong W, Scholes S, Ashton C, Obichere A, Ambler G. Social variations in access to hospital care for patients with colorectal, breast, and lung cancer between 1999 and 2006: retrospective analysis of hospital episode statistics. BMJ. 2010;340.
19. Lemmens VE, van Halteren AH, Janssen-Heijnen ML, Vreugdenhil G, Repelaer van Driel OJ, Coebergh JW. Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity. Ann Oncol. 2005;16(5):767-72.
20. McGory ML, Zingmond DS, Sekeris E, Bastani R, Ko CY. A patient's race/ethnicity does not explain the underuse of appropriate adjuvant therapy in colorectal cancer. Dis Colon Rectum. 2006;49(3):319-29.
21. Paterson HM, Mander BJ, Muir P, Phillips HA, Wild SH. Deprivation and access to treatment for colorectal cancer in Southeast Scotland 2003-2009. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2014;16(2):12442.
22. Gatta G, Capocaccia R, Sant M, Bell CM, Coebergh JW, Damhuis RA, et al. Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high resolution study. Gut. 2000;47(4):533-8.
23. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clinical Epidemiology. 2012;4:283-301.
24. Morris EJ, Forman D, Thomas JD, Quirke P, Taylor EF, Fairley L, et al. Surgical management and outcomes of colorectal cancer liver metastases. The British journal of surgery. 2010;97(7):1110-8. Epub 2010/07/16.
25. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Annals of surgery. 2008;247(1):125-35. Epub 2007/12/25.
26. Wiggans MG, Shahtahmassebi G, Aroori S, Bowles MJ, Stell DA. Socioeconomic status influences the likelihood but not the outcome of liver resection for colorectal liver metastasis. HPB : The Official Journal of the International Hepato Pancreato Biliary Association. 2015;17(2):150-8.
27. Norén A, Eriksson H, Olsson L. Selection for surgery and survival of synchronous colorectal liver metastases; a nationwide study. European Journal of Cancer. 2016;53:105-14.
28. NHS Digital. National Bowel Cancer Audit Report2016 15/01/2017. Available from: http://www.hscic.gov.uk/bowel.
29. World Health Organization: International Statistical Classification of Diseases and Related Health Problems (10th Revision). Geneva: World Health Organization; 1992.
30. Armitage JN, van der Meulen JH. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. The British journal of surgery. 2010;97(5):772-81. Epub 2010/03/23.
31. Noble M MD, Wilkinson K,Whitworth A, Dibben C, Barnes H. The English Indices of Deprivation 2007. London: HMSO, 2008.
32. Vallance AE, vanderMeulen J, Kuryba A, Botterill ID, Hill J, Jayne DG, et al. Impact of hepatobiliary service centralization on treatment and outcomes in patients with colorectal cancer and liver metastases. British Journal of Surgery. 2017:n/a-n/a.
33. NHS Classifications Service: OPCS Classifications of Interventions and Procedures Version 4.4. London: The Stationery Office; 2007.
34. Mackenbach JP. The English strategy to reduce health inequalities. The Lancet. 2011;377(9782):1986-8.
35. National Cancer Transformation Board. Achieving World Class Cancer Outcomes: Taking the strategy forward. 2016 [06/09/2017]; Available from: https://www.england.nhs.uk/wp-content/uploads/2016/05/cancer-strategy.pdf.
36. Nur U, Rachet B, Parmar MKB, Sydes MR, Cooper N, Lepage C, et al. No socioeconomic inequalities in colorectal cancer survival within a randomised clinical trial. British Journal of Cancer. 2008;99(11):1923-8.

37. Abdel-Rahman ME, Butler J, Sydes MR, Parmar MKB, Gordon E, Harper P, et al. No socioeconomic inequalities in ovarian cancer survival within two randomised clinical trials. British Journal of Cancer. 2014;111(3):589-97.
38. Forrest LF, Adams J, Rubin G, White M. The role of receipt and timeliness of treatment in socioeconomic inequalities in lung cancer survival: population-based, data-linkage study. Thorax. 2015;70(2):138-45.
39. Sharrocks K, Spicer J, Camidge DR, Papa S. The impact of socioeconomic status on access to cancer clinical trials. British Journal of Cancer. 2014;111(9):1684-7.
40. Mitry E, Rachet B. [Prognosis of colorectal cancer and socio-economic inequalities]. Gastroenterol Clin Biol. 2006;30(4):598-603.
41. Vallance AE, vanderMeulen J, Kuryba A, Botterill ID, Hill J, Jayne DG, et al. Impact of hepatobiliary service centralization on treatment and outcomes in patients with colorectal cancer and liver metastases. The British journal of surgery. 2017;104(7):918-25.
42. Crawford SM, Sauerzapf V, Haynes R, Zhao H, Forman D, Jones AP. Social and geographical factors affecting access to treatment of lung cancer. Br J Cancer. 2009;101(6):897-901.
43. Cavalli-Björkman N, Qvortrup C, Sebjørnsen S, Pfeiffer P, Wentzel-Larsen T, Glimelius B, et al. Lower treatment intensity and poorer survival in metastatic colorectal cancer patients who live alone. British Journal of Cancer. 2012;107(1):189-94.
44. Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K. Low health literacy and health outcomes: an updated systematic review. Ann Intern Med. 2011;155(2):97-107.
45. National Institute for Health and Care Excellence. Colorectal cancer: diagnosis and management2014 27/02/2017. Available from: https://www.nice.org.uk/guidance/CG131/chapter/1-Recommendations#management-of-metastatic-disease.
46. McBride D, Hardoon S, Walters K, Gilmour S, Raine R. Explaining variation in referral from primary to secondary care: cohort study. BMJ. 2010;341.

AUTHOR DECLARATION

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

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