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for Health Services Research

WORKING GROUP ON ACUTE PURCHASING

Hepatic Resection as a Treatment for Liver Metastases in Colorectal Cancer

July 1999

GUIDANCE NOTE FOR PURCHASERS 99/02

Series Editor: Nick Payne

InterDEC Report No: 02/1999

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authority and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of appropriate evidence, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 13 July 1999 at which this Guidance Note for Purchasers (in a draft form) was considered.

HEPATIC RESECTION AS A TREATMENT FOR LIVER METASTASES IN COLORECTAL CANCER

AUTHORS: Beard SM, Holmes M, Majeed A, Price C. Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1999. Guidance Note for Purchasers: 99/02.

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The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts.

DECISION: The Committee considered that hepatic resection as a treatment for liver metastases in colorectal cancer should be considered as part of the Regional oncology services. It was clear that new surgical techniques offer better opportunities for patients. The Committee recommended the development of the service across Trent, and that it be subject to regular audit and review.

July 1999

HEPATIC RESECTION AS A TREATMENT FOR LIVER METASTASES IN COLORECTAL CANCER

SM Beard
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Trent Institute for Health Services Research
Universities of Leicester, Nottingham and Sheffield

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Conflict of Interest None of the authors of this document has any financial interests in the drug or product being evaluated here.

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ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;
- provides advice and support to NHS staff on undertaking HSR;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor C E D Chilvers (Nottingham); and
Professor M Clarke (Leicester).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (ScHARR).

FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Health Authority and Trust Chief Executives (HATCH) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterDEC, with units in other regions. These are: The Wessex Institute for Health Research and Development and The University of Birmingham Department of Public Health and Epidemiology.

Professor R L Akehurst
Chairman, Trent Working Group on Acute Purchasing

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Colorectal cancer spreads to the liver and the frequency of this metastatic event is high with around 25% of patients having liver metastases at the time of presentation (synchronous metastases) and a further 25-50% of patients developing liver metastases some time during the course of their disease (metachronous metastases).

The standard treatment for patients with hepatic metastases is systemic chemotherapy. This is typically administered using drug regimens based on 5-fluorouracil (5-Fu), which offer modest prolongation of survival, although very rarely leading to a cure, with 5-year survivals reported at less than 5% by the majority of advanced colorectal chemotherapy trials.

Other experimental treatments for liver metastases include local ablation with arterial chemotherapy, embolisation or cryotherapy and surgical removal. With the exception of surgery, none of these treatments has appeared to provide any real impact in terms of overall survival and long-term cure.

Historically, surgical removal, or resection, of liver metastases has been restricted to only a small percentage of patients who have had single, unilobar metastasis because of the technical difficulties of the resection.

There are no published randomised controlled trials which directly compare the role of liver resection against standard treatments for liver metastases. However, there have been a large number of reported case-series spanning a period of over two decades. This review identified 21 independent studies involving more than 100 patients in each case.

Based on the reported survival outcomes for the treated populations as a whole, five year survival following surgical resection ranges between 21-41% (compared with <5% survival in similar patients without such surgical intervention). The best prognosis group are those with single metastases, without evidence of extrahepatic involvement. However, sub-group analysis with case-series suggests that, despite the number and size of tumours, there are clear survival advantages for patients with multiple metastases if the resection can successfully remove all of the metastases without leaving positive margins. The more recent, larger single centred studies report operative mortality rates of around 0-4% and post operative complications rates of 10-30%.

Although some patients already have access to liver resection, particularly in cases of single metastases, it is widely felt that there are many more patients who could benefit potentially who remain either undiagnosed or are receiving purely palliative treatment.

The costs of liver resection are estimated at £6,402 which covers initial work-up, the surgical procedure and the post-surgical management of patients. The typical systemic chemotherapy for non-resected patients is based on 5-FU and is estimated to cost £2,223 per month, with an average three to six months' treatment per patient.

The estimated marginal costs of providing liver resection within a 'typical' health authority of 500,000 population are £130-135,000, based on an estimated 10% of patients being suitable for resection. This assumes that there is no avoidance of chemotherapy costs. In some cases, however, surgical resection would obviate the need for palliative chemotherapy.

Excluding any savings that may be made through avoided chemotherapy treatment, and assuming no differences in salvage treatment for relapses, the cost per life year gained (LYG) for liver resections lies in the range £2,134 to £3,945 per LYG. This figure is dependent on the actual proportion of resections which can be performed with curative intent. The range quoted covers 100% to 50% of resections having curative intent and reflects the range of reported experience from case-series.

If widespread follow-up of colorectal patients were to be adopted, in the light of improved survival following liver resection, then it is likely that cost-effectiveness will increase by an estimated 50% (based on 5-year survival rates and an estimated cost of follow-up including 6-monthly out-patient attendances and ultrasound scans).

ABBREVIATIONS

5-FU	5-Fluorouracil
AUC	Area under the curve
BNF	British National Formulary
CEA	Carcino-embryonic antigen
CT	Computed tomography
CXR	Chest x-ray
ECR	Extra Contractual Referral
EHD	Extrahepatic disease
FUDR	Floxuridine
HAI	Hepatic arterial infusion
HDU	High dependency unit
HRG	Health Care Resource Group
ITU	Intensive treatment unit
LV	Leucovorin
LYG	Life year gained
MRI	Magnetic resonance imaging
MTO 3	Medical Technical Officer Grade 3
PIS	Patient information system
RCT	Randomised controlled trial

1. INTRODUCTION

1.1 Background

Primary cancer of the large bowel - colon and rectum - is the second commonest cancer in the United Kingdom overall with an annual incidence rate of around 57 per 100,000 population per annum.[1] Colorectal cancer spreads to the liver and the frequency of this metastatic event is high. Around 25% of patients who present with colon and rectal cancer have liver metastases at the time of presentation (synchronous metastases). Up to a further 25-50% of patients will develop recurrent tumour in the liver during the course of their disease (metachronous metastases), typically during the first two years following the treatment of the primary cancer.[2,3,4]

Liver metastases are seen as a major cause of death in patients with colorectal cancer.[4] Overall survival for patients with liver metastases is closely related to tumour burden, and untreated patients with single unilobular disease have previously had a median survival of around 21 months.[5] However, the long-term outlook for all such untreated patients, including both single and multiple lesions, is universally recognised as poor with little or no observed five year survival.

Conventional treatments for such liver metastases have either been purely palliative or have involved a range of techniques including: systemic chemotherapy; local ablation with arterial chemotherapy; embolisation or cryotherapy and surgical removal. With the exception of surgery, none of these treatments has appeared to provide any real impact in terms of overall survival and long-term cure. Because of the recognised difficulties in operating on the liver (bleeding etc.), surgical removal has been restricted historically to only a small percentage of patients who have had single, unilobular metastasis.

More recent advances in surgical techniques, coupled with the relative lack of success in non-surgical treatment, has led to an increasing number of more specialist centres operating on a wider group of patients including those with multiple metastases and bilobar disease. Overall survival, following liver resection at such centres, has been suggested to be between 25-35% at five years, with a gradual improvement noted in survival and morbidity over the last 10-15 years since such treatment has been available. Importantly, this more aggressive liver resection can leave patients requiring significant post-surgical care involving high cost Intensive Therapy Unit (ITU) provision.

However, despite the numerous reported case-series, there remains as yet no conclusive randomised controlled trial (RCT) which can clearly define the likely benefits of liver resection for a particular patient group. The proportion of patients who may be suitable for resection remains heavily debated. Many of the published studies attempt to identify independent prognostic factors which may help to categorise levels of expected outcome for patient groups. In particular, the most helpful of these prognostic factors would be those which can be identified before the surgery has begun. Unfortunately, whilst some prognostic factors are well accepted, such as the presence of extra-hepatic disease, others, such as the actual number and position of the metastases, are more contentious.

Although some patients already have access to liver resection, particularly in cases of single metastases, it is widely felt that there are many more patients who could benefit potentially who remain either undiagnosed or are receiving purely palliative treatment.

The purpose of this guidance note is to identify and review the current state of evidence for the effectiveness of liver resection in cases of metastases related to colorectal primary lesions. Where possible, it draws on the likely characteristics of good prognosis groups and the likely impact that such patients may have on NHS resources. Finally, the authors consider the additional primary research which may be required to address the unanswered issues of liver resection, such as the role of more complex surgery, indications for re-resection and the justification for the use of adjuvant chemotherapy as well as follow-up of colorectal cancer patients.

1.2 Surgical Resection of Secondary Liver Cancer

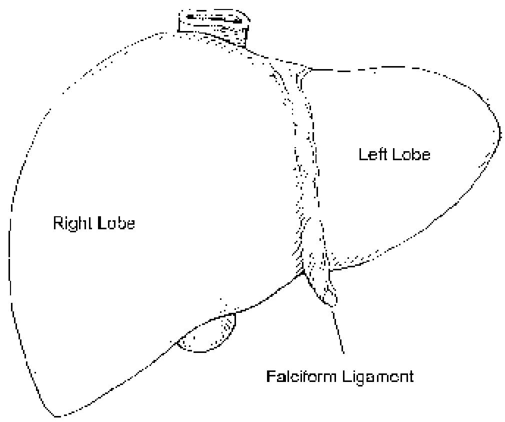
In the early years since its inception, this type of surgery was not very common because of a high operative mortality and morbidity. Over the past 10 years, however, significant technological progress has been made in liver resection, with better understanding of the anatomy of the liver and the physiological and metabolic consequences of major hepatic resections. The advent of intra-operative ultrasonography, ultrasonic dissection, and argon spray coagulation have made it possible to resect large amounts of liver tissue without significant complications. Furthermore, the liver is perhaps the only solid organ with the ability to regenerate completely after resection of even a large percentage of its volume.

For many years the criteria for selection of patients for liver resection for colorectal cancer was considered to be a single metastasis on one or other side of the liver which could be removed surgically with a margin of at least 1cm. This is still the practice in most general hospitals in the UK at present. With technological advancement, some surgeons have extended the criteria to include two to three metastases from one or other lobes of the liver. More recently, specialist liver surgeons have successfully resected fairly extensive disease from both sides of the liver with reports of long-term survival.

1.2.1 Technical Aspects of Hepatic Resection

The human liver is a solid organ anatomically situated in the upper abdomen underneath the diaphragm. Morphologically, it is divided into the right and left lobes demarcated by the falciform ligament (Figure 1).

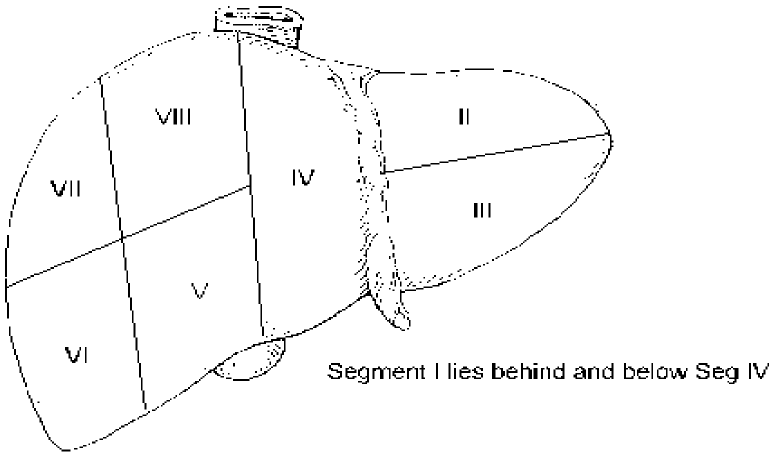
Figure 1 The Lobar Structure of the Liver



The liver has a dual blood supply, approximately 80% of the supply comes from the hepatic portal vein which drains blood from most of the gastro-intestinal tract, and 20% from the hepatic artery which is a branch of the coeliac artery (arising from the aorta). It is an extremely vascular organ with 1.5 litres of blood passing through it each minute (30% of the cardiac output).

There are eight anatomical segments in the liver, segments I, II and III lie to the left of the falciform ligament and are supplied by the left branch of the hepatic portal vein and hepatic artery. Segment IV lies to the right of the falciform ligament and is also supplied by the left hepatic portal vein and hepatic artery. Segments V, VI, VII and VIII lie entirely on the right side with segments V and VI lying below VII and VIII and supplied by the right branch of the hepatic portal vein and hepatic artery. (Figure 2).

Figure 2 The Segmental Structure of the Liver



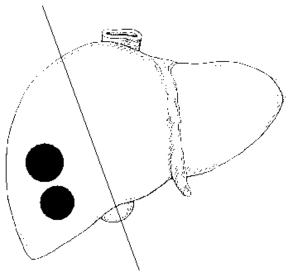
Hepatic resections are classified according to the site of the segments removed. Anatomical resections are further complicated because the nomenclature used is morphological. These are shown in Table 1. There is a different nomenclature in use in North America, which compounds the confusion and will not be discussed here.

As a general rule, anatomical resections are associated with shorter operating time, lower blood loss and quicker recovery with a low risk of liver failure. Extended resections, especially right-sided ones, are associated with a significant risk of liver failure especially if the size of segments II and III is small, however, the development of selective portal vein embolisation has allowed pre-resection hypertrophy and significantly reduces the risk of liver failure despite very extensive resection.

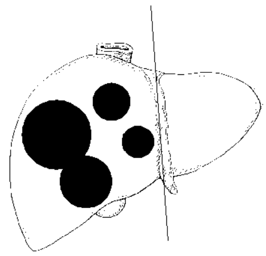
Table 1 Nomenclature of Hepatic Resections

Type of Resection	**Segments Removed**	**Anatomical or Extra-anatomical**
Right hemi-hepatectomy	V,VI, VII and VIII	Anatomical
Left hemi-hepatectomy	II and III	Anatomical
Extended right hemi-hepatectomy	IV, V, VI, VII and VIII	Extra-anatomical
Extended left hemi-hepatectomy	I,II,III and IV	Extra-anatomical
‘Central’ resection	IV with or without I	Extra-anatomical
‘Segmental’ resections	Any segments (single or in combination of adjoining segments) in a single lobe except I and IV	Anatomical
‘Bilobar’ resections	Any segment in both lobes	Extra-anatomical
‘Wedge’ resections	Any segment, superficial tumour	Extra-anatomical

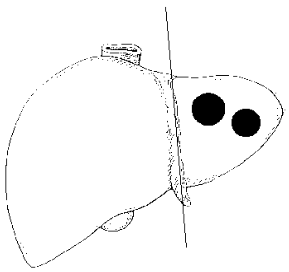
These resections are described in the following illustrations for easier comprehension:



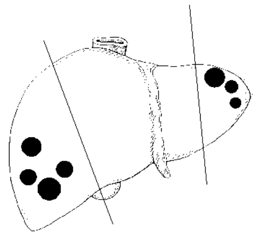
Right hemi-hepatectomy



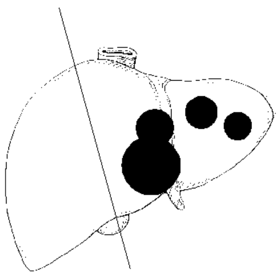
Extended right hemi-hepatectomy



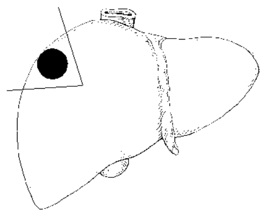
Left hemi-hepatectomy



Bilobar resection



Extended left hemi-hepatectomy



Wedge resection

1.3 Non-surgical Treatment of Secondary Liver Cancer

The lack of clear benefit from the non-surgical treatment of hepatic metastases from colorectal cancer has meant that many patients have been managed symptomatically without attempt to 'cure'. This review has not attempted to evaluate the evidence of clinical effectiveness of the range of alternative treatments which are on offer, but in the review of effectiveness reference has been made to a number of case-series reporting survival for patients who did not receive surgery. In assessing the marginal costs and benefits of liver resection a direct comparison has been made with systemic chemotherapy.

1.3.1 Chemotherapy

A detailed discussion of the role of chemotherapy in colorectal cancer is beyond the scope of this document. In summary, chemotherapy is offered to patients with colorectal cancer in two settings, adjuvant and palliative.

Adjuvant chemotherapy:
Adjuvant chemotherapy is given to patients after resection of the primary colonic or rectal cancer and is usually offered to patients with locally advanced (Dukes C) cancers diagnosed on histological examination of the resected specimen. This has a 'prophylactic' value and has been clearly shown to reduce recurrence and improve survival in this group of patients. The 'De Gramont' regime with 5-fluorouracil (5-FU) and folinic acid (leucovorin) is currently favoured.

Palliative chemotherapy:
Palliative chemotherapy is given to patients who have the following:

- Locally advanced colonic cancers and the colorectal surgeon is unable to clear completely the primary tumour;
- Patients who have synchronous liver metastases which have not been resected;
- Patients who have recurrent abdominal or lung tumours.

The aim of therapy in this group of patients is to prolong survival and alleviate symptoms, although there is no good evidence that either of these goals are achieved.[6]

The choice of therapy depends upon whether the patient has already been given 5-FU as adjuvant treatment, in which case alternative drugs (e.g. Tomudex or oxaliplatin) may be considered.

In the UK, probably the most common form of 5-FU palliative treatment is the 'De Gramont' 2-day regimen. This is based around a daily treatment involving an initial combined 2-hour infusion of leucovorin (200mg/m^2) + bolus 5-FU (400mg/m^2) followed by a 22-hour infusion of 5-FU (400mg/m^2). This regimen is typically repeated every 14 days. A patient may face an average of six cycles of therapy (i.e. a three month active treatment period). An alternative 5-day 'Mayo' 28-day cycle regimen can also be used in some cases, with slight differences in toxicity and drug dosage.

Chemotherapy for liver metastases may also be delivered locally via a hepatic arterial infusion catheter (HAI). The advantages of HAI lie in the more direct administration of chemotherapy drugs to the liver, potentially minimising systemic exposure. A number of trials have reported response and potential survival advantages over systemic chemotherapy and no treatment. However, within the UK the use of HAI would still be regarded as experimental and would not be available outside of a clinical trial.[4,6,7]

Other treatments which may be given alone or in combination with surgery include:

1.3.2 Cryotherapy

Cryotherapy utilises rapid freezing of the tumour. The abdomen is opened and a cryotherapy probe is placed in the centre of the liver metastases. An ice-ball is then formed which is allowed to thaw; one or more freeze/thaw cycles are used to achieve a significant degree of tumour destruction.

1.3.3 Interstitial Laser Therapy

Interstitial laser therapy utilises the delivery of energy to the core of the metastases in order to heat the metastases with a view to destruction. The principles are the same as for cryotherapy; instead high temperature is used for destroying tumours.

1.3.4 Interstitial Radiation

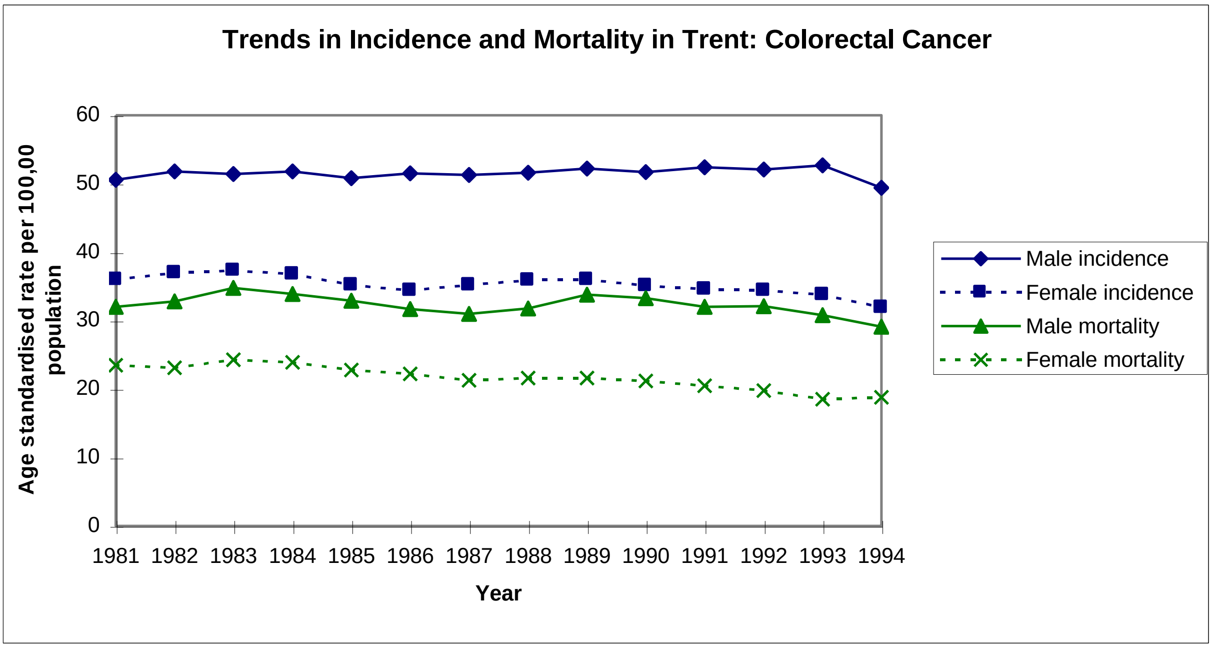
Radiation delivered directly to the metastases by implanted radioactive seeds is another approach to controlling tumour growth.

1.4 Scale of the Problem in a 'Typical' District

The incidence of colorectal cancer (ICD-10: C18/C20) has been recorded at 54.8 per 100,000 population per annum for the Trent region during 1992/94.[8] Given an estimated population of 4.6 million for this period, this represents approximately 2,650 reported cases per annum (270 cases for a 'typical' health authority population of 500,000). This level of incidence fits well with nationally reported rates of 59.5 per 100,000 (male) and 56.3 per 100,000 (female).[1]

The incidence and mortality rates for colorectal cancer have remained steady over the last 15 years, with only a slight reduction in observed mortality rates (Figure 3). Recorded cases of colorectal cancer are apparent from around 35-40 years of age and increase with age steadily, showing a consistently slightly higher incidence in males than females.

Figure 3 Trent Colorectal Cancer Statistics



Around 25% of colorectal patients will present with liver metastases diagnosed at the same time as the primary tumour (synchronous cases). Around 25-50% of patients will develop liver metastases some time after the primary surgery, typically within a 2-year period (metachronous cases). Therefore, within the Trent region around 2,000 new cases of liver metastases, directly related to a primary colorectal cancer would be expected. For a 'typical' health authority of 500,000 population, these figures equate to an expected 270 new cases of colorectal cancer each year, with an estimated 210 cases involving liver metastases (70 synchronous/140 metachronous).

It is possible that these numbers are over-estimations due to the high percentage of patients with colorectal cancer being elderly and the fact that some might, therefore, be unfit for major surgical resections due to significant co-morbidity. Age alone should not be a contra-indication to surgery due to improved outcomes with the use of modern anaesthesia and post-operative care.

In trying to determine the best way to manage these patients a key question is which patients, if any, should receive surgery. The historical clinical view has been that between 5-10% of liver metastases cases are resectable. This implies that within the Trent region there are between 100-200 cases of liver metastases which are potentially resectable. However, more recent case-series from specialist centres have utilised much wider eligibility criteria and, potentially, this could expand the proportion of patients suitable for resection to 20-25%.

In an attempt to try to identify the number of patients undergoing liver resection (as defined by a J02 procedure code) a search of the Trent Patient Information System (PIS) database 1996/97 was conducted. Initially, the analysis was restricted to patients coded as having colorectal primaries. This revealed just four patients undergoing liver resection, of whom only two had a diagnosis coding of secondary liver metastases. The analysis was expanded to include any patient who had either a coding of secondary liver or primary colorectal cancer, as it was felt that coding omissions might explain the low number. This second, wider search, revealed 21 patients undergoing liver resection in the Trent region during 1996/97.

2. HEPATIC RESECTION AS A TREATMENT FOR LIVER METASTASES IN COLORECTAL CANCER: SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Literature Search Strategy

In searching the literature relevant to the treatment of metastases from colorectal primaries, the authors considered all reported reviews and case-series of liver resection over an initial period covering 1990 to July 1998.

The search focused on the following data bases:

- MEDLINE;
- EmBASE;
- COCHRANE LIBRARY;
- HMIC (Dept of Health/ King's Fund/ HELMIS);
- CRD (DARE/NEED/HTA databases);
- 20-25 other information sources, covering web sites, personal contacts and literature databases.

Precise search terms, used in the main searches of Medline and EmBase for evidence of liver resection, are provided below.

EmBASE 1/1990-7/1998

No.	Records	Request
1	28472	explode 'COLON-CANCER'/ all subheadings
2	18384	explode 'RECTUM-CANCER'/ all subheadings
3	32620	#1 or #2
4	7063	'LIVER-METASTASIS'/ all subheadings
5	5088	'LIVER-CANCER'/ all subheadings
6	27909	'METASTASIS'/ all subheadings
7	226	#5 and #6
8	7271	#4 or #7
9	5175	explode 'LIVER-RESECTION'/ all subheadings
10	317	#3 and #8 and #9
11	228	#10 and (PY >= "1990")

MEDLINE 1/1990-7/1998

1	exp colonic neoplasms/ or exp rectal neoplasms/	24,067
2	exp Liver neoplasms/	20,139
3	Hepatectomy/	3,338
4	resection.ti.	6,331
5	3 or 4	9,051
6	((liver or hepatic) adj6 metast$).tw.	5,789
7	1 and 2 and 5	334
8	1 and 6 and 5	301
9	7 or 8	348
10	(animal not human).sh.	699,672
11	9 not 10	342
12	from 11 keep 1-342	342
13	from 12 keep 1-342	342

As a result of the review of this evidence, particularly previous reviews of liver resection, the search was expanded to include case-series dating back to 1984. This was felt necessary as many of the more recent reviews were still referencing larger series reported from this earlier period.

In total 59 case-series were found which reported on the use of liver resection in cases of metastases related to colorectal primary cancer. As resection represents a fairly specialised surgical technique it was felt justified to concentrate on case-series which reported survival results in more than 100 patients. Also, consideration was only given to the latest published data covering specific patient cohorts, as in some cases there were multiple reports of case-series.

Therefore, in total 21 independent case-series were identified, representing different patient cohorts, which had sufficient patient numbers (>100) to be able to infer treatment consequences in terms of overall survival, operative morbidity and/or pre-operative prognostic factors. (see Tables in Appendices.)

2.2 Clinical Effectiveness of Non-surgical Treatment

In evaluating the role of liver resection, it is important to compare results with those achieved with no treatment or with other non-surgical treatment modalities. As already discussed, the standard alternative treatment for patients with liver metastases is systemic chemotherapy based on the use of 5-FU + a modulator, with the most common regimen based on the De Gramont dosage/administration combination.

The ideal evidence of effectiveness would be a direct randomised trial of resection against standard chemotherapy in patients with potentially resectable liver metastases. However, it was not possible to identify any randomised controlled studies which would allow this direct comparison to be made. Given the growing world-wide acceptance of the role of liver resection, as the only potentially curative treatment for liver metastases, the future availability of such randomised comparable data in non-resected patients is very unlikely.

One potential source of indirect comparative data is the existing group of published trials which have considered the relative efficacy of different chemotherapy regimens for patients with advanced colorectal cancer, often involving liver metastases. This body of data has been concerned generally with the comparison of 5-FU with 5-FU + modulator, and evaluating the role of HAI against continuous infusion, often using floxuridine (FUDR) rather than 5-FU.

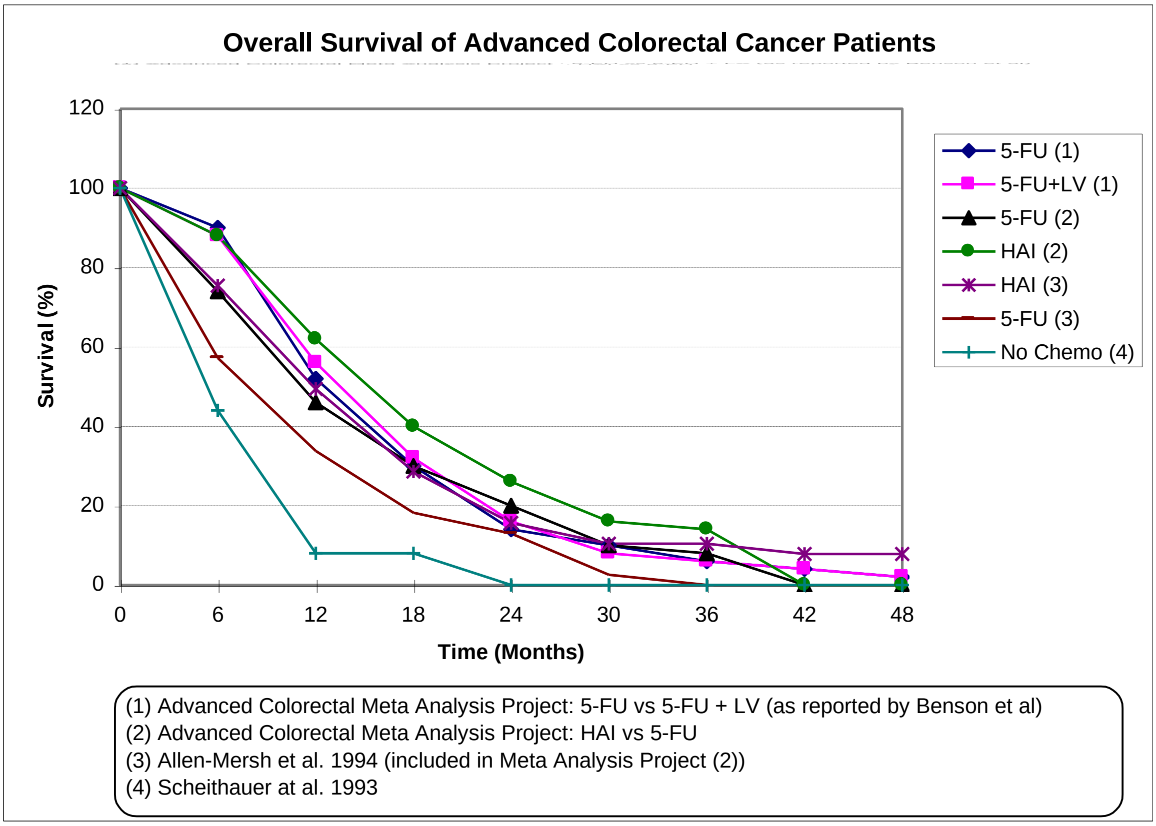
A recent Advanced Colorectal Meta-Analysis project considered the efficacy of 5-FU in the treatment of patients with measurable non-resectable metastases and no evidence of extrahepatic disease.[9] Covering 1,400 patients from nine trials, the results suggested a 23% tumour response rate and an overall median survival of approximately 12 months for 5-FU + leucovorin.

The group went on to consider the role of HAI against continuous infusion in a subsequent meta-analysis of seven trials covering 654 patients.[10] The studies compared HAI based FUDR with a control arm of either intravenous FUDR / 5-FU or no treatment. Overall, 5-FU was associated with a 14% response rate and an overall survival of 12 months. This compared with an HAI tumour response rate of 41%. However, the only significant survival advantage for HAI was discovered when compared to a no-treatment group.

Allen-Mersh et al.[11] considered the efficacy of HAI versus conventional chemotherapy in 100 non-resectable advanced colorectal cancer patients, having no greater than 60% liver involvement and no extrahepatic disease (EHD). The HAI group achieved a median survival of roughly 13 months compared with seven months for the control group.

Scheithauer et al.[12] considered the relative benefits of 5-FU + leucovorin (LV) + cisplatin in 40 previously untreated patients with liver metastases or recurrent primary disease. Compared with non-chemotherapy supportive care only, chemotherapy was associated with a relatively small, but statistically significant, advantage in median survival (11 months versus 5 months).

Figure 4 Survival of Advanced Colorectal Patients - Typical Datasets

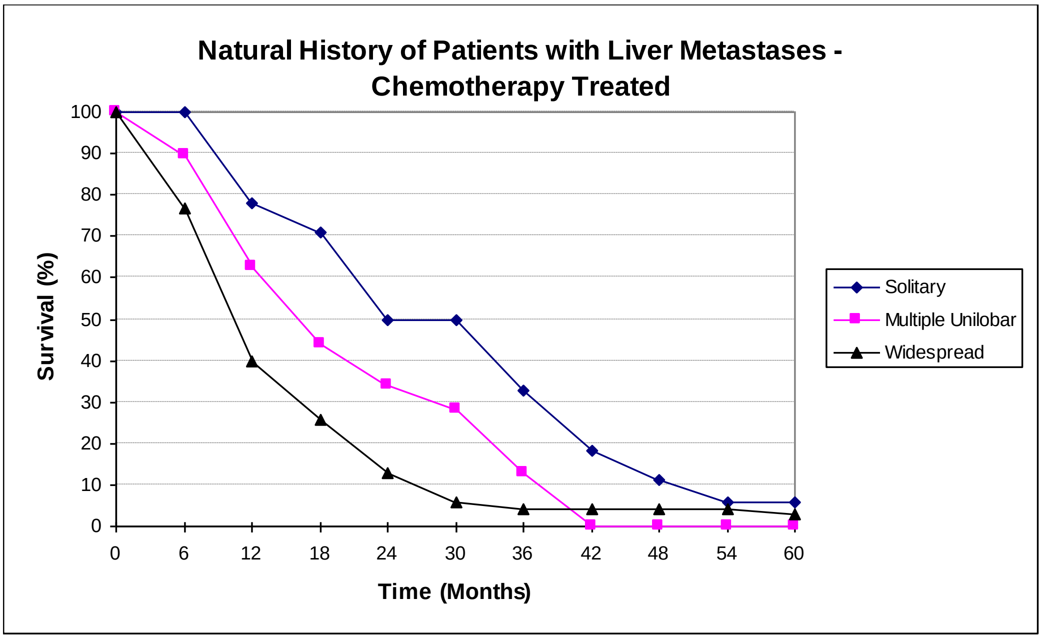


Taken together, this body of data suggests a 12 month overall median survival for patients with advanced colorectal disease, with little or no 5-year survival (Figure 4). However, although randomised, the problem with advanced colorectal trial data is that the patient group is much broader than those with pure isolated liver metastases. Patients with colorectal related liver metastases are currently classified as Dukes Stage D, which also encompasses those with much more widespread metastatic disease. These trials tend to include a range of Dukes C and D patients. As such, the study populations almost certainly include patients with tumour burden and EHD which would exclude them from aggressive liver resection.

An alternative is to derive comparative data from resection case-series themselves as several of the studies have tried to identify a comparison group, often quoting survival outcomes for resected, non-resected and non-curative resected patient groups. It is likely that these non-resected patient groups are more suitable for comparison although, clearly, in the absence of randomised studies, it is difficult to be confident of comparing like with like. Patients going forward for liver resection, even in units which strongly advocate this surgery, are highly selected; i.e. without significant comorbidities, surgically fit with a low chance of perioperative mortality and a pattern of secondaries which is resectable. Patients who are not operated on, by contrast, include all those rejected for surgery because their tumours were too far advanced or they were suffering from other conditions likely to affect the outcome adversely.

The most notable attempt to establish a comparable control group for liver resection comes from Wagner et al.[5,13] in a study analysing the fate of 252 unresected patients. They excluded from this group those with extrahepatic spread and significant comorbidities in order to create a group which could act as historical controls for patients having resections. Even so, the group was likely to have more severe disease than those having resections as only 70 had tumours which were judged as resectable. Median survival for unilobular and multilobular lesions was 21 and 15 months respectively. Over 20% of patients with solitary liver lesions lived for three years or more, but very few survived for more than five years (Figure 5).

Figure 5 Overall Survival in Cases of Unresected Liver Metastases



Source : Excel graph using data taken from published survival curve - Wagner et al.[5]

By contrast, a recent review of the natural history of patients with untreated liver metastases considered the outcome of 172 Swedish patients, all of whom had proven colorectal cancer. The original laparotomy enabled a clear diagnosis of synchronous metastases in 155 (91%) of these patients. The mean age of the patients was 69 years (range: 35 years - 89 years) and, as with many series, a slight bias towards men (83 versus 72) was observed. None of these patients had further treatment other than the surgery for the primary tumour. Median survival on follow-up was 4.5 months; the longest survival was 36 months. Metachronous metastases were observed in 12 of the 172 patients, between 3-26 months following the primary tumour surgery.[3]

Stangl et al.[14] considered the survival experience of 1,099 patients with liver metastases, splitting the group into those receiving resection, regional chemotherapy, systemic chemotherapy and no-treatment. Overall, median survival was 30 months with only 3% (36/1099) achieving a 5-year survival. The curative resection group had a 41% five-year survival rate compared to 0-5% for the remaining patient groups.

Wade et al.[15] analysed the computerised files of the US Department of Veterans Affairs Hospitals from 1988 to 1992 representing over one million admissions per year. They identified 887 patients whose codes indicated that they had a single liver metastasis which was not resected. Mean survival was 11 months, with a projected five-year survival of 2%.

There are clear difficulties in identifying a comparison group which makes drawing firm conclusions about the natural history of untreated, or non-surgically treated hepatic secondaries very difficult. However, it is clear that, whilst there is variation in quoted survivals for these patients for periods of under five years, instances of survival beyond five years for such patients are rare. Even in the group likely to do best, those with a single unresected metastasis, no literature was identified which reported five-year survival of greater than 5%.

The Wade et al. study[15] appears to provide the most appropriate comparative data, as it is stratified by the extent of the liver metastases and the solitary and unilobar group is likely to be closest to representing a group of potentially resectable patients.

2.3 Clinical Effectiveness of Liver Resection

2.3.1 Quantity and Quality of Evidence

To date there have been no reported randomised controlled trials which directly compare the role of liver resection against other treatments. However, there have been a large number of reported case-series spanning a period of over two decades. The majority of these published case-series involve small numbers, but a core group of significant studies was identified, each of which involved more than 100 patients.

Although this group included significant series dating from the mid to late 1980s, including a large series from the Mayo clinic (US)[5,13] and a large multi-centre study from North America and England,[16,17] these tended to have more recently published updates and, as such, they have not been included in the summary of effectiveness. Overall, 21 independent case-series were identified each of which reported survival in over 100 patients. The authors have chosen to concentrate on these series on the basis that larger studies represent best practice and have more potential to identify significant sub-groups with differing chances of survival.

The majority of the studies (20 out of 21) have been published during the last 10 years. Most series come from single centres, although there are multi-centre studies from France,[18,19] the Netherlands[20] and the USA.[15,21,22] Irrespective of the publication year there tends to be great variation in terms of the precise time-period in which the data were collected. A number of the series (9 out of 21) include cases from more than twenty years ago.

Some series have methodological problems in that they rely heavily on retrospective analysis of computerised records of large population groups. This raises concerns firstly in terms of the reliability of such data, and sufficient detail on the type of resection conducted is not easily accessible. Others are predominantly retrospective studies which must carry caveats in terms of the quality of data collection and control of the patient group. Only four series seem to have explicit prospective data collection.[21,23,24,25]

Basic patient characteristics in these studies are broadly similar with mean age at operation around 60 years and similar numbers of men and women. Of more significance are differences between the studies in the criteria used for operation and the criteria used for inclusion and exclusion in the reported series. There are opportunities to exclude patients before, during, or even after the operation. Pre-operative exclusions are designed to identify those patients whom the surgeon considers will benefit from surgery. The types of test used have changed over time with, for example, the introduction of computerised tomography and nuclear magnetic resonance imaging. The criteria used to exclude or include patients for surgery also varies widely over time and between centres. This aspect of patient selection is a key part of the assessment of the procedure which is discussed in Section 2.4 on prognostic indicators.

Most of the series attempted to exclude pre-operatively patients whose cancer had spread outside the liver and in whom the tumour was not resectable. However, the extent to which pre-operative investigations are able accurately to identify these patients is hard to assess from the literature. A large series from Erlangen, Germany[25] reported that of 1,718 patients with hepatic metastases, 80% were subjected to laparotomy, of which 64% did not go forward to resection. Another study[26] excluded a further 20% of cases during surgery on the basis of intra-operative ultrasound and the surgeons' view of tumour resectability. Other series are not clear about the proportions excluded and may have attempted some sort of resection on all the patients selected on pre-operative criteria. In this second instance, patients may be classified post-operatively into groups according to whether the tumour actually was resected completely by the surgeon, either on inspection, or after microscopic examination of the margins of the resected liver.

A further cause of difficulty in comparing studies comes from differences in which patients are selected for reporting, and differences in the treatments patients received after resection. Clearly some series have given adjuvant therapies to some,[23] or all patients.[27] Some series exclude patients who have had repeat resections[28] while others include them. The 859 resections reported by Hughes et al.[17] only included those who survived for 30 days after operation, while most other series include perioperative death in their 5-year survival data.

The type of resections reported in the series is yet another variable, related to the selection of patients for surgery, where the complex nomenclature makes it particularly difficult to make accurate comparison. Finally, variation in the length and completeness of follow-up is particularly important where the main outcome measure is survival. Some series claim 100% follow-up[23,24,25] while in others follow-up is either lower or not mentioned.[27]

2.3.2 Patient Survival

The majority of the studies (16 out of 21) focus on five-year actuarial survival as a primary measure of outcome, with fewer studies using median survival statistics. Based on the reported survival outcomes for the treated populations as a whole, five-year survival ranges between 21% and 41%. (See Table 2).

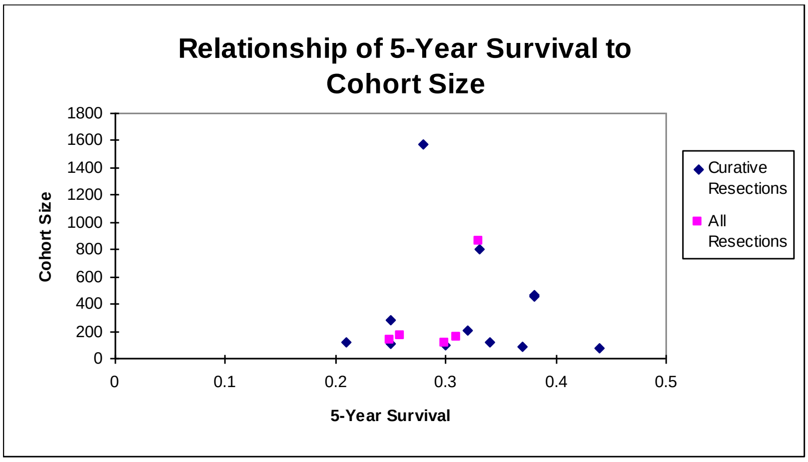
Table 2 Overall 5-Year Survival Rates Following Hepatic Resection

Ref	Potentially Curative Only	Sites	Years	Median Survival	5-Year Survival	Operative Mortality	Operative Morbidity
Fuhrman et al.[26]	Y	Y	14	-	44%	2.8%	-
Bakalakos et al.[27]	N	Y	15	20 mths	-	-	-
Fong et al.[29]	Y	Y	6	-	38%	2.8%	24%
Taylor et al.[30]	N	Y	16	-	34%	0%	28%
Scheele et al.[25]	N	Y	32	33 mths	33%	4.4%	16%
Hughes et al.[22]	N	N	37	-	33%	-	-
Gayowski et al.[31]	Y	Y	11	-	32%	0%	-
Doci et al.[32]	N	Y	10	28 mths	30%	5%	33%
Rees et al.[24]	N	Y	9	-	30%	1%	17%
Nordlinger et al.[19]	N	N	22	-	28%	2.3%	23%
Wade et al.[15]	N	N	14	31 mths	26%	4%	-
Ohlsson et al.[23]	Y	Y	24	25 mths	25%	3.6%	14%
Jenkins et al.[28]	N	Y	18	-	25%	3.8%	18%
Rosen et al.[33]	Y	Y	27	-	25%	2%	-
Van Ooijen et al.[20]	Y	N	10	-	21%	7.6%	34%
Steele et al.[21]	N	N	4	37 mths	-	-	-

Despite differences in patient prognostic grouping and overall patient numbers, the general pattern is one of improving overall survival rates, peri-operative mortality and morbidity. Influences of technical advances in such treatment would appear to explain these improvements particularly as resection has become progressively more aggressive in these series. A few studies cover long periods of time allowing the possibility to consider the influence of improvements in surgical technique over the last 10-20 years. In a series of 111 cases from 1971 to 1995 in a single centre in Sweden, the five-year actuarial survival increased from 19% in the period up to 1984 to 35% thereafter.[23] Reporting on 450 resections, 30 of which were carried out before 1980, Scheele et al. reported only marginal differences in five-year survival of 37% and 39% between the two groups, though the second group appears to have had more radical surgery.[25] Whilst it remains difficult to attribute definite causal relationships to improvements over time-periods, there appears to be some justification for the argument that improvements in surgical technique and post-surgical care are allowing a comparable level of survival in more complex patients.

Another feature is that the longest five-year survivals are from single centres. The main multi-centre studies,[15,19,34] have five-year survivals of 21%-28%. The more numerous single centre studies range from 21% to 44%, which may indicate an effect of surgical expertise concentrated in these centres. The spread of the reported five-year survival data, plotted against the cohort size of the studies, implies that the largest published studies reflect the mid-range of reported survival.

Figure 6 Plot of 5-Year Survival versus Cohort Size

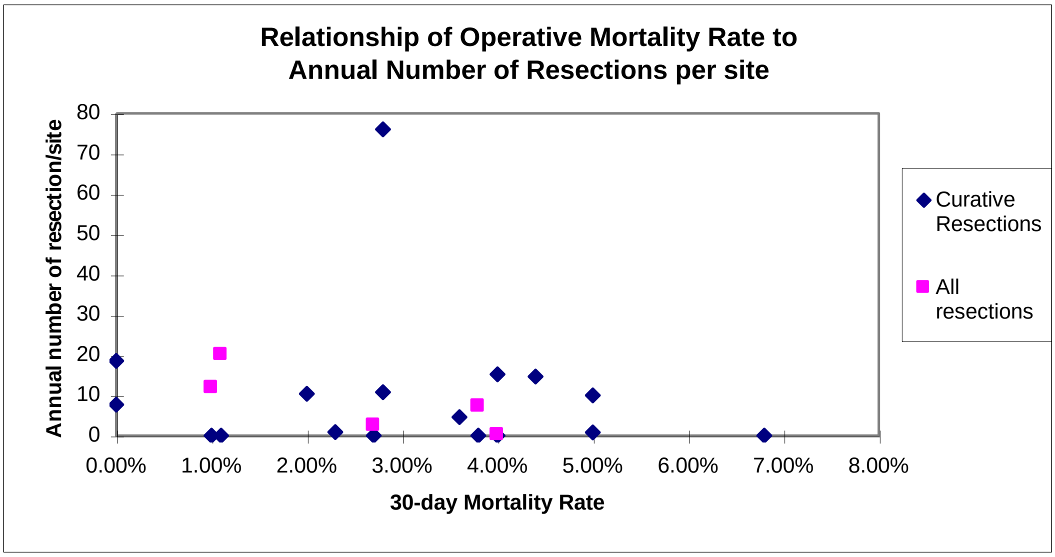


2.3.3 Operative Morbidity and Mortality of Resection

Operative mortality has been a problem previously associated with liver resection, with early series indicating up to 5-10% of cases resulting in death during the 30-day post-operative period. The main causes of mortality following liver surgery tend to relate to bleeding, cardiac arrest, sepsis and liver failure. However, when comparing the mortality rates of the identified resection case-series, it is seen that there has been a marked improvement in 30-day mortality rates over the last 10-20 years. The most recent and larger single centred studies report mortality rates of around 0-4%, in contrast to the higher 4-8% as reported by series from the late 1980s and very early 1990s. (Figure 7 refers).

Again, as some of the larger, and more established, series have run over long periods of time, they are able to quote significant reductions in mortality rate, despite having adopted a more aggressive approach to their surgery. From a series of over 300 resected patients, Scheele et al.[35] reflect on gradual improvements in mortality rates from 11.5% (pre 1980), to 3.5% (post 1980) and more recently to 1.8% during 1992-95. Similarly, Ohlsson et al.[23] report no cases of operative mortality over the last 10 years, compared to a previous rate of 6% for their earlier cases.

Figure 7 Peri-operative Mortality Rates versus Annual Resections



As a parallel issue, post-operative complications can be relatively common with liver surgery. The published series suggest that complication rates range between 10-30% and are on the whole completely recoverable and manageable before discharge from hospital.

2.4 Prognostic Indicators

In reporting survival outcome, the majority of the published case-series have reflected on the ability to identify good prognostic indicators. The objective is to devise a set of pre-surgical criteria which can be applied to identify patients most suitable for resection and, importantly, to identify those for whom resection would provide little or no benefit. A wide range of prognostic factors has been examined. These include factors related to the primary tumour, the amount of spread, grade of tumour, operative factors and personal factors. As expected, those factors which are associated with a more advanced stage of the tumour (both primary and secondary) are associated with lower survival.

Whilst some of the potential factors are generally well supported, such as the presence of EHD, others have proven more contentious with real differences of opinion. An example of such a debated issue is the relevance of the number of metastases to overall outcome, with four or more metastases or bilobar disease often stated as a contraindication. Unfortunately, some of the factors found to be good indicators of survival are only detectable post- or peri-operatively and, as such, cannot really be used by clinicians to influence the decision to conduct a laparotomy. Examples include the histological grade of the liver metastasis and the presence of disease in the margins of the resected tumour.

Appendix D summarises the range of prognostic factors which have been considered by the key published case-series. The table indicates those factors which reach significance as independent factors following multi-variate analysis of survival data. The majority of studies use five-year survival as the main outcome measure, although some have used median and disease-free survival. Again, direct comparison between studies is made difficult as the studies differ in their inclusion criteria, with patients excluded from some of the series when there are important prognostic factors. Not all studies include patients with clear extra-hepatic disease, or those in whom it was not possible to resect all the tumour. The following identifies the main prognostic factors identified by the case-series analysis and considers their relevance to the clinical management of the patient.

2.4.1 Curative versus Non Curative Intent

This issue is in many ways the key to the problem. The concept of a curative or potentially curative resection is frequently used to mean either that at operation the patient appeared to be macroscopically free of tumour, or that, in addition to this, the specimen also had clear resection margins. Several studies excluded patients unless they had a curative resection. Studies where it is possible to examine this can be identified in Appendix B where survival data for key sub-groups are given.[21,24,27,26,28] In all studies there is a clear difference between the two groups. Where median survival has been quoted, the difference ranges from eight months[27] to 25 months[25] survival advantage, and in terms of five-year survival the differences are even more marked with the highest five-year survival for the non-curative resections reported as only 6%[24]. Caution is needed in interpreting these differences, because the two groups are not strictly comparable and the numbers in most studies are small. One study where the non-resected group appears most comparable is that reported by Scheele et al.[25] who identified a group of 65 patients in which there was minimal macroscopic or microscopic evidence of the presence of disease after resection. Median survival in this group was 14 months compared with 40 months for the curatively resected group. No patient survived for five years, compared with a 38% actuarial five-year survival in the curatively resected group.

2.4.2 Extrahepatic Disease

Most series have attempted to exclude patients with extrahepatic disease by pre-operative and intra-operative investigation because of its well recognised contribution to poor prognosis. So in the majority of series those patients with EHD disease were identified during the course of surgery or in the immediate post-operative period. Of the nine studies where this factor was examined, six found it to be significant in the multivariate analysis and two in univariate analysis. In the one study where it was not found to be a significant variable, this finding was based on only four cases with EHD[36]. The magnitude of the effect is large with little evidence of survival advantage in the group EHD over those which are not resected. Most authors conclude that the presence of EHD is an absolute contraindication to liver resection for secondary colorectal cancer.

2.4.3 Clear Resection Margins

Another clearly significant prognostic indicator is the presence or absence of tumour in the margins of the resection specimen examined histologically. Again, there is almost universal agreement that positive margins are a poor to very poor prognostic factor. In the only study listed in Appendix D where it was not found to be a significant factor, it was nevertheless associated with a lower disease-free survival.[37] The importance of clear resection margins is overwhelming, but the influence of margin of clearance on survival is debatable.

2.4.4 Size of Tumour, Number of Metastases and Satellite Lesions

The fundamental difference between the conservative and aggressive approaches to liver resection as a treatment for hepatic metastases from colorectal cancer is in the indications for operation in terms of the size, number and distribution of metastases. Whilst the traditional view is that it is only worth resecting a single small metastasis confined to one lobe, the proponents of surgery have put forward a number of extended criteria based on the number, size and distribution. For example, authors have variously used: less than three metastases; less than four metastases; less than 10cm; unilobar; any number of metastases, but not tumours with satellite metastases; any number and distribution of metastases as long as they can be resected completely without leaving residual tumour.

Nearly all the studies have examined the issue of whether patients with four or more metastases fare worse than those with less than four. Opinion is divided, but there are important differences in the way that the studies have been carried out which may account for some of the difference. For example, most of the studies which have not found the number of metastases to be significant, are those which have also taken the grade of the tumour into account in the multiple regression model. Taking the series overall, the majority of studies find that the number of metastases is related to prognosis and the effect in many is marked. Rosen et al.[33] calculates a five-year survival of 29% for patients with one lesion compared with 17% for those with two or three, and 13% for those with four or more. Doci et al.[32] found that the probability of five-year survival for single tumours was 38% compared with 16% for multiple, and Fong et al.[29] estimated a 47% survival for single tumours compared with 31% for two to three and 24% for four or more. Taylor et al.[30] Calculated that the relative risk of death in those with two or more metastases compared to a single tumour was 2.04. Scheele et al.[38] by contrast found a much smaller difference, with the five-year survival for those with one metastasis being 33%, compared with 27% for those with two or more. However, in this series, patients with satellite metastases around a single focus were included in the 'single' group. As satellite configuration is clearly associated with poor prognosis, this may be relevant. Rees et al.[24] also found no difference in five-year survival for resection of more than one metastasis.

A similar picture emerges for the size of metastases where various size categories have been examined. Some large series have found this to be a significant prognostic indicator, but equally others have not. There seems to be agreement, however, that the presence of satellite metastases is a poor prognostic factor. Satellite metastases tend to be associated with more aggressive, and less well differentiated, types of tumour.

Overall, these studies confirm the view that multiple metastases, larger metastases and satellite lesions do indicate poorer prognosis compared to single, small, non-satellite lesions. In coming to a conclusion about whether they are sufficiently poor indicators of adverse outcome to make surgery unwarranted, the authors still have difficulties owing to the absence of controlled studies or even careful studies of natural history. Regrettably, there are very few detailed studies which allow such comparison.

One study of more than 200 patients who did not have a resection, concluded that the median survivals in those with single and multiple unilobular lesions were 21 and 15 months respectively, with more than 20% with unresected solitary lesions surviving three years or more.[5] By comparison, median survivals in those series which have published these data for patients having liver resection are:

- 28 months in those with less than four metastases and 20 months in more than four;[23]
- 35 months in those with one or two metastases and 39 months in those with three or more;[28]
- 45 months in those with one metastasis (27 months with satellites) and 41 months in those with two or more independent metastases (18 months with satellites);[25]
- 36 months in those with one metastasis, 26 months for two or three metastases and 28 months with four or more metastases.[32]

In selected patients who fulfil the various pre-operative and intra-operative criteria for surgery, the published case-study data would suggest an increased advantage in the median survival of up to approximately 13-26 months. In general, however, because of the selection process for surgery, these figures are likely to be overestimates.

In addition, a proportion of patients with resected multiple metastases can be expected to survive for five years. This proportion varies from being as high as the estimate for single metastases[24,25] or less than half this figure.[30] By comparison, very few, if any, people with known, unresected, multiple metastases can be expected to survive longer than five years.

2.4.5 Metachronous versus Synchronous Metastases

Some studies have considered the relative outcomes of patients with synchronous and metachronous disease, and opinion remains divided. Synchronous metastases are present at the time that the primary is removed. This indicates a more advanced stage of the disease and, other things being equal, one might expect that this situation would also be associated with more aggressive tumours. Furthermore, to remove synchronous metastases at the same time as the primary is to subject the patient to a much bigger operation at one time than in the case of those with metachronous disease, where, by definition the patient is receiving two procedures separated by months, if not years. Schlag et al.[39] concluded that outcomes of resection for patients with synchronous metastases are universally poorer than for those with metachronous metastases. Synchronous metastases were associated with higher rates of multiple recurrence rather than single site recurrences. Other authors have also found that removal of metachronous tumours was associated with longer survivals than synchronous ones,[25] although this has not always been statistically significant[24]. Jenkins et al.[28] report that, among patients with synchronous metastases, those who had a liver resection at the same time as the primary fared significantly worse than those in whom resection was conducted a few weeks later. Although, in several studies, patients with synchronous metastases appear to fare worse than those with metachronous metastases, the magnitude of the effect alone is probably not sufficiently large to have a significant bearing on the decision as whether to operate or not.

2.4.6 Operative Factors

These include the type of resection - whether it was of an anatomical segment or not, the amount of liver removed, the amount of intra-operative blood loss and the use of ultrasound dissector. Traditionally, the type of resection and the proportion of liver removed were important factors, because of high post-operative mortality associated with major non-anatomical resections. Although a few series still find these factors to be important prognostic variables after taking other factors into account, the majority do not find the type of resection or the amount of liver removed to be significant predictors of prognosis. Three studies have found the amount of intra-operative transfusion to be a significant factor, which is as expected. Most centres use ultrasound dissection in order to minimise blood loss and to provide a better means of removing the lesions. Therefore, operative technique is important and this is supported by the tendency of single centres with large numbers of cases to report better results than multiple centres with small numbers of cases.

2.5 Rates of Recurrence

The issue of re-resection is a contentious one, and many of the series have reported high levels of recurrence (typically within two to three years after the initial resection). Although 50-70% of patients may be expected to have an eventual recurrence, only 10-15% of patients will be considered for re-resection having liver only involvement. Some centres carry out additional resections on those patients who experience a recurrence which meets their criteria. Scheele et al.[25] carried out 51 re-resections on 434 people who had had a first resection 'with curative intent'. Rees et al.[24] carried out 7 re-resections from 107 people who had had an initial resection. Ohlsson et al.[23] reported 15 re-resections against 128 initial resections.

This low rate of re-resection reflects the limited amount of liver-only metastases found on recurrence following colorectal related liver metastases.

2.6 Conclusions

No randomised controlled trial data or comparative group studies exist that examine the case for liver resection in the treatment of colorectal liver metastases. The evidence available is based on well conducted published case-series of patients, who have had resection of hepatic metastases for colorectal cancer, and comparisons are limited to historical comparative data about the outcome for patients who have had other forms of non-surgical treatment.

In general, uncontrolled, non-randomised observational studies are more associated with over/under estimation of treatment effects than those that may be suggested through fully randomised controlled trials.[40] When using observational study evidence, conclusions can be drawn using statistical comparisons, such as meta-analysis, however, such methods carry dangers in terms of confounding factors and study bias.[41]

Based on the available evidence, there appears to be clear survival advantage for patients who have liver resection, provided that the surgery renders the patient tumour free (as far as can be judged on the basis of current investigations and microscopic examination of the resection margin) and they have no EHD. Although patients with multiple liver secondaries probably have a worse prognosis than those with a single metastasis, there is evidence of survival advantage from resecting these tumours provided that they have no EHD and all the tumour can be removed. The evidence does not provide good support for a survival advantage from surgery for patients who have liver resection when there is extrahepatic disease or in patients in whom all the tumour is not removed.

There is a significant survival advantage from operative techniques which minimise blood loss.

3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

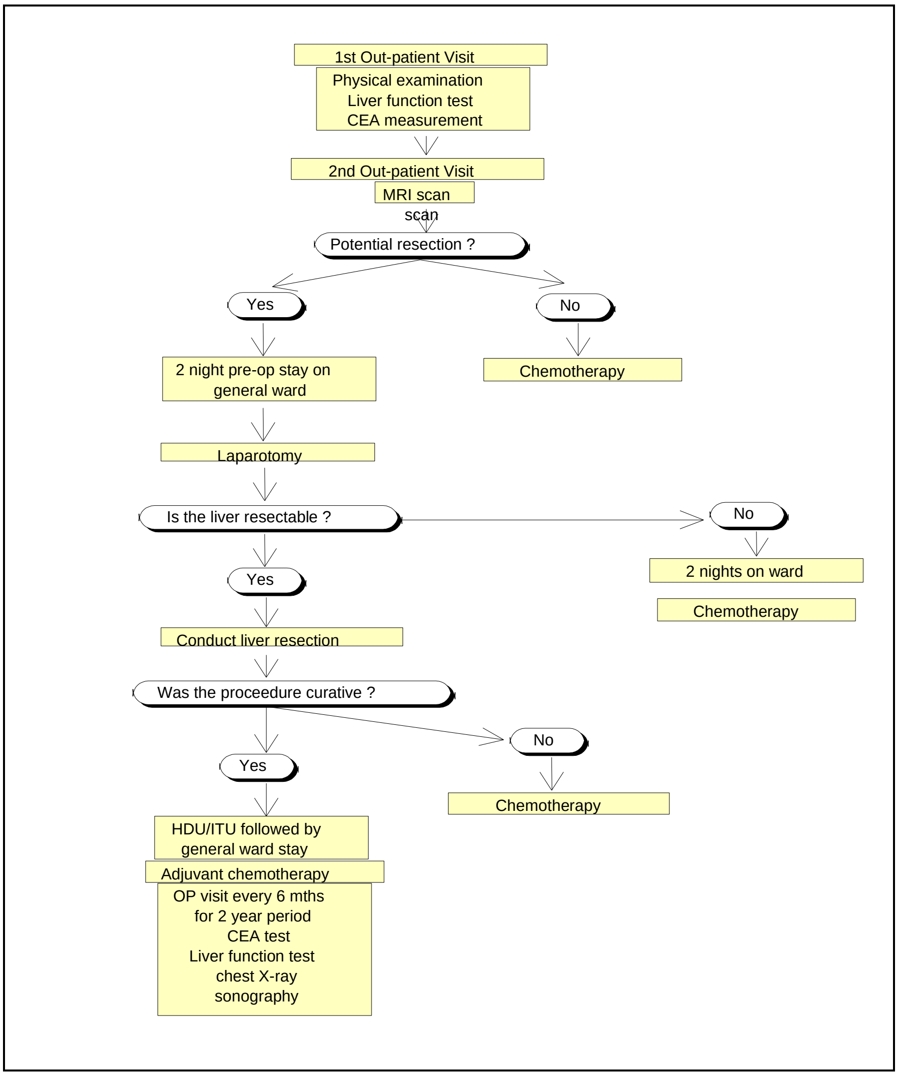
3.1 Analysis of Treatment Costings

3.1.1 Cost of Liver Resection

The treatment pathway for potentially resectable patients is shown in Figure 8. This helps to demonstrate the main cost elements of treatment:

a) pre-operative costs including diagnostic work-up - including Magnetic Resonance Imaging (MRI) scan and measurement of carcino-embryonic antigen (CEA) levels;
b) variable costs of the resection procedure itself;
c) cost of adjuvant therapy (if given - evidence base for this is not conclusive);
d) longer-term follow-up costs.

Figure 8 Treatment Pathway for Potential Liver Resection Patients



The following estimates of average cost are taken from experience of liver resection at the Royal Hallamshire Hospital, Sheffield.

Table 3 Cost of Diagnostic Work-up

Diagnostic Test/Resource	Average Usage	Total Cost
Out-patient clinic - new appointment	12 minutes for an E grade nurse	£2.16
	12 minutes for a consultant	£11.76
	consumables	£5.00
Liver function test - pathology	Per test	£4.60
CEA - pathology	Per test	£6.45
MRI	1 body area (including contrast)	£270.00
Out-patient clinic – follow-up	8 minutes for an E grade nurse	£1.44
	8 minutes for a consultant	£7.84
	consumables	£5.00
TOTAL WORK-UP COST		**£314**

Table 4 Cost of Liver Resection Procedure

Operative Procedure/Resource	Average Usage	Total Cost
Pre-operative admission	2 nights @ £275 per night	£550.00
Theatre list:	F grade 5 hrs	£73.10
Staffing would be for F, E & A grade theatre nurse & an MTO 3 for 5 hrs plus 2 hrs for an E grade recovery nurse	E grade 5 hrs	£63.96
	A grade 5 hrs	£36.41
	MTO 3 5 hrs	£70.67
	E grade 2 hrs	£25.58
Consumables	Drugs, medical & surgical & sterile services	£440.18
HDU (high dependency unit) care	4 nights @ £500 per HDU bed/night	£2,000.00
14% patients also require initial ITU care	5 nights @ £1300 per ITU bed/night plus	£910.00
Ward stay - 5 nights	5 nights @ £275 per night	£1,375.00
Pharmacy – drugs and i.v. fluids		£275.00
TOTAL RESECTION COST		**£5,820.00**

Table 5 Cost of Longer-term Follow-up

Follow-up Resources	Usage	Total Cost
Clinical attendance - review	8 minutes for an E grade nurse 8 minutes for a consultant Consumables	£1.44 £7.84 £5.00
Clinical attendances – follow-up 6 monthly for 2 yrs (i.e. 4 attendances)	For 4 attendances - Staffing (over 2 yrs) 32 minutes for an E grade nurse 32 minutes for a Consultant Consumables	 £5.76 £31.36 £20.00
<u>4 attendance each including:</u> Liver function pathology test (pathology) CEA (pathology) CXR (chest x-ray) Ultrasound of the abdomen	 4 tests at £4.60 per test 4 tests at £6.45 per test 4 tests at £12.04 per test 4 tests at £26.03 per test	 £18.40 £25.80 £48.16 £104.12
TOTAL FOLLOW-UP COST		**£268.00**

NB: Out-patient costs calculated on:

Consultant - Maximum part time - Gross cost £59,245 / E Grade Nurse - Days only - Gross cost £19,003

Bringing these three cost elements together, an overall estimate for the cost at £6,402 can be derived. (see Table 6).

Table 6 Total Average Cost of Resection

Treatment Phase	Total Cost
Cost of Diagnostic Work-up	£314
Cost of Resection Procedure	£5,820
Cost of Long-term Follow-up	£268
Grand Total	£6,402

Importantly, no cost for potential re-resection has been included within this estimate. For the purpose of the analysis, the authors have considered that recurrences would be challenged with conventional salvage chemotherapy.

Although shown in the general treatment pathway diagram as a theoretical option, the cost of adjuvant chemotherapy for patients following resection surgery has not been included. Although some reported series have used adjuvant systemic chemotherapy with hepatic resections, there is no evidence to establish firmly a clear survival advantage in such cases and, as such, this is not current UK practice.

These figures represent bottom-up costings using the typical clinical pathway and procedure as experienced at the Royal Hallamshire Hospital, Sheffield. However, it also helps to consider the costs from a purchaser's viewpoint, by comparison with Extra Contractual Referral (ECR) prices for such liver resection procedures. The NHS 1998 Reference Costs[42] list the national average ECR cost for a complex liver procedure (Health Care Resource Group (HRG) - Code G02) as £3,756 (50% range: £1,865 to £4,890 / 100% range: £296 to £11,530).

However, the key issue with this type of HRG costing is that, due to the relatively low volume of liver resections in most centres, the average costs are diluted with the costs of higher volume, less complex procedures. Therefore, in such cases of new, low volume, complex procedures the ECR prices are often under-estimates of the true cost.

3.1.2 Cost of Conventional Treatment

As previously discussed, the most appropriate comparison of marginal benefits and costs is for patients who could potentially have had a resection. For the purpose of this review the authors have considered that the alternative treatment for these patients would be systemic chemotherapy (administered with palliative rather than curative intent). The typical standard chemotherapy regimen adopted in the UK currently is based on 5-FU following a De Gramont regimen.

The following table presents the typical treatment costs for a patient following such a regimen. The cost structure has been taken from a recent cost-comparison study conducted by the Royal Marsden Hospital.[43] The study recorded patient-specific costs and in-patient/out-patient costs for 31 patients following the De Gramont regimen, including ward stay, chemotherapy drugs, diagnostic tests, consumables and fluids. Current British National Formulary (BNF) drug costs[44] and local in-patient costs have been used to ensure a fairer comparability to the liver resection costings. It has also been assumed that treatment is based on six courses of in-patient administered chemotherapy (i.e. three months of treatment). This is likely to be an under-estimate as patients can experience between three and six months of treatment.

Following this chemotherapy regimen, it is estimated that the total treatment costs would be around £6,669 (see Table 7).

Table 7 Costs of Palliative Chemotherapy

Monthly Resource Usage	**Cost**
4 days in-patient stay @ £275 per day	£1,100.00
Tests Consumables Fluids	£195.03 £25.92 £22.97
Chemotherapy Drug Costs Folinic acid (200mg/m2) 2 hours 5-FU (400mg/m2) 24 hours for 2 day period / repeated every 14 days Concomitant drugs	 £363.92 £39.84 £71.27
Average cost per month (A)	£2,223
Average number of months (B)	3
Total Cost of Treatment (A X B)	£6,669

3.1.3 Marginal Cost of Liver Resection

Accepting the assumptions taken of no adjuvant chemotherapy and identical treatment in later recurrences, a nominal marginal cost of therapy can be estimated by comparing the two costs.

Cost of Liver Resection and Follow-up (A)	£6,402
Cost of Standard Chemotherapy Regimen (B)	£6,669
Marginal Cost Saving (B-A)	£267

However, it is debatable whether the cost of resection does actually displace the cost of chemotherapy. As most patients have recurrence, and the majority of these will be challenged with systemic chemotherapy, it could be argued that resection simply delays the original cost of the chemotherapy until a later date (typically two to three years later). Therefore, the only potential saving would be if those patients who had a liver resection did not have post-hepatectomy chemotherapy and remained free of tumour.

3.2 Analysis of Treatment Benefits

The typical calculations of patient benefits for new drugs/interventions involve the use of either median survival data (usually quoted as a trial outcome), or mean survival data (typically calculated via area under the curve (AUC) methods of survival curve analysis) again taken from published controlled trial evidence. However, in the case of liver resection, there is no such controlled trial evidence available, although there is a relatively large number of case-series reflecting variations in patient groups, surgical techniques and outcome measurement. Therefore, the authors are faced with a difficult decision in selecting an appropriate observational evidence base with which to estimate clinical benefit.

It would seem logical to use case-series which reflect adequately the real life practice of liver resection, rather than a limited analysis of curative only procedures, particularly as there will be real costs incurred in following up non-curative or non-resection patients.

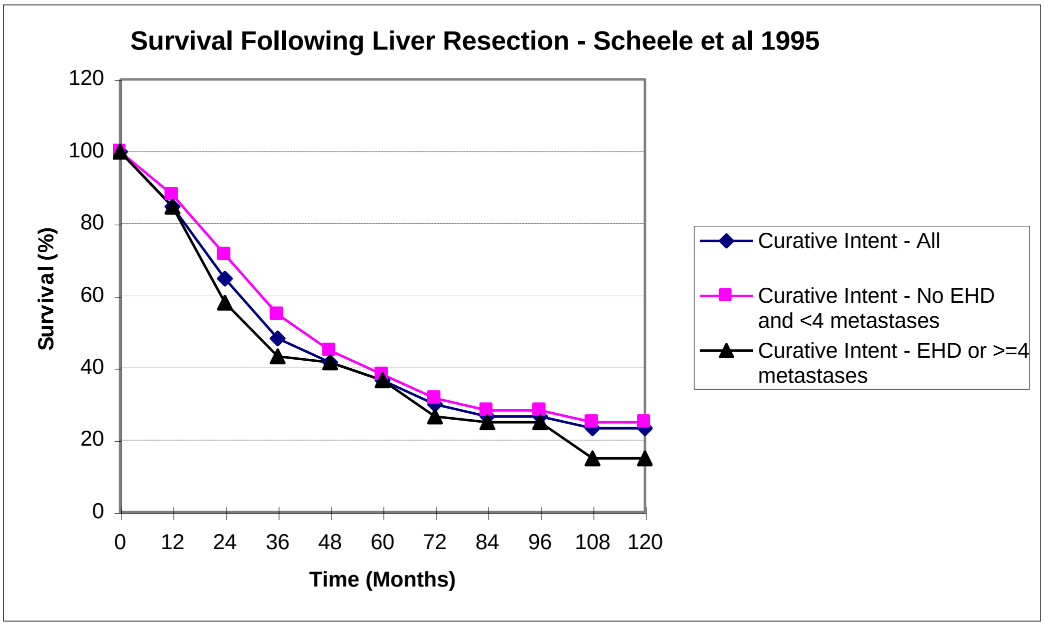
As such, a case-series was selected which was felt to provide a balance in terms of patient numbers, proportion of patients treated curatively, the complexity of the surgical procedures adopted, and availability of full survival curve data.

Scheele et al.[25] report on a large number of patients, of whom 79% had resections of anatomical segments, representing what many clinicians would consider to be the leading, and most complete, case-series on liver resection for metastases.

If the data are restricted to the first five years of survival (i.e. no continued cure is assumed beyond five years), the overall mean survival for patients undergoing resection with curative intent is 38 months. Stratifying the population by number of metastases, and the presence of EHD, it can be seen that for cases of less than four metastases the mean survival period is 39 months compared with 35 months for four or more metastases. This difference was found to fall short of reaching statistical significance (p=0.18). The comparative figures using data for the full ten years are 53 months, 57 months and 50 months respectively. The Scheele data have clearly shown that long-term survival beyond five years is achievable and sustainable. This is further confirmed from the study of long-term survivors conducted by

D'Angelica.[36]

Figure 9 Survival Following Liver Resection



In terms of a comparative set of non-resected survival data, Wagner et al.[5] have been used as a source of expected outcome in a similar patient group treated with standard chemotherapy. Based on an AUC approach, the survival curves have been analysed (Figure 9) and the following mean survivals are estimated: solitary 28 months, multiple unilobar 19 months, widespread 14 months.

Although there are no randomised trial data comparing liver resection to alternative case-series against established control groups, derived from either other large natural history case-series or data from chemotherapy comparison studies (i.e. 5-FU vs. 5-FU + modifiers vs. HAI trials). Whilst this is clearly not ideal, the magnitude of the advantage of liver resection is clear even when using the most optimistic outcome for standard treatment (as in Wagner et al.).[5]

In their analysis the authors matched less than four metastases and no EHD Scheele group with the non-resected multi-unilobar Wagner group. The more than four and/or EHD Scheele group was matched with patients having widespread disease.

Figure 10 Marginal Survival of Liver Resection versus Chemotherapy

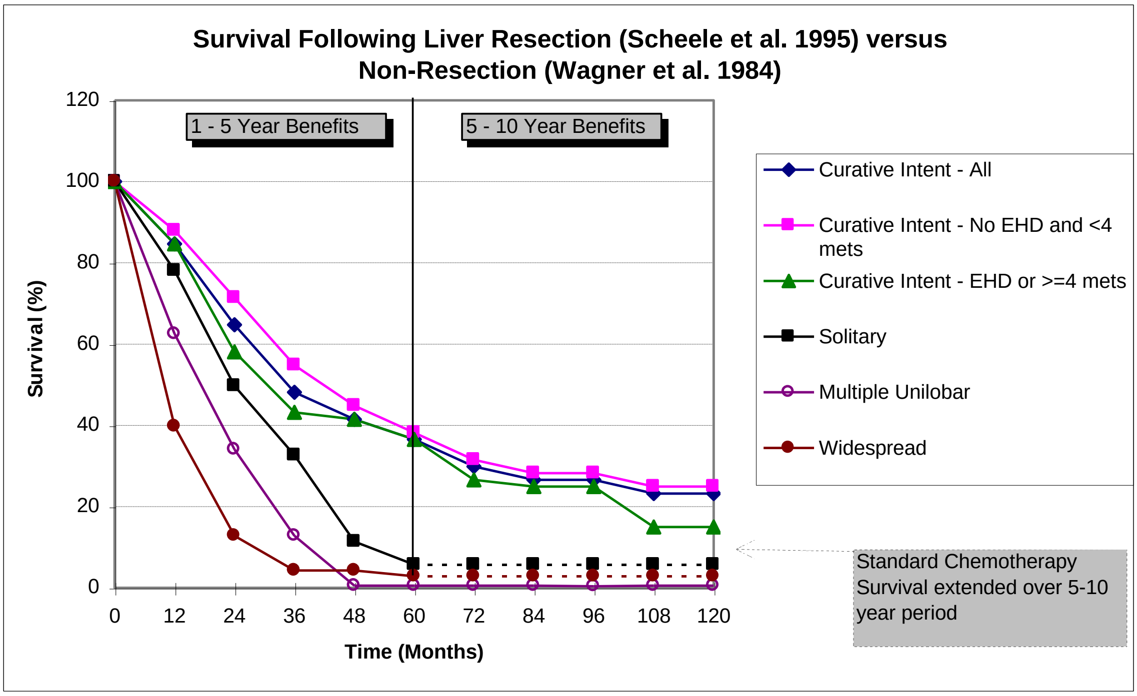


Table 8 Marginal Survival in Cases of Liver Resection

No. of Metastases	Wagner et al. Mean Survival	Scheele et al. Mean Survival		Difference in Survival	
		5 Years' Data	10 Years' Data	5 Years' Data	10 Years' Data
Less than 4	19 months	39 months	57 months	20 months	38 months
4 or more	13 months	35 months	50 months	22 months	37 months

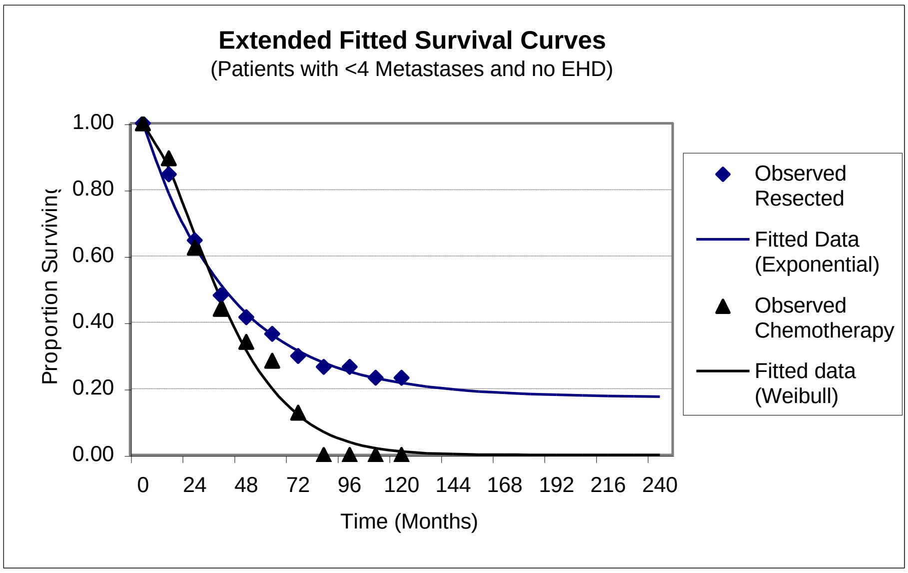
For patients with less than four metastases, the data suggest that over the first five years each patient will have a marginal survival of 1.6 LYG over traditional chemotherapy, increasing to 3.2 LYG when using all 10 years' data. For patients with four or more metastases, the figures are 1.8 LYG and 3.0 LYG respectively. A similar analysis comparing non-resected patients having solitary metastases suggests a 10-year marginal survival benefit of 2.1 LYG.

3.2.1 Sensitivity of Benefit Calculation

As the survival curves for patients having liver resection suggest a much longer-term survival, compared to the non-resected patient groups, there is a clear argument that patient benefits beyond the published 10 year limit should also be considered. Indeed, as part of the Scheele case series analysis, actuarial 20-year survival rates of over 17% have been reported for patients undergoing potentially curative resection.

As part of a sensitivity analysis, the authors of the Guidance Note extrapolated beyond the study data by fitting mathematical curves to the published resection survival data, and extended these out to a 20 year horizon. As there appeared to be a significant plateau in the survival data, suggesting a longer-term curative effect with a reducing hazard rate over time, they fitted an exponential survival curve form. Figure 11 shows the extrapolated fitted curve for the resected and non-resected patient groups, having <4 metastases and no EHD.

Figure 11 Extended Survival Curves



As previously stated, the 5-year survival rates for non-resection patients are <5% and there is clinically no expectation of any survival at 20 years. However, in order to provide a conservative view of resection, curve fitting procedures were also performed and 20-years' survival data extrapolated using the published data for non-resection patients, as suggested by Wagner.

The results of this extended analysis are shown in Tables 9 and 10, and have also been calculated at a discounted rate of 6%. The results clearly show that, if the principle of extrapolating out to include 20-year survival is accepted, then marginal benefits can increase by around 100% from 5-year survival benefits.

Table 9 Survival Benefits for Patients with 4 or more Metastases and/or EHD

Survival Period	Wagner et al.		Scheele et al.		Difference in Overall Survival	
	Discounted (6%) LYG	Not Discounted LYG	Discounted (6%) LYG	Not Discounted LYG	Discounted (6%) LYG	Not Discounted LYG
5-years	1.1	1.1	2.7	2.9	1.6	1.8
10-years	1.1	1.1	3.4	4.1	2.3	3.0
20-years	1.1	1.1	3.8	5.0	2.8	3.9

Table 10 Survival Benefits for Patients with less than 4 Metastases and no EHD

Survival Period	Wagner et al.		Scheele et al.		Difference in Overall Survival	
	Discounted (6%) LYG	Not Discounted LYG	Discounted (6%) LYG	Not Discounted LYG	Discounted (6%) LYG	Not Discounted LYG
5-years	1.6	1.6	2.9	3.2	1.4	1.6
10-years	1.6	1.6	3.9	4.7	2.3	3.1
20-years	1.6	1.6	4.6	6.4	3.1	4.8

3.3 Analysis of Cost-effectiveness

In assessing the cost-effectiveness of an intervention, the most common approach is to use a measure of mean or median survival for a patient group and to combine this with the average cost of the intervention to calculate a cost-effectiveness ratio, typically the cost per LYG.

However, in this case it is also important that the proportion of patients who may be accepted for potential resection, but will eventually have either an abandoned procedure (due to peri-operative findings such as positive resection margins) or who may have a non-curative palliative resection, is taken into account. In these cases it is likely that patients will be offered chemotherapy as an alternative treatment as well as incurring all or part of the costs of resection, without gaining the LYG benefit associated with curatively resected patients.

Estimates of the likely proportion of such patients are difficult to make. The published case-series are varied in their reporting of such cases, with many of the series restricting survival data to curative resections only. However, the paper by Rees et al.[24] may reflect the closest estimate to a typical UK specialist centre with referral and entry criteria resulting in 17% of patients having no-curative therapy.

Table 11 considers the worst, best and most-likely scenarios involving patients who are referred for liver resection, but who are not eventually resected. For non-curative resections, the full cost of work-up and the surgical resection procedure have been included, but not the follow-up costs, as it is assumed that these patients will move on to standard palliative care. For patients in the non-resected treatment group, the costs of work-up and the cost of surgery have been included, but only five nights of general post-operative stay. Again, follow-up costs are not included.

It is assumed that these patients will receive the same chemotherapy regimen that they would have received had they not been considered for resection. Therefore, no additional costs for any adjustment to the chemotherapy regimen have been assumed. It is assumed that these patients will receive no additional benefit beyond that experienced as chemotherapy only patients.

As there is some debate over potential savings through avoided chemotherapy, the liver resections have been costed without any off-set against alternative treatment. This, in effect, takes the conservative assumption that all resected patients will eventually relapse, and that there will be no true long-term disease-free survival. Therefore, the marginal cost of resection is assumed to be the complete cost, as estimated at £6,402 (including follow-up).

Expected benefits have been taken for the five years following resection only, at approximately three LYG (Table 8 refers). This is very much a conservative view against resection. If further extended benefits are included beyond the five-year survival point (i.e.

10-years, or even 20-year survival expectations), then the estimated benefits could be between 3.5-5 LYG.

The cost-effectiveness has been calculated using undiscounted benefits. However, discounted benefit data from Table 9 and Table 10 can be used to repeat the calculation. As the costs of resection are all within the first year of treatment, discounting is not required for costs.

From Table 11 it is clear that, compared with many other health care interventions provided by the NHS, the cost-effectiveness of liver resection is favourable.

It is unlikely that the costs of referral for patients unsuited for liver resection will damage this cost-effectiveness argument. Even if 50% of patients were found eventually to be unsuited for surgery, or only received palliative resection, the survival benefits for the remaining patients are likely to cost around £4,000 per LYG, with an average curatively resected patient expected to benefit by three years' extended survival. For a reasonable proportion of patients this survival is likely to extend well beyond five years. Using Rees et al.[24] as an example of UK clinical practice, around 20% of referred patients might not be expected to proceed to a full curative resection, leading to a cost per LYG figure of around £2,600.

One issue that also needs to be factored into this consideration is the potential cost of the regular follow-up of all patients after colorectal surgery. Whilst previous reports have concluded that there is no cost-effectiveness argument for the regular follow-up of such patients, it is clear that in many cases clinicians are conducting such follow-up. Typically, this is based around six monthly assessments through an ultrasound and a CEA level test, usually for a period of two years, within which most metastases are expected to appear.

If liver resection was to become more widely available, it is likely that colorectal follow-up would be implemented, particularly if the scope for curative surgery continues to widen. The published literature suggests that the proportion of patients with liver metastases who are potentially resectable is 5-10%.

The scenario in Table 12 assumes that all patients are followed up for a two year period. Costs are estimated at £320 (i.e. £80 per session covering the out-patient clinic attendance at £52 and CEA test/ultrasound at £30). It is also assumed that 10% of patients are potentially resectable (i.e. will be referred) and that only 50% of cases will proceed to curative resection at laparotomy, with 40% having non-curative surgery and 10% no resection at laparotomy (i.e. the worst-case scenario of the referral patterns from Table 11).

Table 11 Costs and LYG Benefits of Potentially Resectable Patients

'Best Case' Scenario

Treatment Group	Proportion of Patients	Cost	LYG	Cost per LYG
Curative	100%	£6,402	3.0	£2,134
Non-curative	0%	£6,134	0	-
No resection	0%	£2,624	0	-
Average patient		£6,407	3.0	£2,134

'Likely UK Experience' Scenario

Treatment Group	Proportion of Patients	Cost	LYG	Cost per LYG
Curative	83%	£6,402	3.0	£2,134
Non-curative	17%	£6,134	0	-
No resection	0%	£2,624	0	-
Average patient		£6,619	2.5	£2,658

'Worst-Case' Scenario

Treatment Group	Proportion of Patients	Cost	LYG	Cost per LYG
Curative	50%	£6,402	3.0	£2,134
Non-curative	40%	£6,134	0	-
No resection	10%	£2,624	0	-
Average patient		£5,917	1.5	£3,945

Again, benefits have been limited to undiscounted five-year survival differences.

Table 12 Inclusion of Follow-up Costs

Patient Group	Patient Numbers	Unit Cost	Total Cost
Colorectal patients follow-up	2,000	£320	£640,000
Patients referred	10% of 2,000 = 200 patients		
Curative resections	50% of 200 = 100	£6,402	£640,200
Non-curative resections	40% of 200 = 80	£6,134	£490,720
No resections	10% of 200 = 20	£2,624	£52,480
Total cost of resection and follow-up			£1,823,400
LYG	100 curative patients at 3.00 LYG		300 LYG
Cost per LYG			£6,078

It is clear, therefore, that regular follow-up decreases the cost-effectiveness and, thus, the evidence for its usefulness should be carefully considered if it is to be instituted. Even so, the cost-effectiveness ratio, of around £6,000 per LYG, is well within the range of those for other interventions routinely provided by the NHS.

4. OPTIONS FOR PURCHASERS AND PROVIDERS

The options for purchasers can be summarised as:

Option 1: To Fund Resection in Cases of Single Metastasis Only.

- Health authorities should commission services which allow the identification and surgical treatment of those patients in whom the removal of liver metastases from colorectal cancer have the best predicted outcome and for whom there is a long established agreement that they benefit from surgery. This is the group of patients with a single small metastasis confined to one lobe.

- The surgical treatment of patients outside of this group should not be purchased.

- This option would still require a significant expansion of current services. Consideration would need to be given to having a district level capacity for such surgery or at least several centres within the health region.

Option 2: To Fund Resections for a Wider Set of Indications (which include the presence of Multiple Metastases) for Which Curative Resection can be Realistically Achieved.

- In addition to option 1, health authorities should commission, on the basis of agreed criteria, surgery for an additional group of patients who have multiple or large metastases. These criteria should probably include: absence of extrahepatic disease, absence of other significant comorbidities, pre-operative assessment suggesting that the tumour can be removed with clear resection margins, intra-operative assessment suggesting that the tumour can be removed with clear resection margins.

- The surgical treatment of patients who do not fall within the criteria in this option should only be commissioned as part of properly conducted research studies, designed to evaluate the effectiveness of the procedure in comparison with alternative treatments.

- This option would require an even greater expansion of current services. In order to avoid inequities in service provision during the expansion of the service to fulfil this option, there would have to be strict application of the criteria.

Option 3: To Maintain the Status Quo.

- The current situation is that very few patients with liver metastases, who could potentially benefit from hepatic resection (even those who meet the traditional criteria of a single metastasis) actually receive surgery. This is partly because treating physicians may have a lack of awareness of the value and availability of hepatic resection.

Option 4: Not to Fund Liver Resections and Target Only 5-FU Based Chemotherapy Regimens.

- This option would involve patients being treated with 5-FU based chemotherapy regimens only. Patients could be entered into ongoing trials covering chemotherapy regimes (including HAI-based treatment and prolonged infusion) and other forms of non-surgical therapy (cryosurgery etc.).

- This option would be contrary to the weight of world-wide evidence supporting liver resection as the only potentially curative treatment option for this patient group. Liver resection is offered as a standard treatment across the world and it is extremely unlikely, from an ethical viewpoint, that any future RCT will be conducted for patients with solitary metastases or multiple unilobar disease. There may be potential for further studies (preferably RCTs) of more aggressive forms of liver resection for patients with much more dispersed disease, with high levels of liver involvement or evidence of certain types of extrahepatic disease.

The authors of this Guidance Note recommend: Option 2.

Additional recommendation

The benefits and cost-effectiveness of regular follow-up of colorectal patients should be considered as part of a RCT.

The cost-effectiveness of non-surgical treatment of liver secondaries for colorectal cancer should be evaluated as there appears to be little reliable information on this subject.

5. DISCUSSION AND CONCLUSIONS

5.1 Lack of Randomised Evidence Base

There is an obvious issue about the lack of RCT data in the case of liver resection. This lack of such trial data probably relates to the fact that simple liver resections have been performed for a great number of years and have become an accepted potentially curative technique. The following questions remain:

- Are randomised trial data still necessary in making policy decisions in respect of liver resection?
- If needed, can they be provided technically?
- If so, can they be realistically expected?

The answer in the case of simple resection, such as, single metastasis or multiple unilobar disease, is that RCT evidence is unlikely to be necessary, as the survival benefits have been clearly established from the observational data taken over a significant period of time. Also, the randomised trial data of conventional treatment show only marginal patient benefits. Any suggestion of randomising such patients would be likely to run into ethical problems given this evidence-base. However, it is true that not all patients who could benefit from simple liver resection are actually receiving such treatment.

For more complex liver surgery, there is less clear evidence of effectiveness and in these cases it is fair to say that randomised trial evidence might contribute to the debate, although there may be difficulties in patients' acceptance of randomisation to non-surgical treatment if the metastases are technically resectable. Other issues including adjuvant chemotherapy following resection and the combination of resection with cryosurgery are also clear areas where future randomised evidence is needed.

5.2 Comparative Use of Resection for Other Cancers

Resection is also used as a potentially curative surgical technique for other cancers, in particular cases of pancreatic, oesophageal and other gastrointestinal cancer.

Resection for pancreatic cancer appears limited to around 10-15% of patients depending on the amount of tumour spread, as is the case for liver resection. Median survivals are reported at around 18-20 months and five-year survivals are noted at around 10%.[45] For cases of oesophageal cancer, five-year survival ranges between 20%-30%.[46]

From the available evidence base, liver resection would seem to provide at least comparable benefits to the use of resection in other cancers.

5.3 Can a Set of Indicators be Established Which Clearly Identifies Patients for Referral from District General Hospitals?

It is still difficult to determine a precise definition of 'suitable' patients for liver resection. Many of the prognostic factors suggested in the literature are post-operative or rely on imaging techniques conducted during surgery. The evidence suggests that those patients most suited to resection are likely to have:

- single metastasis, no extrahepatic disease;
- multiple metastases, restricted to a single lobe, no extrahepatic disease.

Given the typical patient profiles of the resection series, this is likely to equate to around 10% of those with liver metastaes.

In all cases the survival will be strongly influenced by the ability of the surgeon to remove the tumour(s) clearly without any involvement in the resection margins. Importantly the clinical experience of the authors suggests that rates of unnecessary laparotomy are likely to be very low indeed (in contrast to some studies).

There needs to be a clear set of referral guidelines for district general hospitals when dealing with cases of liver metastases. These guidelines should define clearly the treatment pathways open to the patient. Suggested referral guidelines have been included in the appendices.

5.4 Service Provision

If liver resection is to be provided for a group of patients with suitable physical status and liver involvement, then there are a number of operational issues which will need to be considered carefully:

- Is there a need to introduce a more formal follow-up procedure for colorectal cancer patients after surgery for the primary tumour?

- Is there a case to train staff and equip local district general hospitals to conduct liver resection procedures or should treatment be based on more experienced centres?

- What should be considered as a sufficient volume of resections to maintain a clinical specialism?

Based on the clinical experience of one author (Ali Majeed) it is estimated that a typical hepatic surgeon, specialising in liver resections, could reasonably be expected to conduct around 50 resections per annum. Ideally, a specialist centre would have two or more surgeons.

5.5 Use of Repeat Liver Resection for Liver Only Recurrences

A number of the reported case-series have used repeated resection, or re-resection, in cases of recurrence which has been restricted to the liver only. Up to 70% of initially resected patients are expected to have some form of recurrence, and in only 10-15% of cases is this restricted to isolated liver cancer. Therefore, the volume of such re-resection patients is relatively low, with less than 20 such cases expected in the Trent region each year, even if all potentially resected patients are in fact initially resected. From the available evidence, the outcomes from re-resected patients appear positive with no additional operative mortality above that of first-time resection.

5.6 Likely Costs of Providing Liver Resection

Overall, it has been estimated that for every 10,000 colorectal patients who have additional liver metastases, roughly 10% will be suitable for initial surgical resection with curative intent. Given the average cost of resection of £64,070 it is estimated that the marginal costs of providing liver resection for this group of patients are around £6,400,000 (equating to £130-135,000 for an average district of 500,000 population).

If the criteria for resections were to be widened, this figure could rise to around £12,800,000 (or £260-£270,000 for a ‘typical’ district) representing 20% of all patients with metastatic disease

Appendix A Description of Key Resection Case-series

Reference	Country	Pubn Year	Time Period	Yrs	No Sites	Design	Method	No Pts	Age Profile[a]	Description	Resections		Adj	Follow-up	
											Potentially Curative	Type		Median (mths)	Cover
Ohlsson et al.[23]	SWE	98	71-95	24	1	Retrospective (Prospective since 1980)	Hospital records review	111	37%<60	No EHD, limited number of mets / intra op clear of tumour	100%	77% anatomic 17% atypical minor 5% atypical major	18%	60.2	100%
Bakalakos et al. [27]	US (Ohio)	98	78-93	15	1	Retrospective	Hospital records review	301	61(25-83)	Intra op clear of tumour and EHD defined curative	79%	80% wedge 20% lobectomy	100%	NS	86%
Fong et al. [29]	US (MSK)	97	85-91	6	1	Retrospective	Hospital records review	456	62(27-87)	No EHD / intra op clear of tumour	100%	27% wedge 13% segmental 3% lateral segmental 44% lobectomy 13% extended	NS	37	NS
D'Angelica et al.[36] (subset of the same pt group as Fong et al.)	US (MSK)	97	85-91	6	1	Retrospective	Hospital records review	96	16%>70	Study of prognostic factors in >5 year survivors of resection	100%	43% lobectomy 47% wedge (or less) 10% extended	NS	NS	NS
Rees et al.[24]	UK	97	86-96	9	1	Prospective	Hospital records review	107	NS	Pre-op no EHD / intra-op assessment of resectablity using ultrasongraphy	83%	89% anatomic 5% atypical/wedge	NS	(12-108)	100%
Jenkins et al. [28]	US (Illinois)	97	75-93	18	1	Retrospective	Hospital records review + telephone follow-up	131	62(30-88)	Curative resection defined as no EHD, >1cm negative margins	81%	70% anatomic 30% wedge	NS	24	NS
Taylor et al. [30]	Canada	97	77-93	16	1	Retrospective	Hospital records review	123	58(30-87)	No EHD / intra-op expectation of 1cm margin <5 metastases/ unclear if subsequent positive tumour margins were excluded.	100%	84% anatomic	60%	NS	95%
Jaeck et al. (subset of Nordlinger et al.)[18]	France	97	59-87	28	85	Retrospective	Questionnaire survey of long-term survival and prognostic data (> 5 years)	747	58 [Mean]	Survival considered for 1818 curative resections. Prognostic analysis restricted to curative resection up to 1987 (i.e. at least 5 years follow-up).	100%	63% major 37% minor	32%	NS	100%
Nordlinger et al.[19]	France	96	68-90	22	85	Retrospective	Questionnaire survey of overall survival	1568	46%<60	Post-op exclusion of EHD and incomplete resection and follow up.	100%	64% major 36% minor	35%	19	97%
Wade et al.[15]	US	96	88-92	14	85	Retrospective	Central patient administration database (22,000 pts)	161	64 [mean]	Complex inclusions based on diagnostic ICD and op codes confirm hepatic metastases and liver resection / synch metastases excluded	NS	57% anatomic	NS	NS	NS
Fuhrman et al. [26]	US (Texas)	95	88-92	14	1	Retrospective	Hospital records review	151	58(?)	Pre-op no EHD. Intra-operative assessmet of resectablity using ultasonography, >4 metastases excluded.	71%	65% anatomic	NS	25	NS
Scheele et al.[25]	Germany	95	60-92	32	1	Retrospective	Hospital records review	469	59(26-91)	469 patients had curative intent / 434 had potentially curative procedure / 350 survived curative resection	100%	45% common anatomic 34% uncommon anatomic 21% non-anatomic	7%	NS	99%
Gayowski et al.[31]	US (Pitts)	94	81-91	11	1	Retrospective	Hospital records review / telephone survey / records	204	60(28-79)	Resections had curative intent. although no clear criteria provided	100%	84% major 16% minor	NS	69	NS

[a] Assume average ages to be median statistics unless expressly indicated otherwise

Reference	Country	Pubn Year	Time Period	Yrs	No Sites	Design	Method	No Pts	Age Profile[a]	Description	Resections: Potentially Curative	Resections: Type	Adj	Follow-up: Median (mths)	Follow-up: Cover
							review								
Van Ooijen et al.[20]	Netherland	92	79-89	10	15	Retrospective	Hospital records review	118	57(28-83)	Pre-op exclusion of EHD, intra-op exclusion of macroscopic disease	100%	74% anatomic 22% wedge 4% combined	NS	NS	99%
Rosen et al. [33] (prev reported by Adson & Wagner et al.)	US (Mayo)	92	60-87	27	1	Retrospective	Hospital records review	280	59(?)	No EHD and all known tumour removed with negative >1cm margins - potentially curative resections	100%		NS	NS	97%
Cady et al.[47]	US (Boston)	92	up to 90	NS	1	Retrospective	Hospital records review	142	61(31-80)	129 survived and were considered curative procedures. Involved use of cryosurgery in 13% of patients	91%	NS	NS	NS	NS
Fegiz et al.[48]	Italy	91	NS	NS	NS (>1)	Retrospective	NS	212	NS	Pre-op exclusion of EHD	100%	47% major 53% minor	NS	NS	NS
Doci et al.[32]	Italy	91	80-89	10	1	Retrospective	Hospital records review	100	57(28-74)	Excluded EHD, >1cm clear margin, no gross residual disease	100%	50% lobectomy 50% non-anatomic	NS	NS	100%
Steele et al.[21]	US (Boston)	91	84-88	4	15	Prospective	Hospital records review	150	63%>60	12% non-curative 42% no resection	46%	37% wedge	NS	37	100%
Schlag et al.[39]	Germany	90	81-89	8	1	Retrospective	Hospital records review	122	59(36-79)	No EHD, single lobe and < 4 metastases Study of synchronous vs. metachronous	100%	37% single lobe seg 23% wedge 35% right or left hemi	NS	22	100%
Hughes et al.[22]	US (Registry of Heaptic Metastases)	86	48-85	37	24	Retrospective	Registry data on curative resections	859	13%>70	Group 1 : 24 patients - presence of nodes Group 2 : 37 patients - presence of EHD Group 3 : 798 - curative removal of isolated metastases	93%	41% major anatomic 35% wedge 24% minor anatomic	NS	21	100%

NS - Not stated

21 studies which provide unique survival and/or prognostic data

Appendix B Summary of Survival Outcomes (all patients)

Reference	Period	Outcome Group	Overall Survival			Disease-free Survival		Operative Mortality Excluded	Complication Rate	Operative Mortality
			Median	3 Yr	5 Yr	3 Yr	5 Yr			
Ohlsson et al.[23]	71-95	Curative	25 mths	37%	25%	22%	19%	NS	14%	3.6%
	71-84	Curative	20 mths		19%		18%	NS		6%
	85-95	Curative	40 mths		35%		21%	NS		0%
Bakalakos et al.[27]	78-93	All	20 mths						17%	1.1%
		Curative	23 mths							
		Non-curative	15 mths							
		Non-resected	13 mths							
Fong et al.[29]	85-91	Curative	46 mths	59%	38%				24%	2.8%
Rees et al.[24]	86-96	All	NS	47%	30%	NS	NS	NS	17%	1%
		Curative	NS	56%	37%					
		Non-curative	NS	11%	6%					
Jenkins et al.[28]	75-93	All	33 mths	42%	25%	34%	16%	NS	18%	3.8%
		EHD	NS		0%					
		+ Margins	NS		0%					
		Synchronous	NS		13%					
		Metachronous	NS		35%					
Taylor et al.[30]	77-93	All	NS		34%		20%	NS	28%	0%
		1 metastasis	NS		47%					
		> 1 metastasis	NS		17%					
		1 met + sat nodes	NS		16%					
Nordlinger et al.[49]	68-90	All	NS	44%	28%	23%	15%	Yes	23%	2.3%
		0-2 risk factors[b]	NS	79%						
		3-4 risk factors[b]	NS	60%						
		5-7 risk factors[b]	NS	43%						

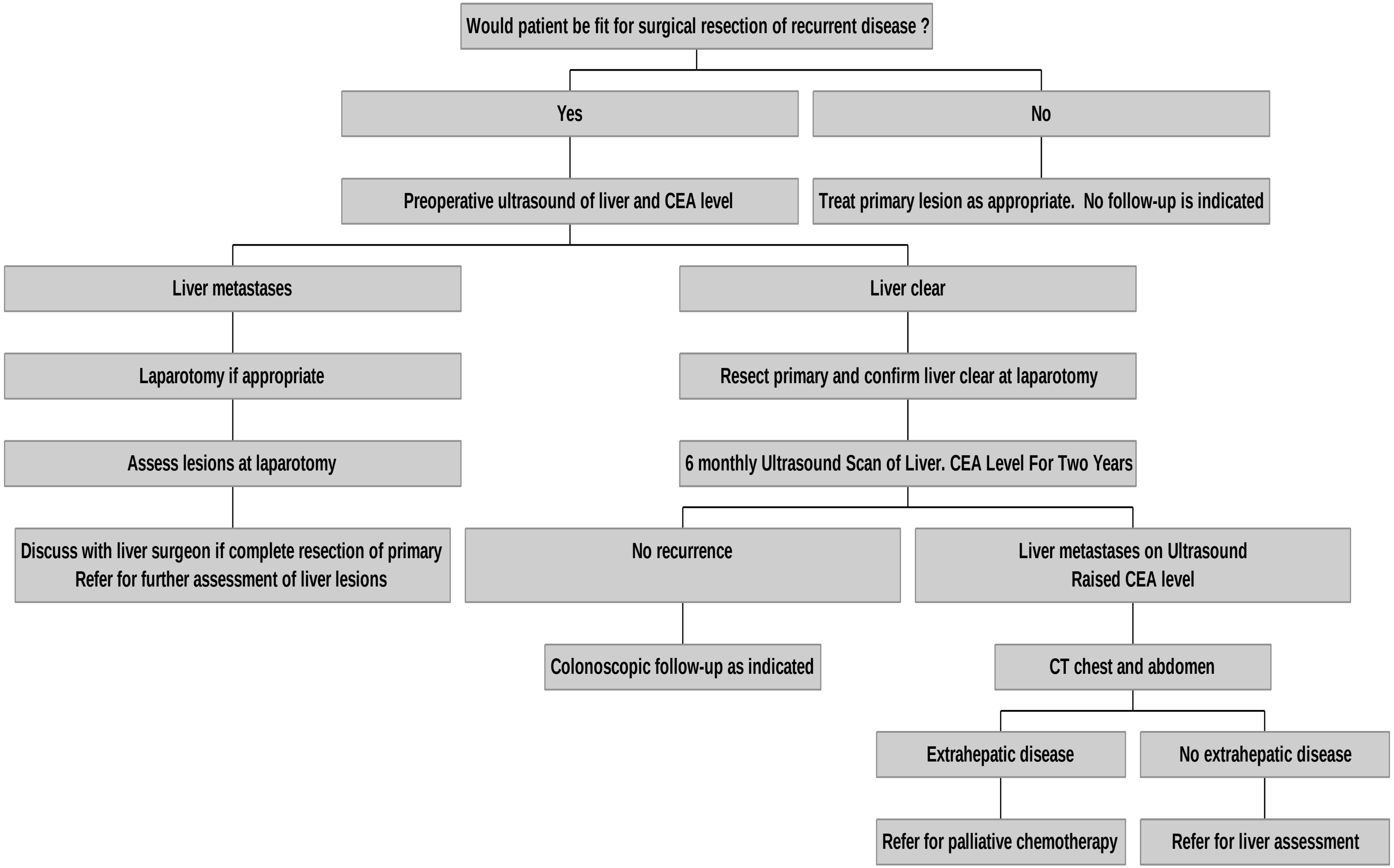
[b] 2-year survival data not 3-year

Reference	Period	Outcome Group	Overall Survival			Disease-free Survival		Operative Mortality Excluded	Complication Rate	Operative Mortality
			Median	3 Yr	5 Yr	3 Yr	5 Yr			
Fuhrman et al.[26]	88-92	All	NS		31%					
		Curative	NS		44%					2.8%
		Un-resected	NS		0%					
		Resected								
Wade et al.[15]	88-92	All	31 mths		26%			NS		4%
Scheele et al.[25]	60-92	All	NS	45%	33%			No	16%	4.4%
		Curative	40 mths		38%		33%			
Gayowski et al.[31]	81-91	Curative	33 mths	43%	32%	29%	25%			0%
Van Ooijen et al.[20]	79-89	Curative	NS		21%		19%		34%	5%
Rosen et al.[33]	60-87	Curative	32 mths	47%	25%				NS	2%
Fegiz et al.[48]	NS	Curative	NS					NS	NS	6.8%
		1 metastasis	NS	34%	20%					
		> 1 metastasis	NS	17%	17%					
		Synchronous	NS	44%	18%					
		Metachronous	NS	32%	22%					
Doci et al.[32]	80-89	Curative	28 mths		30%		11%	Yes	33%	5%
		Dukes B	43 mths		47%					
		Dukes C	27 mths		24%					
Steele et al.[21]	84-88	All							13%	2.7%
		Curative	37 mths		NS					
		Non-cure	21 mths		NS					
		Un-resected	17 mths		NS					
Schlag et al.[39]	81-89	Curative	NS		NS				29%	4%
		Metachronous	32 mths		16%					6.7%
		Synchronous	24 mths		2%					0%
Hughes et al.[17]		All			33%		21%			
		Curative			33%		22%			

NS - Not stated

Appendix C

Initial Presentation with Colorectal Cancer



Appendix D Prognostic Factors Restricted to Latest Reports of Individual Case-series (17 papers) that Provide Information on Prognostic Factors

M = significant from a multivariate analysis / U = significant from a univariate analysis / X = considered, but not significant

References	Age	Sex	No. of Mets (>3)	Satellite Nodes	Size of Mets	Bilobar vs. Unilobar	Synchronous vs. Metachronous	Time interval Primary to LM	Grade of Liver Tumour	Extrahepatic Disease (EHD)	Serosa infiltration	Positive Margins (>1cm)	Pre-op CEA values (>200)	% Liver Removed PLR	Stage of Primary	Site of Primary	Presence of Primary Nodes	Type of Resection - (anatomical)	Blood Transfusion	Year of Resection	Ultrasound Dissector	Method of Detection
Ohlsson et al.[23]			X	X	X	X	X		**M**	**M**		U	M		X			X	**M**	**M**	U	U
Bakalakos et al.[27]			X		X	**M**		X				**M**			X			X	X			
D'Angelica et al.[36 c]	X	**M**	X			**M**		X		X		**M**	X		X	X		X				
Fong et al.[29]	X	X	**M**		**M**	U		**M**		**M**		**M**	U		U	X	U	U	X			
Rees et al.[24]			X		**M**	X	X					**M**			X	U						
Jenkins et al.[28]	X	X	X				**M**			**M**		**M**		X		X		X	X			
Taylor et al.[30]	X	X	**M**	**M**	X		X	X									X	X	U			
Jaeck et al.[50]	X	X	X		X	X	X			**M**	**M**	**M**	**M**			X		X				
Nordlinger et al.[49]	**M**		**M**		U			**M**			**M**	**M**	**M**		**M**		**M**					
Scheele et al.[51]	X	X	X	**M**	**M**	X	**M**	X	**M**	U		U	U		**M**	X	U	**M**		**M**		
Gayowski et al.[31]	U		**M**		X	U	U	U		U		**M**			U			X	X			
Van Ooijen et al.[20 c]		X	**M**			X	X					X			X	X		X	**M**			
Rosen et al.[33]		X	**M**	U	X		U			**M**					U	X						**M**
Cady et al.[52 c d]			U		U	U						U	U	U								U
Fegiz et al.[48 e]	X	X	U			U	U		U					U	U			X				
Doci et al.[53]	X	U	X			U		X	**M**				X		U	**M**		U				
Hughes et al.[17]	X		**M**			X		**M**		**M**		**M**	X		U		**M**					

Mets - Metastases

[c] Prognostic factor related to Disease-free Survival not Overall Survival
[d] univariate analysis only
[e] evaluated against 3 year overall survival

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Appendix E

EXAMPLE OF A PROTOCOL FOR THE FOLLOW-UP OF PATIENTS WITH COLORECTAL CANCER WITH SPECIAL REFERENCE TO LIVER METASTASES

The colorectal surgeon receives the initial referral and investigates the patient. A key determinant of follow-up is whether the patient would be fit for resection of recurrent disease if it is found. Pre-operative liver ultrasonography and determination of CEA levels should be carried out once the diagnosis is confirmed. Resection of the primary should then be carried out.

Synchronous Metastases:

If metastases are discovered before resection of the primary lesion, colo-rectal surgery should proceed and the metastases be assessed. A key determinant of the success of hepatic resection is the clearance of the primary tumour. If the colorectal surgeon considers that residual macroscopic disease is present, the patient should be referred for chemotherapy directly after surgery. If the surgeon considers that the primary colonic cancer has been satisfactorily cleared, and the liver disease is not widespread, patients (of all Dukes stages) should be referred directly for hepatic resection and this will be followed by systemic chemotherapy. Further management of rectal cancer patients will depend on radial resection margins in rectal cancer. Involved margins have a high incidence of local recurrence and these patients should be referred for systemic chemotherapy or radiotherapy and subsequent hepatic resection if imaging confirms the absence of local recurrence.

Metachronous Metastases:

If metastases are not found pre-operatively, colorectal surgery is conducted and entry into one of the adjuvant chemotherapy trials may be considered.

Follow-up of patients with no metastases at the time of removal of the primary is conducted in the colorectal clinic. The following protocol is recommended (in addition to the colonic surveillance program):

> 6-monthly follow-up for two years (90% of patients who develop liver metastases will do so within two years of diagnosis of colorectal cancer). At each visit:

- Ultrasonography of the liver

- Serum CEA level

At any stage of follow-up if the ultrasounds scan or CEA is abnormal, a Computed Tomography (CT) scan of the chest and abdomen should be performed. If there is no evidence of extrahepatic disease, and liver metastases are confirmed, the patient should be referred for further assessment of the liver lesions with a view to resection.

A ‘wait and see’ policy will result in metastases enlargement and hepatic lymphatic spread and is no longer justified.

Appendix F

EXAMPLE OF GUIDELINES FOR REFERRAL FOR HEPATIC RESECTION

The patient should be referred for consideration of liver resection only if the following criteria are fulfilled:

- The patient is fit to undergo hepatic resection (ASA I and II. Rarely ASA III). The morbidity of hepatic resection is low (e.g. same as gastrectomy).
- There is no evidence of extrahepatic disease.

These criteria are best assessed by:

- Anaesthetic assessment by Consultant Anaesthetist;
- Computed Tomography (CT) Scan of the chest and abdomen.

Assessment of Liver Metastases:

Resectability of metastases depends upon their geographical distribution in the liver. Size and number are not relevant. It is recommended that the CT scan should be sent to the liver surgeon for assessment and a decision can be made as to whether further imaging is appropriate.

REFERENCES

1 Office for National Statistics. Cancer statistics: registrations. 1992.

2 Millikan KW, Staren ED, Doolas A. Invasive therapy of metastatic colorectal cancer to the liver. *Surg Clin North Am* 1997; 77: 27-48.

3 Bengtsson G, Carlsson G, Hafstrom L, et al. Natural history of patients with untreated liver metastases from colorectal cancer. *Am J Surg* 1981; 141: 586-589.

4 NHS Executive. Guidance on Commissioning Cancer Services: Improving outcomes in colorectal cancer - the research evidence. 1997.

5 Wagner JS, Adson MA, van Heerden JA, et al. The natural history of hepatic metastases from colorectal cancer. A comparison with resective treatment. *Ann Surg* 1984; 199: 502-508.

6 Benson AB. Therapy for advanced colorectal cancer. *Semin Oncol* 1998; 25: 2-11.

7 NHS Centre for Reviews and Dissemination; University of York. Effective health care: The management of colorectal cancer. 1997.

8 Trent Cancer Registry. Colorectal cancer in Trent - 1992-94. 1998.

9 Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992; 10: 896-903.

10 Bozzetti F, Bignami P, Montalto F, et al. Repeated hepatic resection for recurrent metastases from colorectal cancer. *Br J Surg* 1992; 79: 146-148.

11 Allen-Mersh TG. Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases. *Lancet* 1994; 344: 1255-1260.

12 Scheithauer W. Randomised comparison of combination chemotherapy plus supportive care with suportive care alone in patients with metastatic colorectal cancer. *BMJ* 1993; 306: 752-755.

13 Adson MA, van Heerden JA, Adson MH, et al. Resection of hepatic metastases from colorectal cancer. *Arch Surg* 1984; 119: 647-651.

14 Stangl R. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994; 343: 1405-1410.

15 Wade TP, Virgo KS, Li MJ, et al. Outcomes after detection of metastatic carcinoma of the colon and rectum in a national hospital system. *J Am Coll Surg* 1996; 182: 353-361.

16 Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of indications for resection. Registry of Hepatic Metastases. *Surgery* 1988; 103: 278-288.

17 Hughes KS, Rosenstein RB, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases. A multi-institutional study of long-term survivors. *Dis Colon Rectum* 1988; 31: 1-4.

18 Jaeck D, Bachellier P, Guiguet M, et al. Survival benefit of repeat liver resection for recurrent colorectal metastases: 143 cases. *Wiadomosci Lekarskie* 1997; 50 Su 1 Pt 1: 102-104.

19 Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer* 1996; 77: 1254-1262.

20 Van Ooijen B, Wiggers T, Meijer S, et al. Hepatic resections for colorectal metastases in The Netherlands: A multiinstitutional 10-year study. *Cancer* 1992; 70: 28-34.

21 Steele G, Jr., Bleday R, Mayer RJ, et al. A prospective evaluation of hepatic resection for colorectal carcinoma metastases to the liver: Gastrointestinal Tumor Study Group Protocol 6584. *J Clin Oncol* 1991; 9: 1105-1112.

22 Hughes KS, Simon R, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. *Surgery* 1986; 100: 278-284.

23 Ohlsson B, Stenram U, Tranberg K, et al. Resection of colorectal liver metastases: 25-year experience. *World J Surg* 1998; 22: 268-277.

24 Rees M, Plant G, Bygrave S. Late results justify resection for multiple hepatic metastases from colorectal cancer. *Br J Surg* 1997; 84: 1136-1140.

25 Scheele J, Stang R, Altendorf-Hofmann A, et al. Resection of colorectal liver metastases. *World J Surg* 1995; 19: 59-71.

26 Fuhrman GM, Curley SA, Hohn DC, et al. Improved survival after resection of colorectal liver metastases. *Ann Surg Oncol* 1995; 2: 537-541.

27 Bakalakos EA, Kim JA, Young DC, et al. Determinants of survival following hepatic resection for metastatic colorectal cancer. *World J Surg* 1998; 22: 399-404.

28 Jenkins LT, Millikan KW, Bines SD, et al. Hepatic resection for metastatic colorectal cancer. *Am Surg* 1997; 63: 605-610.

29 Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. *J Clin Oncol* 1997; 15: 938-946.

30 Taylor M, Forster J, Langer B, et al. A study of prognostic factors for hepatic resection for colorectal metastases. *Am J Surg* 1997; 173: 467-471.

31 Gayowski TJ, Iwatsuki S, Madariaga JR, et al. Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. *Surgery* 1994; 116: 703-10.

32 Doci R, Gennari L, Bignami P, et al. One hundred patients with hepatic metastases from colorectal cancer treated by resection: Analysis of prognostic determinants. *Br J Surg* 1991; 78: 797-801.

33 Rosen CB, Nagorney DM, Taswell HF, et al. Perioperative blood transfusion and determinants of survival after liver resection for metastatic colorectal carcinoma. *Ann Surg* 1992; 216: 493-504.

34 Lygidakis NJ, Thodorakopoulou M, Dedemadi G, et al. Resection of unresectable secondary liver tumors--new frontiers in liver surgery. *Hepatogastroenterology* 1997; 44: 1632-1640.

35 Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg* 1990; 77: 1241-1246.

36 D'Angelica M, Brennan MF, Fortner JG, et al. Ninety-six five-year survivors after liver resection for metastatic colorectal cancer. *J Am Coll Surg* 1997; 185: 554-559.

37 Hagmuller E, Beck N, Ockert D, et al. [Adjuvant therapy of liver metastases: active specific immunotherapy]. [German]. *Zentralblatt fur Chirurgie* 1995; 120: 780-785.

38 Scheele J, Stangl R, Altendorf Hofmann A, et al. Indicators of prognosis after hepatic

resection for colorectal secondaries. *Surgery* 1991; 110: 13-29.

39 Schlag P, Hohenberger P, Herfarth C. Resection of liver metastases in colorectal cancer--competitive analysis of treatment results in synchronous versus metachronous metastases. *Eur J Surg Oncol* 1990; 16: 360-365.

40 Jarad AR. BMJ, ed. *Randomised Controlled Trials*. BMJ Books, 1998;

41 Egger M, Plant G, Bygrave S. Late results justify resection for multiple hepatic metastases from colorectal cancer. *Br J Cancer* 1997; 84: 1136-1140.

42 NHS Executive. The new NHS - Modern and Dependable: A National Framework for Assessing Performance. Consultative Document EL(98)4. 1998.

43 Ross P, Heron J, Cunningham D. Cost of treating advanced colorectal cancer: a retrospective comparison of treatment regimes. *Eur J Cancer* 1996; 32A: 13-17.

44 British Medical Association, Royal Pharmaceutical Society. British National Formulary. 1998.

45 Reber HA, Ashley SW, McFadden D. Curative treatment for pancreatic neoplasms - radical resection. *Surg Clin North Am* 1995; 75: 905-912.

46 Middleton G, Cunningham D. Current opinions in the management of gastrointestinal cancer. *Ann Oncol* 1995; 6: 17-26.

47 Cady B, Stone MD, McDermott WV, Jr., et al. Technical and biological factors in disease-free survival after hepatic resection for colorectal cancer metastases. *Arch Surg* 1992; 127: 561-8.

48 Fegiz G, Ramacciato G, Gennari L, et al. Hepatic resections for colorectal metastases: The Italian multicenter experience. *J Surg Oncol* 1991; 48: 144-154.

49 Nordlinger B, Vaillant JC, Guiguet M, et al. Survival benefit of repeat liver resections for recurrent colorectal metastases: 143 cases. Association Francaise de Chirurgie. *J Clin Oncol* 1994; 12: 1491-1496.

50 Jaeck D, Bachellier P, Guiguet M, et al. Long-term survival following resection of colorectal hepatic metastases. *Br J Surg* 1997; 84: 977-980.

51 Scheele J, Altendorf Hofmann A, Stangl R, et al. Surgical resection of colorectal liver metastases: Gold standard for solitary and completely resectabe lesions. *Swiss Surg*

1996; 4-17.

52 Cady B, Stone MD. The role of surgical resection of liver metastases in colorectal carcinoma. *Semin Oncol* 1991; 18: 399-406.

53 Doci R, Bignami P, Montalto F, et al. Prognostic factors for survival and disease-free survival in hepatic metastases from colorectal cancer treated by resection. *Tumori* 1995; 81: 143-146.

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