Cochrane Library

Cochrane Database of Systematic Reviews

Liver resection versus other treatments for neuroendocrine tumours in patients with resectable liver metastases (Review)

Gurusamy KS, Ramamoorthy R, Sharma D, Davidson BR

Gurusamy KS, Ramamoorthy R, Sharma D, Davidson BR.
Liver resection versus other treatments for neuroendocrine tumours in patients with resectable liver metastases.
Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD007060.
DOI: 10.1002/14651858.CD007060.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Liver resection versus other treatments for neuroendocrine tumours in patients with resectable liver metastases

Kurinchi Selvan Gurusamy[1], Rajarajan Ramamoorthy[1], Dinesh Sharma[1], Brian R Davidson[1]

[1]University Department of Surgery, Royal Free Hospital and University College School of Medicine, London, UK

Contact address: Kurinchi Selvan Gurusamy, University Department of Surgery, Royal Free Hospital and University College School of Medicine, 9th Floor, Royal Free Hospital, Pond Street, London, NW3 2QG, UK. kurinchi2k@hotmail.com.

Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: New, published in Issue 1, 2010.

Citation: Gurusamy KS, Ramamoorthy R, Sharma D, Davidson BR. Liver resection versus other treatments for neuroendocrine tumours in patients with resectable liver metastases. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD007060. DOI: 10.1002/14651858.CD007060.pub2.

ABSTRACT

Background

Neuroendocrine tumours are tumours of cells, which possess secretory granules and originate from the neuroectoderm. While liver resection is generally advocated in patients with resectable liver metastases, recent studies have shown good survival in patients with disseminated neuroendocrine tumours who underwent thermal ablation using radiofrequency.

Objectives

To determine the benefits and harms of liver resection versus other treatments in patients with resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours.

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 July 2008 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 interventions (chemotherapy, hormonotherapy, or immunotherapy) and those comparing liver resection and thermal ablation (radiofrequency ablation or cryoablation) in patients with resectable liver metastases from neuroendocrine tumours for the review.

Data collection and analysis

Two authors independently identified trials for inclusion.

Main results

We were unable to identify any randomised clinical trial suitable for inclusion in this review. We were also unable to identify any quasi-randomised studies, cohort studies, or case-control studies that could inform meaningfully.

Authors' conclusions

There is no evidence from randomised clinical trials comparing liver resection versus other treatments in patients with resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours. Liver resection appears to be the main stay curative treatment for neuroendocrine liver metastases based on non-randomised studies. Further randomised clinical trials comparing liver resection alone or in

combination with chemoembolisation or radionuclide therapy are needed. Further randomised clinical trials comparing surgical resection and radiofrequency ablation in selected patients may also be appropriate.

PLAIN LANGUAGE SUMMARY

No evidence from randomised clinical trial for optimal management of resectable liver spread originating from intestinal hormone cells

Liver spread from hormone-producing cancer of intestinal hormone cells is generally treated by liver resection surgery (removing the affected parts of the liver) if it is possible to remove all the cancer deposits and is associated with good long-term survival. However, recently, destroying the tumour using radiofrequency waves has been reported to show reasonably good survival in patients in whom it is not possible to remove the liver spread by surgery. This Cochrane review attempted to answer the question whether surgical resection of the liver tumours is better than other forms of treatment in patients with removable liver spread. We could not find any randomised clinical trials addressing the issue. Currently, there is no evidence from randomised clinical trials comparing liver resection versus other treatments in patients with resectable liver spread originating from intestinal hormone cells. Evidence from retrospective studies has shown prolonged survival after surgery for such patients. There has also been some suggestion that combining treatments such as surgery and chemotherapy or radioactive tracer treatment results in better survival than surgery alone. Therapies such as radiofrequency ablation (heat destruction of the tumours using radiofrequency waves) have been recently evaluated as curative treatment and may be useful in patients with small tumours (smaller than 5 cm in size). However, long-term follow-up data from radiofrequency ablation is not available. Liver resection appears to be the main stay curative treatment for neuroendocrine liver metastases based on non-randomised studies. Further randomised clinical trials comparing liver resection alone or in combination with chemoembolisation or radionuclide therapy are needed. Further randomised clinical trials comparing liver resection and radiofrequency ablation in selected patients may also be appropriate.

BACKGROUND

Neuroendocrine tumours are tumours of cells which possess secretory granules and originate from the neuroectoderm, ie, cells of the ectoblast or epiblast that program the neuroendocrine system (NCBI 2008). These cells commonly produce ectopic hormones (via amine precursor uptake and decarboxylation (APUD cells) (NCBI 2008). Some of the gastro-entero-pancreatic neuroendocrine tumours include carcinoid tumours, insulinomas, gastrinomas, glucagonomas, somastatinomas, and vipomas (Leotlela 2003). They can occur alone or may occur as part of multiple endocrine neoplasia type 1 (MEN type I) syndrome (Leotlela 2003).

The annual incidence of gastro-entero-pancreatic neuroendocrine tumours ranges from 2.5 to 4.5 per 100,000 population (Modlin 2003). There has been a steady increase in the incidence and prevalence of these tumours (Modlin 2003). Carcinoids account for about one fifth of the malignancies of the small intestine (Ito 2003). Ninety per cent of carcinoid tumours arise from the appendix (NCBI 2008b). They secrete the hormones serotonins (5 hydroxytryptamine or 5HT), 5 hydroxytryptophan or 5HTP, bradykinin, tachykinin, histamine, substance P, and several other peptides (Zuetenhorst 2005). Patients develop the malignant carcinoid syndrome (severe flushing of skin, diarrhoeal watery stools, bronchoconstriction, sudden drops in blood pressure, edema, and ascites) (NCBI 2008) when there are metastases (Rubin 1999).

The main hormones secreted by other gastrointestinal neuroendocrine tumours include insulin (insulinoma), gastrin (gastrinomas), glucagon (glucagonoma), somatostatin (somatostatinomas), and vasoactive intestinal peptide (vipomas). The main symptoms and diseases caused by these tumours include hypoglycaemia (insulinomas), diabetes mellitus (glucagonoma, somatostatinoma), erythema (glucagonoma), stomatitis (glucagonoma), glossitis (glucagonoma), weight loss (glucagonoma), severe peptic ulcer (gastrinoma), gallstones (somatostatinoma), steatorrhoea (somatostatinoma), watery diarrhoea (vipomas), hypochlorhydria (somatostatinomas), and hypokalaemia (vipoma). Definitions of the different kind of tumours can be found in the MeSH database on Pub Med (NCBI 2008). The tumours may also be non-secretory (ie, do not secrete any hormone that causes such symptoms).

Advanced neuroendocrine tumours are neuroendocrine tumours, which involve adjacent structures (locally advanced) or distant sites, such as liver (metastatic neuroendocrine tumours). Radical surgery including resection of the primary tumour and the liver metastases has been the main treatment for potentially resectable advanced neuroendocrine tumours metastatic to the liver, with five-year survival rates of 61% to 70% (Coppa 2001; Yao 2001; Sarmiento 2003) and 10-year survival rate of 35% (Sarmiento 2003). Many patients are offered only palliative treatment for liver metastases from neuroendocrine tumours because they are considered unfit for radical surgery or because of misconceptions about the curative potential of liver resection. Others are offered palliative treatment because the liver metastases are unresectable (ie, curative surgery is not possible because of the extent of spread). Various palliative treatment options available to the patient include palliative cytoreductive surgery (Chung 2001), chemotherapy (Oberg 1989; Fjallskog 2001; Sun 2005), liver transplantation (Coppa 2001; Florman 2004), embolisation using gel-foam (Wangberg 1996; Gupta 2005), transarterial chemoembolisation or TACE (Falconi 1999; Yao 2001; Gupta 2005), radionuclide therapy using 111 indium-pentetreotide (Anthony 2002; Nguyen 2004) or meta-iodobenzylguanidine (MIBG) (Mukherjee 2001; Pasieka 2004), immunotherapy (alone (Oberg 1989) or in combination with octreotide (Kölby 2003)), and medical treatment using octreotide (Kölby 2003) or lanreotide (Faiss 2003). Ablative therapies, such as radiofrequency ablation have been reported to be associated with good survival in patients with liver metastases from neuroendocrine tumours considered unresectable (Leblanc 2008).

There have been no meta-analyses or systematic reviews comparing liver resection with other treatments in resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours.

OBJECTIVES

To determine the benefits and harms of liver resection versus other treatments in patients with resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours.

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.

Types of participants

Patients with liver metastases from gastro-entero-pancreatic neuroendocrine tumours (irrespective of the type of gastro-entero-pancreatic neuroendocrine tumour), who were amenable to potentially curative liver resections.

Types of interventions

We planned to include trials comparing liver resection versus thermal ablation (radiofrequency ablation or cryoablation). We also planned to include liver resection (alone or in combination with radiofrequency ablation or cryoablation) versus other treatments (chemotherapy or hormonotherapy or immunotherapy). We also planned to include trials that compared liver resection with adjuvant treatment versus liver resection alone.
Co-interventions were allowed if carried out equally in the trial intervention arms.

Types of outcome measures

Primary outcomes

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

Secondary outcomes

1. Recurrence rate (for comparison of surgery, radiofrequency ablation, and cryoablation).

2. Disease-free survival (for comparison of surgery, radiofrequency ablation, and cryoablation).
3. Treatment-related morbidity (for example, for surgery: 30-day mortality, bile leak, lymphorrhoea, abdominal collections requiring treatment, wound-related complications, such as wound infection, wound dehiscence; for example, for palliative chemotherapy or hormonotherapy or immunotherapy: 30-day mortality bone marrow suppression, nausea, vomiting, diarrhoea, joint pain; radiofrequency ablation or chemoembolisation: liver abscess).
4. Symptom relief (however defined by authors).
5. Quality of life (however defined by authors).
6. Total hospital stay.

Search methods for identification of studies

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register* (Gluud 2008), 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.

We did not identify any randomised trials. We searched the reviews of treatment of neuroendocrine tumours 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 relevant publications and planned to identify the trials for inclusion and list the excluded studies with the 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. Type of neuroendocrine tumour.
6. Operating time.
7. Previous treatments (such as chemotherapy, immunotherapy, hormonotherapy).
8. Other co-interventions (such as portal vein embolisation, chemotherapy, immunotherapy, hormonotherapy).
9. Outcomes (mentioned above).
10. Methodological quality (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 methodological quality

We planned to assess the methodological quality of 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 2008). 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

- Adequate, if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing dice was considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.
- Unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
- Inadequate, if a system involving dates, names, or admittance numbers were used for the allocation of patients. These studies are known as quasi-randomised and we planned to exclude such trials from the review.

Allocation concealment

- Adequate, if the allocation of patients involved a central independent unit, on-site locked computer, or sealed envelopes. In addition, if there was no blinding in the trials, the allocation concealment was considered adequate only if blocked randomisation was not used or if the blocks were of variable size or if the blocks were distributed across multiple centres such that it is not possible to predict the block size in a single centre.
- Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described. In addition, if there was no blinding in the trials, the allocation concealment was considered unclear if it was not clear whether blocked randomisation was used or if the method of blocked randomisation was not described.
- Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised (we planned to exclude such studies). In addition, if there was no blinding in the trials, the allocation concealment was considered inadequate if it was possible to predict future assignments of participants based on previous assignments such as when fixed size blocks were used in a single centre trial. However, we planned to include such trials for the review.

Blinding

It is not possible to blind the health-care provider (surgeon) and patients to the groups. However, it is possible to blind the outcome assessors. So, blinding was considered adequate if the outcome assessors were blinded.

- Adequate, if the outcome assessors were blinded and the method of blinding was described.
- Unclear, if the outcome assessors were blinded and the method of blinding was not described.
- Inadequate, if no attempts were made to blind the outcome assessors or if the outcome assessors could easily identify the group to which the patient belongs.

Incomplete data outcomes

- Adequate, if there were no post-randomisation drop-outs or withdrawals or if the post-randomisation drop-outs were balanced in both groups or reasons for missing data unlikely to be related to true outcome (for example, patients did not undergo surgery after randomisation).
- Unclear, if it is not clear whether there are any drop-outs or withdrawals or if the reasons for these drop-outs are not clear.
- Inadequate, if the reasons for missing data are likely to be related to true outcomes, 'as-treated' analysis was performed, potentially inappropriate application of simple imputation, potential for patients with missing outcomes to induce clinically relevant bias in effect estimate or effect size.

Selective outcome reporting

- Adequate, if survival was reported or if the trial's protocol was available and all of the trial's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
- Unclear, if there is insufficient information to assess whether the risk of selective outcome reporting is present.
- Inadequate, if not all the pre-specified outcomes were reported or if the primary outcomes were changed or if some of the important outcomes were incompletely reported.

Other biases

Baseline imbalance

- Adequate, if there was no baseline imbalance in important characteristics.
- Unclear, if the baseline characteristics were not reported.
- Inadequate, if there was an baseline imbalance due to chance or due to imbalanced exclusion after randomisation.

Early stopping

- Adequate, if sample size calculations were reported and the trial was not stopped or stopped early by formal (or informal) stopping rules.
- Unclear, if sample size calculations were not reported and it is not clear whether the trial was not stopped early.
- Inadequate, if the trial was stopped early without formal stopping rules.

Sponsor bias

- Adequate, if the trial was unfunded or was not funded by an instrument or equipment or drug manufacturer or a third party with vested interest in the results of the trial.
- Unclear, if the source of funding was not clear.
- Inadequate, if the trial was funded by an instrument or equipment or drug manufacturer or a third party with vested interest in the results of the trial.

We considered any trials classified as adequate sequence generation, allocation concealment, blinding, incomplete data outcomes, and selective reporting (see above) as trials of low bias-risk. However, if all-cause mortality is reported, a trial will be considered as low bias-risk for mortality even if blinding was not performed as long as the trial is classified as adequate in adequate sequence generation, allocation concealment, incomplete data outcomes, and selective reporting.

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 2008) using the software package RevMan 5 (RevMan 2008). For dichotomous variables, we planned to calculate the relative risk (RR) with 95% confidence interval. For continuous variables, we planned to calculate the mean difference (MD) (for outcomes such as hospital stay) or standardised mean difference (SMD) (for outcomes such as quality of life when different scales could be used) with 95% confidence interval. For outcomes such as hazard ratio for death, we planned to use generic inverse variance method for the meta-analysis. 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 the fixed-effect model. We planned to explore heterogeneity by chi-squared test with significance set at P value 0.10, and measure the quantity of heterogeneity by I^2 (Higgins 2002). We considered an I^2 of 30% or more to represent heterogeneity.

We planned to perform the analysis on an intention-to-treat basis (Newell 1992) whenever possible. Otherwise, we planned to adopt the 'available case analysis'. In case we found 'zero-event' trials in statistically significant outcomes, 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 results of risk difference.

Subgroup analysis

We planned to perform the following subgroup analyses.

- Trials with low bias-risk (see section 'assessment of methodological quality') compared to trials with high bias risk.
- Surgical resection alone or in combination with radiofrequency ablation, cryoablation.
- Different types of neuroendocrine tumours.

Bias exploration

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

RESULTS

Description of studies

We identified a total of 369 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=15), *MEDLINE* (n=285), *EMBASE* (n=30), *Science*

Citation Index Expanded (n=35) and *LILACS* (n=4). We excluded 45 duplicates. It was clear from reading titles and abstracts that none of the remaining 324 references were randomised clinical trials. Although we would have excluded quasi-randomised studies, we searched for any quasi-randomised study in order to calculate the sample size and outcomes that could be used for any new randomised clinical trial. We were not able to identify any quasi-randomised study either 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

None of the publications 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.

However, given the prolonged survival following the resection of the primaries and liver metastases (five year survival - 61% to 70%; ten-year survival - 35%) (Coppa 2001; Yao 2001; Sarmiento 2003), liver resection should properly be used as the benchmark against which all other treatments for resectable neuroendocrine liver metastases are assessed. Ablative therapies, such as radiofrequency ablation, have been considered by some to be potentially curative for many liver tumours including metastases from neuroendocrine tumours (Leblanc 2008). Five-year survival after radiofrequency ablation in patients with liver metastases deemed unresectable has been reported to be 56% (Mazzaglia 2007). However, there are concerns about an increased recurrence rate after radiofrequency ablation compared with surgical resection (Sutherland 2006; Curley 2008) and cannot be recommended routinely. Long-term survival data on radiofrequency ablation are also not available. Besides, radiofrequency ablation is not suitable for large tumours (> 5 cm to 6 cm) (due to the high incidence of recurrence) and tumours proximal to vital intra-hepatic and extra-hepatic structures (because of the high risk of thermal injury to these structures) (Wood 2000; Garrean 2007). The size of the neuroendocrine liver metastases is frequently larger than 5 to 6 cm in size (Yao 2001). Furthermore, randomised clinical trials comparing liver resection and radiofrequency ablation in selected patients with less than 5 cm tumour size may be appropriate.

Liver resection with adjuvant treatment such as chemoembolisation or radionuclide therapy (Yttrium-90 microspheres) may result in better survival than liver resection alone (Landry 2008). A proportion of patients who underwent adjuvant treatment had the adjuvant treatment at the time of initial resection, and others underwent adjuvant treatment at the time of recurrence. It is expected that patients who developed recurrence after liver resection for neuroendocrine tumours are treated with further liver resection, radiofrequency ablation, or with palliative treatments such as chemotherapy or radionuclide therapy. The palliative treatments such as chemotherapy or radionuclide therapy will also be used for non-resectable liver metastases from neuroendocrine tumours. However, the concept of combining chemoembolisation or microspheres is relatively new and has to be assessed in randomised clinical trials.

One of the methodological problems that the conductors of this trial will face include blinding of patients and health-care providers, which are not possible in most instances. This may result in bias in outcomes like symptom relief and quality of life. Another problem that the conductor of the trial will face is that some metastases deemed resectable by imaging may not be resectable once a laparotomy is performed. These patients may undergo palliative interventions, which may include debulking, ablative procedure, or non-cytoreductive treatment such as chemotherapy. Such patients should be included in the analysis of the outcomes using an intention-to-treat analysis to determine the overall cost-utility of a treatment. An additional analysis excluding such patients will provide information on survival and quality of life in those who completed surgical treatment. The quality of life should be administered at regular time intervals so that quality adjusted life year and cost-utility analysis can be performed. Considering the long follow-up required to assess the survival, it is possible that some patients are lost to follow-up. Adequate steps should be taken to prevent this from happening.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from randomised clinical trials or from quasi-randomised studies, cohort studies, or case-control studies comparing liver resection versus other treatments in patients with resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours.

Implications for research

Future randomised clinical trials of low risk of bias should use liver resection as the benchmark against which all other treatments are assessed in patients with resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours. Such trials should be reported according to the CONSORT Statements (www.consort-statement.org).

ACKNOWLEDGEMENTS

To TC Mahendran, Chennai, India, who was the first surgical teacher of the first author.
To The Cochrane Hepato-Biliary Group for the support that they have provided.

Peer Reviewers: J Klejnen, The Netherlands; V Khatri, USA.
Contact Editor: C Gluud, Denmark.

REFERENCES

Additional references

Anthony 2002

Anthony LB, Woltering EA, Espenan GD, Cronin MD, Maloney TJ, McCarthy KE. Indium-111-pentetreotide prolongs survival in gastroenteropancreatic malignancies. *Seminars in Nuclear Medicine* 2002;**32**(2):123-32.

Chung 2001

Chung MH, Pisegna J, Spirt M, Giuliano AE, Ye W, Ramming KP, et al. Hepatic cytoreduction followed by a novel long-acting somatostatin analog: a paradigm for intractable neuroendocrine tumors metastatic to the liver. *Surgery* 2001;**130**(6):954-62.

Clark 2002

Clark OA, Castro AA. Searching the Literatura Latino Americana e do Caribe em Ciencias da Saude (LILACS) database improves systematic reviews. *International Journal of Epidemiology* 2002;**31**(1):112-4.

Coppa 2001

Coppa J, Pulvirenti A, Schiavo M, Romito R, Collini P, Di Bartolomeo M, et al. Resection versus transplantation for liver metastases from neuroendocrine tumors. *Transplantation Proceedings* 2001;**33**(1-2):1537-9.

Curley 2008

Curley SA. Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial?. *Annals of Surgical Oncology* 2008;**15**(1):11-3.

DeMets 1987

DeMets DL. Methods for combining randomized clinical trials: strengths and limitations. *Statistics in Medicine* 1987;**6**(3):341-50.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177-88.

Egger 1997

Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 1997;**315**(7109):629-34.

Faiss 2003

Faiss S, Pape UF, Bohmig M, Dorffel Y, Mansmann U, Golder W, et al. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors - the International Lanreotide and Interferon Alfa Study Group. *Journal of Clinical Oncology* 2003;**21**(14):2689-96.

Falconi 1999

Falconi M, Bassi C, Bonora A, Sartori N, Procacci C, Talamini G, et al. Role of chemoembolization in synchronous liver metastases from pancreatic endocrine tumours. *Digestive Surgery* 1999;**16**(1):32-8.

Fjallskog 2001

Fjallskog ML, Granberg DP, Welin SL, Eriksson C, Oberg KE, Janson ET, et al. Treatment with cisplatin and etoposide in patients with neuroendocrine tumors. *Cancer* 2001;**92**(5):1101-7.

Florman 2004

Florman S, Toure B, Kim L, Gondolesi G, Roayaie S, Krieger N, et al. Liver transplantation for neuroendocrine tumors. *Journal of Gastrointestinal Surgery* 2004;**8**(2):208-12.

Garrean 2007

Garrean S, Hering J, Helton WS, Espat NJ. A primer on transarterial, chemical, and thermal ablative therapies for hepatic tumors. *American Journal of Surgery* 2007;**194**(1):79-88.

Gluud 2008

Gluud C, Nikolova D, Klingenberg SL, Whitfield K, Alexakis N, Als-Nielsen B, et al. Cochrane Hepato-Biliary Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)). 2008, Issue 3. Art. No.: LIVER.

Gupta 2005

Gupta S, Johnson MM, Murthy R, Ahrar K, Wallace MJ, Madoff DC, et al. Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival. *Cancer* 2005;**104**(8):1590-602.

Higgins 2002

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**(11):1539-58.

Higgins 2008

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Intervention 5.0.0 [updated February 2008]. The Cochrane Colloboration, 2008. Available from www.cochrane-handbook.org.

Ito 2003

Ito H, Perez A, Brooks DC, Osteen RT, Zinner MJ, Moore FD Jr, et al. Surgical treatment of small bowel cancer: a 20-year single institution experience. *Journal of Gastrointestinal Surgery* 2003;**7**(7):925-30.

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982-9.

Kölby 2003

Kölby L, Persson G, Franzén S, Ahrén B. Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours. *The British Journal of Surgery* 2003;**90**:687-93.

Landry 2008

Landry CS, Scoggins CR, McMasters KM, Martin RC 2nd. Management of hepatic metastasis of gastrointestinal carcinoid tumors. *Journal of Surgical Oncology* 2008;**97**(3):253-8. [PUBMED: 18264984]

Leblanc 2008

Leblanc F, Fonck M, Brunet R, Becouarn Y, Mathoulin-Pelissier S, Evrard S. Comparison of hepatic recurrences after resection or intraoperative radiofrequency ablation indicated by size and topographical characteristics of the metastases. *European Journal of Surgical Oncology* 2008;**34**(2):185-90. Epub 2007 Nov 12.

Leotlela 2003

Leotlela PD, Jauch A, Holtgreve-Grez H, Thakker RV. Genetics of neuroendocrine and carcinoid tumours. *Endocrine-related Cancer* 2003;**10**(4):437-50.

Macaskill 2001

Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Statistics in Medicine* 2001;**20**(4):641-54.

Mazzaglia 2007

Mazzaglia PJ, Berber E, Milas M, Siperstein AE. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. *Surgery* 2007;**142**(1):10-9.

Modlin 2003

Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003;**97**(4):934-59. [PUBMED: 12569593]

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**(9128):609-13.

Mukherjee 2001

Mukherjee JJ, Kaltsas GA, Islam N, Plowman PN, Foley R, Hikmat J, et al. Treatment of metastatic carcinoid tumours, phaeochromocytoma, paraganglioma and medullary carcinoma of the thyroid with (131)I-meta-iodobenzylguanidine [(131)I-mIBG]. *Clinical Endocrinology* 2001;**55**(1):47-60.

NCBI 2008

NCBI. MeSH database. http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh (last accessed on 2 September 2008).

Newell 1992

Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *International Journal of Epidemiology* 1992;**21**(5):837-41.

Nguyen 2004

Nguyen C, Faraggi M, Giraudet AL, de Labriolle-Vaylet C, Aparicio T, Rouzet F, et al. Long-term efficacy of radionuclide therapy in patients with disseminated neuroendocrine tumors uncontrolled by conventional therapy. *Journal of Nuclear Medicine* 2004;**45**(10):1660-8.

Oberg 1989

Oberg K, Norheim I, Alm G. Treatment of malignant carcinoid tumors: a randomized controlled study of streptozocin plus 5-FU and human leukocyte interferon. *European Journal of Cancer & Clinical Oncology* 1989;**25**(10):1475-9.

Pasieka 2004

Pasieka JL, McEwan AJ, Rorstad O. The palliative role of 131I-MIBG and 111In-octreotide therapy in patients with metastatic progressive neuroendocrine neoplasms. *Surgery* 2004;**136**(6):1218-26.

RevMan 2008 [Computer program]

Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Royle 2003

Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. *International Journal of Technology Assessment in Health Care* 2003;**19**(4):591-603.

Rubin 1999

Rubin J, Ajani J, Schirmer W, Venook AP, Bukowski R, Pommier R, et al. Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. *Journal of Clinical Oncology* 1999;**17**(2):600-6.

Sarmiento 2003

Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *Journal of the American College of Surgeons* 2003;**197**(1):29-37.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12.

Sun 2005

Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. *Journal of Clinical Oncology* 2005;**23**(22):4897-904.

Sutherland 2006

Sutherland LM, Williams JA, Padbury RT, Gotley DC, Stokes B, Maddern GJ. Radiofrequency ablation of liver tumors: a systematic review. *Archives of Surgery* 2006;**141**(2):181-90.

Sweeting 2004

Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Statistics in Medicine* 2004;**23**(9):1351-75.

Wangberg 1996

Wangberg B, Westberg G, Tylen U, Tisell L, Jansson S, Nilsson O, et al. Survival of patients with disseminated midgut carcinoid tumors after aggressive tumor reduction. *World Journal of Surgery* 1996;**20**(7):892-9.

Wood 2000

Wood TF, Rose DM, Chung M, Allegra DP, Foshag LJ, Bilchik AJ. Radiofrequency ablation of 231 unresectable hepatic tumors: indications, limitations, and complications. *Annals of Surgical Oncology* 2000;**7**(8):593-600.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman GD, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical Research Ed.)* 2008;**336**:601-5.

Yao 2001

Yao KA, Talamonti MS, Nemcek A, Angelos P, Chrisman H, Skarda J, et al. Indications and results of liver resection and hepatic chemoembolization for metastatic gastrointestinal neuroendocrine tumors. *Surgery* 2001;**130**(4):677-85.

Zuetenhorst 2005

Zuetenhorst JM, Taal BG. Metastatic carcinoid tumors: a clinical review. *The Oncologist* 2005;**10**(2):123-31.

APPENDICES

Appendix 1. Search strategies

Database	Period	Search strategy used
The Cochrane Hepato-Biliary Group Controlled Trials Register	July 2008	(metasta* OR secondar* OR spread OR advanced) AND ("neuroendocrine tumor" OR "neuroendocrine tumors" OR "neuroendocrine tumour" OR "neuroendocrine tumours" OR adenoma OR adenomas OR apudoma OR apudomas OR carcinoid or carcinoids OR argentaffinoma OR argentaffinomas OR somatostatinoma OR somatostatinomas OR "islet cell tumor" OR "islet cell tumors" OR "island cell tumour" OR "island cell tumours" OR nesidioblastoma OR nesidioblastomas OR insulinoma OR insulinomas OR "multiple endocrine neoplasia" OR "multiple endocrine adenopathy" OR "multiple endocrine adenopathies" OR "multiple endocrine adenomatoses" OR "multiple endocrine adenomatosis" OR "familial endocrine adenomatoses" OR "familial endocrine adenomatosis" OR "multiple endocrine neoplasms" OR vipoma or vipomas OR "diarrheogenic tumor" OR "diarrheogenic tumors" OR "diarrheogenic tumour" OR "diarrheogenic tumours" OR "VIP secreting tumor" OR "VIP secreting tumors" OR "VIP secreting tumour" OR "VIP secreting tumours" OR "Pancreatic cholera" OR "Verner-Morrison syndrome" OR "Verner Morrison syndrome" OR "watery diarrhea syndrome" OR "watery diarrhoea syndrome" OR WDHA OR WDHH OR "neuroendocrine carcinoma" or "neuroendocrine carcinomas") AND (liver OR hepatic) AND (segmentectomy OR resection OR cryoablat* OR cryosurger* OR radioablat* OR radiofrequency ablat* OR radio-frequency ablat* OR RF ablat* OR thermoablat*)
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Issue 3 2008	#1 MeSH descriptor Neoplasm Metastasis explode all trees in MeSH products #2 (metasta* OR secondar* OR spread or advanced) #3 (#1 OR #2) #4 MeSH descriptor Neuroendocrine Tumors explode all trees #5 MeSH descriptor Apudoma explode all trees #6 MeSH descriptor Carcinoid Tumor explode all trees #7 MeSH descriptor Adenoma, Islet Cell explode all trees #8 MeSH descriptor Insulinoma explode all trees #9 MeSH descriptor Carcinoma, Islet Cell explode all trees #10 MeSH descriptor Gastrinoma explode all trees #11 MeSH descriptor Glucagonoma explode all trees #12 MeSH descriptor Somatostatinoma explode all trees #13 MeSH descriptor Vipoma explode all trees #14 MeSH descriptor Multiple Endocrine Neoplasia explode all trees #15 MeSH descriptor Pancreatic Neoplasms explode all trees #16 "neuroendocrine tumor" OR "neuroendocrine tumors" OR "neuroendocrine tumour" OR "neuroendocrine tumours" OR adenoma OR adenomas OR apudoma OR apudomas

(Continued)

		OR carcinoid or carcinoids OR argentaffinoma OR argentaffinomas OR somatostatinoma OR somatostatinomas OR "islet cell tumor" OR "islet cell tumors" OR "island cell tumour" OR "island cell tumours" OR nesidioblastoma OR nesidioblastomas OR insulinoma OR insulinomas OR "multiple endocrine neoplasia" OR "multiple endocrine adenopathy" OR "multiple endocrine adenopathies" OR "multiple endocrine adenomatoses" OR "multiple endocrine adenomatosis" OR "familial endocrine adenomatoses" OR "familial endocrine adenomatosis" OR "multiple endocrine neoplasms" #17 vipoma or vipomas OR "diarrheogenic tumor" OR "diarrheogenic tumors" OR "diarrheogenic tumour" OR "diarrheogenic tumours" OR "VIP secreting tumor" OR "VIP secreting tumors" OR "VIP secreting tumour" OR "VIP secreting tumours" OR "Pancreatic cholera" OR "Verner-Morrison syndrome" OR "Verner Morrison syndrome" OR "watery diarrhea syndrome" OR "watery diarrhoea syndrome" OR WDHA OR WDHH OR "neuroendocrine carcinoma" or "neuroendocrine carcinomas" #18 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #10 OR #11 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17) #19 (#3 AND #18) #20 MeSH descriptor Malignant Carcinoid Syndrome explode all trees #21 carcinoid syndrome #22 (#19 OR #20 OR #21) #23 MeSH descriptor Liver explode all trees #24 liver OR hepatic #25 (#23 OR #24) #26 segmentectomy OR resection OR debulk* OR cryoablat* OR cryosurger* OR radioablat* OR radiofrequency ablat* OR radio-frequency ablat* OR RF ablat* OR thermoablat* #27 MeSH descriptor Cryosurgery explode all trees #28 (#26 OR #27) #29 (#25 AND #28) #30 MeSH descriptor Hepatectomy explode all trees #31 (#29 OR #30) #32 (#22 AND #31)
MEDLINE (Pubmed)	January 1951 to July 2008	((("Neoplasm Metastasis"[MeSH] OR metasta* OR secondar* OR spread OR advanced) AND ("neuroendocrine tumor" OR "neuroendocrine tumors" OR "neuroendocrine tumour" OR "neuroendocrine tumours" OR adenoma OR adenomas OR apudoma OR apudomas OR carcinoid or carcinoids OR argentaffinoma OR argentaffinomas OR somatostatinoma OR somatostatinomas OR "islet cell tumor" OR "islet cell tumors" OR "island cell tumour" OR "island cell tumours" OR nesidioblastoma OR nesidioblastomas OR insulinoma OR insulinomas OR "multiple endocrine neoplasia" OR "multiple endocrine adenopathy" OR "multiple endocrine adenopathies" OR "multiple endocrine adenomatoses" OR "multiple endocrine adenomatosis" OR "familial endocrine adenomatoses" OR "familial endocrine adenomatosis" OR "multiple endocrine neoplasms" OR vipoma or vipomas OR "diarrheogenic tumor" OR "diarrheogenic tumors" OR "diarrheogenic tumour" OR "diarrheogenic tumours" OR "VIP secreting tumor" OR "VIP secreting tumors" OR "VIP secreting tumour" OR "VIP secreting tumours" OR "Pancreatic cholera" OR "Verner-Morrison syndrome" OR "Verner Morrison syndrome" OR "watery diarrhea syndrome" OR "watery diarrhoea syndrome" OR WDHA OR WDHH OR "neuroendocrine carcinoma" or "neuroendocrine carcinomas" OR "Neuroendocrine Tumors"[MeSH] OR "Apudoma"[MeSH] OR "Carcinoid Tumor"[MeSH] OR "Adenoma, Islet Cell"[MeSH] OR "Insulinoma"[MeSH] OR "Carcinoma, Islet Cell"[MeSH] OR "Gastrinoma"[MeSH] OR "Glucagonoma"[MeSH] OR "Somatostatinoma"[MeSH] OR "Vipoma"[MeSH] OR "Multiple Endocrine Neoplasia"[MeSH] OR "Pancreatic Neoplasms"[MeSH])) OR "Malignant Carcinoid Syndrome"[MeSH] OR carcinoid syndrome)) AND ((("Liver"[MeSH] OR liver OR hepatic) AND (segmentectomy OR resection OR debulk* OR "Cryosurgery"[Mesh] OR cryoablat* OR cryosurger* OR radioablat* OR radiofrequency ablat* OR radio-frequency ablat* OR RF ablat* OR thermoablat*)) OR "Hepatectomy"[MeSH]) AND ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) AND humans [mh])

(Continued)

EMBASE (Dialog Datastar)	January 1974 to July 2008	1 APUDOMA.W..DE. OR CARCINOID#.W..DE. OR MULTIPLE-ENDOCRINE-ADENOMATOSIS.DE. OR MULTIPLE-ENDOCRINE-NEOPLASIA.DE. OR PANCREAS-ISLET-CELL-TUMOR#.DE. 2 NEUROENDOCRINE ADJ TUMOR OR NEUROENDOCRINE ADJ TUMORS OR NEUROENDOCRINE ADJ TUMOUR OR NEUROENDOCRINE ADJ TUMOURS OR ADENOMA OR ADENOMAS OR APUDOMA OR APUDOMAS OR CARCINOID OR CARCINOIDS OR ARGENTAFFINOMA OR ARGENTAFFINOMAS OR SOMATOSTATINOMA OR SOMATOSTATINOMAS OR ISLET ADJ CELL ADJ TUMOR OR ISLET ADJ CELL ADJ TUMORS OR ISLAND ADJ CELL ADJ TUMOUR OR ISLAND ADJ CELL ADJ TUMOURS OR NESIDIOBLASTOMA OR NESIDIOBLASTOMAS OR INSULINOMA OR INSULINOMAS 3 MULTIPLE ADJ ENDOCRINE ADJ NEOPLASIA OR MULTIPLE ADJ ENDOCRINE ADJ ADENOPATHY OR MULTIPLE ADJ ENDOCRINE ADJ ADENOPATHIES OR MULTIPLE ADJ ENDOCRINE ADJ ADENOMATOSES OR MULTIPLE ADJ ENDOCRINE ADJ ADENOMATOSIS OR FAMILIAL ADJ ENDOCRINE ADJ ADENOMATOSES OR FAMILIAL ADJ ENDOCRINE ADJ ADENOMATOSIS OR MULTIPLE ADJ ENDOCRINE ADJ NEOPLASMS 4 VIP ADJ SECRETING ADJ TUMORS OR VIP ADJ SECRETING ADJ TUMOUR OR VIP ADJ SECRETING ADJ TUMOURS OR PANCREATIC ADJ CHOLERA OR VERNER-MORRISON ADJ SYNDROME OR VERNER ADJ MORRISON ADJ SYNDROME OR WATERY ADJ DIARRHEA ADJ SYNDROME OR WATERY ADJ DIARRHOEA ADJ SYNDROME OR WDHA OR WDHH 5 NEUROENDOCRINE ADJ CARCINOMA OR NEUROENDOCRINE ADJ CARCINOMAS 6 1 OR 2 OR 3 OR 4 OR 5 7 METASTA$ OR SECONDAR$ OR SPREAD OR ADVANCED OR LIVER-METASTASIS#.DE. OR METASTASIS#.W..DE. 8 6 AND 7 9 LIVER OR HEPATIC 10 SEGMENTECTOMY OR RESECTION OR DEBULK$ OR CRYOABLAT$ OR CRYOSURGER$ OR RADIOABLAT$ OR RADIOFREQUENCY ABLAT$ OR RADIO-FREQUENCY ABLAT$ OR RF ABLAT$ OR THERMOABLAT$ OR CRYOABLATION#.W..DE. OR RADIOFREQUENCY-ABLATION#.DE. OR THERMOABLATION#.W..DE. 11 9 AND 10 12 HEPATECTOMY OR LIVER-RESECTION.DE. 13 11 OR 12 14 8 AND 13 15 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. 16 14 AND 15
Science Citation Index Expanded (http://apps.isiknowledge.com)	January 1970 to July 2008	#1 TS=(metasta* OR secondar* OR spread OR advanced) #2 TS=("neuroendocrine tumor" OR "neuroendocrine tumors" OR "neuroendocrine tumour" OR "neuroendocrine tumours" OR adenoma OR adenomas OR apudoma OR apudomas OR carcinoid or carcinoids OR argentaffinoma OR argentaffinomas OR somatostatinoma OR somatostatinomas OR "islet cell tumor" OR "islet cell tumors" OR "island cell tumour" OR "island cell tumours" OR nesidioblastoma OR nesidioblastomas OR insulinoma OR insulinomas OR "multiple endocrine neoplasia" OR "multiple endocrine adenopathy" OR "multiple endocrine adenopathies" OR "multiple endocrine adenomatoses" OR "multiple endocrine adenomatosis" OR "familial endocrine adenomatoses" OR "familial endocrine adenomatosis" OR "multiple endocrine neoplasms") #3 TS=(vipoma or vipomas OR "diarrheogenic tumor" OR "diarrheogenic tumors" OR "diarrheogenic tumour" OR "diarrheogenic tumours" OR "VIP secreting tumor" OR "VIP secreting tumors" OR "VIP secreting tumour" OR "VIP secreting tumours" OR "Pancreatic cholera" OR "Verner-Morrison syndrome" OR "Verner Morrison syndrome" OR "watery diarrhea syndrome" OR "watery diarrhoea syndrome" OR WDHA OR WDHH OR "neuroendocrine carcinoma" or "neuroendocrine carcinomas") #4 #3 OR #2 #5 TS=(liver OR hepatic) #6 TS=(segmentectomy OR resection OR cryoablat* OR cryosurger* OR radioablat* OR radiofrequency ablat* OR radio-frequency ablat* OR RF ablat* OR thermoablat*) #7 TS=(random* OR blind*OR placebo* OR meta-analysis)

(Continued)

		#8 #7 AND #6 AND #5 AND #4 AND #1
LILACS	July 2008	(((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized 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$)) Placebos OR Mh OR Tw placebo$ 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)

HISTORY

Protocol first published: Issue 2, 2008
Review first published: Issue 2, 2009

Date	Event	Description
18 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

See sponsors of the review.

SOURCES OF SUPPORT

Internal sources

- none, Not specified.

External sources

- Kleijnen Systematic Reviews Ltd, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

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)

*Hepatectomy; Liver Neoplasms [secondary] [*surgery]; Neuroendocrine Tumors [secondary] [*surgery]

MeSH check words

Humans