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Palliative cytoreductive surgery versus other palliative treatments in patients with unresectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours (Review)

Gurusamy KS, Pamecha V, Sharma D, Davidson BR

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[Intervention Review]

Palliative cytoreductive surgery versus other palliative treatments in patients with unresectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours

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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 alone metastases, the management of patients with liver metastases, which cannot be completely resected, is controversial.

Objectives

To determine if cytoreductive surgery is better than other palliative treatments in patients with liver metastases from gastro-entero-pancreatic neuroendocrine tumours, which cannot be completely resected.

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

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 palliative treatments (chemotherapy or hormone-therapy or immunotherapy) or no treatment in patients with liver metastases from neuroendocrine tumours, which cannot be completely resected, were considered 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.

Authors' conclusions

The literature provides no evidence from randomised clinical trials in order to assess the role of cytoreductive surgery in non-resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours. High-quality randomised clinical trials may become feasible to

perform if their conduct and study design is thoroughly considered in all their practical and methodological aspects. Pilot randomised clinical trials, which can guide the study design of definitive randomised clinical trials, are necessary.

PLAIN LANGUAGE SUMMARY

No evidence for optimal management of patients with unresectable liver spread originating from intestinal hormone cells

Liver metastases (liver spread) from gastrointestinal neuroendocrine tumours (cancer of intestinal hormone cells which originate from the embryonic nerve cells or the embryonic outer coat) are generally treated with surgery if a complete removal is deemed possible. This is associated with a long-term survival. However, more than four-fifths of patients with liver metastases from neuroendocrine tumours cannot undergo resection of all metastatic disease. The treatment of such patients is controversial. Palliative removal of the liver spread (ie, leaving behind a part of the cancerous liver spread) or destroying a significant portion of the cancerous liver spread using radiofrequency waves (collectively called cytoreductive surgeries) are some of the options offering symptomatic relief and possible prolongation of survival. This Cochrane review attempted to answer the question of whether palliative cytoreductive surgery is better than other palliative treatments, but no randomised clinical trials were found, addressing this issue. High-quality randomised clinical trials may become feasible to perform if their conduct and study design is thoroughly considered in all their practical and methodological aspects. Pilot randomised clinical trials, which can guide the study design of definitive randomised clinical trials, are necessary.

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). Gastro-entero-pancreatic neuroendocrine tumours include carcinoid tumours, insulinomas, gastrinomas, glucagonomas, somastatinomas, and vipomas (Leotlela 2003). They can occur alone or may occur as a part of multiple endocrine neoplasia type 1 (MEN type I) syndrome (Leotlela 2003).

The 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). They secrete the hormones serotonin (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, oedema, and ascites) (NCBI 2008) when there are metastases (Rubin 1999).

The main hormones secreted by gastrointestinal neuroendocrine tumours (other than carcinoids) include insulin (insulinoma), gastrin (gastrinomas), glucagon (glucagonoma), somatostatin (somatostatinomas), and vasoactive intestinal peptide (vipomas) (NCBI 2008). 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 hypokalemia (vipoma). Approximately 70% of the neuroendocrine tumours with liver metastases are non-secreting tumours (Nguyen 2007). In such patients, the main symptoms and signs are weight loss, abdominal pain, and abdominal mass (Nguyen 2007).

Radical surgery including resection of the primary tumour and liver metastases is the main treatment for advanced neuroendocrine tumours with five-year and ten-year survival rates of 61% to 70% (Coppa 2001; Yao 2001; Sarmiento 2003) and 35%, respectively (Sarmiento 2003). However, at the time of diagnosis, more than 80% of the liver metastases are bilobar (Chamberlain 2000), and curative resection is not possible. Various palliative treatment options available to these patients include chemotherapy (Oberg 1989; Fjallskog 2001; Sun 2005), liver transplantation (Coppa 2001; Florman 2004), embolisation (Wangberg 1996; Gupta 2005), transarterial chemoembolisation (TACE) (Falconi 1999; Yao 2001; Gupta 2005), radionuclide therapy using 111 indium-pentetreotide (Anthony 2002; Nguyen 2004), Ytrium DOTATOC (Forrer 2007), Lutetium DOTA (Forrer 2007), or meta-iodobenzylguanidine (MIBG) (Mukherjee 2001; Pasieka 2004), immunotherapy alone (Oberg 1989), or in combination with octreotide (Kolby 2003), and medical treatment using octreotide (Kolby 2003) or lanreotide (Faiss 2003). Palliative cytoreduction or debulking by surgical resection (Chung 2001) or cryoablation (Chung 2001; Sheen 2002), radiofrequency ablation (Chung 2001; Henn 2003), or a combination of these have been used for symptom relief in these patients and is generally carried out when it is possible to remove 70% to 90% of the disease (Chung 2001) with adequate remnant liver, ie, without compromising on the liver function (van den Broek 2008). Symptom relief and improved survival can be achieved by cytoreductive surgery (Osborne 2006). However, the patients are exposed to the risks of major liver resection including peri-operative mortality.

We could not find any meta-analyses or systematic reviews comparing palliative cytoreduction surgery with other palliative treatments.

OBJECTIVES

To determine the benefits and harms of palliative cytoreductive surgery versus other palliative treatments in patients with unresectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

Patients with liver metastases from gastro-entero-pancreatic neuroendocrine tumours (irrespective of presence or absence of extrahepatic disease, type of gastro-entero-pancreatic neuroendocrine tumour), who are not amenable to potentially curative liver resections.

Types of interventions

We considered for inclusion liver resection (alone or in combination with radiofrequency ablation or cryoablation) versus other palliative treatments (chemotherapy or hormonotherapy or immunotherapy) or no treatment.

Co-interventions were allowed if carried out equally in the intervention groups.

We excluded trials comparing liver transplantation versus other treatments as this needs further assessment in a separate review.

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.
2. Quality of life (however defined by authors).

Secondary outcomes

1. Estimated progression-free survival.
2. Treatment-related morbidity (surgery - 30-day mortality, bile leak, lymphorrhoea, abdominal collections requiring treatment,

wound related complications, such as wound infection, wound dehiscence; palliative chemotherapy, hormonotherapy, immunotherapy - bone marrow suppression, nausea, vomiting, diarrhoea, joint pain).

3. Symptom relief (however defined by authors).
4. Proportion requiring additional treatment for symptom relief.
5. Total hospital stay (all episodes of hospital admission during the study period).

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) until July 2008. 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 VP), independently of each other, identified the trials for inclusion and planned to list the excluded studies with the reasons for the exclusion.

KSG and VP 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. Reason for unresectability.
7. Operating time.
8. Other co-interventions.
9. Additional therapy used for control of symptoms.
10. Outcomes (mentioned above).
11. Methodological quality and hence risk of bias (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 the outcome assessors were not blinded.

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.
- 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 all the important outcomes (primary outcomes) were 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, 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.
- 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.
- Unclear, if the source of funding was not clear.
- Inadequate, if the trial was funded by an instrument or equipment or drug manufacturer.

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.

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.
- Cytoreductive radiofrequency ablation versus other palliative treatments.
- Cytoreductive cryoablation versus other palliative treatments.
- Different types of neuroendocrine tumours.
- Different methods of palliative treatment.
- Presence or absence of extra-hepatic diseases.

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.

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 trials, we searched for any quasi-randomised trial 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 trials from the retrieved references either.

Risk of bias in included studies

Lack of trials precluded us from assessing the risk of trials.

Effects of interventions

We were unable to identify any studies that studied the interventions of interest for this systematic review.

DISCUSSION

None of the studies identified through the search strategy qualified for this review. We were also unable to identify quasi-randomised studies, which could give information to answer the posed question. Accordingly, we have been unable to identify evidence, which could guide us in the role of cytoreductive surgery in the management of non-resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours.

Although there are no randomised clinical trials or quasi-randomised studies, retrospective cohort studies may give some indications of the outcomes of surgical and non-surgical palliative therapies. A study of meta-iodo-benzyl-guandine therapy, known as MIBG therapy, for gastrointestinal neuroendocrine liver metastases showed a 3-year survival rate of 40% (Pasieka 2004). The 5-year survival rate in patients with gastro-entero-pancreatic neuroendocrine tumours after radiofrequency ablation is 56% (Mazzaglia 2007). The 5-year survival rate in patients with gastro-entero-pancreatic neuroendocrine tumours after palliative debulking surgery followed by hepatic artery chemoembolisation, octreotide, and interferon-α is 57% (Kolby 2003). There are major differences between these studies as regards to the patients and the extent of disease including number and size of metastases; their differentiation; secretory status (and hence receptor status); the primary site of disease; and the distribution of disease sites (liver alone or diffuse metastases). This does not facilitate comparison of survival. For example, the better survival reported after palliative cytoreductive surgery may be related to the patient selection (ie patients with biologically less aggressive metastases are likely to be chosen for palliative cytoreductive surgery and patients with biologically more aggressive metastases are likely to be chosen for other palliative treatments). Thus, cohort studies do not provide data for performing the 'value of information' analysis also (Chilcott 2003). However, to find a difference of 10% improved survival rate by debulking surgery or radiofrequency ablation (or a combination of both) over other palliative treatments (such as radionuclide treatment) with an alpha of 0.05 and power of 0.8, 776 patients are necessary (StatsDirect 2.6). Thus a multicentric trial conducted over many years may be necessary to recruit these patients. Such a trial should include only patients in whom 70% to 90% of the disease is resectable (Chung 2001) with adequate remnant liver, ie, without compromising on the liver function (van den Broek 2008). It may be worth conducting a pilot randomised clinical trial in these patients to guide sample size calculations. This will also give a rough guidance as to whether an adequately powered trial is feasible and will provide data for calculating the 'expected value of perfect information' (Chilcott 2003), which can help in the identification of the priority of a definitive randomised clinical trial. The pilot randomised clinical trial is likely to provide more reliable data than cohort studies by minimising 'selection bias'.

We foresee methodological and procedure-related problems that the conductors of such a trial will face. Blinding of patients and health-care providers regarding symptom relief and quality of life will not be possible in order to avoid bias. It is likely that some metastases deemed unresectable by initial imaging become downstaged and resectable. It may be unethical to refuse potentially curative surgery to such patients. This will result in cross-overs. However, this is likely to happen in a very small proportion of patients. Besides, by adopting an intention-to-treat analysis, it would be possible to determine whether the cytoreductive surgery approach is better than other palliative approaches. The quality of life should be studied at regular time intervals so that quality adjusted life year and cost-utility analysis can be performed. Good survival reported with palliative treatment in patients with neuroendocrine liver metastases necessitates a long follow-up period (of at least 10 to 15 years) to assess the survival properly. This may incur huge expenses depending on the sample size. The 'value of information' analysis (Chilcott 2003) of the pilot trial should give some guidance as to whether such huge expenses are warranted. It is possible that some patients are lost to follow-up because of the long period of follow-up. If this proportion is high, bias due to 'incomplete data outcomes' may arise. Adequate steps should be taken to prevent this from happening. Sequential treatments may be used over a period of years; this may introduce some confusion as to the treatment responsible for the prolonged survival.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence in literature to assess the role of cytoreductive surgery in non-resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours.

Implications for research

High-quality randomised clinical trials to define the role of cytoreductive surgery in non-resectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours may become feasible to perform if their conduct and study design is thoroughly considered in all their practical and methodological aspects. Pilot randomised clinical trials, which can guide the study design of definitive randomised clinical trials, are necessary.

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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

(Continued)

		#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 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

(Continued)

		(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])
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 1945 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 di-

(Continued)

		arrhea 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) #8 #7 AND #6 AND #5 AND #4 AND #1
LILACS (http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i)	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 random$ 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 1, 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. V Pamecha independently assessed the trials for inclusion. D Sharma and BR Davidson critically commented on the review, provided advice for improving the review and advised on a randomised clinical trial design. All authors approved of the final version of the review.

DECLARATIONS OF INTEREST

See sponsors of the review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Kleijnen Systematic Reviews Ltd, UK.

  Requested the preparation of this review.

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 updated methodology stated in the Cochrane Handbook (Higgins 2008). Although, we planned to include the comparison liver resection versus no treatment, we did not state this clearly in the protocol. Now, it is stated clearly.

INDEX TERMS

Medical Subject Headings (MeSH)

*Gastrointestinal Neoplasms; *Pancreatic Neoplasms; Liver Neoplasms [secondary] [*surgery]; Neuroendocrine Tumors [secondary] [*surgery]; Palliative Care [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Humans