

CHEMOSATURATION FOR LIVER METASTASES FROM OCULAR MELANOMA

QUESTION(S) TO BE ADDRESSED:

- 1a) Is chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation clinically effective in the treatment of patients with liver metastases from ocular melanoma?
- 1b) Is chemosaturation more effective than standard treatment in the treatment of patients with liver metastases from ocular melanoma?
- 1c) Is chemosaturation safe to use in the treatment of patients with liver metastases from ocular melanoma?
- 2) Is chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation a cost-effective treatment option for use in patients with liver metastases from ocular melanoma?

SUMMARY:

Background

- Ocular melanoma is rare, affecting 500 to 600 people in the UK per year.
- Liver is often the first and in many cases the only site of metastasis in ocular melanoma patients and these patients have very limited treatment options.
- Chemosaturation via percutaneous hepatic perfusion and hepatic vein isolation is a minimally invasive procedure which can be repeated.
- The procedure aims to deliver the chemotherapy drug directly to the liver in high doses and to filter the blood coming out of the liver to remove much of the drug before returning to the circulation, minimising the systemic toxicity.

Clinical Effectiveness

- No systematic reviews, meta-analyses or randomised controlled trials assessing the effectiveness of chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for metastatic liver cancer metastases from ocular melanoma primaries were identified.
- One evidence review to support NICE guidance (search date 2013) on the treatment of primary and metastatic liver cancer was identified. It included 5 case series, of which one provided evidence on efficacy in ocular melanoma specifically.
- Two case series studies met the inclusion criteria.
- Both the studies included mixed populations with small number of ocular melanoma patients.
- One study (n=5) reported overall survival of between 10 months and about 3.9 years.
- One study (n=5) reported median progression free survival of about 7.6 months.
- The other case series study reported 3 patients with partial responses and 3 patients with stable disease out of the 8 ocular melanoma patients treated.

Cost-Effectiveness

- We found no evidence on the cost effectiveness of the procedure.

Safety

- Evidence on the safety of the procedure is very scarce.
- NICE review reported procedure related mortality rates of between 3.1% and 7.1%. This was based on 5 case series studies with mixed populations i.e. for ocular melanoma and other cancers.

- 11% of those treated with chemosaturation via percutaneous hepatic perfusion experienced gastrointestinal adverse events and 17% experienced cardiovascular adverse events in a large case series (n=121).
- 44% of patients (n=53) experienced hepatic events in the same large case series (n=121).

1 Context

1.1 Introduction

Melanoma is a type of cancer that develops from pigment producing cells called melanocytes. Although melanocytes are predominantly present in the skin, they are also present in other parts of the body, including the eyes.

Eye or ocular melanoma is very rare. The most common type of eye or ocular melanoma is uveal melanoma. This occurs in the area called the uvea – the layer of pigmented tissue between the outer layer of the eye (cornea and sclera) and the inner layer (the retina). Uveal melanoma affects an estimated 500 to 600 people a year in the UK, and is most common in people in their fifties.

The liver is usually the first, and in many cases the only, site of metastasis of uveal melanoma.[1] Treating liver cancer metastases is challenging and depends on the stage and location of the tumour. Treatment also depends on how well liver function is preserved. Treatment options include surgical resection, thermal ablation, systemic chemotherapy, transarterial chemoembolisation and selective internal radiation therapy. Liver transplantation may be appropriate for some patients. For most patients with liver metastases, treatment with curative intent is not possible.[2]

For ocular melanoma liver metastases, UK experts reported to NICE that there is no standard practice other than best supportive care. [2]

Chemosaturation via percutaneous hepatic perfusion and hepatic vein isolation is a relatively new regional treatment option. The procedure aims to allow a high dose of chemotherapy to be delivered directly to the liver without causing severe systemic adverse effects. The procedure used to be carried out in open surgery, but is now performed percutaneous, making it minimally invasive and repeatable. It is typically used in patients who have a poor prognosis and limited treatment options.

1.2 Existing national policies and guidance

There are no current policies or guidance from the National Institute for Health and Care Excellence (NICE) regarding percutaneous hepatic perfusion and hepatic vein isolation for patients with liver metastasis specifically from ocular melanoma.

However, in 2014 NICE provided interventional procedure guidance (IPG488) on the use of the technique for patients with primary or metastatic liver cancer more broadly. This guidance concluded that the evidence available at that point was limited in quality and quantity, and there was a significant incidence of serious adverse effects. Therefore it recommended that:

- The procedure should only be performed within the context of research, which may take the form of observational studies.
- Patient selection should be done by an appropriate multidisciplinary team.
- Hepatic chemosaturation should only be carried out by clinicians with specific training in its use and in techniques to minimise the risk of adverse effects from the procedure.
- Research should document indications for treatment, details of patient selection and details of adjuvant and prior treatments. Outcome measures should include complications, survival and quality of life. Data from well-designed trials comparing the procedure against other forms of

management would be particularly useful, but prospective observational studies may also be of value.

NICE interventional procedures guidance provides safety and efficacy recommendations; compliance is not mandatory.

2 Epidemiology

Uveal melanoma is the most common primary intraocular malignant tumour in adults with an annual incidence of 4.3 new cases per million in the US.[3] Annual incidence is slightly higher in men (4.9 cases per million) when compared to women (3.7 cases per million).[4] Although very rare, between 500 to 600 people are diagnosed with uveal melanoma each year in the UK.[5]

There is no lymphatic drainage in the uvea, therefore if ocular melanoma spreads it does so through blood. Liver metastases are common.[6] According to the Ocular Melanoma Foundation, nearly 80 to 90% of the time, the liver is the first site of metastasis.[7]

3 The intervention

Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation is a minimally invasive procedure which is performed under general anaesthesia.[8]

Three percutaneously inserted catheters are used during the surgery. An infusion catheter is inserted into the femoral artery in the thigh and guided into the hepatic artery which supplies blood to the liver. Anticoagulants are administered throughout the surgery with a goal of reducing the risk of clots forming.[2] The femoral vein is then cannulated and using fluoroscopic guidance, a special multi-lumen, double-balloon isolation-aspiration catheter is inserted into inferior vena cava and across the hepatic veins. The balloons are then inflated and positioned in such a way that the blood leaving the liver via the hepatic vein enters this catheter.

Prior to administering any chemotherapy drug, a contrast media is infused to ensure there is no leakage around these balloons thus confirming that the liver isolation is achieved.

Once that is confirmed, high doses of a chemotherapy drug (melphalan is the commonly used drug) is then infused directly into the liver via the hepatic artery infusion catheter over a period of approximately 30 minutes.[2] During this time, blood leaving the liver is collected via the isolation-aspiration catheter and passes through an extracorporeal filtration system that removes most of the chemotherapy drug before the blood is returned to the circulation via a third catheter in the internal jugular vein.

Throughout the procedure, hemodynamic and arterial pressure monitoring is performed due to the drop in the mean arterial pressure caused by decreased venous return. Patients are also supported with fluids throughout.[8]

Regional treatment of malignant hepatic tumours such as this intervention are reported to be most appropriate when (1) systemic chemotherapy is not effective, (2) the liver is the only dominant site of involvement or (3) there is an urgent need to control local progression of disease for symptom control or palliation.[1]

4 Findings

4.1 Evidence of effectiveness

Medline, Embase, Cochrane, TRIP and NICE Evidence Search were searched from 2005 onwards for systematic reviews, meta-analyses, randomised controlled trials, prospective non-randomised clinical studies and health economics studies to gather evidence on the effectiveness of chemosaturation in terms of overall survival, disease progression and progression-free survival, response using RECIST (Response Evaluation Criteria in Solid Tumours) criteria, and quality of life in patients with liver metastasis from ocular melanoma compared with other standard treatments. Studies that included mixed populations (for example, various locations of primary cancers) were included in this review if they had more than 5 ocular melanoma patients in their cohort.

Overall, the evidence base for this was extremely scarce, and limited to small case series. All of the case series identified which met inclusion criteria included mixed populations; only the effectiveness results for patients with ocular melanoma are described here.

NICE carried out a rapid review of the evidence (search date September 2013) on the use of the intervention for patients with primary or metastatic liver cancer in order to produce interventional procedures guidance.[10] It identified limited evidence, and focused on five case series including 243 patients. Two of these case series were reported to include individuals with ocular melanoma. One case report was a prospective case series included 10 participants with hepatic metastases from ocular melanoma. The second in 121 patients (number with ocular melanoma not specified) was part of a submission to the FDA by the manufacturer of the Delcath chemosaturation system. This submission also described an RCT comparing percutaneous chemosaturation versus best alternative care. As the efficacy results of the RCT had not been fully published in a peer reviewed journal they were not considered by NICE in its appraisal.[10]

No subsequent systematic reviews, meta-analyses or randomised controlled trials were identified. Two subsequent retrospective case studies met the inclusion criteria for this review. Both the studies reported on mixed populations that included ocular melanoma, cutaneous melanoma, gastric cancer, breast cancer, colon cancer and sarcoma. One case series [8] included 5 ocular melanoma patients the other [9] included 8 ocular melanoma patients.

The small size of the studies limits conclusions which can be drawn, as results may not be generalizable to broader groups of patients. In addition, the lack of comparator groups also limits ability to draw conclusions about the effects of the intervention. Ability to obtain larger studies may be hampered somewhat by the relative rarity of the condition, and the limited treatment options and poor prognosis for these patients may also make RCTs less feasible or unethical.

All of the trials used the Delcath System to perform the procedure, and used similar doses of melphalan as the chemotherapy agent. Patients received between 1 and 4 cycles of percutaneous chemosaturation. This variation in number of cycles could have influenced effectiveness results.

The effectiveness results are summarised below and in Table 1 below.

Overall survival

- One study [8] (n=5) reported overall survival of between 10 months and about 3.9 years.

Progression free survival

- One study [8] (n=5) reported median progression free survival of about 7.6 months.

Tumour response

- Tumour response varied across the studies that reported it.
- One study [10] (n=10) included by NICE reported that 20% achieved complete radiographic response, 10% partial response, and 30% minor response; the status of the other 40% of participants was not reported, nor were the criteria for judging response.

- One study [9] (n=8) reported no complete responses, 3 partial responses, and 3 with stable disease (RECIST criteria). Whether the other 2 participants were assessed for response and their response status if so was not reported.
- One study [8] (n=5) reported that one participant (20%) did not respond to treatment, and the other four (80%) had a reduction in tumour volume from baseline. These responses were not classified into RECIST response categories.

Quality of life

None of the included studies reported on quality of life.

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Table 1: Effectiveness of percutaneous chemosaturation for liver metastases from ocular melanoma

Study	Patients	Intervention	Outcomes
<p>NICE Evidence review [10]</p> <p>Prospective case series by Pingpank et al 2005</p> <p>Location: US</p>	<p>28 patients with unresectable liver cancer, including 10 with metastases from ocular melanoma (results reported here). Participants had limited or no extra-hepatic metastases and none had been previously treated with melphalan; most patients were reported to have had previous treatment.</p>	<p>Percutaneous chemosaturation with melphalan (Delcath System). 4 treatments separated by 4 weeks. Doses varied between 2.0mg/kg and 3.5mg/kg.</p>	<p>Follow-up: NR</p> <p>Overall survival: NR</p> <p>Progression free survival: NR</p> <p>Tumour response: Radiographic response rate (not further defined) 20% (2/10) complete response 30% (3/10) partial response 30% (3/10) minor response</p> <p>The complete responses lasted 10 and 12 months. Two patients with partial response were reported to have ongoing responses at 9 and 11 months.</p> <p>Quality of life: NR</p>
<p>Forster et al 2014 [8]</p> <p>Retrospective case series, consecutive patients</p> <p>Location: USA</p>	<p>10 patients with liver metastases, including 5 with ocular melanoma (results reported here). Disease was limited to the liver in all patients.</p> <p>4/5 patients had no previous treatment, and one had previous carboplatin/taxol.</p>	<p>Percutaneous chemosaturation with melphalan (Delcath System).</p> <p>A dose of 3 mg/kg was given adjusted for the patient's ideal body weight.</p> <p>The 4 patients with stable disease or partial response after 6 weeks had repeat treatments every 6-8 weeks, to a total of 3 treatments.</p>	<p>Follow-up: Ranged from 5 months to 35 months.</p> <p>Overall survival: Ranged from 10 months to 46.4 months in the 4 patients who died from the disease. One patient was alive with disease (without progression) at last follow up at 5 months.</p> <p>Progression free survival: Median hepatic progression free survival: 228 days (about 7.6 months; range 0 days to 453 days [about 15.1 months]). One patient's liver disease had not yet progressed by final follow up at 5 months (PFS 166 days).</p> <p>Tumour response: 4/5 (80%) patients had a reduction in tumour</p>

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			<p>size from baseline (range 33.3% to 72.1%), while one patient did not respond and had an increase in tumour volume of 84.9%.</p> <p>Median decrease in hepatic tumour volume in those with stable disease or partial response (RECIST criteria): 48.6%.</p> <p>Quality of life: NR</p>
<p>Vogl et al 2013 [9]</p> <p>Retrospective case series, consecutive patients</p> <p>Location: Frankfurt, Germany and Milan, Italy</p>	<p>14 patients with unresectable hepatic metastases from solid tumours, including 8 with ocular melanoma (results reported here)</p> <p>All patients had prior treatments</p>	<p>Percutaneous chemoablation with melphalan (Delcath Systems)</p> <p>Dose was 3.0 mg/kg ideal body weight for 7 patients (maximum 220 mg/treatment) and 2.0 mg/kg for one patient.</p> <p>Overall, participants received between 1 and 3 treatments, with between 57 and 177 days between treatments.</p>	<p>Follow-up: NR</p> <p>Overall survival: NR</p> <p>Progression free survival: NR</p> <p>Tumour response: Complete response: 0 patients Partial response: 3 patients Stable disease: 3 patients (RECIST criteria)</p> <p>Not clear whether the remaining 2 individuals were assessed for response, therefore % response not calculated.</p> <p>Quality of life: NR</p>

4.2 Trials in progress

We identified no ongoing trial that uses chemosaturation via percutaneous hepatic perfusion and hepatic vein isolation for patients with liver metastasis from ocular melanoma.

4.3 Evidence of cost-effectiveness

We found no evidence of the cost effectiveness of this procedure in our search.

4.4 Safety

Overall, we found very limited evidence on the safety of the procedure. We have summarised findings regarding safety from the NICE evidence review [10] and also the findings of the two subsequent case series included for the effectiveness assessment [8;9]. We have reported safety findings for these studies across the indications for use i.e. for ocular melanoma and other cancers. It is important to note that both the subsequent studies included small numbers of patients which limits ability to assess adverse event rates, particularly uncommon adverse events.

Death

In the largest case series included by NICE (n=121) 4% of participants experienced adverse events resulting in death. These events included ruptured hepatic artery leading to gastrointestinal haemorrhage, gastric perforation, hepatic failure (this patient's liver was 90% tumour), and streptococcal sepsis and neutropaenia. A second included case series (n=46) there were 2 deaths (4.3%) due to hepatic arterial thrombosis associated with infection caused by the catheter system. A third included case series (n=32) reported 1 death (3.1%), due to spontaneous retroperitoneal haemorrhage within 24 hours of the intervention.[10]

In one subsequent case series (n=14, 8 ocular melanoma) one ocular melanoma patient (7.1%) died of retroperitoneal giant hematoma 30 hours after the intervention. The post-mortem revealed multisite vascular bleeding, but no damage to abdominal veins, so the researchers felt it was likely to be attributed to the anticoagulation which was part of the procedure.[9]

The other subsequent case series (n=10, 5 ocular melanoma) included in this review reported no perioperative mortalities.[8]

Gastrointestinal events

The largest case series in the NICE review (n=121) reported that 11% of participants experienced grade 3 or 4 gastrointestinal events (gastritis, ulceration, perforation, bleeding and gall bladder related events). The subsequent case series did not report any adverse gastrointestinal events.[10]

Cardiovascular events

Grade 3 or 4 cardiovascular events occurred in 17% of participants in the largest case series in the NICE review (n=121). The most common event was a troponin or troponin I increase (9 out of 21 events); other events included hypotension, pulmonary embolism, vena cava thrombosis (each in 2 participants), and intracranial haemorrhage, ventricular tachycardia, subendocardial ischaemia, subclavian vein thrombosis, pericardial effusion, somnolence, and impaired pupillary reflex.[10]

One subsequent case series,[8] reported that seven out of the total 10 patients (70%) had mild elevations in their serum troponin levels (a cardiac biomarker) after the treatment, but not EKG or echocardiogram signs of heart attack or dysfunction. One patient experienced non-sustained ventricular tachycardia during their fourth treatment which required it be terminated before the melphalan was infused; there were no cardiac sequelae. The other case series [9] did not report any cardiovascular events.

Haematological events

The largest case series in the NICE review (n=121) reported that [10]:

- 80% of patients experienced thrombocytopenia
- 59% experienced anaemia
- 59% experienced serious neutropenia
- 21% experienced complicated neutropenia (leading to death in two cases described above)

One subsequent case series [8] reported that myelosuppression was the most common adverse event among the 10 patients (absolute risk and event grade not reported) and all cases were treated on an outpatient basis. Six patients (60%) were observed to have neutropenia (grade not reported) after at least one of their chemosaturations treatments.

The other subsequent case series study [9] (n=14) reported various haematological events including nine patients (64%) with grade 3 or 4 pancytopenia, leukocytopenia or thrombocytopenia. One of these patients was reported to develop febrile neutropenia, and another patient not included above developed febrile pancytopenia as a result of a hepatic vascular shunt that avoided drug filtering. There were also a number of grade 1 or 2 haematological events. Some of the events required hospitalisation.

Haemorrhage

The largest case series in the NICE review (n=121) reported that 13% of patients had haemorrhage, 7% of which were grade 3 or 4 events. There were two intracranial haemorrhages in patients with brain metastases, and one of these patients died.[10]

One case series study [9], reported that the intervention had to be stopped prematurely (prior to melphalan infusion) due to vaginal bleeding in one premenopausal patient, they attributed this to systemic heparinisation.

Hepatic events

The largest case series in the NICE review (n=121) reported that 44% of patients (53 in total) experienced hepatic events, leading to 7 patients discontinuing treatment. One patient experiencing hepatic failure died.[10]

One of the subsequent case series [9] reported that 2 patients developed transient grade 1 or 2 increases in liver transaminases in the first few days after treatment. The other subsequent case series [8] did not report any hepatic events.

4.5 Summary of section 4

In the current review we searched for relevant articles from 2005 onwards. No systematic reviews, meta-analyses or randomised controlled trials were identified. Two case series studies met the inclusion criteria. Both the studies included mixed population with very small number of ocular melanoma patients. No studies were found that had a control group. One evidence review to support NICE guidance (search date 2013) on the treatment of primary and metastatic liver cancer was identified.[10] It included 5 case series, of which one provided evidence on efficacy in ocular melanoma specifically. All studies were of poor quality thus there is insufficient evidence to draw firm conclusions.

In a prospective case series study (n=28, 10 ocular melanoma patients) [11] included by the NICE review, 20% (2/10) of treated patients were observed to achieve complete response, 30% (3/10) were observed to achieve partial response and 30% (3/10) were observed to achieve minor response to the intervention.

In a subsequent retrospective case series,[9] percutaneous hepatic perfusion was evaluated in a total of 14 patients which included 8 ocular melanoma patients. Out of the 8 ocular melanoma patients, 3 presented partial response and 3 showed stable disease; the response status of the other two patients was not reported.

In a third retrospective case series,[8] total of 10 patients were included out of which 5 were ocular melanoma patients. The total median percentage decrease in hepatic tumour volume in the patients who had stable disease or partial response was 48.6% for those with ocular melanoma.

Hepatic progression free survival period in this study was about 7.6 months for ocular melanoma patients. Median overall survival ranged from 10 months to about 3.9 years. As this study did not have a control group, it is difficult to assess whether this represents an improvement in expected outcome. The Ocular Melanoma Foundation in the US reports that without treatment median survival is 2 to 8 months for people with metastatic ocular melanoma,[7] but the original source of this estimate was not cited. One case series (n=119) reported that those who had systemic chemotherapy had a median survival of 9.5 months, while those who had surgery or intrahepatic chemotherapy (local treatment) had median survival of 32.4 months.[8] However, caution should be applied when comparing the figures from these sources with those from the included case series, as the populations may not have been comparable and the sample in the included study was very small (n=5).

Overall, previous studies have reported 9 months median overall survival for patients with liver cancer from ocular melanoma.[1] Another study that assessed the course and outcome of metastatic uveal melanoma reported that, patients who received a particularly improved survival (median, 32.4 months), compared with patients who received systemic chemotherapy (median survival, 9.5 months).[8]

In the case series included in the rapid evidence review conducted by NICE in 2013 (5 case series, only two included ocular melanoma patients, n=243) [10] and the subsequent case series, between 3.1% and 7.1% of the patients having the procedure died due to adverse events.[8][10] These events included ruptured hepatic artery leading to gastrointestinal haemorrhage, gastric perforation, hepatic failure (this patient's liver was 90% tumour), and streptococcal sepsis, neutropenia, spontaneous retroperitoneal haemorrhage within 24 hours of the intervention and retroperitoneal giant hematoma 30 hours after the intervention.

The largest case series in the NICE review [11] (n=121) reported that 13% of patients had haemorrhage, 7% of which were grade 3 or 4 events. There were two intracranial haemorrhages in patients with brain metastases, and one of these patients died. This case series also reported 11% of patients had grade 3 or 4 gastrointestinal events, 17% had grade 3 or 4 cardiovascular events, and 44% had hepatic events.

Some of the other reported adverse events included bone marrow suppression, leading to cases of pancytopenia, leukopenia, anemia, and neutropenia.

5 Discussion and conclusions

- 1a) Is chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation clinically effective in the treatment of patients with liver metastases from ocular melanoma?
- 1b) Is chemosaturation more effective than standard treatment in the treatment of patients with liver metastases from ocular melanoma?

We found very limited evidence on the effectiveness of percutaneous hepatic perfusion procedure.

The included studies were small and lacked control groups. No studies were identified of high quality to draw firm conclusions on the effectiveness of the procedure in patients with liver metastasis from ocular melanoma.

- 1c) Is chemosaturation safe to use in the treatment of patients with liver metastases from ocular melanoma?

We found very limited evidence on the safety of percutaneous hepatic perfusion procedure.

No studies were identified of high quality to draw firm conclusions on the safety of the procedure in patients with liver metastasis from ocular melanoma.

- 2) Is chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation a cost-effective treatment option for use in patients with liver metastases from ocular melanoma?

No cost-effectiveness studies were identified to comment on the cost-effectiveness of this procedure.

Competing Interest

All SPH authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare: grants from NHS England to SPH to undertake the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

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7 Search Strategy

Table 6: Population, Intervention, Comparator and Outcomes (PICO)

<p>P- Patients/ population</p> <p>Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?</p>	<p>Patients with ocular melanoma that has metastasised to the liver</p>
<p>I - Intervention</p> <p>Which intervention, treatment or approach should be used?</p>	<p>Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for metastatic liver cancer</p>
<p>C - Comparison</p> <p>What is/ are the main alternative/s to compare with the intervention being considered?</p>	<p>Surgical resection Thermal ablation Systemic chemotherapy Selective internal radiation therapy Transarterial chemoembolization Usual (standard) care</p>
<p>O - Outcomes</p> <p>What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.</p>	<p>Critical for decision-making: RECIST criteria 1 year and 5 year progression free survival 1 year and 5 year overall survival Time to disease progression Side effects and toxicity (particularly GI and CVS events) Quality of life Important for decision-making: Cost-effectiveness</p>
<p>Assumptions/ limits applied to search</p>	<p>Publication Type: Systematic review Meta-analysis Randomised control trails Controlled studies Case series (if no controlled studies identified) Economic study Abstracts were excluded where no clinical outcomes reported, or where the paper was a non-systematic literature review, editorial, letter, laboratory or animal study. Studies published as abstract only (e.g. conference poster) were excluded.</p> <p>Inclusion: Articles published from January 2005 onwards Articles in the English language Articles that included 5 or more ocular melanoma patients</p> <p>Exclusion: Studies with findings of sample reported in more recent publication Studies published in language other than English</p>

Search date: October 2015

Databases searched: Embase, Cochrane, and NICE Evidence Search were searched from 2005 onwards. Letters, editorials, conference abstracts, case reports, cadaver studies, studies in normal hearing and laboratory studies were all excluded.

Embase search strategy

- #1. 'eye melanoma'/exp
- #2. (conjunctiv*:ab,ti or uvea*:ab,ti or eye:ab,ti or ocular:ab,ti) and melanoma:ab,ti
- #3. #1 or #2
- #4. 'liver metastasis'/exp
- #5. liver:ab,ti and metastas*:ab,ti
- #6. #4 or #5
- #7. #3 and #6
- #8. 'cancer chemotherapy'/exp
- #9. chemosaturat:ab,ti
- #10. percutaneous:ab,ti and hepatic:ab,ti and perfusion:ab,ti
- #11. 'high-dose chemotherapy':ab,ti and hepatic:ab,ti
- #12. #8 or #9 or #10 or #11
- #13. #7 and #12
- #14. #13 and [english]/lim and [2005-2015]/py

The search strategy for Cochrane was:

- #1 (conjunctiv* or uvea* or eye or ocular) and melanoma:ti,ab,kw
- #2 MeSH descriptor: [Eye Neoplasms] explode all trees
- #3 #1 or #2
- #4 (liver and metasta*):ti,ab,kw
- #5 MeSH descriptor: [Liver Neoplasms] explode all trees and with qualifier(s): [Secondary - SC]
- #6 #4 or #5
- #7 #3 and #6
- #8 chemosaturat:ti,ab,kw
- #9 "percutaneous hepatic perfusion":ti,ab,kw
- #10 'high-dose chemotherapy' and hepatic:ti,ab,kw
- #11 MeSH descriptor: [Chemotherapy, Cancer, Regional Perfusion] this term only
- #12 #8 or #9 or #10 or #11
- #13 #7 and #12

Guideline crude search:

Guideline.gov (NGC)
NHS Evidence (Types of information>guidelines)
CMA Infobase: Clinical Practice Guidelines (CPGs)
NZGG
Aus NHMRC
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