npg

Surgical resection of hepatic metastases from colorectal cancer: A systematic review of published studies

Clinical Studies

PC Simmonds[1], JN Primrose*[,2], JL Colquitt[1], OJ Garden[3], GJ Poston[4] and M Rees[5]

[1]Cancer Research UK Clinical Centre, MP824, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK; [2]University Surgery, F Level Centre Block (MP816), Southampton General Hospital, Southampton SO16 6YD, UK; [3]Department of Clinical and Surgical Sciences, Royal Infirmary of Edinburgh, 51 Little France Crescent, Old Dalkeith Road, Edinburgh, Scotland EH16 4SA, UK; [4]Department of Surgery, University Hospital Aintree, Longmoor Lane, Liverpool L9 7AL, UK; [5]Hepatobiliary Surgery Unit, North Hampshire Hospital, Aldermaston Road, Basingstoke RG24 9NA, UK

No consensus on the indications for surgical resection of colorectal liver metastases exists. This systematic review has been undertaken to assess the published evidence for its efficacy and safety and to identify prognostic factors. Studies were identified by computerised and hand searches of the literature, scanning references and contacting investigators. The outcome measures were overall survival, disease-free survival, postoperative morbidity and mortality, quality of life and cost effectiveness, and a qualitative summary of the trends across all studies was produced. Only 30 of 529 independent studies met all the eligibility criteria for the review, and data on 30-day mortality and morbidity only were included from a further nine studies. The best available evidence came from prospective case series, but only two studies reported outcomes for all patients undergoing surgery. The remainder reported outcomes for selected groups of patients: those undergoing hepatic resection or those undergoing curative resection. Postoperative mortality rates were generally low (median 2.8%). The majority of studies described only serious postoperative morbidity, the most common being bile leak and associated perihepatic abscess. Approximately 30% of patients remained alive 5 years after resection and around two-thirds of these are disease free. The quality of the majority of published papers was poor and ascertaining the benefits of surgical resection of colorectal hepatic metastases is difficult in the absence of randomised trials. However, it is clear that there is group of patients with liver metastases who may become long-term disease- free survivors following hepatic resection. Such survival is rare in apparently comparable patients who do not have surgical treatment. Further work is needed to more accurately define this group of patients and to determine whether the addition of adjuvant treatments results in improved survival.

Colorectal cancer is the third most common cause of cancer death in the UK (Cancer Research UK Information Resource Centre, 2003). Surgery is the treatment of choice for patients with localised disease but over half of all patients will develop metastases. The liver is often the first site of metastatic disease and may be the only site of spread in as many as 30–40% of patients with advanced disease (Weiss et al, 1986; Hugh et al, 1997a).

It has been postulated that because haematogenous spread usually occurs in a stepwise fashion, initially to the liver, with subsequent intrahepatic spread via the portal vein and further spread to the systemic circulation, surgical resection of isolated hepatic metastases from colorectal cancer may be curative.

The natural history of metastatic colorectal cancer is variable, with a median survival without treatment of only 8 months (Seymour et al, 1997; Simmonds, 2000). Patients with isolated hepatic metastases have a better prognosis than those with more extensive metastatic disease (Goslin et al, 1982; Lahr et al, 1983; Stangl et al, 1994; Rougier et al, 1995) suggesting biological differences in the two settings (Goslin et al, 1982; Lahr et al, 1983; Stangl et al, 1994; Rougier et al, 1995). However, few patients with limited liver-only metastases survive for 5 years (Goslin et al, 1982; Stangl et al, 1994).

A variety of therapeutic approaches have been used in the treatment of metastatic colorectal cancer including surgery, chemotherapy, radiofrequency ablation, cryotherapy or some combination of these (Primrose, 2002). Around 20–30% of patients with liver-only metastases are potentially resectable (Nordlinger et al, 1994; Stangl et al, 1994; Jeffery et al, 2002). The selection criteria for surgery are usually controlled primary tumour, no extra hepatic metastases and that resection is technically feasible with tumour-free margins (Hugh et al, 1997b). A small proportion of patients with completely resectable extrahepatic disease may become long-term survivors (Scheele et al, 1995). Chemotherapy used alone is palliative but may prolong the survival of patients with unresectable disease (de Gramont et al, 2000; Douillard et al, 2000; Saltz et al, 2000; Simmonds, 2000). Used in combination with surgery it may prolong the time to recurrence after resection of hepatic

*Correspondence: Professor JN Primrose;
E-mail: j.n.primrose@soton.ac.uk

metastases (Kemeny *et al*, 2002) or downsize to resectability patients previously judged inoperable (Giacchetti *et al*, 1999). The role of other treatments is poorly defined (Armstrong *et al*, 1994; Donovan, 1995; Adam *et al*, 1997; de Baere *et al*, 1999; Primrose, 2002).

Although there are a large number of published studies reporting the results of surgical resection of hepatic metastases from colorectal cancer, the effectiveness and cost effectiveness of such surgery remains unclear. This systematic review has been undertaken to assess the published evidence for the efficacy and safety of this intervention and, by examining potential prognostic factors, identify patients who may either benefit from surgery or in whom such intervention is inappropriate.

METHODS

Criteria for selecting studies

As randomised trials comparing surgical resection *vs* no surgery have never been conducted, we have attempted to identify all relevant prospective and retrospective series reporting the outcomes of surgical resection with curative intent of colorectal hepatic metastases. Patients undergoing repeat hepatic resection were also included. In order to ensure that the surgical series reviewed reflected the outcomes for patients treated with modern surgical, anaesthetic and supportive care techniques, we have restricted our qualitative analysis to surgical series published after 1980 reporting the outcomes of at least 100 patients. Studies were required to follow patients for at least 30 days for inclusion of data on postoperative morbidity and mortality, and for a median of at least 24 months for inclusion of survival data. No language restriction was applied on searching. All eligible European language studies were translated, but retrospective non-European articles were not.

The outcome measures were overall survival (1 year/3 year/5 year), disease-free survival (1 year/3 year/5 year), operative and postoperative morbidity, operative and postoperative mortality, quality of life and cost effectiveness.

Search strategy

We searched the following electronic databases: Cochrane Controlled Trials Register, Medline, Embase, Cancerlit, Science Citation Index, Edina Biosis, CINAHL and NHS Economic Evaluation Database. Both medical subject heading and free text searching were used to improve the sensitivity of the search. The search strategy was piloted and modified to improve the hit rate, and the sensitivity of the search strategy was tested by hand searching three journals in which a high proportion of identified studies had been published (*Cancer, British Journal of Surgery*, and *Diseases of the Colon and Rectum*, 1998–1999). All relevant studies had been identified, confirming that the search was comprehensive. Searching took place between May 2000 and October 2000. The full search strategy is available from the authors on request.

The following registers were searched for details of ongoing and unpublished studies: National Research Register, Current Controlled Trials, MRC Funded Research database, UKCCCR trials register, Centre Watch Clinical Trials listing, Physician Data Query (USA), National Institutes of Health Clinical Trials (USA), National Health and Medical Research Council (Australia), Trial Amnesty on the Cochrane library, System for Information on Grey Literature in Europe (SIGLE). Investigators of eligible prospective studies and large surgical centres were contacted to find further published, unpublished or ongoing studies, and the reference lists of review articles on this subject and all eligible studies were examined. In order to identify studies that had not been indexed in the above sources, the Proceedings of the American Society of Clinical Oncology (1982–2000) were hand searched.

Review procedures and analysis

All relevant studies were assessed according to the above inclusion criteria using a standard checklist performed independently by two reviewers (one clinical and one non-clinical) and agreement on eligibility was reached. Investigators were contacted for further information where eligibility could not be determined from the published study. Data were extracted from published papers by one reviewer using a standard data extraction sheet and then verified independently by a second reviewer. Data extracted included demographic characteristics of patients, preoperative comorbidities, details of the primary tumour, details of hepatic and extrahepatic metastases, type of resection, nonsurgical therapy and outcomes. When a study had generated multiple publications, the most recent was used to extract data on relevant outcome variables. Earlier publications were used to provide information on baseline characteristics or methodology where necessary. Validity was assessed independently by two reviewers using a standard critical appraisal checklist. For the purposes of this review, items relevant to the assessment of uncontrolled surgical case series were combined from two checklists (Cowley, 1995; Downs and Black, 1998). The checklist was piloted by two reviewers and assessed quality of reporting and internal and external validity. An index of inter-rater agreement was calculated using the Kappa statistic. As all of the eligible published studies were either prospective or retrospective case series, a qualitative summary was produced to identify and describe trends across all studies.

RESULTS

Description of studies identified

Of 529 studies identified by our initial search strategy, 470 were not included in the review, often for more than one reason: 409 (77%) reported less than 100 patients, the median follow-up was less than 24 months in 45 (9%) and unclear in 345 (65%) studies. Other reasons for exclusion were combined data from colorectal and non-colorectal liver metastases (38/529) and lack of mortality and survival data (21/529). The eligibility of 19 publications was unclear, but as these were updated elsewhere the older reports were excluded, and 15 studies were not included because their eligibility remained unclear despite seeking further details from the authors of the original report. A list of excluded studies with reasons for exclusion is available on request from the authors.

Forty-nine published and unpublished studies met all the inclusion criteria, including multiple publications presenting updated information or data on different aspects of the same patient population, providing 30 independent eligible studies. Eighteen of these were single publications (Savage and Malt, 1992; Sugihara *et al*, 1993; Donato *et al*, 1994; Doci *et al*, 1995; Fernandez-Trigo *et al*, 1995; Fuhrman *et al*, 1995; Beckurts *et al*, 1997; Rees *et al*, 1997; Cady *et al*, 1998; Ohlsson *et al*, 1998; Riesener *et al*, 1998; Bradley *et al*, 1999; Harmon *et al*, 1999; Harms *et al*, 1999; Kemeny *et al*, 1999a; Bolton and Fuhrman, 2000; Okano *et al*, 2000; Moroz *et al*, 2002) and in a further 12 cases the data was obtained from multiple publications (Hughes *et al*, 1988, 1989; Hohenberger *et al*, 1990, 1994; Scheele *et al*, 1990, 1991, 1995, 1996; Steele Jr *et al*, 1991, 1995; Rosen *et al*, 1992; Gayowski *et al*, 1994; Stangl *et al*, 1994; Fong *et al*, 1995, 1997, 1999; Leslie *et al*, 1995; Jamison *et al*, 1996, 1997; Jenkins *et al*, 1997; Bakalakos *et al*, 1998a, b; Iwatsuki *et al*, 1999; Minagawa *et al*, 1999; Ambiru *et al*, 1999a; Kemeny *et al*, 1999b, c; Brand *et al*, 2000; DeMatteo *et al*, 2000; Minagawa *et al*, 2000). In addition, data on 30-day mortality and morbidity were included from a further nine studies (one with two publications) in which survival data was excluded owing to insufficient or unclear follow up (Minton and Abou-Issa, 1990; Fegiz *et al*, 1991; Nordlinger *et al*, 1992; van Ooijen *et al*, 1992; Wade *et al*, 1996; Lorenz *et al*, 1997, 1998; Nadig *et al*, 1997; Taylor

et al, 1997; Figueras *et al*, 2001). Details of all studies are tabulated in Appendix A.

Just two studies included all patients presenting with colorectal liver metastases (Scheele *et al*, 1990, 1991, 1995, 1996; Stangl *et al*, 1994; Harms *et al*, 1999) and only three studies presented data on all patients undergoing surgery (radical, nonradical and laparotomy) (Steele Jr *et al*, 1991, 1995; Fuhrman *et al*, 1995; Bakalakos *et al*, 1998a). The majority (27) of studies presented data on resected patients, but while some studies distinguished between R0 resections (no residual disease, histologically clear margins), R1 (histologically involved margins) and R2 resections (macroscopic residual disease), in many this was unclear. Six studies included only a select group of patients undergoing radical resection, and one study included patients undergoing repeat resection only.

Eleven studies were conducted prospectively, three of which were randomised controlled trials comparing surgery alone with surgery plus chemotherapy (Lorenz *et al*, 1998; Kemeny *et al*, 1999a) or comparing two adjuvant chemotherapy regimes (Kemeny *et al*, 1999c). Twenty-five studies were retrospective and the design of three studies was unclear. Twenty-six studies were conducted in single centres, 11 were multicentre studies and two were undertaken by two centres.

No data was found on comorbidity, quality of life, or cost effectiveness of liver resection.

Methodological quality of included studies

There was consistency in validity appraisal between the two reviewers, as indicated by a Kappa statistic of 0.79. The 16-point validity scale was completed for all studies, including one study that was published in abstract form only (Kemeny *et al*, 1999a) (Appendix B). Total scores ranged from 2 to 14 (mean 8.7, median 9).

The quality of reporting was poor in many studies. Eligibility criteria for surgery or inclusion criteria in the study were not reported by 12 (31%) studies. The distribution of principal confounders, such as synchronous or metachronous metastases and curative intent of surgery were not reported by almost a third of studies. Basic demographic information such as mean age and sex distribution was also often missing. Patients were thought to be representative in only a minority of studies (mostly highly selected), and similarly the treatment centres were considered to be unrepresentative (highly specialised).

The primary end points of mortality and survival were not clearly defined in 33 and 74% of studies, respectively; therefore, the comparability of results between studies is unclear. Postoperative mortality was excluded from survival analysis in 21% studies, and patients lost to follow-up were not reported or not included in the appropriate analysis by over half of the studies. Median length of follow-up was not reported by 31% of studies. The outcome of patients receiving surgery alone was reported by just 12 (31%) studies. In 10 (26%) studies patients receiving additional therapies such as adjuvant chemotherapy were not analysed separately. Further, the use of additional therapies was not stated in 17 (44%) studies.

Postoperative mortality

Death within 30 days of hepatic resection was reported by 24 studies, ranging from 0 to 6.6% of patients (median 2.8%). A further nine studies reported perioperative mortality within an undefined time period (1.3–4.6%, median 3.6%), and two studies reported 60-day mortality (3.4–5.5%). Mortality was not reported by four studies. Cause of death was reported by 15 studies for a total of 103 patients (Table 1), including two studies that reported deaths from surgical complications occurring within 90 days (Iwatsuki *et al*, 1999) and 128 days (Scheele *et al*, 1996).

Table I Fatal complications

	No. of studies	No. of patients	% of reported fatalities ($n = 103$)
Bile leak	4	6	5.8
Perihepatic abscess	2	3	2.9
Hepatic failure	10	19	18.4
Renal failure	4	4	3.9
Generalised sepsis	8	17	16.5
Peritonitis	2	3	2.9
GI bleed	3	3	2.9
Deep vein thrombosis	1	1	1.0
Pulmonary embolism	4	7	6.8
Myocardial infarction	3	3	2.9
Cardiac failure	6	12	11.7
Arrhythmia	1	3	2.9
Pneumonia	2	2	1.9
Cerebrovascular accident	2	3	2.9
Urinary tract infection	1	1	1.0
Postoperative haemorrhage	8	18	17.5
Adult respiratory distress syndrome	2	4	3.9
Multisystem organ failure	2	7	6.8
Anastomotic leak/insufficiency	2	6	5.8
Other	8	14	13.6

NB patients may have had more than one cause of death.

Postoperative morbidity

Perioperative complications, including indicators of morbidity such as length of hospital stay, were reported by 29 studies. However, some studies reported fatal complications only (van Ooijen *et al*, 1992; Scheele *et al*, 1996; Lorenz *et al*, 1998; Bolton and Fuhrman, 2000; Moroz *et al*, 2002), length of hospital stay only (Hohenberger *et al*, 1994; Fuhrman *et al*, 1995), blood transfusions only (Jamison *et al*, 1997) or simply reported the number of patients with nonspecified complications (van Ooijen *et al*, 1992; Fernandez-Trigo *et al*, 1995; Scheele *et al*, 1996; Jenkins *et al*, 1997; Taylor *et al*, 1997; Bakalakos *et al*, 1998a; Fong *et al*, 1999; Figueras *et al*, 2001).

The number of studies reporting each complication and the number of patients with the complication is presented in Table 2.

Overall survival

Two studies reported overall survival at 5 years for all patients undergoing surgery (resection and laparotomy only), median 23% (15–31%) (Table 3). Studies in which it was unclear whether resections were R0 or R1/2, or only presented data for both types of resection combined, had a median 5-year survival of 32% (9–63%). Sixteen studies presented 5-year survival for patients undergoing R0 resection, either for the whole study population or for subgroups of patients. Median 5-year survival for these studies was 30% (range 15–67%). Eleven studies reporting 5-year survival for nonradical resections had a median 5-year survival of 7.2% (range 0–30%), and six studies reporting patients who did not undergo resection had a median 5-year survival of 0% (range 0–6%). Survival according to study design is also presented in Table 3. Patients who underwent resection without any additional therapy had a median 5-year survival of 30% (range 20–33.6%), whereas patients who received additional therapy had a median 5-year survival of 35.5% (range 9–63%). Studies in which use of additional therapy was not stated reported 5-year survival between 14 and 58% (median 32.5%). Overall 5-year survival was not reported by three studies (Donato *et al*, 1994; Hohenberger *et al*, 1994; Cady *et al*, 1998), and one study reporting survival from

Table 2 Morbidity (fatal and non-fatal)

	No. of studies	No. of patients in studies	No. of patients with complication	% of patients with complication
Bile leak	15	3746	148	4.0
Perihepatic abscess	11	1755	53	3.0
Hepatic failure	16	3646	102	2.8
Renal failure	6	643	7	1.2
Wound infection	10	1618	88	5.4
Generalised sepsis	12	3312	151	4.6
GI bleed	6	666	12	1.8
Deep vein thrombosis	5	897	7	0.8
Pulmonary embolism	9	935	15	1.6
Myocardial infarction	5	754	11	1.5
Arrhythmia	6	777	22	2.8
Pneumonia	6	933	18	1.9
Pleural effusion	7	1268	55	4.3
Urinary tract infection	5	708	15	2.1
Cerebrovascular accident	5	374	6	1.6
Peritonitis	2	160	3	1.9
Cardiac failure	6	532	13	2.4
Postoperative haemorrhage	15	3913	106	2.7
Other (including complications not specified)	23	6529	1314	20.1
Any blood transfusion	7	1342	863	64.3

			Minimum	Maximum	Median
Units transfused					
Mean	4	572	1	4.4	2.2
Median	6	749	2	6	3
Volume of blood loss (ml)					
Mean	2	238	989	1900	
Median	2	228	425	1700	
Intensive care (days)					
Minimum	1	131			0
Maximum	1	131			38
Median	1	134			1
Mean	2	265	2.5	3.5	
Length of stay (days)	17	2733			
Minimum			1	8	4.5
Maximum			26	100	59
Median			7	17	9.5
Mean			8.8	21	12.5

repeat hepatic resections only was not included in this analysis (Fernandez-Trigo *et al*, 1995).

Disease-free survival

Disease-free survival was reported by fewer studies. Median disease-free survival was 11.6 (Hohenberger *et al*, 1994) and 17 (Doci *et al*, 1995) months (median 14.3 months) for radically resected patients and between 10.8 and 37.4 months (median 17.2 months) for patients with unspecified resections (Jenkins *et al*, 1997; Ohlsson *et al*, 1998; Kemeny *et al*, 1999c; Minagawa *et al*, 2000).

Five-year disease-free survival was reported between 9 and 35% (median 18%) (Doci *et al*, 1995; Scheele *et al*, 1996; Ambiru *et al*, 1999b) and 4–47% (median 21%) (Hughes *et al*, 1989; Jenkins *et al*, 1997; Ohlsson *et al*, 1998; Bradley *et al*, 1999; Iwatsuki *et al*, 1999; Minagawa *et al*, 2000; Okano *et al*, 2000) by studies with radically resected patients and unspecified resections, respectively.

Sites of recurrence

Sites of recurrence following hepatic resection were reported by 13 studies (Table 4). They were classified as liver, extrahepatic or liver plus extrahepatic. Twenty-two percent of all patients experienced recurrence in the liver only, although this is likely to be underestimated as two studies did not specify the proportion of liver-only recurrences. Liver plus extrahepatic recurrences and extrahepatic-only recurrences were experienced by 16 and 24% of patients, respectively. In addition, one study reported recurrences in 235 (62.5%) radically resected patients, although sites of recurrence were not specified.

Prognostic factors

Many studies reported 1-year, 3-year, 5-year and median overall survival and disease-free survival for various potential prognostic factors relating to the characteristics of the primary tumour and/or liver metastases. In general, comparison between studies is limited

Clinical Studies

Table 3 Overall 5-year survival

	Studies	5-year survival (%)		
		Minimum	**Maximum**	**Median**
Patients				
All patients (resected+non resected)	Fuhrman et al, 1995; Harms et al, 1999	15	31	
Resected patients (R0/R1 unclear)	Hughes et al, 1989; Beckurts et al, 1997; Jamison et al, 1997; Ohlsson et al, 1998; Bakalakos et al, 1998a; Bradley et al, 1999; Fong et al, 1999; Harmon et al, 1999; Harms et al, 1999; Iwatsuki et al, 1999; Kemeny et al, 1999a, c; Bolton and Fuhrman, 2000; Minagawa et al, 2000; Moroz et al, 2002) (Jenkins et al, 1997; Okano et al, 2000) (Savage and Malt, 1992; Rees et al, 1997; Scheele et al, 1996	9	63	32
Radical (R0) resection	Savage and Malt, 1992; Sugihara et al, 1993; Doci et al, 1995; Fuhrman et al, 1995; Steele Jr et al, 1995; Scheele et al, 1996; Beckurts et al, 1997; Jenkins et al, 1997; Rees et al, 1997; Riesener et al, 1998; Bakalakos et al, 1998a; Fong et al, 1999; Harms et al, 1999; Iwatsuki et al, 1999; Ambiru et al, 1999b; Okano et al, 2000	15	67	30
Nonradical resection	Lange et al, 1989; Savage and Malt, 1992; Sugihara et al, 1993; Steele Jr et al, 1995; Beckurts et al, 1997; Jenkins et al, 1997; Rees et al, 1997; Bakalakos et al, 1998a; Fong et al, 1999; Harms et al, 1999; Okano et al, 2000	0	30	7.2
Patients not resected	Fuhrman et al, 1995; Steele Jr et al, 1995; Scheele et al, 1996; Bakalakos et al, 1998a; Harms et al, 1999; Moroz et al, 2002	0	6	0
Prospective studies				
Resected (R0/R1 unclear)	Scheele et al, 1996; Beckurts et al, 1997; Rees et al, 1997; Ohlsson et al, 1998; Kemeny et al, 1999a, c	14	63	32.5
Radical	Steele Jr et al, 1995; Scheele et al, 1996; Beckurts et al, 1997; Rees et al, 1997	15	38	30
Non radical	Steele Jr et al, 1995; Beckurts et al, 1997; Rees et al, 1997	0	14	6
Retrospective studies				
Resected (R0/R1 unclear)	Hughes et al, 1989; Savage and Malt, 1992; Jamison et al, 1997; Jenkins et al, 1997; Bakalakos et al, 1998a; Bradley et al, 1999; Fong et al, 1999; Harmon et al, 1999; Iwatsuki et al, 1999; Bolton and Fuhrman, 2000; Minagawa et al, 2000; Okano et al, 2000; Moroz et al, 2002	9	58	32.3
Radical	Savage and Malt, 1992; Doci et al, 1995; Fuhrman et al, 1995; Jenkins et al, 1997; Riesener et al, 1998; Bakalakos et al, 1998a; Fong et al, 1999; Harms et al, 1999; Iwatsuki et al, 1999; Ambiru et al, 1999b; Okano et al, 2000	17	67	30
Non radical	Savage and Malt, 1992; Jenkins et al, 1997; Bakalakos et al, 1998a; Fong et al, 1999; Harms et al, 1999; Iwatsuki et al, 1999; Okano et al, 2000	0	30	7.2
Single centre				
Resected (R0/R1 unclear)	Jamison et al, 1997; Ohlsson et al, 1998; Bakalakos et al, 1998a; Harmon et al, 1999; Kemeny et al, 1999c; Bolton and Fuhrman, 2000; Moroz et al, 2002	9	61	32.3
Radical	Savage and Malt, 1992; Sugihara et al, 1993; Doci et al, 1995; Fuhrman et al, 1995; Scheele et al, 1996; Jenkins et al, 1997; Rees et al, 1997; Riesener et al, 1998; Bakalakos et al, 1998a; Fong et al, 1999; Harms et al, 1999; Iwatsuki et al, 1999; Ambiru et al, 1999b; Okano et al, 2000	17	67	30
Non radical	Savage and Malt, 1992; Sugihara et al, 1993; Jenkins et al, 1997; Rees et al, 1997; Bakalakos et al, 1998a; Fong et al, 1999; Harms et al, 1999; Iwatsuki et al, 1999; Okano et al, 2000	0	30	7.2
Multicentre				
Resected (R0/R1 unclear)	Hughes et al, 1989; Kemeny et al, 1999a; Minagawa et al, 2000	32	63	35
Radical	Steele Jr et al, 1995		23	
Non radical	Steele Jr et al, 1995		14	
Two centres				
Resected (R0/R1 unclear)	Beckurts et al, 1997; Bradley et al, 1999	14	36	
Radical	Beckurts et al, 1997		15	
Resection only	Ohlsson et al, 1998; Harms et al, 1999; Iwatsuki et al, 1999; Kemeny et al, 1999a; Ambiru et al, 1999b	20	33.6	30
Resection+additional therapy	Steele Jr et al, 1995; Jamison et al, 1997; Ohlsson et al, 1998; Riesener et al, 1998; Bakalakos et al, 1998a; Bradley et al, 1999; Fong et al, 1999; Harmon et al, 1999; Harms et al, 1999; Iwatsuki et al, 1999; Kemeny et al, 1999a; Ambiru et al, 1999b; Kemeny et al, 1999c; Bolton and Fuhrman, 2000	9	63	35.5
Resection+use of additional therapy unclear	Hughes et al, 1989; Savage and Malt, 1992; Sugihara et al, 1993; Doci et al, 1995; Fuhrman et al, 1995; Scheele et al, 1996; Beckurts et al, 1997; Jenkins et al, 1997; Rees et al, 1997; Minagawa et al, 2000; Okano et al, 2000; Moroz et al, 2002	14	58	32.5

Table 4 Sites of recurrence

	Patients	Liver (%)	Extrahepatic (%)	Liver+extra hepatic (%)
Ambiru *et al*, 1999a, b (n = 174)	Resection+HAI	14 (17.9)	16 (20.5)	9 (11.5)
	Resection+PVI	5 (16.7)	12 (40)	7 (23.3)
	Resection only	19 (28.8)	20 (30.3)	12 (18.2)
	Total (R0 resection)	38 (21.8)	48 (27.6)	28 (16.1)
Bradley *et al*, 1999 (n = 134)	Resection R0/R1 unclear	36 (26.9)	27 (20.1)	21 (15.7)
Doci *et al*, 1995 (n = 224)	R0 resection	73 (32.6)	57 (25.4)	25 (11.2)
Donato *et al*, 1994 (n = 102)	Resection only	21 (33.9)	5 (8.1)	
	Resection+chemo	15 (37.5)	7 (17.5)	
	Total (R0 resection)	36 (35.3)	12 (11.8)	
Kemeny *et al*, 1999a, b, c (n = 77)	Resection only			24 (53.3)
	Resection+chemo			8 (25.0)
	Total (R0/R1 unclear)			32 (41.6)[a]
Minagawa *et al*, 2000 (n = 234)	R0/R1 unclear		73 (31.2)	98 (41.7)[a]
Ohlsson *et al*, 1998 (n = 111)	R0/R1 unclear	19 (17.1)	19 (17.1)	43 (38.7)
Okano *et al*, 2000 (n = 152)	R0/R1 unclear	38 (25.0)	26 (17.1)	6 (3.9)
Rees *et al*, 1997 (n = 89)	R0 resection	25 (28.1)	27 (30.3)	9 (10.1)
Riesener *et al*, 1998 (n = 109)	R0 resection	18 (30.5)	13 (22.0)	15 (25.4)
	R0 resection+chemo	10 (20.0)	9 (18.0)	12 (24.0)
	Total	28 (25.7)	22 (20.2)	27 (24.8)
MSKCC, 1999 (n = 156)	Resection+combined therapy	7 (9.5)	35 (47.3)	
	Resection+monotherapy	30 (36.6)	44 (51.8)	
	Total (R0/R1 unclear)	37 (23.7)	79 (50.6)	
Steele *et al*, 1995 (n = 150)	All undergoing surgery	28 (18.7)	11 (7.3)	4 (2.7)
Sugihara *et al*, 1993 (n = 109)	R0 resection	34 (31.2)	30 (27.5)	
Total n = 1821		392 (21.5)	431 (23.7)	293 (16.1)

[a]Proportion of patients with recurrence in the liver only not specified.

owing to differences in categorisation of the prognostic factors. A definition of 'synchronous' is not given in most cases, but could mean hepatic resection within 1 month (Hughes *et al*, 1989), 3 months (Jamison *et al*, 1997; Rees *et al*, 1997) or 6 months (Donato *et al*, 1994) of primary surgery. Time interval between resection of the primary tumour and metastases has been classified into five different categories. Categories for number and size of liver metastases are also extremely varied, and reporting of the type of liver resection is inconsistent. Results from multivariate analysis, which identified prognostic factors independently associated with overall survival, are shown in Table 5. As the factors included in the model differed for each study these cannot be directly compared.

Repeat resections

In studies that reported this outcome, between 3.6 and 17% (median 9%) of patients underwent repeat hepatic resection (Scheele *et al*, 1996; Rees *et al*, 1997; Ohlsson *et al*, 1998; Bakalakos *et al*, 1998a; Bradley *et al*, 1999; Iwatsuki *et al*, 1999; Ambiru *et al*, 1999b; Kemeny *et al*, 1999c; Minagawa *et al*, 2000). Three hepatic resections were performed on 0.9–4% (median 3.8%) of patients (Ohlsson *et al*, 1998; Bakalakos *et al*, 1998a; Minagawa *et al*, 2000), and just 0.4% underwent four resections (Minagawa *et al*, 2000). The Repeat Hepatic Registry reported a series of 170 patients undergoing repeat resection, of which 4.7% underwent a third

resection (Fernandez-Trigo *et al*, 1995). Median and 5-year overall survival from the date of second liver resection for the 170 patients was 34 months and 32%, respectively.

DISCUSSION

Although the prognosis of metastatic colorectal cancer is poor with few patients surviving for 5 years or more (Stangl *et al*, 1994) long-term survival has been reported following surgical resection of isolated hepatic metastases (Fong and Salo, 1999; Geoghegan and Scheele, 1999). The nature of the published studies of surgical resection for colorectal liver metastases did not allow for a quantitative analysis to be performed and we have thus undertaken a qualitative systematic review to summarize the available evidence for the effectiveness of this intervention.

Surgical resection of hepatic metastases from colorectal cancer can be undertaken safely in the majority of patients. The median postoperative (30 day) mortality reported by 24 studies was only 2.8% (0–6.6%). There was patchy reporting of the causes of postoperative death, with the most frequent causes being hepatic failure, postoperative haemorrhage, and sepsis. It is likely that current surgical and anaesthetic practice is associated with perioperative mortalities nearer to 1% as demonstrated in a recent multicentre trial (Nordlinger *et al*, 2005). Operative morbidity was more difficult to quantify as many studies reported only fatal

Clinical Studies

Table 5 Prognostic factors by multivariate analysis

	Significant (improved prognosis)	Nonsignificant
Age	—	Hohenberger et al, 1994; Moroz et al, 2002
Female	Donato et al, 1994	Moroz et al, 2002
Male	Hohenberger et al, 1994	
Primary tumour		
Site of primary tumour	—	Sugihara et al, 1993; Hohenberger et al, 1994; Rees et al, 1997; Kemeny et al, 1999c; Moroz et al, 2002
Low grade of primary tumour	Scheele et al, 1996	Sugihara et al, 1993; Hohenberger et al, 1994; Beckurts et al, 1997; Rees et al, 1997; Harms et al, 1999
No regional lymph node metastases of primary tumour (Duke's stage A or B)	Doci et al, 1995; Fong et al, 1999; Minagawa et al, 2000	Sugihara et al, 1993; Hohenberger et al, 1994; Beckurts et al, 1997; Rees et al, 1997; Harms et al, 1999
Liver tumour		
Metachronous	Sugihara et al, 1993; Donato et al, 1994; Beckurts et al, 1997; Harms et al, 1999	Hohenberger et al, 1994; Rees et al, 1997; Okano et al, 2000
Time interval from primary (months)	Hohenberger et al, 1994 >12 (Fong et al, 1999) >30 (Iwatsuki et al, 1999)	0−3 vs ≥4 (Minagawa et al, 2000)
Size of liver metastases (cm)	Bolton and Fuhrman, 2000 <8 cm (Rees et al, 1997) <5 cm (Scheele et al, 1996; Fong et al, 1999; Okano et al, 2000)	≤2 vs 2.1−5. vs ≥5 cm (Sugihara et al, 1993) <5 vs ≥5 cm (Kemeny et al, 1999c)
Number of liver tumours	<8 (Moroz et al, 2002) 1 (Fong et al, 1999; Minagawa et al, 2000) <3 (Iwatsuki et al, 1999; Okano et al, 2000)	Harms et al, 1999; Bolton and Fuhrman, 2000 1 vs 2−4 vs ≥5 (Sugihara et al, 1993) 1 vs 2−3 vs >3 (Hohenberger et al, 1994; Doci et al, 1995; Rees et al, 1997) 1 vs >1 (Beckurts et al, 1997) ≤7 vs >7 (Moroz et al, 2002)
Absence of satellite metastases	Scheele et al, 1996	—
Percent hepatic replacement (less involvement)	Hohenberger et al, 1994; Doci et al, 1995	—
Unilobar distribution of liver tumour	Iwatsuki et al, 1999	Sugihara et al, 1993; Hohenberger et al, 1994; Rees et al, 1997; Fong et al, 1999; Harms et al, 1999; Okano et al, 2000; Moroz et al, 2002
Fewer hepatic segments involved	Bolton and Fuhrman, 2000	—
Low/moderate grade of liver tumour	Ohlsson et al, 1998	—
Nodes at hepatoduodenal ligament not involved	Beckurts et al, 1997; Harms et al, 1999; Minagawa et al, 2000	Okano et al, 2000
Local invasion of hepatic disease absent	Moroz et al, 2002	—
Vascular invasion absent	Okano et al, 2000	—
Intrahepatic bile duct invasion absent	—	Okano et al, 2000
Extrahepatic disease absent	Ohlsson et al, 1998; Fong et al, 1999; Iwatsuki et al, 1999	—
Presence of fibrous pseudocapsule	Okano et al, 2000	—
Low preoperative CEA level (ng/ml)	Ohlsson et al, 1998 <200 (Fong et al, 1999)	≤5 vs 5.1−30 vs ≥30.1 (Sugihara et al, 1993) <50 vs ≥50 (Minagawa et al, 2000) <5 vs >5 (Hohenberger et al, 1994)
Low postoperative CEA level (ng/ml)	(Hohenberger et al, 1994)	—
Increased resection margin	>5 mm (Rees et al, 1997)	≥1 cm vs ≤0.9 cm (Scheele et al, 1996)
Ro resection	Ro (Fong et al, 1999; Harms et al, 1999; Iwatsuki et al, 1999; Okano et al, 2000)	—
Type of hepatic surgery	Anatomical (Scheele et al, 1996)	(Sugihara et al, 1993; Doci et al, 1995; Bolton and Fuhrman, 2000)
No intraoperative blood transfusion	(Ohlsson et al, 1998)	—
Year of resection more recent	1985−95 vs 1971−84 (Ohlsson et al, 1998)	—
Complex vs simple disease	—	Bolton and Fuhrman, 2000
Additional treatment		
Chemotherapy vs none	—	Donato et al, 1994; Bolton and Fuhrman, 2000
Combined therapy vs monotherapy	(Kemeny et al, 1999c)	—

morbidity or a very limited range of postoperative complications. It was therefore difficult to determine the proportion of patients experiencing operative morbidity and thus its overall impact on patients in the majority of studies. Some studies presented information on outcomes that may be surrogate markers for operative morbidity. Two studies reported information on the duration of stay in intensive care following surgery, the median time in one study was 1 day, while the mean from the two studies

was 3 days. These limited results suggest that most patients require only a short period of intensive care following hepatic resection for colorectal metastases. The median or mean length of hospital stay reported by 17 studies ranged from 7–21 days indicating that while most patients made a rapid recovery following surgery, some experienced a more prolonged hospital stay possibly as a result of complications from their surgery. None of the studies included in this review presented information on recovery of patients' functional status or quality of life following discharge from hospital.

Two studies presented outcome data for all patients with isolated colorectal hepatic metastases who underwent surgery, resection and laparotomy only, with 15 and 31% of patients surviving 5 years, respectively (Fuhrman *et al*, 1995; Harms *et al*, 1999). Studies including only patients who underwent resection reported a survival of around 30% at 5 years for patients undergoing potentially 'curative' resection of isolated hepatic metastases and the majority are disease free at this time. The survival of patients undergoing R0 resections were substantially better (32% at 5 years) than for patients undergoing R1 resections (7.2% at 5 years) and those who did not undergo resection (0% at 5 years).

Patients undergoing surgery may have a better prognosis than other patients with metastatic colorectal cancer as their disease is both confined to the liver and circumscribed within it. The patients are also more likely to be of good performance status and have little or no comorbidity. Identifying a comparable control group in the absence of randomised trials is difficult. Goldberg *et al* (1998) identified 548 patients with recurrent colorectal cancer in a longitudinal study, of whom 222 (41%) were thought to be suitable for 'curative intent' surgery. Potentially curative surgery was performed in 109 (20%) and of these 28 (5%) were performed for isolated liver metastases. The estimated recurrence-free survival of patients following liver resection was 32% at 5 years, similar to survival after lung resection and complete resection of local recurrence. The 5-year survival after curative surgery at other sites and multiple sites appeared worse (16 and 0%, respectively). Although not stated, the survival of the patients not treated surgically or who had palliative surgery was by implication poor, but two out of 19 patients with circumscribed disease liver or lung disease treated nonsurgically were alive at final follow-up. A small number of retrospective studies have attempted to determine the natural history of patients with isolated liver metastases. In a review of 484 untreated patients with liver metastases from colorectal cancer, those with the best prognosis (≤25% liver involvement, primary tumour grade 1/2, no extra hepatic tumour and no mesenteric nodal involvement), had a median survival of 21.3 months, compared with 30 months in patients undergoing hepatic resection in the same institution (Stangl *et al*, 1994). In a group of 125 patients with liver-only metastases, most of whom had had no therapy, the median survival was 12.5 months. All patients died within 5 years. Survival correlated with the extent of liver disease. The presence of three or fewer liver metastases was associated with a median survival of 24 months (Goslin *et al*, 1982). Lahr *et al* (1983) studied 175 untreated patients with liver metastases from colorectal cancer. The median survival of these patients was 6.1 months and the longest survivor lived for 67 months. Patients with 1–4 liver metastases lived longer than those with five or more metastases (median survival 11.8 *vs* 4 months) (Lahr *et al*, 1983). A study of 113 patients with hepatic metastases from colon cancer, reported a mean survival of 3 months in patients with widespread liver disease (Wood *et al*, 1976). Patients with metastases localised to a segment or lobe had a mean survival of 17 months, compared with 25 months for patients with a solitary liver metastases. The overall 1-year survival rates were 6, 27, and 60%, respectively. Another study attempted to distinguish potentially resectable from unresectable disease (Wagner *et al*, 1984). Three groups

of untreated patients were studied. Patients with solitary ($n = 39$), multiple unilateral ($n = 31$) and widespread ($n = 182$) had 3-year survivals of 21, 6 and 4%, respectively. However by 5 years virtually all were dead (3, 0 and 2% survival, respectively). Some small studies have examined the outcome of patients with unresected synchronous hepatic metastases (Bengtsson *et al*, 1981; Boey *et al*, 1981; Finan *et al*, 1985; Gorog *et al*, 1997). The median survival of patients in these series ranged from 4.5 to 10.3 months. These studies suggest that there is a small select group of patients with isolated liver metastases from colorectal cancer who may live a long time without surgical intervention. However, their prognosis remains poor because of the inexorable hepatic progression and extrahepatic spread.

Disease recurrence is common after resection of colorectal hepatic metastases indicating that in the majority of cases the extent of the metastatic disease is underestimated by pre and intraoperative staging investigations. Around one-third of patients experienced disease recurrence in the liver alone and may be candidates for repeat resection. The remainder experienced recurrence concurrently in the liver and extrahepatic sites or in extrahepatic sites only. It may be that biological features in the tumour itself may be important as optimal imaging and this requires further study.

Identification of prognostic factors that predict the outcome following surgical resection of colorectal hepatic metastases would assist in the identification of those patients most likely to benefit from this intervention, or more importantly assist in the identification of patients who were unlikely to benefit. Comparison of the different studies included in this review was hampered by differing definitions of the prognostic factors considered for univariate or multivariate analyses. However, some potential prognostic factors were found to be significant in more than half of the studies. We are currently attempting to evaluate these potential prognostic factors using a large prospectively collected data set contributed by multiple centres. This will be published in due course.

This review was performed deliberately on series published up to the millennium as in recent years major changes have occurred in the management of colorectal liver metastases. These factors will almost certainly impact increasingly on the reported outcomes after 2000 (Poston *et al*, 2005). Firstly modern chemotherapy using cytotoxic agents alone offers extension of median survival to 2 years in patients with nonresectable disease (Cals *et al*, 2004; Goldberg *et al*, 2004; Grothey *et al*, 2004; Tournigand *et al*, 2004). When monoclonal biological agents are added to cytotoxic chemotherapy, the prospect of median survival now extends beyond 2 years, and 20% of patients will still be alive 4 years after detection of unresectable liver disease (Cunningham *et al*, 2004; Hurwitz *et al*, 2004; Saltz *et al*, 2004). It is therefore inevitable that the combination of surgical resection and chemotherapy, which is becoming commonplace, will impact on the survival in the surgical series. The EORTC EPOC trial which is the first to randomise liver resection patients to receive additional, modern, chemotherapy is due for reporting in 2007 (Nordlinger *et al*, 2005). Secondly, novel surgical strategies such as preoperative portal vein embolisation to increase residual acceptably safe volume, or two-stage hepatectomy to allow compensatory hepatic hyperplasia before completion of R0 resection (Abdalla *et al*, 2002; Pawlik *et al*, 2005; Poston *et al*, 2005), have also widened the number of resectable patients including those with extensive liver-only disease. These changes in the definition of resectability means that >20% of patients with liver metastases can now be considered for surgery with curative intent at the outset. It is unclear what the long-term outcome of these strategies will be but the results appear encouraging (Abdalla *et al*, 2002; Pawlik *et al*, 2005; Poston *et al*, 2005). This present review should both set the standard for the reporting of subsequent surgical series and provide baseline results to which they may be compared.

In summary there is a substantial body of evidence from prospective and retrospective case series summarised in this review demonstrating that resection of colorectal hepatic metastases can be performed safely with a low mortality rate and around one-third of patients will survive for 5 years or more. These outcomes in highly selected patients exceed those normally associated with metastatic colorectal cancer. Randomised trials comparing surgical resection with nonsurgical treatment are not now possible. Further information must come from well-documented prospective studies examining consecutive series of patients with colorectal cancer and randomised trials comparing liver resection alone with liver resection plus additional chemotherapy.

ACKNOWLEDGEMENTS

REFERENCES

Abdalla EK, Barnett CC, Doherty D, Curley SA, Vauthey JN (2002) Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. *Arch Surg* **137:** 675–680

Adam R, Akpinar E, Johann M, Kunstlinger F, Majno P, Bismuth H (1997) Place of cryosurgery in the treatment of malignant liver tumors. *Ann Surg* **225:** 38–39

Ambiru S, Miyazaki M, Isono T, Ito H, Nakagawa K, Shimizu H, Kusashio K, Furuya S, Nakajima N (1999a) Hepatic resection for colorectal metastases: analysis of prognostic factors. *Dis Colon Rectum* **42:** 632–639

Ambiru S, Miyazaki M, Ito H, Nakagawa K, Shimizu H, Nakajima N (1999b) Adjuvant regional chemotherapy after hepatic resection for colorectal metastases. *Br J Surg* **86:** 1025–1031

Armstrong JG, Anderson LL, Harrison LB (1994) Treatment of liver metastases from colorectal cancer with radioactive implants. *Cancer* **73:** 1800–1804

Bakalakos EA, Kim JA, Young DC, Martin Jr EW (1998a) Determinants of survival following hepatic resection for metastatic colorectal cancer. *World J Surg* **22:** 399–404

Bakalakos EA, Young DC, Martin Jr EW (1998b) Radioimmunoguided surgery for patients with liver metastases secondary to colorectal cancer. *Ann Surg Oncol* **5:** 590–594

Beckurts KT, Holscher AH, Thorban S, Bollschweiler E, Siewert JR (1997) Significance of lymph node involvement at the hepatic hilum in the resection of colorectal liver metastases. *Br J Surg* **84:** 1081–1084

Bengtsson G, Carlsson G, Hafstrom L, Jonsson PE (1981) Natural history of patients with untreated liver metastases from colorectal cancer. *Am J Surg* **141:** 586–589

Boey J, Choi TK, Wong J, Ong GB (1981) Carcinoma of the colon and rectum with liver involvement. *Surg Gynecol Obstet* **153:** 864–868

Bolton JS, Fuhrman GM (2000) Survival after resection of multiple bilobar hepatic metastases from colorectal carcinoma. *Ann Surg* **231:** 743–751

Bradley AL, Chapman WC, Wright JK, Marsh JW, Geevarghese S, Blair KT, Pinson CW (1999) Surgical experience with hepatic colorectal metastasis. *Am Surg* **65:** 560–566

Brand MI, Saclarides TJ, Dobson HD, Millikan KW (2000) Liver resection for colorectal cancer: liver metastases in the aged. *Am Surg* **66:** 412–415

Cady B, Jenkins RL, Steele Jr GD, Lewis WD, Stone MD, McDermott WV, Jessup JM, Bothe A, Lalor P, Lovett EJ, Lavin P, Linehan DC (1998) Surgical margin in hepatic resection for colorectal metastasis: a critical and improvable determinant of outcome. *Ann Surg* **227:** 566–571

Cals L, Rixe O, Francois E, Favre R, Merad L, Deplanque G, Laadem A, Juin P, Bereder JM, Bernardini D, Herait P (2004) Dose-finding study of weekly 24-h continuous infusion of 5-fluorouracil associated with alternating oxaliplatin or irinotecan in advanced colorectal cancer patients. *Ann Oncol* **15:** 1018–1024

Cancer Research UK Information Resource Centre (2003) CancerStats. http//:info cancerresearchuk org/cancerstats

Cowley DE (1995) Prostheses for primary total hip replacement. A critical appraisal of the literature. *Int J Technol Assess Health Care* **11:** 770–778

Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van CE (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* **351:** 337–345

de Baere T., Elias D, Ducreux M, Dromain C, Kuach V, Gamal El Din M, Sobotka A, Lasser P, Roche A (1999) Percutaneous radiofrequency ablation of hepatic metastases. Preliminary experience. *Gastroenterol Clin Biol* **23:** 1128–1133

de Gramont A., Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N., Louvet C, Hendler D, de Braud F., Wilson C, Morvan F, Bonetti A (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* **18:** 2938–2947

DeMatteo RP, Palese C, Jarnagin WR, Sun RL, Blumgart LH, Fong Y (2000) Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases. *J Gastrointest Surg* **4:** 178–184

Doci R, Bignami P, Montalto F, Gennari L (1995) Prognostic factors for survival and disease-free survival in hepatic metastases from colorectal cancer treated by resection. *Tumori* **81:** 143–146

Donato N, Dario C, Giovanni S, Virgilio B, Paolo DP, Roberto L, Gianfranco P, Mario L, Daniela P, Angelo T (1994) Retrospective study on adjuvant chemotherapy after surgical resection of colorectal cancer metastatic to the liver. *Eur J Surg Oncol* **20:** 454–460

Donovan TB (1995) Interstitial treatment of colorectal metastases to the liver. *Appl Radiol* **24:** 41–44

Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* **355:** 1041–1047

Downs SH, Black N (1998) The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* **52:** 377–384

Fegiz G, Ramacciato G, Gennari L, Doci R, Pezzuoli G, Leggeri A, Peracchia A, Montorsi W, D'Angelo F, Aurello P (1991) Hepatic resections for colorectal metastases: the Italian multicenter experience. *J Surg Oncol Suppl* **2:** 144–154

Fernandez-Trigo V, Shamsa F, Sugarbaker PH (1995) Repeat liver resections from colorectal metastasis. Repeat Hepatic Metastases Registry. *Surgery* **117:** 296–304

Figueras J, Valls C, Rafecas A, Fabregat J, Ramos E, Jaurrieta E (2001) Resection rate and effect of postoperative chemotherapy on survival after surgery for colorectal liver metastases. *Br J Surg* **88:** 980–985

Finan PJ, Marshall RJ, Cooper EH, Giles GR (1985) Factors affecting survival in patients presenting with synchronous hepatic metastases from colorectal cancer: a clinical and computer analysis. *Br J Surg* **72:** 373–377

Fong Y, Blumgart LH, Fortner JG, Brennan MF (1995) Pancreatic or liver resection for malignancy is safe and effective for the elderly. *Ann Surg* **222:** 426–434

Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, Marrero AM, Prasad M, Blumgart LH, Brennan MF (1997) Liver resection for colorectal metastases. *J Clin Oncol* **15:** 938–946

Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* **230:** 309–318

Fong Y, Salo J (1999) Surgical therapy of hepatic colorectal metastasis. *Semin Oncol* **26:** 514–523

Fuhrman GM, Curley SA, Hohn DC, Roh MS (1995) Improved survival after resection of colorectal liver metastases. *Ann Surg Oncol* **2:** 537–541

Gayowski TJ, Iwatsuki S, Madariaga JR, Selby R, Todo S, Irish W, Starzl TE (1994) Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. *Surgery* **116:** 703–710

Geoghegan JG, Scheele J (1999) Treatment of colorectal liver metastases. *Br J Surg* **86:** 158–169

Giacchetti S, Itzhaki M, Gruia G, Adam R, Zidani R, Kunstlinger F, Brienza S, Alafaci E, Bertheault-Cvitkovic F, Jasmin C, Reynes M, Bismuth H, Misset JL, Levi F (1999) Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. *Ann Oncol* **10:** 663–669

Goldberg RM, Fleming TR, Tangen CM, Moertel CG, Macdonald JS, Haller DG, Laurie JA (1998) Surgery for recurrent colon cancer: strategies for identifying resectable recurrence and success rates after resection. Eastern Cooperative Oncology Group, the North Central Cancer Treatment Group, and the Southwest Oncology Group. *Ann Intern Med* **129:** 27–35

Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR (2004) A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* **22:** 23–30

Gorog D, Toth A, Weltner J (1997) Prognosis of untreated liver metastasis from rectal cancer. *Acta Chir Hung* **36:** 106–107

Goslin R, Steele Jr G, Zamcheck N, Mayer R, MacIntyre J (1982) Factors influencing survival in patients with hepatic metastases from adenocarcinoma of the colon or rectum. *Dis Colon Rectum* **25:** 749–754

Grothey A, Sargent D, Goldberg RM, Schmoll HJ (2004) Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* **22:** 1209–1214

Harmon KE, Ryan Jr JA, Biehl TR, Lee FT (1999) Benefits and safety of hepatic resection for colorectal metastases. *Am J Surg* **177:** 402–404

Harms J, Obst T, Thorban S, Busch R, Fink U, Heidecke CD, Roder JD, Siewert JR (1999) The role of surgery in the treatment of liver metastases for colorectal cancer patients. *Hepatogastroenterology* **46:** 2321–2328

Hohenberger P, Schlag P, Schwarz V, Herfarth C (1990) Tumor recurrence and options for further treatment after resection of liver metastases in patients with colorectal cancer. *J Surg Oncol* **44:** 245–251

Hohenberger P, Schlag PM, Gerneth T, Herfarth C (1994) Pre- and postoperative carcinoembryonic antigen determinations in hepatic resection for colorectal metastases. Predictive value and implications for adjuvant treatment based on multivariate analysis. *Ann Surg* **219:** 135–143

Hugh TJ, Kinsella AR, Poston GJ (1997a) Management strategies for colorectal liver metastases – Part I. *Surg Oncol* **6:** 19–30

Hugh TJ, Kinsella AR, Poston GJ (1997b) Management strategies for colorectal liver metastases – Part II. *Surg Oncol* **6:** 31–48

Hughes K, Scheele J, Sugarbaker PH (1989) Surgery for colorectal cancer metastatic to the liver. Optimizing the results of treatment. *Surg Clin North Am* **69:** 339–359

Hughes KS, Rosenstein RB, Songhorabodi S, Adson MA, Ilstrup DM, Fortner JG, Maclean BJ, Foster JH, Daly JM, Fitzherbert D (1988) Resection of the liver for colorectal carcinoma metastases. A multi-institutional study of long-term survivors. *Dis Colon Rectum* **31:** 1–4

Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* **350:** 2335–2342

Iwatsuki S, Dvorchik I, Madariaga JR, Marsh JW, Dodson F, Bonham AC, Geller DA, Gayowski TJ, Fung JJ, Starzl TE (1999) Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. *J Am Coll Surg* **189:** 291–299

Jamison RL, Donohue JH, Nagorney DM, Rosen CB, Harmsen WS, Ilstrup DM (1996) Hepatic resection for metastatic colorectal carcinoma results in the cure of some patients. *Gastroenterology* **110:** A1394

Jamison RL, Donohue JH, Nagorney DM, Rosen CB, Harmsen WS, Ilstrup DM (1997) Hepatic resection for metastatic colorectal cancer results in cure for some patients. *Arch Surg* **132:** 505–510

Jeffery GM, Hickey BE, Hider P (2002) Follow-up strategies for patients treated for non-metastatic colorectal cancer. The Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD002200. DOI: 10.1002/14651858.CD002200

Jenkins LT, Millikan KW, Bines SD, Staren ED, Doolas A (1997) Hepatic resection for metastatic colorectal cancer. *Am Surg* **63:** 605–610

Kemeny MM, Adak S, Gray B, Macdonald JS, Smith T, Lipsitz S, Sigurdson ER, O'Dwyer PJ, Benson III AB (2002) Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy – an intergroup study. *J Clin Oncol* **20:** 1499–1505

Kemeny MM, Adak S, Lipsitz S, Gray B, MacDonald J, Benson II AB (1999a) Results of the Intergroup [Eastern Cooperative Oncology Group (ECOG) and Southwest Oncology Group (SWOG)] prospective randomized study of surgery alone versus continuous hepatic artery infusion of fudr and continuous systemic infusion of 5fu after hepatic resection for colorectal liver metastases. *Proc Am Soc Clin Onc* **18** (Meeting abstract 1012)

Kemeny N, Cohen A, Huang Y, Shi W, Blumgart L, Turnbull A, Sullivan D, Stockman J, Fong Y (1999b) Randomized study of hepatic arterial infusion (HAI) and systemic chemotherapy (SYS) versus sys alone as adjuvant therapy after resection of hepatic metastases from colorectal cancer. *Proc Am Soc Clin Onc* **18** (abstract 1011)

Kemeny N, Huang Y, Cohen AM, Shi W, Conti JA, Brennan MF, Bertino JR, Turnbull AD, Sullivan D, Stockman J, Blumgart LH, Fong Y (1999c) Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* **341:** 2039–2048

Lahr CJ, Soong SJ, Cloud G, Smith JW, Urist MM, Balch CM (1983) A multifactorial analysis of prognostic factors in patients with liver metastases from colorectal carcinoma. *J Clin Oncol* **1:** 720–726

Lange JF, Leese T, Castaing D, Bismuth H (1989) Repeat hepatectomy for recurrent malignant tumors of the liver. *Surg Gynecol Obstet* **169:** 119–126

Leslie KA, Rossi R, Hughes K, Tsao J (1995) Survival expectancy of patients alive 5 years after hepatic resection for metastatic colon carcinoma: report from the registry of hepatic metastases. *Proc Am Soc Clin Onc* **14** (abstract 477)

Lorenz M, Muller HH, Schramm H, Gassel HJ, Rau HG, Ridwelski K, Hauss J, Stieger R, Jauch KW, Bechstein WO, Encke A (1998) Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folinic acid for liver metastases of colorectal cancer. German Cooperative on Liver Metastases (Arbeitsgruppe Lebermetastasen). *Ann Surg* **228:** 756–762

Lorenz M, Staib-Sebler E, Koch B, Gog C, Waldeyer M, Encke A (1997) The value of postoperative hepatic arterial infusion following curative liver resection. *Anticancer Res* **17:** 3825–3833

Minagawa M, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, Yamamoto J, Imamura H (2000) Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. *Ann Surg* **231:** 487–499

Minagawa M, Takayama T, Makuuchi M (1999) Late results justify resection for multiple and bilateralhepatic metastasis from colorectal cancer. *Gastroenterology* **116:** G2043

Minton JP, Abou-Issa H (1990) Resection of hepatic metastases of colorectal carcinoma. *Ohio Med* **86:** 191

Moroz P, Salama PR, Gray BN (2002) Resecting large numbers of hepatic colorectal metastases. *ANZ J Surg* **72:** 5–10

Nadig DE, Wade TP, Fairchild RB, Virgo KS, Johnson FE (1997) Major hepatic resection. Indications and results in a national hospital system from 1988 to 1992. *Arch Surg* **132:** 115–119

Nordlinger B, Jaeck D, Guiget M, Vaillant JC, Balladur P, Schaal JC (1992) Surgical resection of hepatic metastases: multicentric retrospective study by the French Association of Surgery. In *Treatment of Hepatic Metastases of Colorectal Cancer*, Nordlinger B, Jaeck D (eds), pp 129–161. Paris: Springer-Verlag

Nordlinger B, Sorbye H, Debois M, Praet M, Glimelius B, Poston GJ, Schlag PM, Walpole ET, Bechstein W, Gruenberger T (2005) Feasibility and risks of pre-operative chemotherapy (CT) with Folfox 4 and surgery for resectable colorectal cancer liver metastases (LM). Interim results of the EORTC Intergroup randomized phase III study 40983. *Proc Am Soc Clin Oncol* **23** (abstract 3528)

Nordlinger B, Vaillant JC, Guiguet M, Balladur P, Paris F, Bachellier P, Jaeck D (1994) Survival benefit of repeat liver resections for recurrent colorectal metastases: 143 cases. Association Francaise de Chirurgie. *J Clin Oncol* **12:** 1491–1496

Ohlsson B, Stenram U, Tranberg KG (1998) Resection of colorectal liver metastases: 25-year experience. *World J Surg* **22:** 268–276

Okano K, Yamamoto J, Kosuge T, Yamamoto S, Sakamoto M, Nakanishi Y, Hirohashi S (2000) Fibrous pseudocapsule of metastatic liver tumors

Clinical Studies

from colorectal carcinoma. Clinicopathologic study of 152 first resection cases. *Cancer* 89: 267 – 275

Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, Curley SA, Loyer EM, Muratore A, Mentha G, Capussotti L, Vauthey JN (2005) Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 241: 715 – 722 (discussion)

Poston GJ, Adam R, Alberts S, Curley S, Figueras J, Haller D, Kunstlinger F, Mentha G, Nordlinger B, Patt Y, Primrose J, Roh M, Rougier P, Ruers T, Schmoll HJ, Valls C, Vauthey NJ, Cornelis M, Kahan JP (2005) OncoSurge: a strategy for improving resectability with curative intent in metastatic colorectal cancer. *J Clin Oncol* 23: 7125 – 7134

Primrose JN (2002) Treatment of colorectal metastases: surgery, cryotherapy, or radiofrequency ablation. *Gut* 50: 1 – 5

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

Riesener KP, Winkeltau G, Kasperk R, Cheng L, Schumpelick V (1998) Adjuvant regional arterial port chemotherapy after resection of colorectal liver metastases. *Chirurg* 69: 741 – 746

Rosen CB, Nagorney DM, Taswell HF, Helgeson SL, Ilstrup DM, van Heerden JA, Adson MA (1992) Perioperative blood transfusion and determinants of survival after liver resection for metastatic colorectal carcinoma. *Ann Surg* 216: 493 – 504

Rougier P, Milan C, Lazorthes F, Fourtanier G, Partensky C, Baumel H, Faivre J (1995) Prospective study of prognostic factors in patients with unresected hepatic metastases from colorectal cancer. Fondation Francaise de Cancerologie Digestive. *Br J Surg* 82: 1397 – 1400

Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LL (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 343: 905 – 914

Saltz LB, Meropol NJ, Loehrer Sr PJ, Needle MN, Kopit J, Mayer RJ (2004) Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol* 22: 1201 – 1208

Savage AP, Malt RA (1992) Survival after hepatic resection for malignant tumours. *Br J Surg* 79: 1095 – 1101

Scheele J, Altendorf-Hofmann A, Stangl R, Schmidt K (1996) Surgical resection of colorectal liver metastases: Gold standard for solitary and radically resectable lesions. *Swiss Surg*, Suppl 4: 4 – 17

Scheele J, Stang R, Altendorf-Hofmann A, Paul M (1995) Resection of colorectal liver metastases. *World J Surg* 19: 59 – 71

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

Scheele J, Stangl R, Altendorf-Hofmann A, Gall FP (1991) Indicators of prognosis after hepatic resection for colorectal secondaries. *Surgery* 110: 13 – 29

Seymour MT, Stenning SP, Cassidy J (1997) Attitudes and practice in the management of metastatic colorectal cancer in Britain. Colorectal Cancer Working Party of the UK Medical Research Council. *Clin Oncol (R Coll Radiol)* 9: 248 – 251

Simmonds PC (2000) Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group. *BMJ* 321: 531 – 535

Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J (1994) Factors influencing the natural history of colorectal liver metastases. *Lancet* 343: 1405 – 1410

Steele Jr G, Bleday R, Mayer RJ, Lindblad A, Petrelli N, Weaver D (1991) A prospective evaluation of hepatic resection for colorectal carcinoma metastases to the liver: Gastrointestinal Tumor Study Group Protocol 6584. *J Clin Oncol* 9: 1105 – 1112

Steele Jr G, Mayer R, Lindblad AA (1995) A prospective evaluation of hepatic resection for colorectal carcinoma metastases to the liver: follow-up report. *J Hepatic Biliary Pancreatic Surg* 2: 122 – 125

Sugihara K, Hojo K, Moriya Y, Yamasaki S, Kosuge T, Takayama T (1993) Pattern of recurrence after hepatic resection for colorectal metastases. *Br J Surg* 80: 1032 – 1035

Taylor M, Forster J, Langer B, Taylor BR, Greig PD, Mahut C (1997) A study of prognostic factors for hepatic resection for colorectal metastases. *Am J Surg* 173: 467 – 471

Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de GA (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 22: 229 – 237

van Ooijen B, Wiggers T, Meijer S, van der Heijde MN, Slooff MJ, van de Velde CJ, Obertop H, Gouma DJ, Bruggink ED, Lange JF (1992) Hepatic resections for colorectal metastases in The Netherlands. A multi-institutional 10-year study. *Cancer* 70: 28 – 34

Wade TP, Virgo KS, Li MJ, Callander PW, Longo WE, Johnson FE (1996) Outcomes after detection of metastatic carcinoma of the colon and rectum in a national hospital system. *J Am Coll Surg* 182: 353 – 361

Wagner JS, Adson MA, van Heerden JA, Adson MH, Ilstrup DM (1984) The natural history of hepatic metastases from colorectal cancer. A comparison with resective treatment. *Ann Surg* 199: 502 – 508

Weiss L, Grundmann E, Torhorst J, Hartveit F, Moberg I, Eder M, Fenoglio-Preiser CM, Napier J, Horne CH, Lopez MJ (1986) Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies. *J Pathol* 150: 195 – 203

Wood CB, Gillis CR, Blumgart LH (1976) A retrospective study of the natural history of patients with liver metastases from colorectal cancer. *Clin Oncol* 2: 285 – 288

Appendix A

Tabulation of eligible studies is illustrated in Table A1.

Appendix B

Results of quality assessment in 39 studies are shown in Table A2.

Table A1 Tabulation of eligible studies

Study and reference(s)	Recruitment period	Study design	Selection of patients	Characteristics of patients	Subgroups	Postoperative mortality	Overall survival Median (months)	1 year (%)	3 year (%)	5 year (%)
Ambiru, 1999 Japan (Ambiru et al, 1999a, b)	1984–1998	Retrospective Single centre	Patients undergoing radical (R0) resection only	n = 174 Age range 21–80 years, median 63 years Men 108, women 66	(a) Total patients 174 (b) HAI chemo following resection 78 (c) PVI chemo following resection 30 (d) Resection only 66	60 days (a) 6/174 (3.4%) (b) 1/78 (1.3%) (d) 4/66 (6.1%)	(b) — (c) — (d) —	83 83 65	56 25 32	40 17 20
Bakalakos, 1998 USA (Bakalakos et al, 1998a, b)	1978–1993	Retrospective Single centre	All patients undergoing surgery	n = 301 Age range 25–83 years, median 61 years Men 144, women 157	(a) Total 301 patients (b) Resected group, rendered free of gross tumour 238 (i) Histopathological margins clear 94 (ii) Histopathological margins indeterminate 74 (iii) Histopathological margins involved 65 (c) Nonresected group, underwent exploration without resection because of extent or location of hepatic or EH tumour 73 (d) Incomplete resection group, had liver resections but left with gross disease in remaining liver or abdominal cavity 33	Perioperative (a) 4/301 (1.3%)	(a) 20.6 (b) 23.2 (i) 29.9 (ii) 20.5 (iii) 19.4 (c) 13 (d) 14.8	— 82 88 74 76 51 68	— 28 40 14 26 5 9	— 9 20 4 6 0 0
Beckurts, 1997 Germany (Beckurts et al, 1997)	1987–1994	Prospective Two centres	Patients undergoing resection	n = 126 Age range 38–80 years, median 61 years Men 77, women 49	(a) Total patients 126 (b) Radical resection 119 (c) Nonradical resection 7	30 days 2/126 (1.6%)	(a) — (b) — (c) —	— — —	— 31 34 —	14 15 0
Bolton, 2000 USA (Bolton and Fuhrman, 2000)	Up to 1999	Retrospective Single centre	Patients undergoing resection	n = 165 Age range 25–90 years, median 63 years Men and women not reported	(a) Total patients 165 (b) Simple hepatic metastases (1–3 metastatic lesions in a unilobar distribution 121 (c) Complex hepatic metastases (≥4 distinct and separate lesions within one lobe or at least 2 distinct and separate lesions in opposite lobes) 44	Within 30 days or during same hospital stay (a) 10/165 (6.1%) (b) 6/121 (5.0%) (c) 4/44 (4.7%)	(a) —[a] (b) 43[a] (c)[a] 39	— — —	— — —	36 36 37
Bradley, 1999 USA (Bradley et al, 1999)	1977–1999	Retrospective Two centres	Patients undergoing resection	n = 134 Age range not reported, mean 62 years Men 70, women 64		Perioperative 6/134 (4.5%)	—	81	50	36

Surgery for colorectal liver metastases
PC Simmonds et al

Table A1 (Continued)

Study and reference(s)	Recruitment period	Study design	Selection of patients	Characteristics of patients	Subgroups	Postoperative mortality	Overall survival			
							Median (months)	1 year (%)	3 year (%)	5 year (%)
Cady, 1998 USA (Cady et al, 1998)	Up to 1996	Retrospective Single centre	Patients undergoing resection	n = 253 Age not reported Men and women not reported		30 days 9/253 (3.6%)	[a]	Disease-free survival presented for prognostic factors only		
Doci, 1995 Italy (Doci et al, 1995)	1980–1993	Unclear design Single centre	Patients undergoing radical (R0) resection only	n = 224 Age range and median not reported Men and women not reported		From post surgical complications 5/224 (2.2%)	[a] 30	87	62	24
Donato, 1994 Italy (Donato et al, 1994)	1977–1990	Retrospective Multicentre	Patients undergoing radical (R0) resection only	n = 102 Age range 35–84 years, median not reported Men 56, women 46	(a) Total patients 102 (b) Post surgical treatment: none 62 (c) Post surgical treatment: chemotherapy 40	Not reported	(a) 29 (b) 25 (c) 35	88 — —	36 — —	— — —
Fegiz, 1991 Italy (Fegiz et al, 1991)	Not reported	Retrospective Multicentre	Patients undergoing resection	n = 212 Age range and median not reported Men and women not reported		1 month 14/212 (6.6%)		Not eligible		
Fernandez-Trigo, 1995 USA, Norway, Netherlands, Sweden, Germany, France, Italy, Spain (Fernandez-Trigo et al, 1995)	Not reported	Retrospective Multicentre	Patients undergoing repeat hepatic resection	n = 170 Age range 28–84 years, Mean 58 years Men and women not reported		Not reported	34 From second resection	—	45	32
Figueras, 2001 Spain (Figueras et al, 2001)	1991–1998	Prospective Single centre	Patients undergoing resection	n = 150 Age range not reported, mean 60 years		30 days 7/150		Not eligible		
Fong, 1999 USA (Fong et al, 1995, 1997, 1999; DeMatteo et al, 2000)	1985–1998	Retrospective Single centre	Patients undergoing resection	n = 1001 Age range 27–87 years, median 61 years Men 581, women 420	(a) Total patients 1001 (b) Radical resection 895 (c) Nonradical resection 106	30 days 28/1001 (2.8%)	(a) 42 (b) 53 (c) 23	89 — —	57 — —	37 37 20
Fuhrman, 1995 USA (Fuhrman et al, 1995)	1988–1992	Retrospective Single centre	All patients undergoing surgery	n = 151 Age range not reported, median 58.2 years Men 69, women 82	(a) Satisfied pre-op criteria 151 (b) Radical resection 107 (c) Excluded from resection 44	30 days a) 3/107 (2.8%)	(a) — (b) — (c) —	80 90 58	40 55 5	31 44 0
Harmon, 1999 USA (Harmon et al, 1999)	1978–1998	Retrospective Single centre	Patients undergoing resection	n = 110 Age range 41–90 years, mean 63 years Men 65, women 45		30 days 5/110 (4.5%)	42	—	—	46

Study and reference(s)	Recruitment period	Study design	Selection of patients	Characteristics of patients	Subgroups	Postoperative mortality	Overall survival Median (months)	1 year (%)	3 year (%)	5 year (%)
Harms, 1999 Germany (Harms et al, 1999)	1987–1998	Retrospective Single centre	All patients presenting with colorectal liver metastases	n = 449 Age range 25–87 years, median 61.3years Men 253, women 196	(a) Total 449 patients (b) Resection 245 (i) Resection only 86 (ii) Resection+regional chemo 54 (iii) Resection+systemic chemo 105 (iv) Radical resection 225 (v) Nonradical resection 20 (c) No resection 204 (i) No treatment 50	30 day b) 4/245 (1.6%)	(a) 25 (b) 35 (i) — (ii) — (iii) — (iv) 64 (v) 25 (c) 16 (i) 11	78 92 91 82 95 98 70 66 —	25 38 35 35 45 45 18 15 —	15 30 30 17 35 30 11 2 —
Hohenberger, 1994 Germany (Hohenberger et al, 1990, 1994)	1981–1991	Prospective Single centre	Patients undergoing radical (R0) resection only	n = 141 Age range 30–79 years, median 59 years Men 99, women 67		Post op 6/166 (3.6%)	[a] 30	—	—	
Hughes, 1989 USA, Germany, England (Hughes et al, 1988, 1989; Leslie et al, 1995)	1948–1985	Retrospective Multicentre	Patients undergoing resection	n = 862 Age range and median not reported Men 418, women 327	(a) Metastatic disease isolated to liver 800 (b) Metastatic disease in liver+hepatic/coeliac nodes 25 (c) Simultaneous resection of extra hepatic metastases 37	Not reported	(a)[a] (b)[a] (c)[a]			32 4 20
Iwatsuki, 1999 USA (Gayowski et al, 1994; Iwatsuki et al, 1999)	1981–1996	Retrospective Single centre	Patients undergoing resection	n = 305 Age range 26–82 years, mean 60 years Men 178, women 127	(a) All patients undergoing resection (b) Resection margin >1 cm (c) Resection margin ≤1 cm (d) Resection margin involved	30 days 0/305 (0%) (3 deaths within 90 days)	(a) — (b) — (c) (d)	94 —	47 54.2 48.4 20.9	32.3 38.4 31.4 8.4
Jamison, 1997 USA (Rosen et al, 1992; Jamison et al, 1996, 1997)	1960–1987	Retrospective Single centre	Patients undergoing resection	n = 280 Age range not reported, mean 59 years Men 173, women 107		30 days 5/280 (1.8%) (10 died within 60 days)	n = 269 32.4	84	46	27
Jenkins, 1997 USA (Jenkins et al, 1997; Brand et al, 2000)	1975–1993	Retrospective Single centre	Patients undergoing resection	n = 131 Age range 30–88 years, mean 62 years Men 72, women 59	(a) Total patients 131 (b) Radical resection 107 (c) Positive margins 14 (d) Extra hepatic disease 10	In-hospital mortality a) 5/131 (3.8%) 6/167 (3.6%)	(a) 33 (b) 36 (c) 21 (d) 18	— — —	42 50 11 29	25 30 0 0
Kemeny, 1999 USA (abstract)	Not reported	Prospective Multicentre	Patients undergoing resection	n = 109 Age not reported	(a) Total patients 109 (b) Resection only 56	Operative death a) 2/109 (2.6%)	(b) 47.5 (c) 34.2	91	66	32

Clinical Studies

Table A1 (*Continued*)

Study and reference(s)	Recruitment period	Study design	Selection of patients	Characteristics of patients	Subgroups	Postoperative mortality	Overall survival Median (months)	1 year (%)	3 year (%)	5 year (%)
(Kemeny et al, 1999a)				Men and women not reported	(c) Resection only after withdrawals 45 (d) Resection+CHAI of FUDR and systemic infusion of 5FU 53 (e) Resection+CHAI after withdrawals 32		(d) (e)	90	72	63
Lorenz, 1997 Germany (Lorenz et al, 1997)	1982–1993	Prospective Single centre	Patients undergoing resection	n = 110 Age range 35–85 years, median 62 years Men 53, women 57	(a) Total 110 pats (b) Radical resection 81 (c) Nonradical resection 29	60 days 6/110 (5.5%)			Not eligible	
Lorenz, 1998 Germany (Lorenz et al, 1998)	1991–1996	Prospective Multicentre	Patients undergoing resection	n = 219 Age range 30–76 years, median 61 years Men 126, women 93	(a) Total patients 219 (b) Surgery only 111 (c) Surgery+HAI infusion 108	30 days a) 12/219 (5.5%) b) 3/111 (2.7%)c) 9/108 (8.3%)			Not eligible	
Minagawa, 2000 Japan (Minagawa et al, 1999)	1980–1997	Retrospective Multicentre	Patients undergoing resection	n = 235 Age range 30–80 years, median 59.2 years Men 148, women 87		30 days 0/235 (0%)	37.2	92	51	38
Minton, 1990 USA (Minton and Abou-Issa, 1990)	1977–1989	Unclear design Single centre	Patients undergoing resection	n = 239 Age range and median not reported Men and women not reported		30 days 0/239 (0%)			Not eligible	
Moroz, 2000 Australia (unpublished) (Moroz et al, 2002)	Not reported	Retrospective Single centre	Patients undergoing resection	n = 123 Age range 30–87 years, median not reported Men 76, women 47	(a) 123 patients curative resection (b) 36 consecutive patients treated with selective internal radiation therapy+hepatic arterial chemotherapy. More advanced disease, not respectable	30 days a) 1/123 (0.8%)	(a) 38 (b) 16	88 64	53 19	31 6
MSKCC, 1999 USA (Kemeny et al, 1999b, c)	Not reported	Prospective Single centre	Patients undergoing resection	n = 156 Age range 28–79 years, median 59 years Men 91, women 65	(a) Total 156 pats (b) Combined therapy (HAI + systemic chemotherapy) 74 (c) Monotherapy (systemic chemotherapy) 82	Died before starting chemo (a) 5/156 (3.2%)	(a) — (b) 72.2 (c) 59.3	— — —	— — —	— — —
Nadig, 1997 USA (Nadig et al, 1997)	1987–1992	Retrospective Multicentre	Patients undergoing resection	n = 275 Age not reported Men and women not reported		30 days 11/275 (4%)			Not eligible	
Nordlinger, 1992 France (Nordlinger et al, 1992)	1959–1991	Retrospective Multicentre	Patients undergoing resection	n = 1818 Age range not reported, mean 60 years Men 1041, women 777		30 days 43/1818 (2.4%)			Not eligible	

Table A1 (*Continued*)

Study and reference(s)	Recruitment period	Study design	Selection of patients	Characteristics of patients	Subgroups	Postoperative mortality	Overall survival Median (months)	1 year (%)	3 year (%)	5 year (%)
Ohlsson, 1998 Sweden (Ohlsson et al, 1998)	1971–1995	Prospective Single centre	Patients undergoing resection	$n = 111$ Age not reported Men 60, women 51	(a) Total patients 111 (b) Operative mortality excluded 107 (c) 1971–1984 68 (d) 1985–1995 43	30 days (a) 4/111 (3.6%) (c) 4/68 (5.9%) d) 0/43 (0%)	(a) 25.2 (b)[a] — (c)[a] 21.6 (d)[a] 40.8	— — — —	37 — — —	25 — 19 35
Okano, 2000 Japan (Okano et al, 2000)	1992–1996	Retrospective Single centre	Patients undergoing resection	$n = 152$ Age range 35–87 years, mean 59.5 years Men 104, women 48	(a) Total 152 patients (b) Thick fibrous pseudocapsule (10 or more bundles) 47 (c) Thin fibrous pseudocapsule (several layers of collagen bundles in histologic sections) 46 (d) No fibrous pseudo capsule 59 (e) Radical resection 121 (f) R1 resection 21 (g) R2 resection 10	Within 1 month after surgery a) 0/152 (0%)	(a) — (b) — (c) — (d) — (e) (f) (g)	91 100 93 86 96 71 80	65 88 71 41 71 44 38	58 88 64 31 67 30 25
Rees, 1997 UK (Rees et al, 1997)	1986–1996	Prospective Single centre	Patients undergoing resection	$n = 107$ Age not reported Men and women not reported	(a) Total group 107 (b) Radical resection 89 (c) Nonradical resection 18	30 days (a) 1/107 (0.9%)	(a) — (b) — (c) —	87 94 56	47 56 11	30 37 6
Riesener, 1998 Germany (Riesener et al, 1998)	1986–1995	Retrospective Single centre	Patients undergoing radical (R0) resection only	$N = 109$ Age range 23–83 years, mean 62 years Men 64, Women 45	(a) Total patients 109 (b) Resection only 59 (c) Resection+ chemotherapy 50	In-hospital a) 5/109 (4.6%)	(b) — (c) —	— —	— —	24 21
Savage, 1992 USA (Savage and Malt, 1992)	1962–1988	Retrospective Single centre	Patients undergoing resection	$n = 104$ Age range 28–79 years, mean 60.1 years Men 53, women 51	(a) Total patients 104 (b) Radical resection 76 (c) Nonradical resection 28	Not reported	(a) 25 (b) 30 (c) 21	76 80 66	36 42 17	18 23 0
Scheele, 1996 Germany (Scheele et al, 1990, 1991, 1995, 1996; Stangl et al, 1994)	1960–1993	Prospective Single Centre	All patients presenting with colorectal liver metastases	$n = 1751$ Age range 26–91 years, median 59 years Men 258, women 215	(a) Total patients 1715 (b) Total resections 498 (c) Palliative debulking 35 (d) Curative intent 463 (e) Radical resection 394 (i) Radical resection excluding operative mortality 376 (f) Non radical resection 69	30 days (b) 25/498 (5.0%) (c) 3/35 (8.6%) (e) 18/394 (4.6%) (f) 4/69 (5.8%)	(c)[a] 16 (d) — (e) — (i)[a] 41.3 (f)[a] 14.8 (g) 7.4 (h)[a] 16.3	— — — — — — —	— 46 52 55 — — —	0 33 38 39 — 0 5

997

Table A1 (*Continued*)

Study and reference(s)	Recruitment period	Study design	Selection of patients	Characteristics of patients	Subgroups	Postoperative mortality	Overall survival			
							Median (months)	1 year (%)	3 year (%)	5 year (%)
					(g) Unresectable, not resected 1145 (h) Resectable, not resected 102					
Steele *et al*, 1995 USA (Steele Jr *et al*, 1991, 1995)	1984–1988	Prospective Multicentre	All patients undergoing surgery	*n* = 150 Age range and median not reported Men 92, women 58	(a) Total patients = 150 (b) Radical resection = 69 (c) Nonradical resection = 18 (d) Laparotomy only = 63	30 days (a) 4/150 (2.7%)	(b) 35.7 (c) 21.2 (d) 16.5	90 70 70	50 25 12	23 14 0
Sugihara, 1993 Japan (Sugihara *et al*, 1993)	1978–1989	Unclear design Single centre	Patients undergoing radical (R0) resection only	*n* = 159 Age range 34–82 years, mean 57.7 years Men 62, women 45	(a) Total patients = 159 (b) Radical resection = 109 (c) Positive resection margins = 17 (d) Extra hepatic metastases = 19	Postop period 2/49 (4.1%) with hepatic surgery only	(b)[a] — (c) — (d) —	90 70 70	57.2 17 0	47.9 12 0
Taylor, 1997 Canada (Taylor *et al*, 1997)	1977–1993	Unclear design Single centre	Patients undergoing resection	*n* = 123 Age range 30–87 years, mean 58.1 years Men 67, women 56		30 days 0/123 (0%)			Not eligible	
van Ooijen, 1992 The Netherlands (van Ooijen *et al*, 1992)	1979–1989	Retrospective Multicentre	Patients undergoing resection	*n* = 118 Age range 28–83 years, mean 57 years Men 71, women 47		30 day 6/118 (5.1%) 1–4 months another 3 died from late complications			Not eligible	

[a]Operative mortality excluded.

Table A2 Results of quality assessment in 39 studies

Item	No. of studies with response (%)		
	Yes	**No**	**Unclear**
Is the hypothesis/aim/objective of the study clearly described?	37 (94.9)	2 (5.1)	NA
Are the characteristics of patients included in the study clearly described?	27 (69.2)	12 (30.8)	NA
Is the age range and mean/median of patients reported?	27 (69.2)	12 (30.8)	NA
Are the numbers of men and women reported?	30 (76.9)	9 (23.1)	NA
Are the distributions of the principal confounders clearly described?	27 (69.2)	12 (30.8)	NA
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	3 (7.7)	33 (84.6)	3 (7.7)
Were the staff, places and facilities where the patients were treated representative of the treatment the majority of patients receive?	11 (28.2)	3 (7.7)	25 (64.1)
Were data collected prospectively?	11 (28.2)	25 (64.1)	3 (7.7)
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	34 (87.2)	5 (12.8)	n/a
Were the main outcome measures used clearly defined and accurate?			
Operative mortality	26 (66.7)	13 (33.3)	NA
Survival or recurrence	10 (25.6)	29 (74.4)	NA
Are the main findings of the study clearly described?	13 (33.3)	26 (66.7)	NA
Is the length of follow-up reported (median/mean and range/standard deviation)?	27 (69.2)	12 (30.8)	NA
Has the number of patients lost to follow up been reported and included in the appropriate analysis?	17 (43.6)	22 (56.4)	NA
Was operative/postoperative mortality included in the survival analysis?	26 (66.7)	8 (20.5)	5 (12.8)
Was surgery the only intervention received by patients in this study?	12 (30.8)	10 (25.6)	17 (43.6)

Clinical Studies