Original article

Surgical management and outcomes of colorectal cancer liver metastases

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Background: **This population-based study investigated the frequency of hepatic resections for colorectal cancer metastases across England and their outcome.**

Methods: **Individuals who underwent surgery for colorectal cancer between January 1998 and June 2004 within the English National Health Service were identified via the National Cancer Data Repository. All episodes of care in the 3 years after the initial operation were examined to determine the frequency of liver resection. Variations in the use of liver resection and survival were assessed.**

Results: **Some 114 155 individuals underwent surgery for colorectal cancer over the study period, of whom 3116 (2·7 per cent) subsequently had one or more hepatic resections. The hepatectomy rate increased from 1·7 per cent in 1998 to 3·8 per cent in 2004. There was significant variation in the rate of liver resection across cancer networks (range 1·1–4·3 per cent) and hospitals (range 0·7–6·8 per cent). The crude 5-year survival rate after liver resection was 44·2 (95 per cent confidence interval (c.i.) 42·4 to 46·1) per cent from the time of hepatectomy and 45·9 (95 per cent c.i. 44·1 to 47·7) per cent from the time of colectomy. This was comparable to the 5-year survival rate of patients with stage III disease (42·2 (95 per cent c.i. 41·7 to 42·7) per cent).**

Conclusion: **The rate of resection of liver metastases increased over the study period but varied significantly across the country. Patients who underwent liver resection had 5-year survival comparable to that of patients with stage III colorectal cancer.**

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Introduction

Colorectal cancer is the third commonest cancer in England, with 30 000 new cases and 13 000 deaths every year[1]. Around 20–25 per cent of patients have liver metastases at diagnosis and a large proportion go on to develop them. Untreated patients with such disease have very poor survival[2,3]. Evidence from case series suggests that survival can be improved significantly if patients with potentially operable liver metastases undergo hepatic resection[4]. This observation has led the English National Health Service (NHS) to recommend that all patients with such resectable disease be referred to specialist multidisciplinary liver teams for management[5,6].

A randomized trial examining the efficacy of surgical resection of liver metastases is now ethically unfeasible as over 500 published single-centre series have demonstrated the benefits of the intervention[4]. However, many of these studies contained highly selected groups of patients from specialist centres who may not be representative of the population as a whole and, as such, the outcomes may not translate to the general population. Further population-based evidence is required to help quantify the survival benefit of this treatment.

The evidence surrounding what constitutes resectable disease is also broad and no strong consensus exists on the appropriate clinical indications for surgical resection of colorectal liver metastases[4,7]. It is possible that referral practice might vary significantly between centres and that not all patients with potentially resectable disease are referred to liver specialists for the appropriate management of metastatic disease.

The aim of this retrospective population-based study was to investigate patterns and outcomes of surgical management of colorectal cancer liver metastases across a population of 49 million people covered by the English NHS. It sought to determine whether there are systematic differences in the proportion of patients undergoing liver resection across hospitals and cancer networks (regional networks in the UK in which all NHS cancer services – general practitioner, local and specialist hospitals – are grouped to ensure that consistent high-quality care is offered across the country) to determine the impact of resection of liver metastases on the long-term survival of patients with colorectal cancer.

Methods

The National Cancer Data Repository (NCDR)[8] is a new resource that contains information on the management and outcome of all individuals diagnosed with cancer in England. It consists of pooled English Cancer Registry data linked to an extract (covering the interval April 1997 to June 2007 and including episodes of care for individuals with a diagnosis of cancer in any episode) of the administrative data set Hospital Episode Statistics (HES). Linkage uses all or combinations of the identifiers: NHS number, date of birth, postcode at diagnosis and sex. The registry contains information on all tumours diagnosed in England whereas HES contains information on all treatments administered to patients in NHS hospitals; the linked resource allows the processes and outcomes of care to be traced for all patients with cancer treated within the English NHS.

Information was extracted for all individuals who underwent major resection, defined as surgical excision of a section of the large bowel, for a primary colorectal cancer between 1 January 1998 and 30 June 2004 in England. This cut-off date was chosen to ensure that 3 years of HES follow-up were available for all patients. Basic information (age, sex, American Joint Committee on Cancer (AJCC) stage, dates of diagnosis and death, NHS number and postcode at diagnosis) for all colorectal cancers (International Classification of Diseases (ICD, 10th revision, C18–20)[9] was taken from the registry data set, whereas information about patient management was derived from HES. All inpatient episodes of care for each patient identified in the registry extract and linked to the HES data set were searched to identify the first major surgical resection for colorectal disease. This was done by searching for the first appearance (after the date of diagnosis of the colorectal tumour) of the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision) (OPCS4) codes for major colorectal resection[10,11]: emergency excision of appendix (H01), excision of appendix (H02), panproctocolectomy (H041), total colectomy (H05), extended right hemicolectomy (H06), right hemicolectomy (H07), transverse colectomy (H08), left hemicolectomy (H09), sigmoid colectomy (H10), colectomy (H11), subtotal excision of colon (H29), excision of rectum (H33) and total exenteration of pelvis (X14). Information about the initial managing hospital and cancer network for each patient was derived from this episode of care. If a patient received two or more such operations within different episodes, the first operation was used. If a patient received two or more procedures in the same episode, the most radical and extensive procedure was used.

All treatment episodes in the 3 years after the initial colorectal resection were then searched for the liver resection codes for right hemihepatectomy (J021), left hemihepatectomy (J022), resection of segment of liver (J023), wedge excision of liver (J024), partial excision of liver (J028/9), excision of lesion of liver (J031) and extirpation of lesion of liver (J038/9). Patients with such codes were deemed to have undergone resection of one or more colorectal cancer liver metastases.

A Charlson co-morbidity score[12,13] was calculated for each individual based on the diagnostic reasons (excluding cancer) for any hospital admissions in the year before diagnosis of the colorectal tumour, excluding any episodes spanning the time of diagnosis. The cancer component of the Charlson index was derived for each patient from the cancer registry information in the NCDR. Any cancers diagnosed in the year before diagnosis of the colorectal tumour were scored and added to the scores obtained from HES data. Increasing scores indicated increasing co-morbid disease. Patients were grouped into Charlson score categories of 0, 1, 2, and 3 or greater.

Statistical analysis

The frequency of liver resections was assessed in relation to the year of colorectal cancer resection, patient age, sex, AJCC stage of the primary tumour at diagnosis, quintile of the income domain of the Index of Multiple Deprivation (IMD) 2004 (derived from each patient's postcode of residence at diagnosis)[14], Charlson score, and cancer network and hospital where the initial colorectal resection took place. The statistical significance of any differences in liver resection rates across groups were assessed using the χ^2 test.

Survival was calculated from date of surgery of the initial primary colorectal tumour or the date of first liver resection to the date of death or when censored (30 June 2008). Perioperative deaths were included in these survival analyses. Kaplan–Meier survival graphs were used to illustrate 5-year survival and log rank tests to assess whether survival differences were statistically significant. Survival analyses were performed for four groups: all patients, patients with stage III or stage IV disease at diagnosis who did not undergo liver resection, and patients who had a liver resection.

Increasing survival times were associated with a greater likelihood of hepatic resection so traditional survival analyses would induce a bias in favour of resection. Therefore, a landmark analysis[15–17] was also undertaken. This included individuals who survived a minimum of 1 year after colorectal resection (the landmark time was determined *a priori*) and who had stage IV disease at diagnosis. It compared survival between those who did and did not undergo hepatic resection.

A multilevel (random-effects) binary logistic regression model was used to determine factors associated with the use of resection for colorectal cancer liver metastases. The model was built with a hierarchy of patients being clustered within hospitals (level 2), within cancer networks (level 3), so allowing correlations among patient outcomes. The dependent variable, use of liver resection, was coded as a binary outcome with patients who received a liver resection coded as 1 and those who did not as 0. Co-variables (explanatory variables) included age (per 10-year increase), sex, IMD quintile, year of initial colorectal resection, stage at diagnosis, Charlson co-morbidity score and site of the initial colorectal primary. To determine whether the variation in the odds of use of these operations across networks and hospitals was independent of case mix, the residuals of the model were examined. All models were developed with MLwiN software[18].

Results

Over the study interval, 114 155 patients were identified within the NCDR who underwent major resection for a colorectal tumour. Of these, 3116 (2·7 per cent) had one or more liver resections within 3 years of removal of the colorectal primary. Characteristics of the study population are summarized in *Table 1*. Some 280 patients (9·0 per cent) had multiple liver resections within 3 years, giving a total of 3434 hepatic resections; 243 patients had two hepatic resections, 36 patients had three and one patient had four resections.

The rate of hepatectomy increased from 1·7 per cent of all patients who had a primary colorectal cancer resected in 1998 to 3·8 per cent in the first half of 2004 (*Fig. 1*). There was significant variation in the proportion of patients having a liver resection across cancer networks, with rates ranging from 1·1 to 4·3 per cent of those whose primary colorectal cancer had been resected (*Fig. 2a*). The variation was even greater across hospitals, the proportion ranging from 0·7 to 6·8 per cent (*Fig. 2b*).

Table 2 shows the results of the logistic regression model used to determine the odds of liver resection. The odds increased by 15 per cent per year of the study (odds ratio (OR) 1·15 (95 per cent confidence interval (c.i.) 1·13 to 1·18)). They were also increased in those with more advanced disease stage at diagnosis (OR 12·99 (95 per cent c.i. 10·35 to 16·30) for stage IV *versus* stage I) and with tumours in the rectosigmoid (OR 1·37 (95 per cent c.i. 1·21 to 1·55)) or rectum (OR 1·13 (95 per cent c.i. 1·03 to 1·23)) compared with the colon. Older patients (OR per 10-year increase 0·64 (95 per cent c.i. 0·63 to 0·65)), women (OR 0·78 (95 per cent c.i. 0·72 to 0·84)), those with co-morbid disease (OR 0·51 (95 per cent c.i. 0·32 to 0·81) for Charlson score 3 or more *versus* 0) and those in the more deprived socioeconomic quintiles (95 per cent c.i. OR 0·70 (0·61 to 0·80) for most deprived compared with most affluent) were all significantly less likely to receive a hepatic resection.

Fig. 3 shows the variability in the odds of liver resection among hospitals and networks over the study period after adjusting for case mix. Patients in four hospitals and networks were identified as having liver resection significantly more frequently than those treated in other organizations, independently of case mix. No organization used the procedure significantly less frequently after adjustment for case mix.

The crude 5-year survival rate from the date of the initial colorectal resection for the entire study population was 50·6

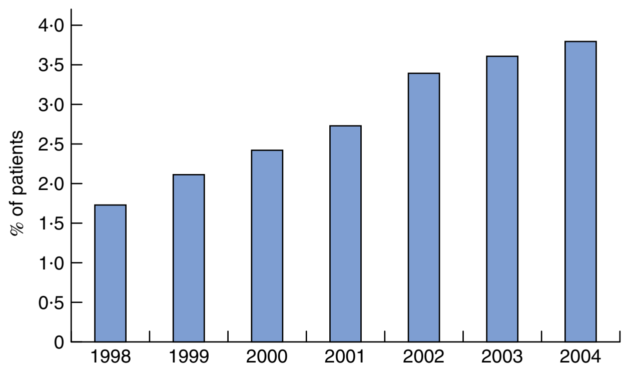


Fig. 1 Proportion of patients having major surgery for colorectal cancer between 1 January 1998 and 30 June 2004 who underwent one or more hepatic resections within 3 years of initial resection

Table 1 Characteristics of the study population

	No liver resection (n = 111 039)	Liver resection (n = 3116)	Total (n = 114 155)
Tumour site			
Colon	71 853 (64·7)	1871 (60·0)	73 724 (64·6)
Rectosigmoid	9327 (8·4)	356 (11·4)	9683 (8·5)
Rectum	29 859 (26·9)	889 (28·5)	30 748 (26·9)
Sex			
M	60 825 (54·8)	1933 (62·0)	62 758 (55·0)
F	50 214 (45·2)	1183 (38·0)	51 397 (45·0)
Age at resection of primary colorectal tumour (years)			
≤ 60	21 017 (18·9)	1192 (38·3)	22 209 (19·5)
61–70	29 991 (27·0)	1197 (38·4)	31 188 (27·3)
71–80	40 387 (36·4)	680 (21·8)	41 067 (36·0)
> 80	19 644 (17·7)	47 (1·5)	19 691 (17·2)
Stage at diagnosis of colorectal primary			
I	11 721 (10·6)	91 (2·9)	11 812 (10·3)
II	36 973 (33·3)	630 (20·2)	37 603 (32·9)
III	34 805 (31·3)	1192 (38·3)	35 997 (31·5)
IV	9459 (8·5)	821 (26·3)	10 280 (9·0)
Unknown	18 081 (16·3)	382 (12·3)	18 463 (16·2)
IMD quintile			
1 (most affluent)	21 244 (19·1)	672 (21·6)	21 916 (19·2)
2	23 958 (21·6)	726 (23·3)	24 684 (21·6)
3	23 713 (21·4)	672 (21·6)	24 385 (21·4)
4	22 311 (20·1)	566 (18·2)	22 877 (20·0)
5 (most deprived)	19 557 (17·6)	469 (15·1)	20 026 (17·5)
Unknown	256 (0·2)	11 (0·4)	267 (0·2)
Year of resection of colorectal primary			
1998	17 561 (15·8)	308 (9·9)	17 869 (15·7)
1999	17 538 (15·8)	379 (12·2)	17 917 (15·7)
2000	17 650 (15·9)	436 (14·0)	18 086 (15·8)
2001	16 684 (15·0)	465 (14·9)	17 149 (15·0)
2002	16 601 (15·0)	580 (18·6)	17 181 (15·1)
2003	16 689 (15·0)	622 (20·0)	17 311 (15·2)
2004	8316 (7·5)	326 (10·5)	8642 (7·6)
Charlson co-morbidity score			
0	95 574 (86·1)	2852 (91·5)	98 426 (86·2)
1	9438 (8·5)	169 (5·4)	9607 (8·4)
2	4214 (3·8)	75 (2·4)	4289 (3·8)
≥ 3	1813 (1·6)	20 (0·6)	1833 (1·6)

Values in parentheses are percentages. IMD, Index of Multiple Deprivation.

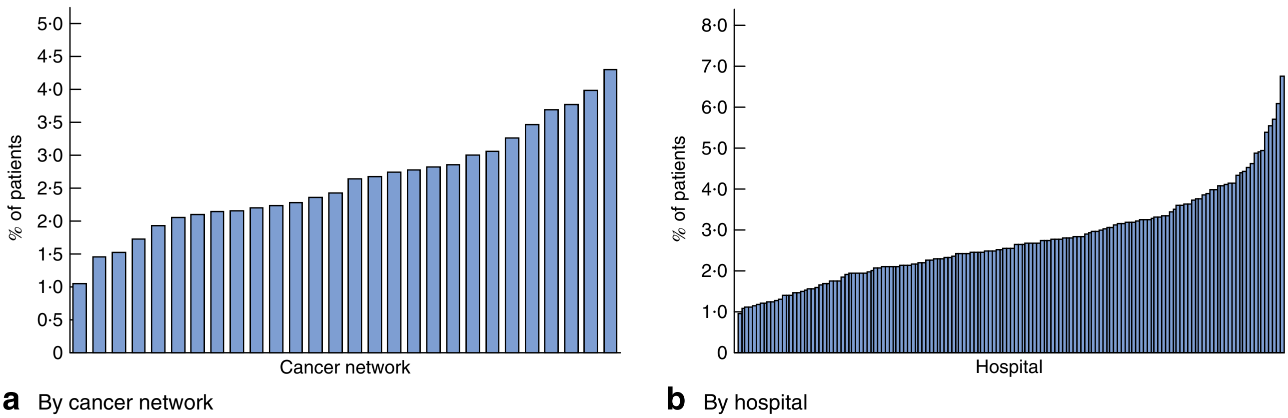


Fig. 2 Proportion of patients who underwent one or more hepatic resections within 3 years of diagnosis across **a** English cancer networks and **b** English National Health Service hospitals

Table 2 Odds of having a liver resection within 3 years of initial colorectal tumour resection

	Odds ratio	*P**	*P*†
Year of resection of colorectal primary	1·15 (1·13, 1·18)	< 0·001	< 0·001
Age at resection of colorectal primary (per 10-year increase)	0·64 (0·63, 0·65)	< 0·001	< 0·001
Sex			< 0·001
M	1·00		
F	0·78 (0·72, 0·84)	< 0·001	
IMD quintile			< 0·001
1 (most affluent)	1·00		
2	1·01 (0·90, 1·12)	0·916	
3	0·96 (0·86, 1·08)	0·490	
4	0·85 (0·76, 0·96)	0·009	
5 (most deprived)	0·70 (0·61, 0·80)	< 0·001	
Unknown	1·17 (0·62, 2·21)	0·619	
Stage of primary tumour at diagnosis			< 0·001
I	1·00		
II	2·55 (2·03, 3·21)	< 0·001	
III	4·55 (3·65, 5·68)	< 0·001	
IV	12·99 (10·35, 16·30)	< 0·001	
Unknown	2·65 (2·07, 3·38)	< 0·001	
Tumour site			< 0·001
Colon	1·00		
Rectosigmoid	1·37 (1·21, 1·55)	< 0·001	
Rectum	1·13 (1·03, 1·23)	0·007	
Charlson co-morbidity score			< 0·001
0	1·00		
1	0·73 (0·62, 0·87)	< 0·001	
2	0·75 (0·59, 0·96)	0·021	
≥ 3	0·51 (0·32, 0·81)	< 0·001	

Values in parentheses are 95 per cent confidence intervals. IMD, Index of Multiple Deprivation. *Individual subcategory *versus* reference; †across groups (binary logistic regression analysis).

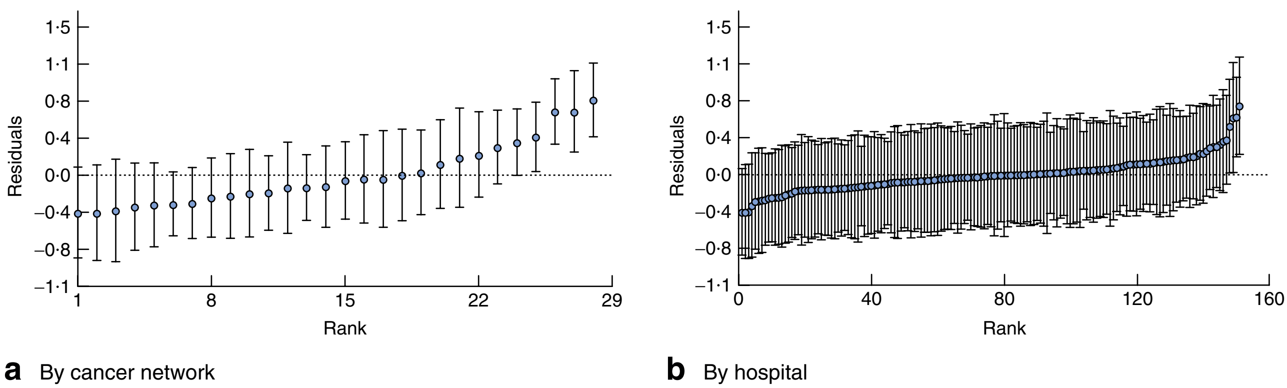
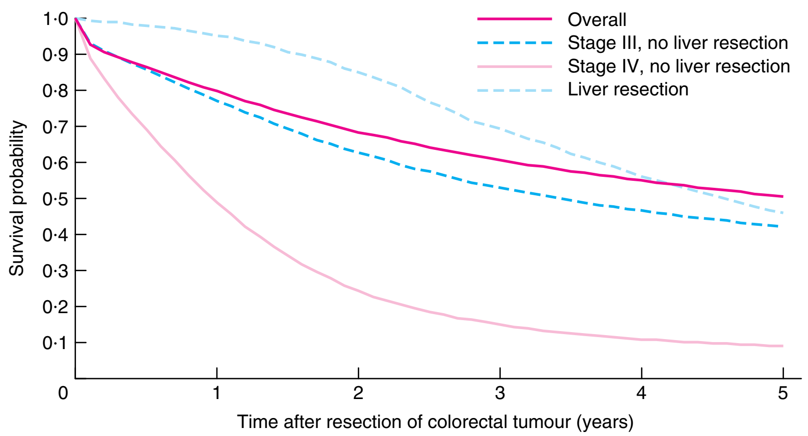


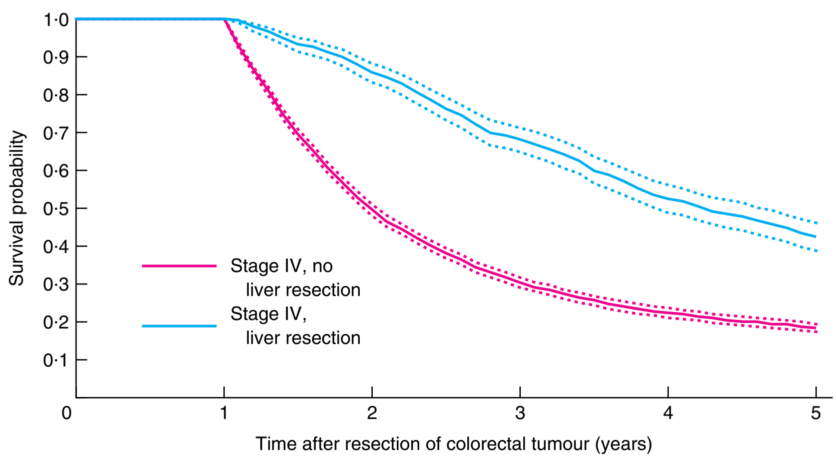
Fig. 3 Variability in the use of resection for colorectal cancer liver metastases by **a** English cancer network and **b** English National Health Service hospital adjusted for patient age, sex, Index of Multiple Deprivation quintile, stage at diagnosis, year of resection of colorectal primary, Charlson co-morbidity score and site of colorectal primary tumour. The dotted line represents the average use of the procedure across the population. Each symbol represents a hospital or network and the bars are 99·9 per cent confidence intervals. The patients in organizations whose confidence intervals do not cross the dotted line were likely to undergo resection for hepatic metastases significantly more or less frequently than the rest of the population, independently of case mix

(95 per cent c.i. 50·3 to 50·9) per cent (*Fig. 4*). Five-year survival following liver resection was 45·9 (95 per cent c.i. 44·1 to 47·7) per cent from the date of resection of the colorectal primary and 44·2 (95 per cent c.i. 42·4 to 46·1) per cent from the date of liver resection. This compared favourably with the 5-year survival rate among patients with stage III disease who did not undergo hepatic resection (42·2 (95 per cent c.i. 41·7 to 42·7) per cent) and



No. at risk						
Overall	114 155	90 868	78 122	69 186	62 668	48 188
Stage III, no liver resection	34 805	26 846	21 803	18 413	16 210	12 241
Stage IV, no liver resection	9459	4613	2297	1398	1030	701
Liver resection	3116	2973	2657	2169	1748	1108

Fig. 4 Kaplan–Meier survival curves for study population overall, patients with stage III or IV disease who did not have liver resection, and for those who had liver resection



No. at risk						
Stage IV, no liver resection	9459	4613	2297	1398	1030	701
Stage IV, liver resection	821	761	657	520	401	257

Fig. 5 Landmark survival analysis of patients with stage IV disease at diagnosis who survived 1 year and did or did not undergo liver resection. Dotted lines represent 95 per cent confidence intervals

was significantly better than that of patients with stage IV disease who did not have hepatic metastases resected (9·0 (95 per cent c.i. 8·4 to 9·6) per cent; $P < 0.001$).

In the landmark analysis of patients with stage IV disease at diagnosis who survived 1 year after operation, 5-year survival was 42·5 (95 per cent c.i. 38·9 to 46·1) and 18·4 (95 per cent c.i. 17·2 to 19·5) per cent for those who did and did not have liver resection respectively (*Fig. 5*). Survival was significantly better for those who had a hepatic resection ($P < 0.001$). The characteristics of the patients included in this analysis are presented in *Appendix 1* (supporting information).

Discussion

This retrospective population-based study provided a national perspective on the surgical management and outcomes of patients with colorectal cancer liver metastases. It demonstrated the long-term survival benefit of hepatectomy for patients with resectable disease compared with those not undergoing liver surgery. Overall, the survival of patients who had liver metastases resected was comparable to that of patients with stage III tumours.

The study also demonstrated inequities in the use of this treatment. The rate of hepatic resection following colorectal cancer surgery increased between 1998 and 2004 across the English NHS, but there was significant variation in its application across cancer networks and hospitals that was independent of case mix. Women, older patients and those who resided in the most deprived areas were significantly less likely to undergo liver resection, probably because individuals in these groups were more likely to be inappropriate surgical candidates. However, the effects remained after adjustment for the Charlson co-morbidity score, suggesting that access to this potentially beneficial surgical treatment is inequitable across the population.

Despite the lack of randomized trial evidence, there has been a growing conviction that the radical treatment of hepatic metastases from colorectal cancer can lead to significantly improved survival. The increase in hepatic resection rates across the present study interval provides evidence that this conviction is being translated into practice, but significant variation in practice was found. The reliability of these findings is limited by the fact that no information was available regarding the actual number of individuals who had potentially resectable metastases, but there is no reason to suspect that the numbers are likely to vary geographically and so it seems unlikely that this would explain the variation observed. It is therefore anticipated that the observed differences in the rates of resection of liver metastases are real. They may reflect inequitable access to multimodal care or a lack of consensus regarding what constitutes resectable disease. In addition, the definition of resectable disease may have changed within individual liver surgery units during the study period. The varying referral practices between multidisciplinary teams may reflect inconsistent use of potentially downstaging chemotherapy or use of different thresholds to determine which patients should be considered for resection. This variation may indicate referral bias and must be minimized to ensure that radical treatment is not denied to any patient who might benefit from it.

To date most studies examining the impact of resection of hepatic colorectal metastases have been small, single-centre case series. A recent systematic review[4] on the subject concluded that the quality of the currently available research was poor and that ascertaining the true benefit of this treatment was difficult in the absence of randomized trials. Of 529 studies identified for review, only 30 were included. Of these, the best evidence came from prospective case series but was still poor. A few population-based studies[19,20] have demonstrated good outcomes after resection of liver metastases in suitable patients, but none has been able to give a national perspective on the management of such hepatic disease. The present study, which was based on all patients with colorectal cancer operated on within the NHS in England from January 1998 to June 2004, has provided strong evidence to support the benefit of the surgical removal of liver metastases.

Previous studies have shown that survival from colorectal cancer differs across the population[21,22] with, for example, those residing in more affluent areas having better survival than patients from more deprived regions. However, in a recent randomized trial in which patients were given equal treatment this gradient disappeared[23], suggesting that the socioeconomic disparities in survival across the general population were due to inequalities in treatment. The present findings support this theory, with rates of hepatic resection varying considerably both geographically and across socioeconomic groups independently of other case-mix factors. Equalizing access to liver surgery for colorectal metastases may help reduce socioeconomic disparities in cancer survival.

A major criticism of the study is that it was based on linked routine cancer registry and HES data, whose accuracy of coding has been questioned[24]. HES has been validated for such national audit processes by comparing it with information submitted to national clinical audits; strong agreement has been observed, suggesting that the linked data set is representative[25,26] and the present results robust. In addition, the process of linkage enables the identification of duplicates in both data sets, so their combination improves the overall quality of the data available.

Another criticism is that the adequacy of case-mix adjustment was limited owing to the routine nature of the data. Patients selected for liver resection may have a better prognosis than other patients with stage IV colorectal cancer who do not have surgery as their disease is both confined to the liver and circumscribed within it. The patients are also more likely to have good performance status and minimal co-morbidity. Unfortunately the NCDR does not contain detailed information about the extent of liver disease, and records only limited details of concomitant illnesses that may make liver resection unfeasible. Adjustment for these factors is therefore impossible. It seems unlikely that the extent of liver disease would vary substantially across hospitals and cancer networks, yet there was significant variation in practice. This suggests that patients are being denied access to a potentially curative treatment that could significantly improve their survival.

Chemotherapy is becoming increasingly successful at rendering inoperable liver metastases resectable[25,27–29]. The present study interval encompassed the introduction of oxaliplatin-based regimens that are more effective than earlier drug treatments. Monitoring the administration of adjuvant treatments and their impact on outcome is essential. Currently, the NCDR does not contain good data regarding adjuvant treatment as the information available relates to inpatient and day-case hospital episodes. Chemotherapy is often administered in the outpatient setting (and as such not captured within the HES data set), so data on its use are limited. It is planned to incorporate information from chemotherapy prescribing systems into the NCDR to improve its scope and the clinical validity of the analyses it enables.

This study has provided good evidence that, after colorectal cancer surgery, patients who have stage IV metastatic disease amenable to radical treatment can have a 5-year survival equivalent to that of patients with lymph node metastases (stage III). The current staging systems for colorectal cancer do not reflect the difference in outcome between resectable and unresectable metastatic disease, and a new staging system that takes these differences into account has been called for[7]. The present findings provide strong evidence to support this view. A revised staging system capable of identifying patients likely to benefit from hepatic resection could help reduce the variation in practice and ensure that all those eligible can benefit from surgery.

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Supporting information can be found in the online version of this article.

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