Evaluation of the introduction of a standardised protocol for the staging and follow-up of colorectal cancer on resection rates for liver metastases

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ABSTRACT

INTRODUCTION In 2004, an audit in our unit demonstrated wide variation in liver resection rates for colorectal cancer (CRC) metastases within the cancer network. Subsequently, a network-wide CT-based follow-up and referral policy was introduced for all patients. A second audit was performed to assess the impact of the guidelines on liver resection rates.

SUBJECTS AND METHODS Analysis of prospective liver resection database between 1997 and 2004 and after the introduction of standardised guidelines between January 2005 and April 2008.

RESULTS A total of 362 patients underwent liver resection for CRC metastases between 1997 and 2008, 237 prior to the introduction of the referral guidelines and 125 after. Liver resection rates according to referring hospital varied from 0.92 to 2.32 per 100,000 population before guidelines were introduced. After 2005, resection rates from the four district hospitals standardised (1.68–1.84 per 100,000 population), but the central unit rate (Sheffield) remained significantly higher (2.67 per 100,000 population). No significant difference in 1-year disease-free survival between patients from Sheffield and the out-lying hospitals was found ($P = 0.553$).

CONCLUSIONS Introduction of a referral protocol standardised resection rates from the four district hospitals, but these remain lower compared to the specialist centre. The wide-spread adoption of a policy to discuss all patients with liver metastases at an advanced disease multidisciplinary team meeting, in the presence of hepatobiliary specialists, may further increase resection rates across the UK.

KEYWORDS

Liver – surgery – Healthcare rationing – Colorectal cancer – Metastases

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Despite significant advances in cancer treatment over the past decade, colorectal cancer (CRC) remains a major source of cancer-related mortality, being the second commonest malignancy in the UK and accounting for 10% of all cancer-related deaths.¹ The majority of these deaths result from the development of metastatic disease. Approximately one-third of patients with CRC present with synchronous liver or lung metastases, with a further 8–25% developing metachronous disease following primary tumour resection.^{2,3} Changes in surgical and radiological techniques, in addition to new chemotherapeutic regimens, now enable patients with advanced disease, whose only option in the

past would have been palliation, to be considered for potentially curative treatment.⁴

The so-called ‘postcode’ provision of healthcare services and treatments in the UK has been investigated and highlighted across a range of medical specialities.^{5–10} However, the majority of these studies have been conducted on a national level, subdividing populations into either strategic health authorities, primary care trusts or medical speciality.^{5,6,10} Few investigators have examined the potential inequality of provision at a truly local level within one region. Inequalities in access to healthcare services have previously caused conflict between patients and healthcare

providers.⁹ The National Institute for Health and Clinical Excellence (NICE), whose remit is to produce guidelines which ensure equal access to cost-effective treatments, aims to standardise care across the UK. Implementation of these guidelines at the local level depends upon their dissemination to all clinicians involved in the care pathway, as well as their acceptability to patients.

Following the sub-specialisation of surgical services, the provision of liver surgery in the UK has been limited to several large centralised units.¹¹ Hepatobiliary surgical expertise has become confined to these centres, which in turn are fed by a group of smaller regional hospitals, forming individual cancer 'networks'. This is the case in the North Trent Cancer Network, where Sheffield Teaching Hospitals NHS Trust provides liver and pancreatic surgical services to Sheffield itself and a group of four district hospitals (Fig. 1). In 2004, an audit of referral patterns for liver resection highlighted a wide variation in resection rates for colorectal liver metastases in different populations throughout the region. Guidelines were introduced within the network for the staging, follow-up and referral of patients with colorectal liver metastases with reference to previous NICE and British Society of Gastroenterology guidance,^{12,15} and a further prospective audit commenced. Here, we present the results of our most recent audit and examine the possible reasons behind the inequalities in resection rates across the region.

Subjects and Methods

Prior to the introduction of standardised network guidelines in 2005, patients in the North Trent Cancer Network with colorectal cancer were staged and followed up according to the preferences of their local hospital. There was wide variation in practice in the staging of colorectal cancers, with thoracic disease being assessed mainly by chest X-ray and

liver disease by ultrasonography. An initial audit was conducted by retrospectively analysing a database which recorded all patients undergoing liver resection up to 2004. Patients who had undergone liver resection were sub-divided according to their referring hospital. Population statistics were retrieved from the government census data and used to standardise the resection rate in each area per 100,000 populations per year. Demographic data, such as age and sex, were also available from the database.

A network-wide staging and referral protocol for CRC liver metastases was then introduced in 2005, which stated that all patients presenting electively with primary CRC should undergo staging CT scan of the chest, abdomen and pelvis (CAPCT) prior to colonic resection. Patients presenting as an emergency should have the primary tumour managed acutely (resection or stenting) with staging CAPCT the first intervention. Following potentially curative resection of the primary lesion, follow-up with 3 monthly carcinoembryonic antigen (CEA) levels and CAPCT at 9 months and 2 years, was recommended. A flow diagram of the proposed care pathway after the detection of liver metastases is shown in Figure 2. Following the introduction of these guidelines, all multidisciplinary team (MDT) records were prospectively collected and examined to identify patients undergoing first-time liver resection for CRC liver metastases up to April 2008. Patient case notes were retrieved and the referring unit identified from the initial letter received by the hepatobiliary unit, along with demographic and operative data. This was then cross-referenced with the hospital's patient administration system (PAS) to ensure accuracy.

The first audit in 2004 had indicated a much higher resection rate for liver metastases in Sheffield patients compared to those from the other hospitals. Our concern was, therefore, that we may be being too aggressive in offering surgery to too many people from the Sheffield MDT. We have, therefore, in addition to the main study, prospectively collected data to assess early recurrence after liver resection of colorectal metastases, as demonstrated on CAPCT at 6 and 12 months following resection of the liver metastases, which are routinely undertaken as part of our post-resection follow-up protocol.

Statistical analysis

All data were entered into Microsoft Excel spreadsheets (Microsoft, Redmond, WA, USA). Data analysis for statistical significance was performed using the statistical software package SPSS v.16.0 (SPSS Inc, Chicago, IL, USA).

Averages stated are mean values (range) and non-parametric tests (chi-squared and Kruskal-Wallis) were used to compare demographic and disease-free survival differences between the five regions in the North Trent Cancer Network and between the original audit (1997–2004) and the more recent data (2005–2008). Results were taken to be significant when $P \leq 0.05$.

Results

Our original audit of patients undergoing liver resection for CRC metastases between 1997 and December 2004 identified 237 patients. The male-to-female ratio was 143:95, with a mean age of 63 years (range, 33–89 years). Of these, 102 patients were from the Sheffield region, the rest of the referrals originating from the surrounding districts. Following the introduction of the standardised cancer network referral guidelines (Fig. 2), our 2008 study identified 125 patients who had undergone primary liver resection for CRC liver metastases between January 2005 and April 2008. Of these patients, 51 were from the Sheffield catchment area and 74 were from the surrounding district hospitals.

There were 81 males and 45 females, with a mean age of 65 years (range, 37–81 years). The age and sex distribution of the patients were well matched across all regions in both the first and second audits (Table 1). Comparison of demographic factors between the patients in the original audit (1997–2004) and those from 2005–2008 showed no significant difference in the male:female ratio and age distribution ($P = 0.702$ and 0.351 , respectively, chi-squared test).

The resection rates per 100,000 populations for the different units, from both the 2004 and 2008 audits, are shown in Table 2. The first audit demonstrated a wide variation in resection rates between 1997 and 2004, ranging from 2.32 resections per 100,000 population for Sheffield compared to 0.92 per 100,000 for region 2. Following the introduction of

Table 1 Liver resection patient demographics according to referring hospital between 1997–2004 and 2005–2008

Study period	Demographic	All patients	Sheffield	Region 1	Region 2	Region 3	Region 4	P-value
1997–2004								
	Sex Ratio (M:F)	143:95	64:38	24:8	12:7	26:24	17:17	0.190 ^a
	Mean age (years)	63 [33–90]	67 [37–90]	59 [33–75]	59 [42–76]	62 [40–76]	59 [33–82]	0.720 ^b
2005–2008								
	Sex ratio (M:F)	81:45	32:19	13:10	12:3	14:9	7:6	0.604 ^a
	Mean age (years)	65 [37–81]	65 [45–82]	65 [50–81]	63 [47–78]	67 [40–80]	62 [35–75]	0.790 ^b

All P-values are for each district tested against all others, [age ranges are given in brackets].

^aKruskal-Wallis test; ^bchi-squared test.

Table 2 Colorectal liver metastases resection rates per 100,000 populations per year

North Trent Region	Resection rate 2004 audit	Resection rate 2008 audit	Age-standardised incidence of colorectal cancer
Sheffield	2.32	2.67	37.8
Region 1	1.11	1.84	41.9
Region 2	0.92	1.75	40.2
Region 3	1.52	1.68	46.0
Region 4	1.93	1.77	49.2

Age standardised incidence of colorectal cancer taken from the Trent Cancer Registry, 1999.

the network-wide staging and referral policy in 2005, resection rates in three of the four district hospitals increased, and all four standardised at approximately 1.8 resections per 100,000 populations per year. However, the resection rates from these hospitals remained significantly lower than that of Sheffield, despite Sheffield having the lowest incidence of colorectal cancer.

Six-month and 1-year disease-free survival in the post 2005 patients (as evaluated by follow-up CT scanning) is shown in Table 3. There was no significant difference in the disease-free survival between patients from Sheffield and those referred in from the district hospitals ($P = 0.396$ and 0.553 at 6 and 12 months, respectively), indicating that it is unlikely that we are being overly aggressive in offering liver surgery to patients from Sheffield.

Discussion

Prior to 2005, we found substantial variability in liver resection rates for colorectal cancer metastases across our region. We suspected that the major factor influencing this was the varied primary tumour staging and follow-up policies adopted by each hospital in the region, plus variations in which patients were referred for consideration of liver resection. For this reason, network guidelines were introduced in an attempt to standardise the surveillance for, and referral of, colorectal liver metastases to the central liver resection MDT. This study highlights the success of the introduction of these guidelines, with the standardisation of resection rates from the four regional hospitals. However, there remains a significant difference in resection rates between the central unit (Sheffield) and the district hospitals, the reasons for which are unclear.

Initially, we were concerned about being overly-aggressive in our selection policy in the Sheffield colorectal MDT meeting. At this forum, unlike in the district hospitals, there is always at least one hepatobiliary surgeon present, and all

patients with liver metastases have their imaging reviewed by a specialist surgeon prior to decisions about therapy. If we were being over-aggressive in our selection of patients suitable for liver surgery from Sheffield, then this should be apparent in poor outcomes for the Sheffield patients compared with the patients from the district hospitals. For this reason, we analysed the disease-free survival of all the patients at 6 and 12 months post liver resection (Table 3), and found no significant difference between Sheffield patients and patients from the regional hospitals ($P = 0.396$ and 0.553 , respectively). This has re-assured us that the higher resection rate and potentially more aggressive patient selection in Sheffield do not appear to have had an adverse impact on outcome, in the form of early postoperative recurrence. Our disease-free survival is in-line with experience in the literature and suggests that our selection of patients for surgery is appropriate.^{14–16} It is our intention to monitor this continually and we shall, in the future, have 2- and 3-year disease-free and, ultimately, 5-year survival data for comparison.

We considered whether or not variations in patient co-

Table 3 Comparison of disease-free survival in patients originating from Sheffield and regional hospitals 2005–2008

	Disease-free survival	
	6 months post-resection	12 months post-resection
Sheffield patients	79.6%	63.8%
Regional patients	72.5%	57.9%
P -value ^a	0.396	0.553

^aChi-squared test.

Table 4 Average multiple deprivation score in the North Trent Cancer Network according to local authority

Local authority	Average multiple deprivation score
Sheffield	27.84
Chesterfield	25.75
Doncaster	30.84
Rotherham	26.71
Barnsley	30.48

morbidity between each region may have affected referral and, therefore, resection rates. Our region historically has depended on manufacturing industries as its main source of employment and economic growth. Due to the relative decrease in manufacturing base throughout Britain in recent years, our cancer network serves some of the most deprived populations in the UK.¹⁷ No direct co-morbidity data from our cohort of patients is presented here. However, according to the indices of multiple deprivation scores 2007 (Table 4), the deprivation and morbidity appear to be relatively evenly spread across our cancer network regions.¹⁷ This would suggest that variations in co-morbidity alone cannot account for the discrepancy in resection rates between Sheffield and the outlying hospitals.

The principal difference in the care pathway of the patients from Sheffield and those from outside is the presence of specialist hepatobiliary surgeons at the Sheffield colorectal MDT meetings. In the district hospitals, the local MDT decide upon referral of patients with liver metastases based upon the North Trent Cancer Network guidelines (Fig. 2). It is our impression that, as a result of specialist hepatobiliary input and a close collaborative working relationship with the Sheffield colorectal surgeons and oncologists, patients discussed in the Sheffield colorectal MDT (which has a specific section to discuss patients with liver metastases) are more likely to be considered for liver resection or pre-operative down-staging techniques including chemo- and radiological therapies.

It is worthy of note that the increase in resection rates in the regional hospitals and within Sheffield is probably not due to the introduction of a referral protocol alone. Increased use of induction chemotherapy for initially inoperable metastases, following the publication by Bismuth and colleagues,¹⁸ and a more aggressive surgical strategy in the treatment of advanced disease, have inevitably lead to more resections being undertaken. Other new strategies, such as pre-operative portal vein embolisation and two-stage hepatectomy are also considered in some cases in an

attempt to render even more patients suitable for surgery.⁴ Whereas 10 years ago, bi-lobar or multiple liver metastases in themselves would have been a relative contra-indication to resection, the assessment of the operability of liver metastases is now much more complicated.⁴ It would seem pertinent that all decisions regarding suitability for induction chemotherapy and resection are made by a specialist hepatobiliary MDT that is familiar with these advances in surgical and oncological techniques. With this in mind, we are in the process of changing our local guidelines for referral with a view to assessing all patients with liver metastases within the central MDT, even in the presence of significant extrahepatic disease, and plan to perform a further prospective audit to monitor any change in resection patterns.

Conclusions

Discussing all cases of CRC hepatic metastases at our specialist hepatobiliary MDT is associated with a higher resection rate with no adverse effect on early recurrence in our cancer network. We, as yet, have no data regarding the effect of increased liver resection rates on mortality for colorectal cancer, and we will need to continue to monitor the outcome of surgery closely in all groups to ensure that we are not offering liver resection inappropriately. However, the wide-spread adoption of a policy to discuss all patients with colorectal liver metastases within a specialist MDT should help to standardise treatment, increase resection rates and potentially reduce the mortality from colorectal cancer across the UK. Healthcare providers and resource managers may need to be prepared for a significant increase in hepatic resection for colorectal liver metastases.

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