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Surgical resection versus non-surgical treatment for hepatic node positive patients with colorectal liver metastases (Review)

Gurusamy KS, Ramamoorthy R, Imber C, Davidson BR

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[Intervention Review]

Surgical resection versus non-surgical treatment for hepatic node positive patients with colorectal liver metastases

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ABSTRACT

Background

Involvement of hepatic lymph node in patients with colorectal liver metastases is associated with poor prognosis.

Objectives

To determine the benefits and harms of curative liver resection with lymphadenectomy versus other treatments for colorectal liver metastases with hepatic node involvement.

Search methods

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register*, the *Cochrane Central Register of Controlled Trials (CENTRAL)* in *The Cochrane Library*, *MEDLINE*, *EMBASE*, *Science Citation Index Expanded,* and *LILACS* until September 2009 for identifying the randomised trials.

Selection criteria

We considered only randomised clinical trials (irrespective of language, blinding, or publication status) comparing liver resection (alone or in combination with radiofrequency ablation or cryoablation) versus other treatments (neo-adjuvant chemotherapy, chemotherapy, or radiofrequency ablation) in patients with colorectal liver metastases with hepatic node involvement.

Data collection and analysis

Two authors independently identified trials for inclusion.

Main results

We were unable to identify any randomised clinical trial fulfilling the inclusion criteria of this review. We were also unable to identify any quasi-randomised or cohort studies, which could meaningfully answer this important issue.

Authors' conclusions

There is no evidence in the literature to assess the role of surgery versus other treatments for patients with colorectal liver metastases with hepatic node involvement. High quality randomised clinical trials are feasible and are necessary to determine the optimal management of patients with colorectal liver metastases with hepatic node involvement.

PLAIN LANGUAGE SUMMARY

No evidence from randomised clinical trials for optimal management of patients with large bowel cancer spread to lymph glands draining the liver

Nearly a third of patients with large bowel cancers (colorectal cancer) spread to the liver (liver metastases) within five years of diagnosis of bowel cancer. The affected part of the liver can be removed surgically in a quarter of such patients who develop liver spread from bowel cancer. About a seventh of these patients, in whom the affected part of the liver is suitable for removal, develop cancer involvement of lymph glands draining the liver (hepatic lymph node). Such patients are associated with poor survival even after removal of the affected part of the liver and the involved nodes. This Cochrane review attempted to answer the question of whether removing the part of the liver is better than other forms of treatment (such as no treatment, chemotherapy, heat destructive therapy using radiofrequency waves, ie, radiofrequency ablation) in such patients but did not find any randomised clinical trial addressing the issue. Currently, there is no evidence from randomised clinical trials for optimal management of these patients. High quality randomised clinical trials are feasible and are necessary to determine the optimal management of patients with colorectal liver metastases with hepatic node involvement.

BACKGROUND

Colorectal cancer is the third commonest malignancy in the United Kingdom with an estimated 34,000 patients diagnosed every year (Wood 2005). It is the second most common cause of cancer mortality (next only to lung cancer) accounting for nearly a tenth of cancer deaths in UK (Wood 2005) and for 1 in 40 deaths from all causes (Wood 2005). Nearly 16,000 people die annually due to colorectal cancer (Wood 2005).

Nearly a third of patients with colorectal cancers develop spread to the liver (liver metastases) within five years (Manfredi 2006). Of these metastatic deposits, 20% to 32% are resectable (Adam 2001; Tepper 2003; Adam 2004). The five-year survival after liver resection varies between 16% and 30% (Beckurts 1997; Ambiru 1999; Adam 2004; Mutsaerts 2005; Vassiliou 2007). Cancer seed to hepatic lymph nodes identified during liver resection is considered as a poor prognostic factor (Rodgers 2000; Abdalla 2006), with five-year survival after liver resection varying between 0% and 4.3% (Beckurts 1997; Jaeck 2002; Laurent 2004). In studies of patients with liver metastases who underwent routine lymphadenectomy, about 14% to 15% of patients with nodes (draining the liver) considered uninvolved macroscopically are infiltrated by tumour cells microscopically (Jaeck 2002; Laurent 2004). Patients who have involvement of common hepatic and coeliac artery nodes (considered as group 2 nodes) (Jaeck 2003) have been reported to have a poorer prognosis than the patients with involvement of hepato-duodenal or retro-pancreatic group of nodes (considered as group 1 nodes) (Jaeck 2003). Approximately half of the microscopic disease is in the hepato-duodenal and the retro-pancreatic group (Jaeck 2003) and therefore amenable to radical lymphadenectomy.

The mechanism for development of hepatic node involvement is not known, nor whether they represent spread from the liver metastases (Beckurts 1997) or the primary bowel cancer. In people with positive nodes, after adjusting for different factors, such as tumour number (Beckurts 1997; Kokudo 1998; Jaeck 2002; Tocchi 2004), size (Kokudo 1998; Jaeck 2002; Tocchi 2004), distribution (Jaeck 2002; Tocchi 2004), and surgical resection margin (Kokudo 1998), survival after liver resection are similar to those in patients with unresectable colorectal metastasis who underwent hepatic infusion chemotherapy (Bennett 2005; Kemeny 2005). Median survival after systemic chemotherapy with leucovorin, 5-fluorouracil, oxaliplatin, and irinotecan has been recently reported to be around 20 months (Kemeny 2006; Falcone 2007) with an estimated three-year survival of about 10% (Kemeny 2006). In light of this, hepatic node involvement detected pre-operatively or during surgery is generally considered a contra-indication for liver resection for liver secondaries from colorectal primary (Irie 1999; Imamura 2001). With the improving results of resection of extra-hepatic disease (five-year survival of 18%) following neo-adjuvant chemotherapy, ie, chemotherapy followed by surgery followed by chemotherapy (Adam 2001), hepatic node involvement as a contra-indication for liver resection for colorectal liver metastases requires to be reconsidered. Regional nodal involvement in other cancers, such as oesophageal cancers (Tsuchiya 2002; Yano 2006) and rectal cancers (Onaitis 2001; Stipa 2004), have been treated with pre-operative chemotherapy in order to down-stage the disease, which may improve the median survival (Tsuchiya 2002). Down-staging the disease in patients with colorectal liver metastases associated with hepatic nodal involvement may improve the survival.

Besides the heterogeneity arising due to the involvement of different groups of nodes, other factors such as the method used for determining nodal involvement, the number of nodes examined, whether routine or selective lymphadenectomy was performed may contribute to the heterogeneity in the patients included in the studies. In spite of this clinical heterogeneity, the prognosis for patients with hepatic node involvement who underwent liver resection is poor (Gurusamy 2008) and the optimal management of these patients remains unclear. Recently, there have been reports that radiofrequency ablation for colorectal metastases is associated with reasonable survival even in patients with colorectal liver metastases deemed unresectable (Oshowo 2003; Leblanc 2008). Radiofrequency ablation has been suggested as an alternative to surgical resection even in patients with resectable disease (Mulier 2008).

There has been no meta-analysis or systematic review of randomised clinical trials comparing potentially curative liver resection with lymphadenectomy and other potentially curative or palliative modalities of treatment of colorectal liver metastases with hepatic node involvement.

OBJECTIVES

To determine the benefits and harms of potentially curative liver resection with lymphadenectomy versus other potentially curative or palliative treatments of patients with colorectal liver metastases with hepatic node involvement.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised clinical trials (irrespective of language, blinding, publication status, or sample size) for inclusion.

Quasi-randomised studies (where the method of allocating participants to a treatment are not strictly random, for example, date of birth, hospital record number, alternation) were not included regarding assessment of benefit but were considered for inclusion regarding assessment of harm.

Types of participants

Patients with colorectal liver metastases, who are found to have hepatic node involvement (irrespective whether group 1 or group 2 nodes) and otherwise resectable (however defined by authors).

Types of interventions

We planned to study the following interventions.

1. Potentially curative surgical liver resection (liver resection where all macroscopic disease is removed) with lymphadenectomy versus other potentially curative (radiofrequency ablation) or palliative treatment (where potentially curative surgical resection or radiofrequency ablation is not possible; including chemotherapy and radiofrequency ablation).
2. Potentially curative surgical resection or ablation with lymphadenectomy or lymph node ablation as part of neo-adjuvant chemotherapy versus palliative treatment.

We planned to allow co-interventions if carried out equally in the trial groups.

Types of outcome measures

Primary outcomes

1. Mortality
   a. Proportion dead after one, three, five, and ten years.
   b. Estimated median survival.
   c. Hazard ratio for death.

Secondary outcomes

1. Proportion with recurrence of liver metastases (for comparison of surgery, radiofrequency ablation, and cryoablation).
2. Disease-free survival.
3. Treatment-related morbidity (surgery - 30-day mortality, bile leak, lymphorrhoea, abdominal collections requiring treatment, wound related complications, such as wound infection, wound dehiscence; chemotherapy - systemic effects, such as bone marrow suppression, nausea, vomiting, diarrhoea; hepatic infusion chemotherapy - systemic adverse effects of chemotherapy and other toxicities, such as peptic ulceration, chemical hepatitis, and biliary sclerosis (Cohen 2003)).
4. Blood transfusion requirements.
5. Total hospital stay.
6. Quality of life (however defined by authors).

Search methods for identification of studies

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register* (Gluud 2009), the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library*, *MEDLINE*, *EMBASE*, *Science Citation Index Expanded* (Royle 2003) and *LILACS* (Clark 2002). We have given the search strategies in Appendix 1 with the time span for the searches. The last search was performed on the 6th of September 2009. We also searched the reviews of treatment of colorectal liver metastases for references to identify relevant trials.

Data collection and analysis

Trial selection and extraction of data

Two authors (KSG and RR), independently of each other, searched for trials and planned to group the identified trials into included or excluded, and to list the latter with reasons for the exclusion.

KSG and RR planned to independently extract the following data.

1. Year and language of publication.
2. Country.
3. Year of study.
4. Inclusion and exclusion criteria.
5. Method of diagnosing nodal involvement (radiological, laparoscopic or open surgical).
6. Method of confirmation of nodal involvement (histopathology, immunocytochemistry).
7. Synchronous or metachronous metastases.
8. Mean number of tumours.
9. Mean size of tumours.
10. Unilobar or bilobar metastases.
11. First resection or repeat liver resection.
12. Pre-operative chemotherapy.
13. Post-operative chemotherapy.
14. Operating time.
15. Other co-interventions (such as portal vein embolization).
16. Outcomes (mentioned above).
17. Risk of bias in trials (described below).

We planned to seek any unclear or missing information by contacting the authors of the individual trials. If there was any doubt whether the trials share the same patients - completely or partially (by identifying common authors and centres), we planned to contact the authors of the trials to clarify whether the trial report had been duplicated.

We resolved any differences in opinion through discussion or arbitration of the third author (BRD).

Assessment of risk of bias

We planned to assess the risk of bias in the trials independently, without masking of the trial names. We planned to follow the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) and the *Cochrane Hepato-Biliary Group Module* (Gluud 2009). Due to the risk of biased overestimation of intervention effects in randomised trials with inadequate methodological quality (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008), we planned to look at the influence of methodological quality of the trials on the results by evaluating the reported randomisation and follow-up procedures in each trial. If information was not available in the published trial, we planned to contact the trial authors in order to assess the trials correctly.

Sequence generation

- Low risk of bias (the methods used is either adequate (eg, computer generated random numbers, table of random numbers) or unlikely to introduce confounding).
- Uncertain risk of bias (there is insufficient information to assess whether the method used is likely to introduce confounding).
- High risk of bias (the method used (eg, quasi-randomised trials) is improper and likely to introduce confounding).

Allocation concealment

- Low risk of bias (the method used (eg, central allocation) is unlikely to induce bias on the final observed effect).
- Uncertain risk of bias (there is insufficient information to assess whether the method used is likely to induce bias on the estimate of effect).
- High risk of bias (the method used (eg, open random allocation schedule) is likely to induce bias on the final observed effect).

Blinding

It is not possible to blind the health-care provider (surgeons or radiologists or oncologists) to the groups. However, it is possible to blind the patients (for comparisons such as liver resection versus open radiofrequency ablation) and the outcome assessors.

- Low risk of bias, if the patients (whenever possible) and outcome assessors were blinded and the method of blinding was described.

- Uncertain risk of bias, if the patients (whenever possible) and outcome assessors were blinded and the method of blinding was not described.
- High risk of bias, if the patients (whenever possible) or outcome assessors were not blinded.

Incomplete outcome data

- Low risk of bias (the underlying reasons for missingness are unlikely to make treatment effects departure from plausible values, or proper methods have been employed to handle missing data).
- Uncertain risk of bias (there is insufficient information to assess whether the missing data mechanism in combination with the method used to handle missing data is likely to induce bias on the estimate of effect).
- High risk of bias (the crude estimate of effects (eg, complete case estimate) will clearly be biased due to the underlying reasons for missingness, and the methods used to handle missing data are unsatisfactory).

Selective outcome reporting

- Low risk of bias (the trial protocol is available and all of the trial's pre-specified outcomes that are of interest in the review have been reported or similar or all of the primary outcomes in this review have been reported).
- Uncertain risk of bias (there is insufficient information to assess whether the magnitude and direction of the observed effect is related to selective outcome reporting).
- High risk of bias (not all of the primary outcomes in this review have been reported and not all of the trial's pre-specified outcomes that are of interest in the review have been reported).

Baseline imbalance

- Low risk of bias (there was no baseline imbalance in important characteristics).
- Uncertain risk of bias (the baseline characteristics were not reported).
- High risk of bias (there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation).

Early stopping

- Low risk of bias (sample size calculation was reported and the trial was not stopped or the trial was stopped early by a formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was low).
- Uncertain risk of bias (sample size calculations were not reported and it is not clear whether the trial was stopped early or not).
- High risk of bias (the trial was stopped early due to an informal stopping rule or the trial was stopped early by a formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was high).

Academic bias

- Low risk of bias (the author of the trial has not conducted previous trials addressing the same interventions).
- Uncertain risk of bias (It is not clear if the author has conducted previous trials addressing the same interventions).
- High risk of bias (the author of the trial has conducted previous trials addressing the same interventions).

Source of funding bias

- Low risk of bias (the trial's source(s) of funding did not come from any parties that might have conflicting interest (eg, instrument or drug manufacturer).
- Uncertain risk of bias (the source of funding was not clear).
- High risk of bias (the trial was funded by an instrument or drug manufacturer).

We considered trials to be of low risk of bias if we assessed them to have low risk of bias in all the above domains.

Statistical methods

We planned to perform the meta-analyses according to the recommendations of The Cochrane Collaboration (Higgins 2008) and the Cochrane Hepato-Biliary Group Module (Gluud 2009) using the software package RevMan 5 (RevMan 2008). For dichotomous variables, we planned to calculate the risk ratio with 95% confidence interval. For continuous variables, we planned to calculate the mean difference (for outcomes like hospital stay) and standardised mean difference (for outcomes like patient quality of life where different scales can be used). For calculation of time to event outcomes such as survival or recurrence, we planned to extract the logarithm of hazard ratios (ln(HR)) and the standard error (SE) of ln(HR) using the methods described by Parmar et al (Parmar 1998) using the excel sheet provided by Tierney et al (Tierney 2007). We planned to use a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987). In case of discrepancy between the two models we planned to report both results; otherwise we planned to report only the results from the fixed-effect model. We planned to explore heterogeneity using a chi-squared test with significance set at P value 0.10, and measure the quantity of heterogeneity by I^2 (Higgins 2002) set at 30%.

We planned to perform the analysis on an intention-to-treat analysis (Newell 1992) whenever possible. Otherwise, we planned to adopt the 'available case analysis'. In case we found 'zero-event' trials for outcomes that are statistically significant without including the 'zero-event' trials, we planned to perform a sensitivity analysis with and without empirical continuity correction factors as suggested by Sweeting et al (Sweeting 2004). We also planned to report the risk difference if the results were different from risk ratio.

Subgroup analysis

We planned to perform subgroup analyses for trials with low risk of bias compared to those with high risk of bias.

Bias exploration

We planned to use a funnel plot to explore bias (Egger 1997; Macaskill 2001). We planed to perform linear regression approach described by Egger et al to determine the funnel plot asymmetry (Egger 1997).

RESULTS

Description of studies

We identified a total of 3986 references through electronic searches of *The Cochrane Hepato-Biliary Group Controlled Trials Register*

and the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* (n = 170), *MEDLINE* (n = 1358), *EMBASE* (n = 1772), *Science Citation Index Expanded* (n = 686) and *LILACS* (n = 0). We excluded 906 duplicates. It was clear from reading titles and abstracts that none of the remaining 3080 references were randomised clinical trials. Although we would have excluded quasi-randomised trials for survival, we searched for any quasi-randomised trial in order to calculate the sample size and outcomes that can be used for any new randomised clinical trial. We were not able to identify any quasi-randomised study also from the retrieved references.

Risk of bias in included studies

None of the studies identified through the search strategy qualified for inclusion in this review. We were also unable to identify any cohort studies or any case-control studies that could meaningfully try to answer the questions posed in this systematic review.

Effects of interventions

None of the studies identified through the search strategy qualified for this review.

DISCUSSION

The involvement of hepatic lymph node in patients with colorectal liver metastases is associated with poor prognosis irrespective of whether these are evident macroscopically or microscopically (Gurusamy 2008). Some surgeons consider involvement of hepatic lymph node to be a contra-indication for liver resection (Irie 1999; Imamura 2001). This review was undertaken to address the issue of optimal management of such patients.

None of the studies identified through the search strategy qualified for this review. We were also unable to identify non-randomised controlled studies (where the controls were similar in characteristics to the liver resection group), which could give information to facilitate the design of a randomised clinical trial.

Traditionally liver resection has offered better survival than other treatments for colorectal liver metastases. However, this was before the advent of the new modalities of treatment. Now the new modalities of treatment are reserved for patients who are not eligible for surgery. Thus, a fair comparison between surgical resection and other new modalities is not possible as surgical resection is performed in patients with favourable features, and the other treatments are performed in patients with unfavourable features. There is ethical dilemma in such situations. However, a previous review by our group showed that involvement of hepatic lymph node in patients with colorectal liver metastases is associated with poor prognosis even after liver resection combined with lymphadenectomy (Gurusamy 2008). Thus, there seems to be no ethical dilemma for the surgeon in randomising such patients to resection versus other treatments.

We considered various comparisons for a randomised clinical trial on surgical resection. One possible comparison is the comparison of neo-adjuvant chemotherapy plus surgical resection (chemotherapy followed by surgery followed by chemotherapy) versus chemotherapy alone in patients with colorectal liver metastases with hepatic node involvement. Regional nodal involvement in other cancers, such as oesophageal cancers (Tsuchiya 2002; Yano 2006) and rectal cancers (Onaitis 2001; Stipa 2004), have been treated with pre-operative chemotherapy for down-staging the disease, which may improve the median survival (Tsuchiya 2002). Down-staging the disease in patients with colorectal liver metastases associated with hepatic nodal involvement may improve the survival. However, this would necessitate a pre-operative diagnosis of nodal involvement and, therefore, only patients with macroscopic positive hepatic lymph nodes (available to biopsy) could be included in this trial. The incidence of macroscopically positive hepatic lymph nodes is 4.8% in patients with otherwise resectable colorectal hepatic metastases (Beckurts 1997). Approximately 50% of the patients with hepatic node disease are alive at one year (Gurusamy 2008). In order to demonstrate an improvement of median survival from 12 months to 18 months with a recruitment period of 24 months and an additional follow-up period of 24 months with an alpha error of 0.05 and a power of 80%, an overall sample size of 240 patients are required (120 patients in each group). However, in such a trial, there will be a high percentage of cross-over between the groups as patients, who progress in spite of chemotherapy in the surgery group and may no longer be resectable. It may also be unethical to refuse surgery for patients belonging to the chemotherapy group, whose disease has been down staged by chemotherapy. However, these patients could be considered for a longitudinal study involving surgical resection for patients responding to systemic chemotherapy. It is important that hepatic node involvement of the patients included in such a study is identified by histological examination rather than imaging since a significant proportion of patients considered to have hepatic node positive disease by computerised tomogram (CT scan) turned out to have no nodal involvement on histological examination (Beckurts 1997).

Another trial that can be performed is neo-adjuvant chemotherapy versus liver resection with hepatic lymphadenectomy (with or without post-operative chemotherapy) in hepatic node positive patients. Again, the patients included in the trial must have a histological confirmation of hepatic node involvement before randomisation. Some patients in the neo-adjuvant chemotherapy group may have cancer progression in spite of chemotherapy. Such patients may no longer have resectable cancer. Patients in the direct surgery group may be found to have unresectable cancer on laparotomy. It is likely that a proportion of patients in both groups would not undergo surgical resection. However, these patients should be included for all the outcomes on an intention-to-treat analysis, which will provide necessary information to perform a cost-utility analysis between neo-adjuvant chemotherapy and direct surgery. Blinding of health-care providers and patients is not possible in such a trial, and the trial is likely to suffer from high bias-risk for outcomes such as quality of life. However, the primary outcome of survival is likely to be free from bias due to lack of blinding (Wood 2008).

Another trial that can be performed is comparison of surgical resection versus radiofrequency ablation in this group of patients. Both groups can be combined with chemotherapy. Routine or selective lymph node dissection is likely to result in a higher morbidity than just liver resection. Radiofrequency ablation has been reported to provide a two-year survival of 75% and three-year survival of 50% of patients with unresectable colorectal liver metastases (Oshowo 2003; Leblanc 2008). Radiofrequency ablation is generally considered to be associated with lower morbidity than major liver resection. However, there are concerns

about a higher recurrence rate after radiofrequency ablation than surgical resection (Sutherland 2006; Curley 2008). Considering the low survival after resection in patients with hepatic node positive colorectal liver metastases, radiofrequency ablation may provide an equivalent survival in these patients with lower morbidity. However, if percutaneous radiofrequency ablation is contemplated, it is important that hepatic node involvement is identified by histological examination as mentioned previously. Blinding of health-care providers (surgeon or radiologist) is not possible. Blinding of patients is possible only in a comparison of surgical resection versus open radiofrequency ablation and not in a trial comparing surgical resection and percutaneous radioablation (after confirmation of hepatic node involvement by CT guided biopsy). Although it is possible to blind the outcome assessors for all the outcomes, lack of patient blinding is likely to introduce bias in quality of life. However, a properly conducted trial is likely to provide a low-bias risk estimate of survival.

Another trial that we considered was that of surgical resection versus no treatment (no chemotherapy but palliation of symptoms such as pain, nausea, vomiting etc will be allowed) for this group of patients. Studies on the natural history of patients with colorectal liver metastases who did not undergo resection or chemotherapy show widely varying results from 10% one-year survival to 40% one-year survival in patients with disseminated metastases (Bengtsson 1981; Wagner 1984). This is in comparison with approximately 50% one year survival in the patients eligible for surgical resection (ie, good general medical condition and metastases confined to the liver or resectable extra-hepatic spread). Besides, there was no difference in the survival between patients who underwent chemotherapy and those who did not undergo chemotherapy after adjusting for the extent of the metastases in one of the studies (Wagner 1984). However, these studies were conducted more than 25 years ago and we decided that a comparison of surgical resection versus no treatment might be unethical, given the recent advances in chemotherapy including oxaliplatin. Besides, it is unlikely that patients agree to participate in such a trial. Trials assessing neo-adjuvant chemotherapy plus surgical resection versus chemotherapy alone; neo-adjuvant chemotherapy versus surgical resection with or without post-operative chemotherapy; and/or surgical resection versus radiofrequency ablation (both groups may or may not have adjuvant chemotherapy) are likely to be ethical and patients may be more willing to participate in such trials.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence in the literature to assess the role of resection versus other treatments for patients with colorectal liver metastases with hepatic node involvement.

Implications for research

High quality randomised clinical trials are feasible and are necessary to determine the optimal management of patients with colorectal liver metastases with hepatic node involvement. Such trials ought to be reported according to the Consort Statement (http://www.consort-statement.org).

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APPENDICES

Appendix 1. Search strategy

Database	Period	Search strategy used
The Cochrane Hepato-Biliary Group Controlled Trials Register	September 2009	(metasta* OR secondar* OR spread OR cancer OR carcinoma OR tumour Or tumor OR neoplasm) AND (colon Or colonic OR colorect* OR rectal OR rectum OR gut OR intestine OR bowel) AND (liver OR hepatic) AND (segmentectomy OR resection)
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (Wiley)	Issue 3, 2009	#1 MeSH descriptor Neoplasm Metastasis explode all trees in MeSH products #2 metasta* OR secondar* OR spread OR cancer OR carcinoma OR tumour Or tumor OR neoplasm in All Fields in all products #3 (#1 OR #2) #4 MeSH descriptor Intestine, Large explode all trees #5 MeSH descriptor Colorectal Surgery explode all trees #6 MeSH descriptor Intestinal Neoplasms explode all trees #7 colon Or colonic OR colorect* OR rectal OR rectum OR gut OR intestine OR bowel #8(#4 OR #5 OR #6 OR #7)

(Continued)

		#9 MeSH descriptor Liver explode all trees #10 MeSH descriptor Liver Neoplasms explode all trees #11 MeSH descriptor Liver Diseases explode all trees #12 liver OR hepatic #13 (#9 OR #10 OR #11 OR #12) #14 segmentectomy OR resection #15 (#13 AND #14) #16 MeSH descriptor Hepatectomy explode all trees #17 (#15 OR #16) #18 (#3 AND #8 AND #17)
MEDLINE (Pubmed)	January 1951 to September 2009	("Neoplasm Metastasis"[MeSH] OR metasta* OR secondar* OR spread OR cancer OR carcinoma OR tumour Or tumor OR neoplasm) AND (colon Or colonic OR colorect* OR rectal OR rectum OR gut OR intestine OR bowel OR "Intestine, Large"[MeSH] OR "Colorectal Surgery"[MeSH] OR "Intestinal Neoplasms"[MeSH]) AND ((("Liver"[MeSH] OR "Liver Neoplasms"[MeSH] OR "Liver Diseases"[MeSH] OR liver OR hepatic) AND (segmentectomy OR resection)) OR "Hepatectomy"[MeSH]) AND ((randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) AND humans [mh])
EMBASE (OvidSP)	January 1974 to September 2009	1 LIVER-METASTASIS#.DE. OR METASTASIS#.W..DE. OR metasta$ OR secondary$ OR spread OR cancer OR carcinoma OR tumour OR tumor OR neoplasm 2 COLORECTAL-CANCER#.DE. OR colon OR colonic OR colorect$ OR rectal OR rectum OR gut OR intestine OR bowel 3 liver OR hepatic 4 segmentectomy OR resection 5 3 AND 4 6 hepatectomy OR LIVER-RESECTION.DE. 7 5 OR 6 8 1 AND 2 AND 7 9 RANDOM$ OR FACTORIAL$ OR CROSSOVER$ OR CROSS ADJ OVER$ OR PLACEBO$ OR DOUBL$ ADJ BLIND$ OR SINGL$ ADJ BLIND$ OR ASSIGN$ OR ALLOCAT$ OR VOLUNTEER$ OR CROSSOVER-PROCEDURE#.MJ. OR DOUBLE-BLIND-PROCEDURE#.DE. OR SINGLE-BLIND-PROCEDURE#.DE. OR RANDOMIZED-CONTROLLED-TRIAL#.DE. 10 8 AND 9
Science Citation Index Expanded (http://apps.isiknowledge.com)	January 1970 to September 2009	#1TS=(metasta* OR secondar* OR spread OR cancer OR carcinoma OR tumour Or tumor OR neoplasm) #2 TS=(colon Or colonic OR colorect* OR rectal OR rectum OR gut OR intestine OR bowel) #3 TS=(liver OR hepatic) #4 TS=(segmentectomy OR resection) #5 TS=(random* OR blind*OR placebo* OR meta-analysis) #6 #5 AND #4 AND #3 AND #2 AND #1
LILACS (http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F)	September 2009	(((Pt randomised controlled trial OR Pt controlled clinical trial OR Mh randomised controlled trials OR random Mh allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (animal Ct AND NOT (Ct human and animal Ct)) OR (Former clinical Pt trial OR E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Placebos OR Mh OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw bad luck OR Tw aleator$) OR Mh research design) AND NOT (animal Ct AND NOT (Ct human and animal Ct)) OR (Ct comparative Former study OR E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (animal Ct AND NOT (Ct human and animal Ct)))) AND (liver OR hepato$ OR hepatic)

CONTRIBUTIONS OF AUTHORS

KS Gurusamy wrote the review and assessed the trials for inclusion. R Ramamoorthy independently assessed the trials for inclusion. C Imber and BR Davidson critically commented on the review, provided advice for improving the review and the design of the randomised clinical trials. All authors approved of the final version of the review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The interventions that will be included for this review have been clarified. The outcomes have now been classified into primary and secondary outcomes. The method of assessment of bias-risk has been updated in line with the methodology stated in the Cochrane Handbook (Higgins 2008).

INDEX TERMS

Medical Subject Headings (MeSH)

*Colorectal Neoplasms; *Lymph Nodes [pathology] [surgery]; Liver; Liver Neoplasms [secondary] [*therapy]; Lymphatic Metastasis

MeSH check words

Humans