

Impact of hepatobiliary service centralization on treatment and outcomes in patients with colorectal cancer and liver metastases

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Background: Centralization of specialist surgical services can improve patient outcomes. The aim of this cohort study was to compare liver resection rates and survival in patients with primary colorectal cancer and synchronous metastases limited to the liver diagnosed at hepatobiliary surgical units (hubs) with those diagnosed at hospital Trusts without hepatobiliary services (spokes).

Methods: The study included patients from the National Bowel Cancer Audit diagnosed with primary colorectal cancer between 1 April 2010 and 31 March 2014 who underwent colorectal cancer resection in the English National Health Service. Patients were linked to Hospital Episode Statistics data to identify those with liver metastases and those who underwent liver resection. Multivariable random-effects logistic regression was used to estimate the odds ratio of liver resection by presence of specialist hepatobiliary services on site. Survival curves were estimated using the Kaplan–Meier method.

Results: Of 4547 patients, 1956 (43.0 per cent) underwent liver resection. The 1081 patients diagnosed at hubs were more likely to undergo liver resection (adjusted odds ratio 1.52, 95 per cent c.i. 1.20 to 1.91). Patients diagnosed at hubs had better median survival (30.6 months compared with 25.3 months for spokes; adjusted hazard ratio 0.83, 0.75 to 0.91). There was no difference in survival between hubs and spokes when the analysis was restricted to patients who had liver resection ($P = 0.620$) or those who did not undergo liver resection ($P = 0.749$).

Conclusion: Patients with colorectal cancer and synchronous metastases limited to the liver who are diagnosed at hospital Trusts with a hepatobiliary team on site are more likely to undergo liver resection and have better survival.

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Introduction

Evidence has emerged over the past decade that centralization of specialist surgical services, to create higher-volume units, improves patient outcomes^{1,2}. This has had a significant effect on both organizational infrastructure and clinical practice within the National Health Service (NHS)^{3,4}. In recently published plans to improve cancer services, the NHS in England has recommended an evaluation of whether cancer surgery would benefit from further centralization⁵.

Colorectal cancer is the third most common cancer worldwide, with over 40 000 new cases diagnosed each year in the UK⁶. Synchronous liver metastases are present

in up to 20 per cent of newly diagnosed patients with colorectal cancer^{7,8}. Median survival with chemotherapy alone is 6–22 months⁹. Liver resection in suitable patients is the only curative treatment modality and 5-year survival rates varying from 44 to 74 per cent have been reported following resection^{10–12}. Wide variation in regional liver resection rates have been demonstrated across England¹¹.

The English Department of Health¹³ published guidelines in 2001 recommending that hepatobiliary surgery services should be delivered by units with sufficiently large catchment populations. As a result, hepatobiliary services have been centralized in a hub-and-spoke arrangement, and they are now present on site in 27 (19.0 per cent) of the

142 NHS hospital Trusts that diagnose and treat patients with colorectal cancer¹⁴.

The UK National Institute for Health and Care Excellence (NICE)¹⁵ has recommended that if a colorectal cancer multidisciplinary team (MDT) considers both primary and metastatic tumours potentially resectable, the patient should be referred to a specialist hepatobiliary surgery team. If referral pathways are working effectively, patients diagnosed with colorectal cancer and liver metastases at hospital Trusts with a specialist hepatobiliary team on site should have similar liver resection rates and survival as those diagnosed at hospital Trusts without a specialist hepatobiliary team.

The aim of this cohort study was to compare the liver resection rate and survival outcomes in patients diagnosed with primary colorectal cancer and synchronous metastases limited to the liver at a centralized hepatobiliary centre (hub) with those at hospital Trusts without hepatobiliary services (spokes).

Methods

Data from the National Bowel Cancer Audit (NBOCA)¹⁴ of patients diagnosed with primary colorectal cancer between 1 April 2010 and 31 March 2014 who underwent a major colorectal cancer resection (right hemicolectomy, extended right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoid colectomy, anterior resection, abdominoperineal excision of rectum (including exenteration of pelvis), Hartmann's procedure, total colectomy and ileorectal anastomosis, total excision of colon and rectum, total excision of colon and rectum plus anastomosis of ileum to anus plus pouch creation) in English NHS hospitals were linked to Hospital Episode Statistics (HES), an administrative database of all admissions to NHS hospitals¹⁶. The NBOCA database contains data on patients diagnosed with colorectal cancer in England. A patient is registered in the NBOCA database at the hospital of colorectal cancer diagnosis. Data entry is prospective and mandatory.

Data regarding surgical urgency (elective/scheduled or urgent/emergency), ASA fitness grade⁸, pathological staging and cancer site were obtained from NBOCA database. Admission type (elective or emergency) and co-morbidity information were obtained from the linked HES records. The date of death was available for patients who died before 1 April 2015 and was obtained from linked data from the Office for National Statistics (ONS)¹⁷.

Patient socioeconomic status was derived from the Index of Multiple Deprivation (IMD)¹⁸. The IMD ranks 32 482 geographical areas of England, each of which covers a mean population of around 1500 people or 400 households,

according to their level of deprivation measured across seven domains. Patients are grouped into five socioeconomic categories based on quintiles of the national ranking of these areas. The Royal College of Surgeons Charlson co-morbidity score¹⁹ was used to identify co-morbid conditions in the HES records in the preceding year.

The site of metastases was identified from HES data using diagnostic information coded according to ICD-10 (C780–C784, C786–C787, C790–C797)²⁰. Patients were considered to have metastatic disease at diagnosis if a HES code was recorded up to 1 year before and 30 days after diagnosis of colorectal cancer. A year before colorectal cancer diagnosis was chosen to include patients who are found to have metastases before determining the site of the primary colorectal cancer.

Procedure information is captured in HES according to OPCS-4²¹. All HES records including admissions up to 31 March 2015 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).

Data regarding the presence of a specialist hepatobiliary team were collected in November 2015 by a national NBOCA-led survey¹⁴. This was undertaken using an electronic questionnaire about the organization and structure of colorectal cancer services. All 142 English hospital Trusts treating more than ten patients with colorectal cancer per year responded. For hospital Trusts not offering hepatobiliary services, the Trust to which the majority of patients were referred was ascertained. This allowed the hospital Trusts with and without a specialist hepatobiliary team on site to be mapped in a hub-and-spoke model. The mapping arrangement was validated using NBOCA and HES records linked at patient level.

Statistical analysis

The statistical significance of differences in patient characteristics in hub and spoke hospital Trusts were assessed using the χ^2 test. Multivariable random-effects logistic regression was used to estimate the odds ratio of liver resection by presence of specialist hepatobiliary services on site, adjusted for the following risk factors: sex, cancer site, IMD quintile, age group, admission type, surgical urgency, Charlson co-morbidity score, T category, N category and ASA fitness grade. A random intercept was modelled for each hospital Trust to reflect the possible clustering of results within Trusts²². Missing values

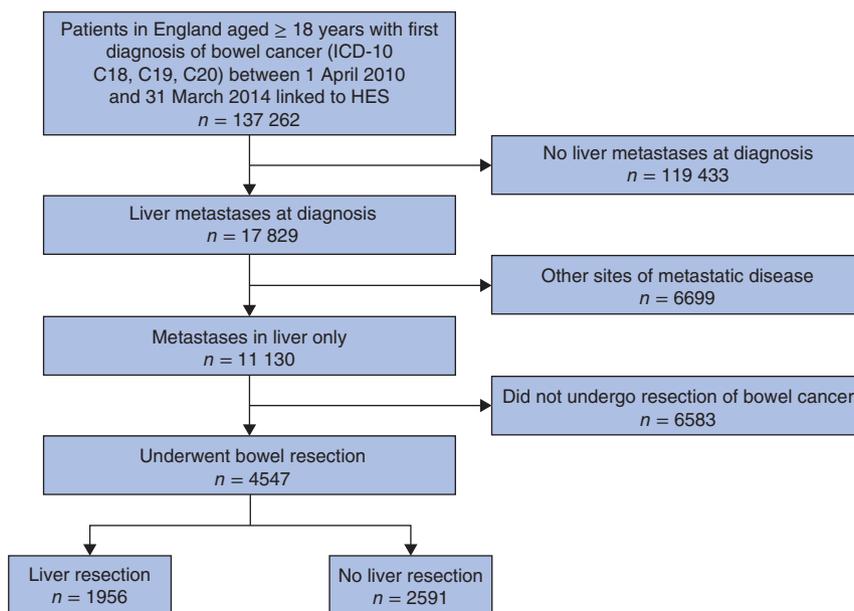


Fig. 1 Flow chart showing inclusion of patients in study

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 sets²³.

Survival was compared between patients with liver metastases diagnosed at hospital Trusts with *versus* those without a specialist hepatobiliary team. To avoid the need to censor patients, survival analyses were restricted to patients diagnosed before 1 April 2013 (with a minimum follow-up of 2 years from the last date of death available from ONS data). Survival curves were estimated using the Kaplan–Meier method and differences 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 hospitals²². STATA[®] version 14.1 (StataCorp, College Station, Texas, USA) was used for all analyses.

Results

Liver metastases were identified in HES data because the NBOCA records only the presence, but not the site, of metastatic disease. Of all patients undergoing major surgery for colorectal cancer identified in the NBOCA database to have metastatic disease at diagnosis, 41.1 per cent (4098 of 9966) had a metastasis code recorded in HES data. Despite the under-reporting of liver metastases in HES, odds ratios still represent a valid measure of the impact of the presence of a specialist hepatobiliary

team on the liver resection rate, in the same way that an odds ratio provides a valid measure of relative risk in case–control studies²⁴. This approach was valid as long as patients recorded in HES data as having liver metastases were representative of all patients with liver metastases. This was evaluated by two methods: first, by comparing the completeness of recording of metastases in HES between hub and spoke hospital Trusts, and, second, by comparing the characteristics of patients with metastases, irrespective of their site, identified in the NBOCA database and corresponding patients in the HES database.

Of the 9966 patients who underwent resection of the primary colorectal cancer and had a record of metastatic disease in the NBOCA data set, 41.1 per cent of those from spoke hospital Trusts (3141 of 7644) and 41.2 per cent of those from hub hospital Trusts (957 of 2322) had a metastasis code recorded in HES. Therefore, the recording of metastases appeared to be consistent between both types of hospital.

Slightly more patients who had an emergency admission, urgent surgery and T4 disease were identified in the HES database with metastatic disease than in the NBOCA, but patient characteristics were otherwise similar (Table S1, supporting information).

Patients

The NBOCA contained linked HES records of 137 262 patients aged 18 years or more with a primary colorectal cancer diagnosed between 1 April 2010 and 31 March 2014.

Table 1 Demographic, clinical and tumour characteristics of patients with liver metastases undergoing colorectal cancer resection according to whether a specialist hepatobiliary surgery team was available on site

	Spoke hospitals (n = 3466)	Hub hospitals (n = 1081)	P*
Age (years)			0.150
0–64	1319 (38.1)	449 (41.5)	
65–74	1161 (33.5)	376 (34.8)	
75–84	813 (23.5)	217 (20.1)	
≥ 85	173 (5.0)	39 (3.6)	
Sex ratio (M:F)	2059:1407	633:448	0.636
Index of Multiple Deprivation			<0.001
1 (least deprived)	450 (13.1)	224 (20.7)	
2	657 (19.1)	225 (20.8)	
3	729 (21.2)	219 (20.3)	
4	792 (23.1)	210 (19.4)	
5 (most deprived)	806 (23.5)	202 (18.7)	
Missing	32	1	
Admission			0.474
Elective	2227 (66.0)	702 (67.2)	
Emergency	1145 (34.0)	342 (32.8)	
Missing	94	37	
Urgency of colorectal cancer resection			0.152
Elective/scheduled	2256 (66.0)	721 (68.4)	
Urgent/emergency	1161 (34.0)	333 (31.6)	
Missing	49	27	
Charlson co-morbidity score			0.336
0	2400 (70.6)	760 (72.0)	
1	776 (22.8)	220 (20.8)	
≥ 2	222 (6.5)	76 (7.2)	
Missing	68	25	
ASA fitness grade			0.026
I	404 (13.3)	100 (10.1)	
II	1603 (52.6)	524 (53.0)	
III	871 (28.6)	316 (32.0)	
IV or V	168 (5.5)	49 (5.0)	
Missing	420	92	
Cancer site			0.212
Ascending colon	388 (11.2)	110 (10.2)	
Caecum	665 (19.2)	191 (17.7)	
Rectosigmoid	273 (7.9)	75 (6.9)	
Descending colon	126 (3.6)	37 (3.4)	
Hepatic flexure	156 (4.5)	52 (4.8)	
Rectum	551 (15.9)	194 (17.9)	
Sigmoid colon	938 (27.1)	326 (30.2)	
Splenic flexure	112 (3.2)	26 (2.4)	
Transverse colon	257 (7.4)	70 (6.5)	
T category at diagnosis			0.727
T0	22 (0.7)	7 (0.7)	
T1	32 (1.0)	6 (0.6)	
T2	156 (4.7)	50 (4.8)	
T3	1577 (47.4)	507 (48.9)	
T4	1540 (46.3)	466 (45.0)	
Missing	139	45	
N category at diagnosis			0.889
N0	819 (24.6)	249 (24.1)	
N1	1136 (34.1)	361 (34.9)	
N2	1374 (41.3)	425 (41.1)	
Missing	137	46	

Values in parentheses are percentages. * χ^2 test.

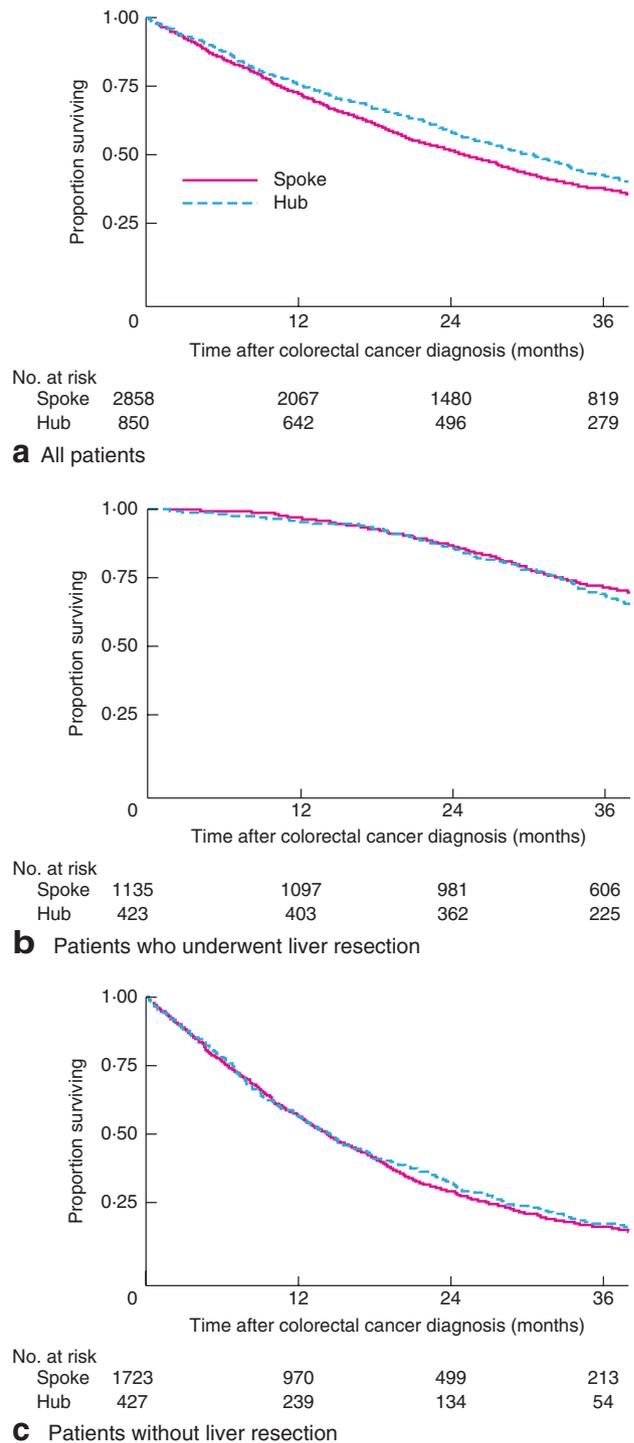


Fig. 2 Kaplan–Meier curves showing survival after colorectal cancer diagnosis in patients with synchronous liver metastases, according to diagnosis at hub (hospital Trust with on-site hepatobiliary surgical services) or spoke (hospital Trust without on-site hepatobiliary surgical services): **a** all patients, **b** patients who had liver resection and **c** patients who did not undergo liver resection. **a** $P < 0.001$, **b** $P = 0.620$, **c** $P = 0.749$ (log rank test)

Some 17 829 patients (13.0 per cent) with a code of secondary malignant neoplasm of the liver (C787) recorded up to 1 year before and 30 days after a diagnosis of colorectal cancer were identified. Of these, 6699 patients with a HES code of another site of metastasis (C780–C784, C786, C790–C796) were excluded. A further 6583 patients who did not have a colorectal cancer resection were excluded. As a result, data from 4547 patients were available for analysis (Fig. 1). Liver resection was performed in 1956 of these patients (43.0 per cent).

Patients diagnosed in hubs tended to have higher ASA grade ($P=0.026$) and lower deprivation ($P<0.001$ for IMD quintile) compared with those diagnosed elsewhere (Table 1). There was no statistically significant difference in any other patient or tumour characteristic.

Liver resection

Liver resection was performed more frequently in hubs: 545 of 1081 patients (50.4 per cent) who were diagnosed in the 27 hospital Trusts with a specialist hepatobiliary surgery team had a liver resection, compared with 1411 of 3466 (40.7 per cent) diagnosed elsewhere (crude odds ratio 1.48, 95 per cent c.i. 1.29 to 1.70). With adjustment for differences between the patient groups, those diagnosed at hubs remained more likely to undergo liver resection (adjusted odds ratio 1.52, 1.20 to 1.91).

A difference in liver resection rates between hubs and spokes was seen across most regions of the country. Comparison of liver resection rates in hubs with the mean rates in spokes that referred to them indicated that 21 of 27 hubs had higher liver resection rates than their respective spoke's mean.

Survival

Median follow-up for surviving patients was 41.9 months. Survival was better in hubs (median 30.6 months compared with 25.3 months in spokes) (Fig. 2a), and remained so when differences in patient and tumour characteristics were taken into account (adjusted hazard ratio 0.83, 95 per cent c.i. 0.75 to 0.91).

There was no difference in median survival between patients diagnosed at hubs and spokes when the analysis was restricted to patients who had liver resection ($P=0.620$) or those who did not undergo liver resection ($P=0.749$) (Fig. 2b,c).

Discussion

In this national cohort of patients with colorectal cancer and liver metastases, those who were diagnosed at hospital

Trusts with specialist hepatobiliary services on site (hubs) were more likely to undergo liver resection and have better survival than patients diagnosed elsewhere (spokes), after adjusting for patient and tumour characteristics. This discrepancy was present in over three-quarters of hubs and spokes in the country. As there was no difference between hubs and spokes in the survival of patients in this cohort who underwent liver resection and in those who did not, the improved overall survival for patients diagnosed at hubs was likely to be due to the increased rate of liver resection.

Case ascertainment in the NBOCA is reported to be 94 per cent¹⁴. This high value reduced the risk of selection bias and yielded a large study cohort. The linkage of the NBOCA data set to HES enabled the identification of liver resection, and adjustment for differences in patient and tumour characteristics between patients diagnosed in hub and spoke hospital Trusts. Linkage to ONS mortality data allowed robust outcome ascertainment. The data set was also linked to data from an organizational survey regarding access to hepatobiliary services, which was validated using information on the surgical provider contained in HES data.

It is a limitation of this study that the presence of liver metastases is under-recorded in HES data for patients who did not have a liver resection. Some 13.0 per cent of patients with colorectal cancer were found to have a HES code recorded for liver metastases at the time of diagnosis, whereas others^{7,8} have reported corresponding percentages ranging from 14 to 20 per cent. Although this produces an underestimate of the risk ratio – the ratio of the observed percentage of patients who had a liver resection following diagnosis in a hub (50.4 per cent) and the corresponding percentage in spokes (40.7 per cent) – it does not affect the odds ratio presented. This odds ratio is a valid measure of the relative risk if patients with liver metastasis recorded in HES are representative, and if the likelihood that a liver metastasis is recorded in HES is the same in hub and spoke hospitals. If liver metastases were more likely to be recorded in the hubs than in the spokes (which is the most probable situation if the assumption is not met), this would underestimate the odds ratio and only further strengthen the conclusion that liver resection rates are higher in hospital Trusts with specialist hepatobiliary services.

A further limitation of HES is that it does not contain information regarding the volume and distribution of liver metastases. It is therefore not possible to know which of the patients who did not undergo liver resection had potentially operable disease. It is, however, unlikely that the burden of liver metastases in patients would vary substantially between hospital Trusts after risk adjustment for IMD quintile. As chemotherapy is often administered on

an outpatient basis, reliable information regarding its use is also not available in HES and therefore unknown for this patient cohort. Patients undergoing radiofrequency or microwave ablation without liver resection have not been included as the overall rates were so low (0.05 per cent of the total study cohort).

Only patients undergoing major resection of primary colorectal cancer were included in the study cohort. The rate of major resection of primary colorectal cancer in this cohort was the same in hubs and spokes. A comparison of survival of all patients with liver metastases (regardless of primary colorectal cancer resection) between hubs and spokes found the same increased survival in the hubs as when the analysis was restricted to those undergoing major resection of the primary colorectal cancer.

These results mirror those of a study²⁵ of 95 818 patients diagnosed with lung cancer in English NHS Trusts between January 2008 and March 2012. The study demonstrated differences in access to surgery according to hospital of diagnosis; 16.7 per cent of patients who were first seen in a 'surgical centre' underwent resectional surgery compared with 12.2 per cent of those who were first seen in a 'non-surgical centre'. The present study of patients with colorectal cancer and liver metastases demonstrates not only differences in access to liver surgery between patients diagnosed in hospital Trusts with and without a specialist team, but also significant differences in patient survival.

A population-based study¹¹ of all patients with colorectal cancer who had a major resection in the English NHS between 1998 and 2004 reported variation in liver resection rates from 1.1 to 4.3 per cent across Trusts. The results of the present study, similarly conducted at a national level, confirm the findings of previous single-centre or single-region studies^{26–29} demonstrating the need to improve referral rates from spoke to hub hospital Trusts with specialist hepatobiliary services on site. A national study³⁰ of 27 990 patients with colorectal cancer treated in Sweden between 2007 and 2011 also demonstrated higher liver resection rates in patients treated at hub hospitals with on-site hepatobiliary services. However, they did not find improved patient survival in hub hospitals compared with those diagnosed at spoke hospitals.

In the present study, the patients diagnosed in spoke hospitals were more socially deprived than those diagnosed in hub hospitals. This may reflect the demography of the areas served by the spoke hospitals, or may indicate that less deprived patients are more likely to be referred to a specialist hub unit. Comparisons of the liver resection rates and survival across spokes and hubs were risk-adjusted for deprivation and other factors, so this difference in deprivation did not bias the results.

The present study, restricted to patients with colorectal cancer and synchronous liver metastasis at diagnosis, demonstrates that variation in the rate of liver resection in England is still present. Furthermore, it indicates that hepatobiliary service centralization, with the existence of a hub-and-spoke arrangement, may be part of the explanation. Any further centralization of cancer services should take into consideration the impact on equity of access to services. These findings suggest that access to specialist hepatobiliary services is inadequate for patients diagnosed in spoke hospital Trusts.

A possible explanation for this disparity may relate to the complexity of managing patients with colorectal cancer and synchronous liver metastases. Colorectal multidisciplinary teams at hospital Trusts with no on-site hepatobiliary services may have less awareness of the availability of novel chemotherapy agents and sophisticated interventional radiological techniques, which have resulted in a widening of the definition of resectable liver metastases³¹. The routine referral of all patients diagnosed with colorectal cancer and liver metastases for discussion at a hepatobiliary MDT meeting would be an effective strategy for improving equality of access. However, as many patients with metastatic colorectal cancer would not benefit from resection but rather palliative treatment, this strategy would also prove resource intensive. The present study highlights the need for standardization of the assessment and onward referral of patients with metastatic colorectal cancer by colorectal MDTs. Clearly defined and nationally agreed referral protocols, increased attendance of hepatobiliary surgeons at spoke colorectal cancer MDT meetings, education programmes from hepatobiliary MDTs to colorectal cancer surgeons, and the use of video-conferencing between hepatobiliary and colorectal cancer MDTs may aid this⁴.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Comparison of characteristics of patients recorded as having metastatic disease at diagnosis in the National Bowel Cancer Audit compared with those with a metastasis code in Hospital Episode Statistics, restricted to patients undergoing major resection (Word document)

Editor's comments

This research implies that patients with liver metastases should be referred to a specialized centre (i.e. a hospital with an on-site specialized MDT). This seems to be a straightforward conclusion that is likely embraced by specialized centres. Of more interest, however, is that an explanation for this difference in resection rates and outcome after surgery remains largely unknown. What is the contribution of non-surgical disciplines that take part in the MDT, including radiology for interventional techniques or medical oncology for chemotherapy?

Similar results have been shown for the surgical treatment of oesophagogastric cancer in the Netherlands suggesting that the findings this study may be applicable to other cancer types and healthcare systems.

A weakness of the study is that only presence of liver metastases was known and not the site of metastatic disease. It is therefore not known which of the patients who did not undergo liver resection had potentially operable disease. This is a strong plea for registering all patients with colorectal liver metastases independent of treatment, including patients that received palliative care only.

B. P. L. Wijnhoven
Editor, BJS