SIR-Spheres for the treatment of non-resectable liver tumours

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Assessment report

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Ms Silke Walleser, Ms Felicity Allen, Ms Alisa Higgins, Ms Kirsten Howard and Dr Sarah Lord from the NHMRC Clinical Trials Centre. The report was edited by Matthew Stevens, Science Scape Editing. The report was endorsed by the Minister for Health and Ageing on 28 November 2005.

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SIR-Spheres are used to treat patients with hepatic metastases secondary to colorectal cancer (CRC) in the absence of extrahepatic metastases, when the hepatic metastases are not amenable to surgery or radiofrequency ablation. They may be used in combination with systemic chemotherapy or hepatic arterial chemotherapy (HAC). SIR-Spheres are also used to treat primary non-resectable, non-ablatable hepatocellular carcinoma (HCC); however, this indication is not as common as colorectal liver metastases (CLM) in Australia.

Medical Services Advisory Committee—role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from the National Health and Medical Research Council (NHMRC) Clinical Trials Centre was engaged to conduct a systematic review of literature on SIR-Spheres for the treatment of non-resectable liver tumours. An Advisory Panel with expertise in this area then evaluated the evidence and provided advice to MSAC. This review updates MSAC's assessment of SIR-Spheres published in 2002.

MSAC's assessment of SIR-Spheres

The evaluation team worked with members of the Advisory Panel to develop specific questions addressing the use of SIR-Spheres for the treatment of non-resectable, non-ablatable liver tumours secondary to CRC, and for the treatment of non-resectable, non-ablatable HCC. The following two research questions were developed and are assessed in this review:

1st indication

What are the safety, effectiveness and cost-effectiveness of SIR-Spheres used alone or in addition to chemotherapy for treating non-resectable, non-ablatable hepatic metastases secondary to CRC compared with HAC treatment or systemic chemotherapy?

2nd indication

What are the safety, effectiveness and cost-effectiveness of SIR-Spheres for treating non-resectable, non-ablatable HCC compared with transarterial chemoembolisation (TACE) or ^{131}I-lipiodol?

A comprehensive search strategy was developed to identify relevant studies and reviews of the safety, effectiveness and cost-effectiveness of SIR-Spheres. In addition to electronic database searches, reference lists of identified publications were hand-searched, and publications were provided by the applicant. A total of eight studies, six (two randomised controlled trials [RCTs], four case series) for the CLM indication and two (case series) for the HCC indication, met criteria for inclusion in the review of effectiveness. An additional eight case series were included for the safety evaluation.

Clinical need

Colorectal metastases of the liver

CRC is the most common cancer after non-melanomatous skin cancer and the third most common cause of cancer death reported to Australian cancer registries. In 2001, CRC accounted for 14.5 per cent of all new cases of cancer and 13.1 per cent of cancer deaths (excluding non-melanocytic skin cancer) (AIHW & AACR 2004). In 2001, premature death from CRC was responsible for an estimated 29 768 person-years of life lost before the age of 75, making it second only to lung cancer for this measure of disease burden (AIHW & AACR 2004).

Approximately 50 per cent of patients with CRC will develop liver metastases within 5 years and 20 per cent of patients will already have liver metastases at the time of primary diagnosis (COSA & CAN 1999). If untreated, liver metastases from CRC show a very poor prognosis, with a median survival of 19 to 21 months, and no patients surviving 5 years (Liu et al. 2003).

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. The three major risk factors for development of HCC are alcoholic liver disease, chronic hepatitis B (HBV) infection and chronic hepatitis C (HCV) infection. In 2001, there were 853 new cases of primary liver cancer and 777 deaths (AIHW & AACR 2004), most of which can be attributable to HCC. The incidence rate of HCC in Australia has been steadily increasing in the past two decades, and it is thought that this can be partially explained by the increase in the prevalence of HBV and HCV (Law et al. 2000). Current estimates suggest that there are more than 242 000 Australians who are infected with HCV, and that another 14 499 are infected each year (National Centre in HIV Epidemiology and Clinical Research 2004). Therefore, it can be expected that the incidence rates of HCC will continue to rise in the future.

Safety

The assessment of the safety of SIR-Spheres is based on information from seven of the eight included studies of SIR-Spheres in CLM and HCC patients, eight additional case series included for the safety assessment (3 evaluating SIR-Spheres and 5 evaluating other Selective Internal Radiation Therapies [SIRTs]), TGA data, and information provided by the applicant. Minor complications and side-effects associated with the use of SIR-Spheres include including gastrointestinal (GI) side-effects (abdominal pain, nausea, vomiting and diarrhoea), fever, a transient decrease in haemoglobin and abnormal liver function tests. Major complications which have been reported include death, radiation hepatitis, radiation gastritis, radiation pneumonitis, radiation-induced cirrhosis, hepatic necrosis and GI ulceration. In the included SIR-Spheres safety information seven deaths occurred due to fatal radiation hepatitis, radiation gastritis, acute hepatic necrosis and sepsis associated with neutropaenia. Of these seven deaths, five were reported in the included studies which evaluated a total of 503 patients. In addition, a small number of cases of radiation pneumonitis, radiation-induced cirrhosis, non-fatal radiation gastritis and GI ulceration were found in the included studies.

There is limited comparative evidence available to enable an assessment of the safety of SIR-Spheres compared to other therapies used in the treatment of liver tumours. Of the two comparative studies identified, one found no difference in the rate of Grades 3 (severe) and 4 (life-threatening) toxicities between patients treated with SIR-Spheres and HAC and patients treated with HAC alone (Gray et al. 2001), while the other found 13 Grades 3 and 4 toxicities in patients treated with SIR-Spheres and systemic chemotherapy compared to five Grades 3 and 4 toxicities in patients treated with systemic chemotherapy alone (van Hazel et al. 2004).

In addition to the safety of patients treated with SIR-Spheres, safety issues arise for personnel involved in implanting SIR-Spheres and handling the device. From the available information it appears that the doses of radiation delivered to personnel are reasonably low and are within ranges recommended by the National Occupational Health and Safety Commission (National Occupational Health and Safety Commission 1995). SIR-Spheres should be implanted in approved centres to ensure that these safety standards are met.

Effectiveness

Effectiveness of SIR-Spheres for treatment of liver metastases of colorectal cancer

Two small RCTs (level II evidence) and four uncontrolled case series reports (level IV evidence) were identified for inclusion in the evaluation of the effectiveness of SIR-Spheres in CLM patients. The two RCTs evaluated the use of SIR-Spheres and HAC and of SIR-Spheres and systemic chemotherapy. In the trial comparing SIR-Spheres and HAC to HAC alone, no statistically significant survival benefit was found, however the trial was underpowered to detect a survival difference (Gray et al. 2001). In the trial comparing SIR-Spheres and systemic chemotherapy to chemotherapy alone, a statistically significant increase in survival was seen in patients treated with SIR-Spheres and systemic chemotherapy (29.4 months vs 12.8 months, HR 0.33; 95% CI 0.12–0.91; $P = 0.025$). This trial, however, used systemic chemotherapy regimens which no longer represent current practice. The survival advantage when SIR-Spheres are used in combination with current chemotherapy regimens is unknown.

All six included studies demonstrated anti-tumour activity of SIR-Spheres, but only the small van Hazel et al. (2004) trial used standardised criteria to measure tumour response. This study found a statistically significant increase in tumour response rates in patients treated with SIR-Spheres and systemic chemotherapy compared to those treated with systemic chemotherapy alone (van Hazel et al. 2004).

Effectiveness of SIR-Spheres for the treatment of hepatocellular carcinoma

Two case series of fair quality were identified for inclusion in the evaluation of the effectiveness of SIR-Spheres in HCC. Both case series reported partial or complete tumour response in up to 50 per cent of patients, demonstrating that SIR-Spheres have anti-tumour activity. This provides weak evidence for the effectiveness of SIR-Spheres in patients with non-resectable, non-ablatable HCC. Without comparative studies, however, it is not possible to draw any conclusions about the effectiveness of SIR-Spheres compared to other existing treatments in patients with HCC.

Cost-effectiveness

Cost-effectiveness of SIR-Spheres for treatment of liver metastases of colorectal cancer

A trial-based economic model supplied by the applicant and an exploratory economic evaluation were used to evaluate the cost-effectiveness of SIR-Spheres and systemic chemotherapy in patients with CLM. The trial-based economic model is based on the van Hazel et al. (2004) trial, which compared SIR-Spheres and 5-fluorouracil plus leucovorin systemic chemotherapy (5-FU/LV) to 5-FU/LV systemic chemotherapy alone. This economic model showed that the addition of SIR-Spheres to 5-FU/LV results in an incremental cost per life-year gained of $21 524 compared to 5-FU/LV alone. Sensitivity analyses show that this cost per life-year gained may range from $12 270 to $88 119; the wide range indicates that the incremental cost-effectiveness ratio is particularly sensitive to changes in survival estimates.

As the van Hazel et al. (2004) trial used a systemic chemotherapy regimen that is no longer considered current practice, an economic model comparing SIR-Spheres and current systemic regimens (FOLFOX6 and FOLFIRI; see Glossary) to current chemotherapy regimens alone was developed. Assuming 3 different scenarios for the magnitude of survival benefits, two alternative follow-up regimens associated with adding SIR-Spheres to current chemotherapy regimens and two different schedules of chemotherapy cycles (10 and 20 cycles), the cost per life-year gained ranged from $8009 for the 'best-case scenario' (incremental survival benefit of 1.65 years with less intensive follow-up and 10 cycles of FOLFOX/FOLFIRI) to $133 653 for the 'worst-case scenario' (incremental survival benefit of 0.3 years with more intensive follow-up and 20 cycles of FOLFOX/FOLFIRI) when compared to the current chemotherapy regimens alone.

These estimates are based on the assumption that SIR-Spheres will be used in the same manner with current chemotherapy regimens as they were used with 5-FU/LV in the van Hazel et al. (2004) trial. Due to the lack of trial data about the effectiveness of SIR-Spheres in combination with current chemotherapy regimens, the results of the exploratory economic evaluation should be viewed as an exploration of the possible costs and benefits associated with the use of SIR-Spheres alongside current chemotherapy regimens.

Cost-effectiveness of SIR-Spheres for the treatment of hepatocellular carcinoma

As the effectiveness of SIR-Spheres as a treatment for patients with HCC has not been established, cost-effectiveness could not be established, and an economic evaluation was not conducted.

Recommendations

1st indication

MSAC recommends that on the strength of evidence pertaining to the treatment of patients with hepatic metastases secondary to colorectal cancer which are not suitable for resection or ablation, interim public funding should be supported for first line treatment by administration of SIR-Spheres in combination with systemic chemotherapy using 5FU and leucovorin, with the collection of survival data. This data should be reported to MSAC within three years.

- The Minister for Health and Ageing endorsed this recommendation on 28 November 2005

2nd indication

As there is currently insufficient evidence pertaining to the treatment of non-resectable, non-ablatable hepatocellular carcinoma with SIR-Spheres, MSAC recommends that public funding should not be supported at this time.

- The Minister for Health and Ageing endorsed this recommendation on 28 November 2005

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of Selective Internal Radiation Therapy (SIRT) using SIR-Spheres, a therapeutic device for the treatment of hepatic metastases secondary to colorectal cancer (CRC) and hepatocellular carcinomas (HCC) that are not amenable to surgery or radiofrequency ablation. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are presented in Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine, general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of the current evidence for SIRT using SIR-Spheres for two indications—firstly, for the treatment of non-resectable, non-ablatable hepatic metastases secondary to CRC in combination with hepatic arterial chemotherapy or systemic chemotherapy, and secondly, for the treatment of non-resectable, non-ablatable HCC.

Background

Selective internal radiation therapy

This evaluation was undertaken in response to an application from Sirtex Medical Ltd for the listing of Selective Internal Radiotherapy Therapy (SIRT) using SIR-Spheres under the Australian Medicare Benefits Scheme (MBS). It updates the previous MSAC assessment report, *Selective Internal Radiation Therapy for Hepatic Metastases using SIR-Spheres* (MSAC application 1034, 2002). For the purposes of this review, the term SIR-Spheres will be used to describe the technology, yttrium-90 microspheres and SIRT.

The procedure

The following information comes from the *Australian SIR-Spheres Users Manual* (Sirtex Medical Ltd. 2000a; Sirtex Medical Ltd. 2000b). SIR-Spheres are intended for implantation into malignant liver tumours for the purpose of selectively delivering high doses of ionising radiation to the tumour. They are beta-emitting yttrium-90 microspheres with a diameter of between 20 and 40 μm. Yttrium-90 (^{90}Y) is a high-energy pure beta-emitting isotope with no primary gamma emission.

SIR-Spheres are injected into the hepatic artery for delivery to the liver. This requires catheterisation of the hepatic artery via either a trans-femoral catheter or a permanently implanted hepatic artery port with a catheter.

Following embolisation into the hepatic artery by catheter, SIR-Spheres become concentrated in the microvasculature of liver cancer, where they have a local radiotherapeutic effect. The ^{90}Y delivers 94% of the radiation dose within 11 days; the inert resin microspheres remain implanted in tissue. As tumours within the liver derive their blood supply almost exclusively from the hepatic artery, the SIR-Spheres are preferentially delivered in greater amounts to the tumour rather than via the normal liver parenchyma, which is supplied by both the hepatic artery and the portal vein. Some limited concurrent damage to healthy tissue is caused by radiation that escapes tumour boundaries and from SIR-Spheres that fail to become embedded in tumours.

In about 3 per cent of patients with liver tumours there will be significant arteriovenous shunts in the tumour, which will mean that more than 10 per cent of the SIR-Spheres injected into the hepatic artery will pass through the liver and lodge in the lungs. As this may cause radiation damage to the lungs, a nuclear medicine breakthrough scan must be performed in all patients to assess this possibility. A standard dose of technetium-99-labelled macroaggregated albumin (MAA) is injected either into the surgically implanted port or via the hepatic artery catheter that is used to perform the pretreatment hepatic angiogram. The patient is then placed under a gamma camera, which delineates the liver and lungs. The ratio of MAA particles that pass through the liver and lodge in the lungs can then be calculated. The percentage of MAA that has escaped through the liver and lodged in the lungs can then be expressed as a 'lung/liver ratio'. Normally this is less than 10 per cent. If the lung/liver ratio is more than 10 per cent, then the amount of SIR-Spheres delivered to the patient must be reduced, according to a standard protocol.

Microspheres

There are two commercial forms of ^{90}Y microspheres available—SIR-Spheres (Sirtex Medical Ltd) and TheraSpheres (Theragenics, Atlanta, GA, USA). Both products use the same radioisotope (^{90}Y) and have the same target dose (100 Gy). However, they differ in microsphere size profile, base material and the size of commercially available doses. TheraSpheres are embedded in glass, whereas SIR-Spheres use resin. The US Food and Drug Administration (FDA) granted premarket approval for SIR-Spheres to treat unresectable hepatic metastases from CRC, whereas TheraSpheres were approved to treat unresectable HCC under the humanitarian device exemption. The use of TheraSpheres is not considered in this report.

Intended purpose

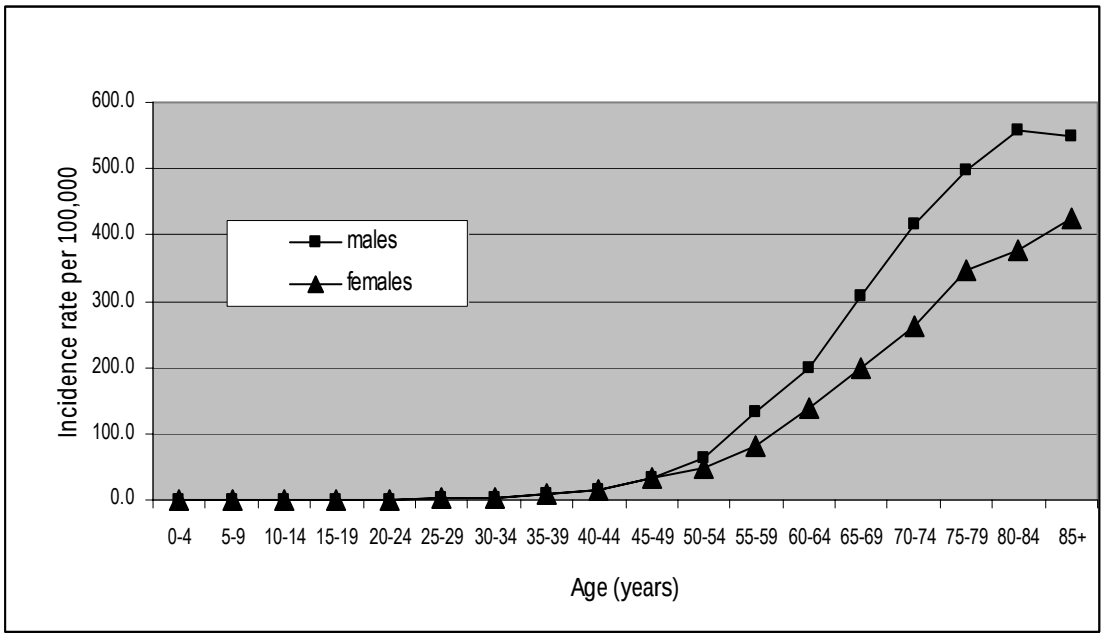
SIR-Spheres are used to treat patients with hepatic metastases secondary to CRC (CLM) in the absence of extrahepatic metastases, when the hepatic metastases are not amenable to surgery or radiofrequency ablation. They may be used in combination with systemic chemotherapy or hepatic arterial chemotherapy (HAC). SIR-Spheres are also used to treat primary non-resectable, non-ablatable HCC; however, this indication is not as common as CLM in Australia.

Clinical need / burden of disease

Colorectal metastases of the liver

Colorectal cancer is the most common cancer after non-melanomatous skin cancer and the third most common cause of cancer death reported to Australian cancer registries. In 2001, there were 12 844 cases of CRC reported and 4 754 deaths, accounting for 14.5 per cent of all new cases of cancer and 13.1 per cent of cancer deaths (excluding non-melanomatous skin cancer) (AIHW & AACR 2004). In 2001, premature death from CRC was responsible for an estimated 29 768 person-years of life lost before the age of 75, making it second only to lung cancer for this measure of disease burden (AIHW & AACR 2004).The incidence rates of CRC have increased since 1990 by an average of 0.4 per cent in males and 0.1 per cent in females per year, but mortality rates have fallen steadily by 0.9 per cent per year in males and 1.4 per cent in females over the previous decade (AIHW & AACR 2004).Figure 1 shows the incidence rates for colorectal cancer by age and sex for 2001.

Figure 1 Age-specific incidence rates for colorectal cancer in Australia, by sex, 2001



Source: Cancer in Australia 2001 (AIHW & AACR 2004).

There are a number of primary tumours, such as breast cancer, bronchogenic carcinoma and malignant melanoma, that frequently develop liver metastases; however, the incidence of spread to the liver is particularly high in the case of CRC (Conte et al. 1999). Approximately 50 per cent of patients with CRC will develop liver metastases within 5 years and 20 per cent of patients will already have liver metastases at the time of primary diagnosis (COSA & CAN 1999). Liver metastases tend to develop very quickly. If untreated, liver metastases from CRC show a very poor prognosis, with a median survival of 19 to 21 months and no patients surviving 5 years (Liu et al. 2003). It has been estimated that only 25 per cent of patients with CLM are candidates for liver resection (Liu et al. 2003). Resection of CLM improves long-term survival: up to 58 per cent of patients with 5-year survival have been reported in specialised centres (Abdalla et al. 2004; Choti et al. 2002).

Australia's age-standardised incidence of CRC is 50 per 100 000 population, which is high compared with the average of 37 per 100 000 in other developed countries (AIHW & AACR 2004). Australia's male and female mortality rates for CRC are also high by world standards, being higher than those of Canada, the USA and the UK (AIHW & AACR 2004). Known predisposing factors include a diet high in calories and rich in animal fats, reduced physical activity and a family history of the disease (AIHW & AACR 2004).

Hepatocellular carcinoma

There are two main types of primary malignant liver cancer: HCC, the most common primary liver cancer, and cholangiocarcinoma. HCC arises from hepatocytes, the major cell type of the liver, whereas cholangiocarcinoma arises in the cells lining the bile duct of the liver. The three major risk factors for development of HCC are alcoholic liver disease, chronic hepatitis B (HBV) infection and chronic hepatitis C (HCV) infection. In

2001, there were 853 new cases of primary liver cancer and 777 deaths (AIHW & AACR 2004), reflecting the high fatality rate of this disease. These figures include all primary cancers of the liver and intrahepatic bile ducts (International Classification of Diseases, 10th version, Australian Modification [ICD-10-AM] C 22) but, as non-HCC causes of primary liver cancer are rare, they can be used to approximate current HCC incidence and mortality rates in Australia. The incidence rate of HCC in Australia has been steadily increasing over the past two decades and it is thought that this can be partially explained by the increase in the prevalence of HBV and HCV (Law et al 2000). Current estimates suggest that there are more than 242 000 Australians who are infected with HCV, and that another 14 499 are infected each year (National Centre in HIV Epidemiology and Clinical Research 2004). Therefore, it can be expected that the incidence rates of HCC will continue to rise in the future.

Patient prognosis is influenced by the stage of the tumour, its histological pattern and coexistent cirrhosis (Balis & Lauwers 2004). Symptoms range from dull abdominal pain to the rapid development of jaundice, ascites, weight-loss and fever (Badvie 2000). Death is most commonly due to gastrointestinal haemorrhage, hepatic failure or metastatic disease (Badvie 2000).

Untreated patients rarely live longer than 3 to 6 months after the onset of symptoms, but this varies with stage of disease (Badvie 2000). Resected patients have a 5-year survival rate of around 30 per cent, and tumour size is suggested to represent a significant determinant of survival (Badvie 2000).

HCC recurrence has been reported as varying between 20 and 70 per cent (Badvie 2000). Five-year survival rates for transplantation are similar to resection, in the range of 30 per cent, although transplantation achieves a better recurrence-free survival (Badvie 2000). However, as transplantation is suitable only for the small number of patients with small HCC (tumour size < 5 cm), and only 15 to 30 per cent of patients are potentially resectable, such therapies are not available to most HCC patients (Gennari et al. 1995).

The extent of HCC and the degree of liver impairment is recorded using various staging classification systems. There is no agreement on the best staging system worldwide (Llovet & Beaugrand 2003). The most common systems used to stage HCC in clinical trials include the TNM (tumour, node, metastasis) system for liver cancer, the Okuda classification system for HCC and the Barcelona Clinic Liver Cancer system. The most commonly used system for classifying liver function in cirrhotic patients with HCC is the Child–Pugh system. The TNM, Okuda and Child–Pugh systems are described in Appendix I.

Health service usage

In Australia in 2002–2003, there were 5220 separations for the treatment of hepatic metastases (ICD-10-AM code C78.7) (AIHW 2004). This figure indicates all treatment episodes and thus does not accurately reflect patient numbers, because some patients may have received several treatment episodes during this period. It also includes patients with hepatic metastases secondary to non-colorectal primary cancers. The number of patients with hepatic metastases from CRC would therefore be only a proportion of this figure. In 2003–2003, there were 1314 separations for the treatment of primary liver cancer (ICD-10-AM code C22, predominantly HCC) (AIHW 2004).

Australian hospital data for ^{90}Y use (ICD10-AM 16009-00) is not available by CLM or HCC indications, and thus it is not possible to specify the number of SIR-Spheres procedures performed annually for these indications. Similarly, numbers on usage of other treatments currently used for the treatment of CLM and HCC, such as chemotherapy, transarterial chemoembolisation (TACE) and ^{131}I-lipiodol, cannot be estimated.

Existing procedures for the treatment of colorectal liver metastases

The existing procedures for the treatment of CLM include surgical resection, ablation (radiofrequency ablation, cryotherapy and laser photocoagulation), systemic chemotherapy and HAC. Where possible, surgical resection or ablation are the treatments of choice, as outlined briefly below. The patient group of interest in this report includes those patients with CLM who are not eligible for resection or ablation. The treatments for these patients include systemic chemotherapy and HAC, which are outlined in more detail in the following pages.

Surgical resection

The NHMRC Clinical Practice Guidelines state that CLM should be considered for resection in patients with up to four hepatic metastatic lesions that can safely be removed with an adequate margin, and with no evidence of extrahepatic disease (COSA & CAN 1999).

While early attempts at liver resection had high rates of morbidity and mortality, the mortality of liver resection in non-cirrhotic patients is now considerably less than 5 per cent in most major units (COSA & CAN 1999).

Since 1995, results from RCTs have become available that provide evidence of the benefits of resection of hepatic colorectal metastases. One of these trials reports 40 per cent survival at 5 years after complete resection of hepatic metastases, and tumour-free survival rates of 60 and 100 per cent in patients surviving 2 and 7 years, respectively (Vauthey et al. 2004).

More recently, case series have shown higher long-term survival following liver resection, with up to 58 per cent of patients surviving 5 years in specialised centres (Abdalla et al. 2004; Choti et al. 2002). In one of these studies, 10-year survival was 26 per cent (Choti et al. 2002).

Radiofrequency ablation

Radiofrequency ablation (RFA) is a recently developed technique for the local ablation of HCC or metastatic liver tumours in patients who are not suitable for curative surgical resection due to the number or location of tumour lesions, the presence of extrahepatic disease or poor liver function (MSAC 2003). An RFA needle is inserted into the tumour under radiographic guidance, and radiofrequency waves are used to generate heat around the device, which results in thermal coagulation and necrosis of the surrounding tissue (Vauthey et al. 2004; Garcea et al. 2003). RFA can be applied percutaneously (usually by

radiologists), laparoscopically or intraoperatively. In Australia, RFA is reimbursed under the MBS for the percutaneous treatment of non-resectable HCC (MSAC 2003).

Clinical data on the effectiveness of RFA are scarce, and effectiveness has been assessed mainly in case series with short follow-up times. These series indicate superiority in safety and tumour eradication when compared to percutaneous ethanol injection (PEI) and cryotherapy (Garcea et al. 2003). A recent prospective series of laparoscopic RFA has reported a median survival of 28.9 months in patients with CLM (Berber et al. 2005). The complication rate following RFA has been reported at 3.3 per cent (Garcea et al 2003). Common minor complications include abdominal discomfort and fever. More serious complications include liver abscess, which is potentially fatal, and adverse events related to thermal injury of adjacent tissues such as colon, bile ducts and skin (Garcea et al. 2003).

Cryotherapy

Cryotherapy is another local ablative technique used to treat primary and metastatic liver tumours in patients who are not eligible for surgical resection. A cooled insulated probe is inserted into the tumour under radiographic guidance. The aim is to destroy the tumour tissue by a process of freezing and thawing without damaging the normal liver parenchyma (Vauthey et al. 2004). A complication rate of 27 per cent and a mortality rate of up to 4 per cent have been reported (Garcea et al. 2003). Major complications include hypothermia, biliary fistula, infection and coagulopathy (Vauthey et al. 2004).

The comparison of cryotherapy to surgical resection is limited by the fact that few comparative studies have long-term survival data. There has been one RCT of 123 patients with liver metastases which compared the use of variations of the technique (cryoextirpation, cryoresection and cryodestruction) with liver resection (Korpan 1997). The trial reported a 5-year survival of 44 per cent in the treatment group (cryoextirpation, cryoresection and cryodestruction) compared to a 5-year survival of 36 per cent in the control group (standard surgical resection). The patients in this trial, however, were eligible for surgical resection, and thus the trial results are unlikely to be applicable to the patient population of interest in this report.

In addition to that RCT, many case series have reported five year survivors (Morris et al. 1996; Onik et al. 1991; Onik et al. 1993; Shafir et al. 1996; Weaver et al. 1995; Yeh et al. 1997). In a recent review, Garcea et al. (2003) reported a median survival of between 22 and 42 months, and 5-year survival rates of between 20 and 30 per cent following cryotherapy (Garcea et al. 2003).

Laser photocoagulation

Laser photocoagulation uses the local delivery of laser light under radiographic control to generate heat for tumour ablation (Garcea et al. 2003). The NHMRC Clinical Practice Guidelines for CRC state that while percutaneous laser photocoagulation may be an easier method than cryotherapy, it has, to date, had quite limited value due to the small volume of tissue that can be destroyed (COSA & CAN 1999). Clinical data on both tumour marker normalisation and survival are very limited. A recent review of long-term survival data identified two case series reporting a 3-year survival of 42 per cent and a median

survival of 16 months, respectively, after laser photocoagulation in patients with CLM (Garcea et al. 2003).

Systemic chemotherapy

Systemic chemotherapy has been given to patients with advanced CRC with the aim of relieving tumour-related symptoms, improving overall quality of life and prolonging survival. Although there are few studies comparing systemic chemotherapy with supportive care alone in patients with CRC, those studies that have been performed show a survival benefit (COSA & ACN 1999). The standard systemic chemotherapy protocols currently used for the treatment of CLM have changed since the previous MSAC report (MSAC 2002). At that time, the standard systemic treatment for advanced CRC was 5-fluorouracil plus leucovorin (5-FU/LV) (COSA & CAN 1999). Recent large-scale RCTs have demonstrated the benefit of additional chemotherapy agents to this regimen, particularly oxaliplatin (de Gramont et al. 2000; Goldberg et al. 2004; Tournigand et al. 2004) and irinotecan (Saltz et al. 2000; Douillard et al. 2000). There are different combinations of these agents with 5-FU and leucovorin—for irinotecan, these are the FOLFIRI, AIO and IFL (or Saltz) regimens; for oxaliplatin, the FOLFOX4 and FOLFOX6 regimens are used (see Appendix G for detailed description of regimens). These combinations are now considered standard for the treatment of advanced CRC (NCI 2005).

Current standard first-line chemotherapy regimens for advanced CRC in Australia are (Advisory Panel March 2005):

- oxaliplatin plus 5-FU and leucovorin administered as FOLFOX6 regimen (see Appendix G)
- irinotecan plus 5-FU and leucovorin administered as FOLFIRI regimen (see Appendix G)

Capecitabine is also used as a single agent in elderly patients or in patients with comorbidities, on account of its favourable side-effect profile (Van Cutsem et al. 2004).

Safety

The side-effects of chemotherapy depend upon the drug, the dosage and the administration schedule. Two trials have raised concerns about the toxicity of the newer systemic combination regimens (Delaunoit et al. 2004; Rothenberg et al. 2001). A randomised multicentre trial to evaluate various combinations of 5-FU/LV administered with either irinotecan or oxaliplatin showed unexpectedly high levels of toxicity and mortality in two treatment arms—the arm receiving bolus 5-FU/LV plus oxaliplatin and the arm receiving sequential 5-FU/LV plus irinotecan (IFL or Saltz regimen) (Delaunoit et al. 2004). An independent panel examining the unexpected high levels of mortality in this and a second trial found that the 60-day mortality rates were especially high in the study groups receiving 5-FU/LV plus irinotecan, and that the majority of deaths were attributable to either multiple gastrointestinal toxicities (diarrhoea, nausea, vomiting, anorexia and abdominal cramping) or sudden unexpected thromboembolic events (Rothenberg et al. 2001).

It has been suggested that the toxicities observed with the IFL regimen in these studies are associated with the bolus administration of 5-FU, independent of irinotecan (NCI

2005). Following these studies, it has been recommended to use oxaliplatin and irinotecan with regimens using 5-FU/LV infusions rather than daily bolus 5-FU/LV treatments to minimise toxicity-related symptoms (Delaunoit et al. 2004).

FOLFOX6 and FOLFIRI, the currently used regimens in Australia, follow this recommendation and administer the chemotherapeutic agents via ambulatory pump and infusion (except for the loading dose of 5-FU) (NCI 2005).

Despite the recommendations to minimise toxicity, specific side-effects associated with the new chemotherapeutic agents oxaliplatin and irinotecan remain. Oxaliplatin can induce a neurotoxicity characterised by numbness and tingling of the hands and feet and an increased sensitivity to cold temperatures, which manifests itself as painful spasms of the throat (Gill et al. 2003; Maindrault-Goebel et al. 2004). The common side-effects of 5-FU, leucovorin and irinotecan are diarrhoea, mucositis and low blood counts. These events are more severe with irinotecan (Gill et al. 2003).

In a crossover trial comparing FOLFIRI with FOLFOX6, Tournigand et al. (2004) observed more severe or life-threatening toxicities (Grades 3 and 4—refer to http://ctep.cancer.gov/reporting/ctc.html for more details) in patients treated with FOLFOX6 (74%) than with FOLFIRI (53%). However, they reported that the frequency of serious adverse events was higher in patients treated with FOLFIRI (14% vs 5%). FOLFOX6 is now generally preferred over FOLFIRI (Advisory Panel March 2005).

Effectiveness

The addition of the newer agents oxaliplatin and irinotecan have shown increased survival times compared to the older standard regimens of 5-FU/LV. A three-arm RCT comparing 5-FU/LV plus irinotecan to 5-FU/LV and irinotecan alone in 683 patients with metastatic liver disease reported significantly longer progression-free survival (median 7.0 vs 4.3 months; $P = 0.004$), a higher rate of confirmed response (39% vs 21%, $P < 0.001$), and longer overall survival (median 14.8 vs 12.6 months; $P = 0.04$) for the three-drug combination of 5-FU/LV plus irinotecan than with 5-FU/LV alone. Grade 3 (severe) toxicities were also more common with the three-drug combination. However, Grade 4 (life-threatening) adverse events and quality of life scores were similar in the two groups (<8%) (Saltz et al. 2000).

Two trials comparing 5-FU/LV with the addition of oxaliplatin (FOLFOX4 regimen) with 5-FU/LV alone reported significantly improved response rates and median progression-free survival with FOLFOX4. However, the observed increases in median survival from 14.7 to 16.2 months (de Gramont et al. 2000) and from 19.4 to 19.9 months (Giachetti et al. 2000) did not reach statistical significance. More recently, a three-arm trial comparing the FOLFOX4 regimen with 5-FU/LV and irinotecan (IFL) and a combination of irinotecan and oxaliplatin (IROX) reported a statistically significant survival advantage with FOLFOX4 over the other two regimens (Goldberg et al. 2004).

Recent efforts to simplify 5-FU/LV administration have resulted in new oxaliplatin and irinotecan regimens, FOLFOX6 and FOLFIRI, which have been compared in a crossover trial conducted by Tournigand et al. (2004). In this trial, the regimens showed similar response rates (56% for FOLFIRI and 54% for FOLFOX6), median time to first progression (8.5 months vs 8 months) and overall median survival (21.5 vs 20.6 months) (Tournigand et al. 2004). On the basis of these results, these two regimens can now be considered standard treatment in Australia (Advisory Panel March 2005).

Hepatic arterial chemotherapy (HAC)

Hepatic arterial chemotherapy (HAC) involves the administration of chemotherapy agents directly into the liver via the hepatic artery. Established hepatic metastases derive their blood supply mainly from the hepatic artery, whereas blood is supplied to normal hepatic tissue mainly via the portal vein. This allows the delivery of a higher drug concentration to the liver than can be achieved by intravenous chemotherapy (COSA & CAN 1999). In addition, this approach allows larger doses of agents that are subject to extensive first-pass metabolism in the liver (such as floxuridine and fluoropyrimidines such as 5-FU) without increasing systemic concentrations and subsequent toxicity (Elias et al. 2004; NHMRC 1999).

The main disadvantage of HAC is that it has limited ability to effectively treat extrahepatic disease, particularly if agents with high first-pass liver metabolism are used. It also requires implantation of a catheter into the hepatic artery and connection to a port, which is cumbersome for the patient and precludes its use in patients who are not well enough to undergo a laparotomy for catheter insertion (COSA & CAN 1999).

Three methods of delivery may be used: (i) via an angiographically placed catheter into the hepatic artery; (ii) via surgically implanted infusion ports with an external pump; and (iii) via surgically implanted infusion pumps (Vauthey et al. 1996).

Safety

Different safety issues are associated with HAC, depending on the approach used to deliver the chemotherapeutic agents.

(i) Hepatic artery catheterisation is a minimally invasive technique compared to the laparotomy required for port and pump implantation. However, complications associated with repeated arterial puncture, and poor patient acceptance due to frequent catheter migration and the need for hospitalisation and confinement to bed, has limited its use (Vauthey et al. 1996).

(ii) Arterial ports with an external infusion pump require a laparotomy (and attendant risks) for arterial cannulation and the placement of the infusion pump. The main complication with an external port is the 30 to 42 per cent incidence of catheter or hepatic artery thrombosis, which may necessitate stopping treatment in up to 20 per cent of patients (Vauthey et al. 1996), although at least one other study has reported rates as low as 6 per cent (Barnett & Malafa 2001).

(iii) The surgical implantation of the infusion pump is a newer technique that has demonstrated improved hepatic artery patency compared to the use of an arterial port and external pump (Vauthey et al. 1996). Complications include operative mortality (<1%), mechanical problems relating to the catheter (5%), vascular problems such as catheter–artery thrombosis or aneurysm formation (5%), and an 8 per cent rate of pump-related problems such as pocket haematoma, seroma or infection. The complication rate has been shown to be associated with the prior experience of the surgeon in the technique (Vauthey et al. 1996)

The NHMRC Clinical Practice Guidelines recommend that implantation of a port or infusion pump include a routine cholecystectomy to avoid chemical cholecystitis. Particular attention should be paid to the ligation of hepatic artery branches which perfuse the

stomach, common bile duct and pancreas, to prevent complications such as peptic ulceration resulting from inadvertent perfusion of the stomach with chemotherapeutic agents (COSA & ACN 1999).

In addition to the technical complications described above, HAC is also associated with toxicity of the chemotherapy agents. The NHMRC Clinical Practice Guidelines for CRC report that the toxicities from intrahepatic chemotherapy may include sclerosing cholangitis (10%), which may be fatal in some cases, chemical gastritis or cholecystitis (10%), peptic ulceration (5%) or diarrhoea (5%) (COSA & ACN 1999). Regimens including 5-FU are specifically associated with an increased risk of gastrointestinal symptoms and bone marrow toxicity (Barnett & Malafa 2001).

Effectiveness

A meta-analysis of six of the seven randomised controlled trials published between 1988 and 1993, which compared HAC with intravenous chemotherapy, has shown a significantly higher tumour response rate in favour of HAC (41% vs 14%). The effect of HAC on survival is less clear—when the data of studies comparing HAC with intravenous chemotherapy were pooled, no significant survival benefit was observed (Meta-analysis Group in Cancer 1996). Many of these studies, although RCTs, had a sample size that was insufficient to detect any significant survival advantage.

Two trials have compared HAC with a control group managed with supportive care that could include intravenous chemotherapy. Both indicated a significant survival benefit from HAC (Allen-Mersh et al. 1994; Rougier et al. 1997). However, only 20 per cent (Allen-Mersh et al. 1994) and 50 per cent (Rougier et al. 1997) of control group patients received any chemotherapy.

Conflicting results have further been reported in two recent trials that compared fluoropyrimidine-based HAC with systemic chemotherapy. Whereas a large European trial (MRC/EORTC trial) did not observe any survival benefit of a 5-FU/LV regimen given as HAC compared with the same regimen given as systemic chemotherapy, a smaller American study demonstrated significant benefits using a regimen of floxuridine, LV and dexamethasone (Chan & Kerr 2003). The relative benefits of systemic versus hepatic chemotherapy in current practice are difficult to assess, as trial data comparing HAC with the newer systemic chemotherapy regimens are limited.

New regimens have been designed that combine intra-arterial administration of chemotherapeutic agents with systemic chemotherapy, although no published data are available to date (Elias et al. 2004).

Existing procedures for the treatment of hepatocellular carcinoma

The existing procedures for the treatment of HCC include surgical resection, liver transplantation, systemic chemotherapy, HAC, ablative therapies, hormonal therapy, transcatheter arterial chemoembolisation and ^{131}I-lipiodol. Each of these treatments is outlined below. As previously reported, the patient group of interest in this report is those patients who are not eligible for resection or ablation.

Surgical resection

Surgery, either resection or liver transplantation, offers the only proven potentially curative procedure for HCC (Ryder 2003). Surgical resection has been associated with a 5-year survival of 35 to 50 per cent (Choti 2002). In cirrhotic patients, prognosis is less favourable, with 5-year survival rates of 25 to 30 per cent (Badvie 2000). The size of the tumour is a significant factor determining survival, with 5-year survival rates of up to 85.3 per cent for tumours ≤ 3 cm in one large case series (Badvie 2000). Only patients with a single tumour ≤ 5 cm or up to 3 lesions ≤ 3 cm should be considered for resection according to guidelines developed by the British Society of Gastroenterology (Ryder 2003). Due to the high proportion of cases with inoperable tumours, extrahepatic spread or cirrhosis, fewer than 20 per cent of HCC patients are suitable for surgical resection (Badvie 2000). Recurrence rates of 50 to 60 per cent at 5 years after resection have been reported, with the majority of recurrence being intrahepatic (Ryder 2003).

Liver transplantation

Liver transplantation is the treatment of choice for resectable HCC, but few patients receive transplants due to the limited availability of donor organs. In selected cases, transplantation has been shown to have similar or superior survival rates compared with partial hepatic resection (Choti 2002). Patients with a single tumour ≤ 5 cm or up to 3 lesions ≤ 3 cm are suitable for transplantation (Ryder 2003). Selecting patients according to these guidelines, a 4-year survival rate of 75 per cent has been reported in patients with cirrhosis and unresectable tumours after total hepatectomy and transplantation (Choti 2002). Furthermore, transplantation has been shown to achieve a better recurrence-free survival than resection (Badvie 2000).

Systemic chemotherapy

Systemic chemotherapy has not demonstrated any survival benefit and has a limited role in the treatment of HCC. There is no proven advantage of single-agent or combination chemotherapy, and any agents used in HCC should be given in the context of clinical trials (Ryder 2003).

Hepatic arterial chemotherapy

HAC is most commonly used in conjunction with embolisation agents and is discussed below with transcatheter arterial chemoembolisation.

Ablative therapies

Ablative therapies suitable for HCC patients with inoperable disease include cryotherapy, laser photocoagulation and radiofrequency ablation. These techniques are described in the previous section. Controlled evidence of these therapies for the treatment of HCC is lacking, and therefore the role of these techniques in the treatment of HCC remains unclear (Choti 2002).

Percutaneous ethanol injection (PEI) is another ablative technique used in the treatment of HCC. It is administered by introducing a needle percutaneously into a liver tumour and slowly injecting absolute or 95 per cent ethanol into the lesion under radiographic guidance (Berry & Maddern 2000; Siperstein & Berber 2001). As the ethanol diffuses into the cells, it induces non-selective protein degradation and cellular dehydration, resulting in local areas of coagulation necrosis within and around the tumour (Berry & Maddern 2000).

Several large series of PEI have been reported, but controlled evidence comparing PEI with hepatic resection in HCC is lacking. A review of the current evidence has found an approximate 5-year survival of 30 per cent. As the effectiveness of PEI in inducing total tumour necrosis is largely dependent on tumour size, PEI has been used mainly in patients with tumours smaller than 3 cm. The effectiveness of PEI is also dependent on the severity of cirrhosis (Garcea et al. 2003).

Hormonal therapy

Hormonal agents, in particular tamoxifen, have been used in the treatment of HCC on the basis of observations that HCC tissues contain oestrogen and androgen receptors (Badvie 2000). A meta-analysis of tamoxifen studies in treating HCC has shown no antitumoral effect and no survival benefit (Llovet & Bruix 2003).

Transcatheter arterial chemoembolisation (TACE)

Transcatheter arterial chemoembolisation (TACE) is a combination of targeted chemotherapy and arterial embolisation, causing both ischaemic and chemotherapeutic effects on HCC (Rindani et al. 2002).

The procedure

The femoral artery is catheterised under local anaesthesia, and hepatic arteriography and superior mesenteric portovenography are performed before the procedure to define the size and location of tumour nodules. The arteries supplying the tumours are catheterised under the guidance of fluoroscopy, and the chemotherapeutic emulsion is generally injected first, followed by the embolisation agent, until a reduced flow is observed. The embolic material used is often gelatine foam powder or particles (Badvie 2000). The chemotherapeutic agents most commonly used are doxorubicin, mitomycin and cisplatin (Llovet & Beaugrand 2003). The intermittent occlusion of the hepatic artery by embolic material increases the contact time between drug and tumour and induces massive tumour necrosis by ischaemia (Badvie 2000).

TACE can be repeated every 2 to 3 months depending on the status of the patient (Dodd et al. 2000).The patients most suited to TACE are those with preserved liver

function and multinodular tumours without vascular invasion or extrahepatic spread (Llovet & Beaugrand 2003).

Safety

The side-effects of TACE are associated with the chemotherapy agent used and procedure complications associated with TACE, such as pain, fever and hepatic decompensation (Ryder 2003). Serious complications are estimated to occur in around 3 to 5 per cent of patients (Ryder 2003). Common side-effects following TACE include transient fever, abdominal pain and elevation of liver enzymes (Huo et al. 2003).

The three most frequent serious treatment complications are liver failure, sepsis (cholecystitis, liver abscess) and gastrointestinal bleeding (Camma et al. 2002). Liver failure occurs when there is ischaemic damage to the functioning liver tissue (Llovet & Beaugrand 2003).

Effectiveness

A scoping search (further described in the 'Approach to Assessment' section) identified two recently published systematic reviews that examined the use of TACE in patients with HCC (Llovet & Bruix 2003; Reidy & Schwartz 2004). These reviews identified seven RCTs that assessed the survival benefits of transcatheter arterial embolisation (TAE) or TACE compared to conservative management or suboptimal treatments for treating unresectable HCC. An overview of the seven included RCTs is provided in the following section—results of the data extraction process are presented in Appendix C. Three of the seven RCTs assessed embolisation alone (Lin et al. 1988; Bruix et al. 1998; Llovet et al. 2002), while four assessed chemoembolisation, one with doxorubicin (Pelletier et al. 1990) and three with cisplatin (Groupe d'étude 1995; Lo et al. 2002; Pelletier et al. 1998). Gelfoam was the embolisation agent used in all studies.

The underlying cause of liver disease varied across the studies. The majority of patients in four of the studies from Europe had HCV- or alcohol-related cirrhosis, whereas the two Asian studies included mainly patients with HBV-induced liver disease. Two of the most recently published trials (Lo et al. 2002; Pelletier et al. 1998) have demonstrated survival benefits favouring chemoembolisation. A systematic review by Llovet and Bruix (2003) included a meta-analysis of six of the seven RCTs that reported on 2-year survival and showed a significant improvement in the TACE group (503 patients) compared with the control group (OR 0.53, 95% CI 0.32–0.89; $P = 0.017$). When all seven trials were included, the 1-year survival rates showed an OR of 0.64 (95% CI, 0.41–1.01; $P = 0.051$) in favour of TACE. In particular, RCTs that selected patients with Child–Pugh A patients and Okuda stage I rather than patients with advanced stages of HCC reported a survival advantage for TACE (Llovet & Bruix 2003).

^{131}I–lipiodol

Lipiodol is a radio-opaque substance that is derived by iodination of poppy seed oil. It contains 37 to 39 per cent iodine by weight (Rindani et al. 2002). In 1983, it was reported that lipiodol was selectively retained in vascular hepatomas when injected directly into the hepatic artery (Rindani et al. 2002). This led to the development of a radiotherapy treatment for unresectable HCC in which the iodine was replaced with radioactive ^{131}I (Rindani et al. 2002). Studies have shown that ^{131}I-lipiodol is retained by HCC for several

weeks, whereas it is cleared from normal liver tissue within days. ^{131}I-lipiodol emits both β and γ rays, making it suitable for both therapeutic and imaging purposes (Rindani et al. 2002).

The procedure

This description of the ^{131}I-lipiodol procedure is based on information from the study by Rindani et al. (2002), who treated 12 patients with this technique at the Royal North Shore Hospital in Sydney. Patients are pretreated with Lugol's iodine to block the effect of ^{131}I ions on the thyroid gland. Patients undergo catheterisation of the hepatic artery, and a dose of approximately 2 GBq ^{131}I-lipiodol is administered. Following administration, patients are kept in a lead-lined single room for around 5–7 days until their radiation levels are acceptable. During hospitalisation, tolerance is estimated clinically and from liver function tests on day 1 and before discharge. In addition, a planar scintiscan of the liver and thorax are performed 24 hours after administration and before discharge. Repeat treatments are given depending on patient progress.

Safety

Reported side-effects of ^{131}I-lipiodol include fever, mild abdominal pain, nausea and radiation hepatitis (Keng & Sundram 2003). The limited safety data available indicate that ^{131}I-lipiodol is well tolerated with minimal side-effects.

Effectiveness

The evidence for the effectiveness of ^{131}I-lipiodol is limited by the lack of large-scale RCTs. A scoping search found two case series evaluating ^{131}I-lipiodol (Leung et al. 1994; Rindani et al. 2002) and one RCT comparing ^{131}I-lipiodol with TACE in a total of 129 patients (Raoul et al. 1997). In the RCT, survival rates at 1 year were 38.5 per cent for ^{131}I-lipiodol and 42.2 per cent for TACE. At 4 years, no patients in the TACE group survived, compared with 10.2 per cent in the ^{131}I-lipiodol group. These differences in survival between ^{131}I-lipiodol and TACE at 4 years were not statistically significant (Raoul et al. 1997).

Comparators

The choice of comparators for the purposes of this review was decided by identifying the current treatments and describing the current best conventional care for the CLM and HCC indications (MSAC guidelines). According to the expert opinion of the Advisory Panel, SIR-Spheres would not be used in patients eligible for resection or ablation, and thus these treatments were not considered as comparators.

For the CLM indication, both systemic chemotherapy and HAC have been identified as comparators. There is strong evidence for improved survival by using systemic chemotherapy for this indication (Tournigand et al. 2004). HAC is used less commonly, as evidence regarding its effectiveness conflicts (Meta-analysis Group in Cancer 1996; Allen-Mersh et al. 1994; Chan & Kerr 2003). In Australian clinical practice, it is likely that SIR-Spheres would supplement and not replace these therapies. It was the expert opinion of the Advisory Panel, however, that there would be instances when SIR-Spheres would be used as a standalone treatment, and thus this context was considered in the report.

For the HCC indication, TACE and ^{131}I-lipiodol were chosen as comparators, as the Advisory Panel stated that these are currently used in clinical practice as treatments for HCC, and their use is supported at least to some extent by existing evidence demonstrating their efficacy (Leung et al. 1994; Llovet et al. 2002; Llovet & Bruix 2003; Raoul et al. 1997; Rindani et al. 2002). Systemic chemotherapy for HCC was not considered to be a suitable comparator, as existing evidence has not established that it has any benefits in this patient group (Lau et al. 1998; Leung et al. 1994; Ryder 2003). Palliative care was not considered to be a comparator because it is used in patients who have untreatable HCC or in patients who choose to stop active treatment.

Therefore, based on the advice of the Advisory Panel, the following comparators were chosen for this review:

For metastatic colorectal cancer tumours (CLM)

- systemic chemotherapy
- hepatic arterial chemotherapy (HAC).

For hepatocellular carcinoma (HCC)

- transarterial chemoembolisation (TACE)
- ^{131}I-lipiodol.

Definition of study outcomes

The effect of treatment for CLM and HCC can be assessed by evaluating survival, disease progression, tumour response and quality of life outcomes. Tumour response can be assessed from changes in tumour area, tumour volume and tumour markers (including carcinoembryonic antigen [CEA] for liver tumours). Standard methods for assessing changes in tumour area, recorded as changes in cross-sectional diameters of lesions, are considered the conventional method for determining tumour response. Other (non-standard) methods use tumour volume and CEA (Advisory Panel, December 2004). Assessing tumour area is the method considered in the 'Response Evaluation Criteria in Solid Tumours' (RECIST), which are the current generally accepted criteria to objectively evaluate and document tumour response to treatment, developed by the European Organization for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) of the United States and the National Cancer Institute of Canada Clinical Trials Group (see Appendix H for further details).

Marketing status of the device

The device used for the delivery of SIRT using SIR-Spheres is listed with the Australian Therapeutic Goods Administration, with the listing number of AUST L 63369.

Current reimbursement arrangement

SIRT using SIR-Spheres is not currently reimbursed, and there is no MBS item number for this procedure.

Approach to assessment

The research questions

The evaluation team worked with members of the Advisory Panel to develop specific questions addressing the use of SIR-Spheres for the treatment of non-resectable, non-ablatable liver tumours. Two research questions were developed, one addressing the treatment of non-resectable, non-ablatable liver tumours secondary to CRC, the other addressing the treatment of non-resectable, non-ablatable HCC. These questions were formulated *a priori* from information from the Advisory Panel on current practice, the disease area and the purpose of the therapy. Flow charts (Appendix F) depicting the clinical pathways for treating non-resectable, non-ablatable liver tumours secondary to CRC and for the treatment of HCC were developed in conjunction with the Advisory Panel. These flow charts were used to define the role of SIR-Spheres in the treatment of non-resectable, non-ablatable liver tumours and the comparable treatment options for each condition.

Two review questions are covered in this report:

1st indication

What are the safety, effectiveness and cost-effectiveness of SIR-Spheres used alone or in addition to chemotherapy for treating non-resectable, non-ablatable hepatic metastases secondary to CRC compared with HAC treatment or systemic chemotherapy?

2nd indication

What are the safety, effectiveness and cost-effectiveness of SIR-Spheres for treating non-resectable, non-ablatable HCC compared with TACE or ^{131}I-lipiodol?

Review of literature

MSAC's recommendations are based primarily on the findings of a systematic literature review conducted by the NHMRC Clinical Trials Centre. The medical literature was searched to identify relevant studies and reviews published in the period between 1966 and January 2005. Searches were conducted via electronic databases, as listed in Table 1.

Table 1 Electronic databases searched in the scoping search

Database	Period covered
Medline	1966 – January 2005
EMBASE	1980 – January 2005
Premedline	As at 11 January 2005
Current Contents	11 January 2005 (previous 6 months)
The Cochrane Library	Issue 4, 2004

Search strategy

The search strategies were developed using the key elements of the clinical questions. The primary search strategy to identify studies on SIR-Spheres in patients with liver metastases secondary to CRC and HCC is shown in Tables 2, 3 and 4. This search was used to identify papers on SIR-Spheres in the various databases outlined in Table 1. A secondary scoping search was carried out to identify studies evaluating TACE and ^{131}I-lipiodol to enable an indirect comparison between these comparators and SIR-Spheres when used in HCC study populations only. In addition, the Advisory Panel advised on the most recent treatment regimens for systemic chemotherapy in colorectal patients with liver metastases so that a scoping search would retrieve the most relevant literature in this area.

Table 2 Medline and the Cochrane Library search strategy

Number	Search strategy
1	exp microspheres/
2	exp Yttrium radioisotopes/
3	microsphere$.mp.
4	SIRT.mp.
5	(SIR-Sphere$ or (SIR adj Sphere$)).mp.
6	(select$ adj3 intern$ adj3 (radiat$ or radiother$)).mp.
7	or/ 1–6
8	exp Liver Neoplasms/
9	exp Neoplasm Metastasis/
10	((liver or hepatic) adj3 (cancer or neoplasm)).mp.
11	((liver or hepatic) adj3 metasta$).mp.
12	or/8–11
13	7 and 12

Table 3 EMBASE search strategy

Number	Search history
1	exp Microsphere/
2	exp Yttrium/
3	exp Yttrium 90/
4	exp Radioisotope Therapy/
5	microsphere.mp.
6	SIRT.mp.
7	(SIR-Sphere$ or (SIR adj Sphere$)).mp.
8	(select$ adj3 intern$ adj3 (radiat$ or radiother$)).mp.
9	or/ 1–8
10	exp Liver Tumour/
11	exp Liver Metastasis/
12	((liver or hepatic) adj5 (cancer or neoplasm)).mp.
13	((liver or hepatic) adj3 metasta$).mp.
14	or/8–13
15	9 and 14

Table 4 Premedline and Current Contents search strategy

Number	Search history
1	microsphere.mp.
2	SIRT.mp.
3	(SIR-Sphere$ or (SIR adj Sphere$)).mp.
4	(select$ adj3 intern$ adj3 (radiat$ or radiother$)).mp.
5	or/ 1–4
6	((liver or hepatic) adj5 (cancer or neoplasm)).mp.
7	((liver or hepatic) adj3 metasta$).mp.
8	or/ 6–7
9	5 and 8

Reference lists of publications were also searched for additional relevant citations that may have been inadvertently missed in searches of major databases. In addition to the databases listed in Table 1, the websites of international health technology assessment (HTA) agencies listed in Table 5 were also searched. The applicant's submission was also reviewed to ensure that all relevant literature was included.

Table 5 Electronic databases and Heath Technology Assessment websites searched in this review

Organisation	Database/website
NHS Centre for reviews and dissemination databases (UK)	
Economic Evaluation Database (EED)	www.york.ac.uk/inst/crd/
Database of Abstracts of Reviews of Effectiveness (DARE)	
Heath Technology Assessment (HTA)	
International Network of Agencies for Health Technology Assessment (INAHTA)	www.inahta.org
British Columbia Office of Health Technology Assessment (Canada)	www.chspr.ubc.ca
Swedish Council on Technology Assessment in Healthcare (Sweden)	www.sbu.se
Oregon Health Resources Commission (US)	www.ohppr.state.or.us/index.html
Minnesota Department of Health (US)	www.health.state.mn.us/htac/index.htm
Canadian Coordinating Office for Health Technology Assessment (Canada)	www.ccohta.ca
Alberta Heritage Foundation for Medical Research (Canada)	www.ahfmr.ca
Veteran's Affairs Research and Development Technology Assessment Program (US)	www.va.gov/resdev
National Library of Medicine Health Service / Technology Assessment text (US)	www.ncbi.nlm.nih.gov
Office of Health Technology Assessment Archive (US)	www.wws.princeton.edu/~ota
Institute for Clinical Evaluative Science (Canada)	www.ices.on.ca
German Institute for Medical Documentation and Information (DIMDI) (Germany)	www.dimdi.de
National Information Centre of Health Services Research and Health Care Technology (US)	www.nlm.nih.gov/nichsr/nichsr
Finnish Office for Health Technology Assessment (FinOHTA) (Finland)	www.stakes.fi/finohta/linkit/
Institute of Medical Technology Assessment (Netherlands)	www.bmg.eur.nl/imta/
Agence nationale d'accreditation et d'évaluation en santé (France)	www.anaes.fr
Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) (Canada)	www.aetmis.gouv.qc.ca/en/index.php
Health Technology Board for Scotland (UK)	www.htbs.co.uk/home.asp?did = 6
National Coordinating Centre for HTA (NCCHTA) (UK)	www.hta.nhsweb.nhs.uk
Centre for Health Program Evaluation (Australia)	chpe.buseco.monash.edu.au

Search results

Existing reviews

The searches of the UK National Health Service (NHS) databases and HTA agency websites (Table 5) did not identify any systematic reviews or health technology reports meeting criteria for inclusion in this review.

Published literature

The search strategy retrieved a total of 574 non-duplicate citations. The numbers of non-duplicate citations retrieved from each database are presented in Table 6.

Table 6 Numbers of non-duplicate citations retrieved from each database for the primary SIR-Spheres search

	Medline	Premedline	Current Contents	Embase	Cochrane Library	Total
Number of citations	452	11	2	27	82	574

Eligibility criteria for SIR-Spheres studies

The 574 non-duplicate citations were evaluated independently by two reviewers to determine whether they met the eligibility criteria outlined in Table 7. There was agreement between reviewers in 565 of the 574 citations (98.4%). Discrepancies in the results of this screening process were resolved by discussion.

Table 7 Study exclusion criteria

1. Not a clinical study

   Reports excluded described animal, laboratory or scientific studies, editorials, letters, case reports and case series of fewer than 10 patients. Non-systematic narrative reviews and conference abstracts were also excluded.

2. Wrong patient group

   Studies had to include patients with non-resectable, non-ablatable hepatic metastases secondary to CRC or patients with non-resectable, non-ablatable HCC.

3. Wrong intervention

   Studies had to use SIR-Spheres as the intervention.

4. Wrong comparator

   Studies had to use HAC, systemic chemotherapy, TACE or ^{131}I-lipiodol as the comparator.

5. Wrong outcomes

   Studies had to report on at least one of the following:

   - survival
   - progression
   - tumour response
   - tumour markers
   - safety and toxicity
   - quality of life
   - costs

6. Not in English

   Only studies published in English were eligible for inclusion.

On the basis of these criteria, 566 citations were excluded from the review. The reasons for exclusion are listed in Table 8.

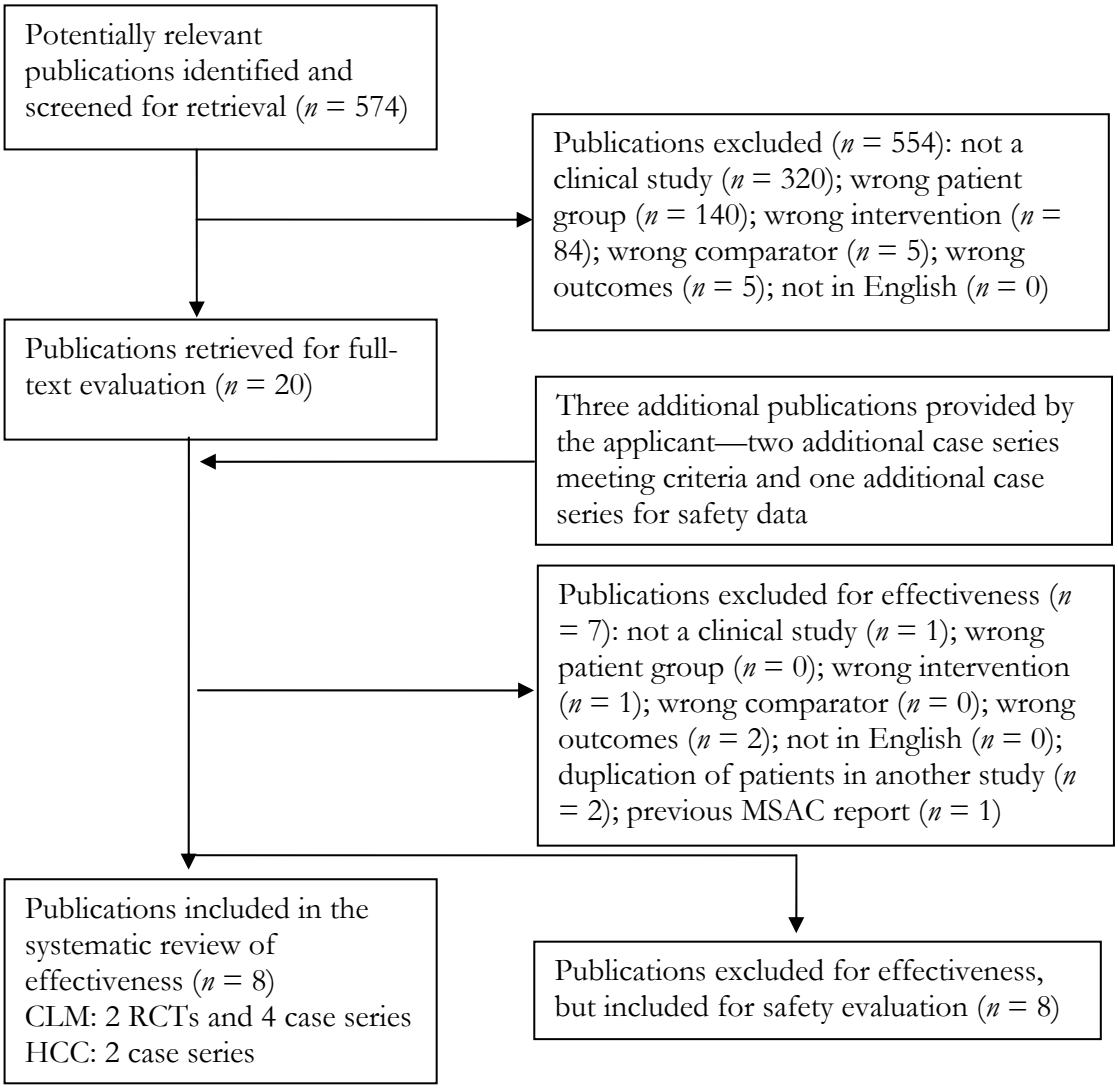
Table 8 Reasons for exclusion

Reason for exclusion	Frequency	%[1]
1. Not a clinical study	323	56.3
2. Wrong patient group	140	24.4
3. Wrong intervention	88	15.3
4. Wrong comparator	6	1.0
5. Wrong outcomes	8	1.4
6. Not in English	0	0
7. Other[2]	1	0.2
Total	566	98.6

[1]Percentage of frequency is calculated as a percentage of the total 574 citations identified.
[2]The previous MSAC report which this review is updating was excluded.

The QUOROM flow chart (Moher et al 1999) summarises the results of the literature search and the application of the study exclusion criteria (Figure 2).

Figure 2 QUOROM flow chart[1] summarising the results of the literature search and the application of entry criteria



1. modified from Moher et al (1999)

Figure 2 shows that three additional publications not identified by the literature search were provided by the applicant. Two of these studies (Lim et al. 2005a, b) were unpublished case series of patients with CLM. Patients in these two studies were found to overlap, so only the study by Lim et al. (2005a) was included in this report. This trial by Lim et al. (2005a) has subsequently been published in the *Internal Medicine Journal*. The additional publication provided by the applicant was a report of the use of SIR-Spheres in patients with CLM. This publication did not meet criteria for inclusion in the systematic review of effectiveness (as it is not a clinical trial), but it was included in the safety evaluation of this review (Gray et al. 2000). A further publication (Stubbs et al. 2001a) identified during the literature search was excluded after the lead author verified that the study population in the paper was included in another study by the same authors (Stubbs et al. 2001b) (Stubbs R.S., Wakefield Hospital, Wellington, New Zealand, personal communication, Feb 2005)

In total, two randomised controlled trials and four case series evaluating the use of SIR-Spheres in patients with CLM met criteria for inclusion in this review, and two case series evaluating the use of SIR-Spheres in patients with HCC met criteria. For the evaluation of safety of SIR-Spheres, an additional eight case series were included; four of these investigated SIRT technologies other then SIR-Spheres. Among the eight additional case series included in the safety evaluation, two appear to report on the same patient population (Leung et al. 1995; Ho et al. 1997), but as both provide safety data, both were retained in the review.

Scoping search for TACE and ^{131}I-lipiodol studies

A scoping literature search was carried out to retrieve articles on the comparators TACE and ^{131}I-lipiodol so as to enable an indirect comparison between these treatments and SIR-Spheres in patients with HCC. The eligibility criteria for TACE were restricted to systematic reviews and RCTs that compared TACE to palliative care or symptomatic treatment. As levels I and II evidence for the use of ^{131}I-lipiodol is limited, case series were also included for the evaluation of ^{131}I-lipiodol. The patient group was restricted to those with non-resectable, non-ablatable HCC. This search identified a total of 733 articles (Table 9). The reasons for exclusion are summarised in Table 10.

Table 9 Number of non-duplicate citations identified from each database for the TACE / lipiodol search

	Medline	Premedline	Current Contents	Embase	Cochrane Library	Total
Number of citations	278	7	46	393	9	733

Table 10 Reasons for exclusion

Reason for exclusion	Frequency	%[1]
1. Not a clinical study	170	23.2
2. Wrong patient group	190	26.0
3. Wrong intervention	281	38.4
4. Wrong comparator	10	1.4
5. Wrong outcomes	70	9.5
6. Not in English	–	
Total	721	98.5

[1] Percentage of frequency is calculated as a percentage of the total 733 citations identified.

The TACE / ^{131}I-lipiodol search identified a total of 12 eligible articles (9 TACE, 3 ^{131}I-lipiodol) from a total of 733 abstracts. The evidence for TACE is based on two systematic reviews and seven RCTs evaluating TACE against symptomatic treatment. The evidence for ^{131}I-lipiodol comes from one RCT comparing TACE with ^{131}I-lipiodol and two case-series evaluating ^{131}I-lipiodol.

Study appraisal

Assessment of eligible studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the NHMRC (2000). These dimensions (Table 11) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 11 Evidence dimensions

Type of evidence	Definition
Strength of evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design (see Table 12).
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *P*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

The three subdomains (level, quality and statistical precision) collectively measure the strength of the evidence. The designations of the levels of evidence are shown in Table 12.

Table 12 Designations of levels of evidence[1]

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pretest/post-test

[1]Modified from NHMRC (1999).

Quality appraisal

Study quality refers to the extent to which the methods used within a chosen study design are adequate to avoid potential bias. A structured appraisal to assess the quality of all included studies was performed. Well-defined, standard NHMRC criteria were used to appraise the quality of the included randomised controlled trials (Table 13).

For the quality assessment of included case series, criteria from the NHS Centre for Reviews and Dissemination (2001) were adopted. For each study, representativeness of the sample was assessed by considering whether consecutive patients were enrolled in the study. The relevance of the population was considered in terms of the applicability of the study population to the population under study in this report. An adequate length of follow-up to observe occurrence of important events was defined as 3 months. Quality of outcome assessment was determined in relation to whether outcome measures were objective (survival, CEA, tumour area response) or subjective (tumour response by tumour volume) and whether outcome assessors were blinded (Table 13).

Table 13 Quality assessment of randomised controlled trials[1] and case series[2]

RANDOMISED CONTROLLED TRIALS

Randomisation and allocation concealment

- Study reported as randomised and appropriate method of allocation concealment described
- Study reported as randomised and inappropriate method of allocation concealment described
- Study reported as randomised and no method of allocation concealment described or method unclear
- Study not reported as randomised

Outcome assessment

- All patients received standardised assessment
- No standardised assessment or not mentioned/unclear

Blinding

- Blinding of outcome assessor and patient and care giver
- Blinding of outcome assessor or patient and care giver
- Blinding not done

Follow-up

- Intention to treat analysis and full follow-up
- Intention to treat analysis and <15% loss to follow-up
- Analysis by treatment received only or no mention of withdrawals
- Analysis by treatment received only and no mention of withdrawals or >15% withdrawal/loss to follow-up/post-randomisation exclusions

CASE SERIES

- Was the study based on a representative sample selected from a relevant population?
- Were the criteria for inclusion and exclusion explicit?
- Did all subjects enter the study at a similar point in their disease progression?
- Was follow-up long enough for important events to occur?
- Were the techniques used adequately described?
- Were outcomes assessed using objective criteria or was blinding used?
- If comparisons of subseries were made, was there sufficient description of the series and of the distribution of prognostic factors?

[1]Modified from NHMRC 1999

[2]Modified from NHS Centre for Reviews and Dissemination 2001

Data analysis

The characteristics of the study population, type of intervention and co-therapies, study quality and relevant endpoints were extracted for each trial. Data were extracted independently by two reviewers, and any discrepancies were resolved by discussion or by a third reviewer if required. The quality assessment and data extraction tables for the included studies are provided in Appendix D. Sufficient data for meta-analysis were not available for this review.

Expert advice

An Advisory Panel with expertise in clinical oncology, surgery and radiation medicine was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the Advisory Panel is provided in Appendix B.

Results of assessment

Included studies

Eight publications were identified as meeting the criteria for inclusion in this review. Of these publications, six evaluated the use of SIR-Spheres in patients with CLM, and two evaluated the use of SIR-Spheres in patients with HCC. The six publications on patients with CLM represent two RCTs (Gray et al. 2001; van Hazel et al. 2004) and four case series (Gray et al. 2000; Gray et al. 1992; Lim et al. 2005a; Stubbs et al. 2001b). Of the RCTs, one compares SIR-Spheres with systemic chemotherapy (van Hazel et al. 2004) and the other compares SIR-Spheres with HAC (Gray et al. 2001). The two publications on patients with HCC are both case series (Lau et al. 1998; Lau et al. 1994).

In addition to the eight publications listed above, an additional eight case series were included for the evaluation of the safety of SIR-Spheres in patients with liver tumours (Andrews et al. 1994; Blanchard et al. 1989; Carr 2004; Dancey et al 2000; Herba et al. 1988; Ho et al. 1997; Leung et al. 1995; Stubbs and Wickremesekera 2004). As previously described, two of these case series (Ho et al. 1997; Leung et al. 1995) report on the same population of patients, but as both provide information on the safety of SIR-Spheres, both were retained in the review.

Appendix D summarises patient characteristics, effectiveness and safety data, and study quality of all included studies. The characteristics and quality appraisal of the included studies and the results of effectiveness are reported separately for the CLM and HCC indications. Within the CLM indications, the characteristics, quality appraisal and results on effectiveness are reported separately for the RCTs and the case series.

Characteristics of included studies: Colorectal metastases indication

Characteristics of RCTs

1. Van Hazel et al. (2004): SIR-Spheres vs systemic chemotherapy

This phase II trial compared SIR-Spheres and 5-FU/LV chemotherapy with 5-FU/LV chemotherapy alone in patients with previously untreated CLM either with or without extrahepatic metastases. The primary outcomes were response rate, time to progressive disease (PD) and toxicity. The secondary outcomes were survival and quality of life measures. The trial was designed to presage a large phase III trial that would evaluate survival as the main endpoint, however as newer systemic chemotherapy regimens are now in use, that trial was not undertaken.

The study enrolled 21 patients with histologically proven colorectal adenocarcinoma and CT scan evidence of liver metastases that could not be treated by resection or ablation. Patients with cerebral metastases were excluded. Patient characteristics are described in Table 14.

Systemic chemotherapy consisted of 5-fluoruracil 425 mg/m^2 body surface area (BSA)/day plus leucovorin 20 mg/m^2/day for 5 consecutive days, repeated at 4-weekly intervals. Chemotherapy was continued in both patient groups until evidence of unacceptable toxicity, patient request or disease progression. Patients randomised to the combination arm had SIR-Spheres administered into the hepatic artery via a trans-femoral catheter on the 3rd or 4th day of the second cycle of chemotherapy. The first five patients received a standard dose of 2.5 GBq of ^{90}Y activity. Doses in the subsequent six patients were administered according to a formula based on body surface area and percentage tumour involvement. Once protocol treatment ceased, further cancer treatment was allowed, including non-protocol chemotherapy and other supportive treatment.

Tumour response was measured using the RECIST criteria (Therasse et al. 2000) (Appendix H). Response was reported as 'first integrated response' and 'best confirmed response'. Patients lost to follow-up or dying before any follow-up scans had been performed were regarded as having had tumour progression in the liver at the time of death. Toxicity in all patients was recorded using standard Union internationale contre la Cancer (UICC) criteria. Quality of life was measured at randomisation, and then at 3-monthly intervals using the validated 23-point FLIC (Functional Living Index—Cancer) questionnaire. Clinicians also reported an assessment of the patients' wellbeing at the same intervals using the Spitzer index.

2. Gray et al. (2001): SIR-Spheres vs HAC

The objective of this phase III trial was to evaluate the additional patient benefit of adding SIR-Spheres to hepatic arterial chemotherapy (HAC) in patients with CLM against HAC alone. Benefits were measured in terms of tumour response rate, time to disease progression in the liver, survival, treatment-related toxicity and change in quality of life.

The trial was originally designed to enter 95 patients, but was closed early in 1997 with 74 patients, of whom 70 were eligible for trial entry and were treated and followed according to the trial protocol. Patients in the study had confirmed non-resectable and non-ablatable bi-lobar liver metastases from primary adenocarcinoma of the large bowel. In addition, patients with metastases in the porta hepatis lymph nodes were eligible for inclusion. Patients who had already received systemic chemotherapy for treatment of their metastases were included if they had not received radiotherapy to the liver (14%). The patient characteristics are summarised in Table 14.

HAC was administered as a continuous infusion of floxuridine at 0.3 mg/kg of body weight/day into a hepatic artery port for 12 days repeated at 4-weekly intervals. HAC protocol treatment was delivered for 18 cycles or until evidence of tumour progression, development of extrahepatic metastases, unacceptable toxicity, port failure or patient request. A single injection of SIR-Spheres was given. The injeciton was given at the time of insertion of the access port in the first patient, and after recovery from surgery in subsequent patients, but within 4 weeks of insertion of the access port. The dosage of SIR-Spheres was determined by tumour size, and ranged from 2 to 3 GBq activity. After protocol treatment, non-protocol chemotherapy and other supportive treatments were allowed.

Tumour response was measured in three ways: (i) tumour volume, (ii) serum carcinoembryonic antigen (CEA) levels and (iii) tumour area.

i) Tumour volume: Tumour volume is calculated by manually tracing the outline of tumours on serial CT scans and then digitising the tracings on a graphics tablet. Data are then transferred to a data-handling computer program that calculates the total tumour and liver volumes. Serial CT scans on all patients were independently evaluated by two medical practitioners not associated with the trial. If any recording of a tumour volume varied by more than 10 per cent from the mean of the two measurements, then the scans were independently traced by a third medical practitioner. Tumour volume was then taken as the mean of the two closest values.

ii) Serum CEA changes: Tumour response was also calculated from changes in serum CEA levels. The assay for CEA changed during the trial, although it is not clear how this affected results or whether the reference ranges changed over the course of the trial. Tumour response using CEA was used only for patients in whom the serum CEA was elevated before the start of protocol treatment.

iii) Tumour area: Tumour area was measured by calculating the sum of the products of cross-sectional diameters of all measurable lesions seen on serial CT scans.

Definition of response

Tumour response was not measured using the RECIST criteria, but was defined in the publication to allow for 3-monthly follow-up CT scans instead of monthly CT scans.

A Partial Response (PR) was defined as an objectively measured decrease in tumour size, measured for both areas and volumes, by 50 per cent or more on two successive CT scans performed after randomisation, not less than 3 months apart, before evidence of progressive disease in the liver and before any non-protocol treatment had been given.

A Complete Response (CR) was defined as the disappearance of all tumour on two successive CT scans performed after randomisation, not less than 3 months apart, before evidence of progressive disease in the liver and before any non-protocol treatment had been given.

A CEA complete response (CEA CR) was defined a decrease in serum CEA into the normal range on any occasion after randomisation but before evidence of progressive disease and before any non-protocol treatment had been given.

A CEA partial response (CEA PR) was defined as a decrease in serum CEA by 50 per cent or more, but not into the normal range, on any occasion after randomisation but before evidence of progressive disease and before any non-protocol treatment had been given.

Progressive disease in the liver (PD) used the same three objective measures that determine response to treatment, and was defined as (i) an increase in tumour area or tumour volume by 25 per cent or more, (ii) the development of new lesions in the liver or (iii) an increase in serum CEA by 25 per cent or more over the nadir for those patients with an elevated CEA at the time of randomisation.

No change (NC) was defined as either a decrease in tumour area, volume or CEA that is less than required for a Partial Response, or an increase that is less than that required for Progressive Disease.

Not assessable (NA) was attributed to those patients who either (i) had no follow-up CT scans, (ii) had unmeasurable index lesions for estimating cross-sectional tumours areas, or (iii) did not have an elevated CEA at the time of randomisation.

Quality of life was recorded at 3-monthly intervals using a validated 13-point linear analogue self-assessment scale by Priestman and Baum (1976). The paper indicates that an attempt was made to determine patient quality of life by using a linear analogue self-assessment scale of 11 questions. The trial was not powered to detect a difference in any quality of life measures.

Characteristics of case series

Four case series were included for the evaluation of SIR-Spheres in patients with CLM. These series were conducted in Australia and New Zealand and included patient numbers ranging from 29 to 71. Three of the case series were restricted to patients with liver metastases secondary to CRC, however one study (Lim et al. 2005a) included 14 patients (of a total of 46) who had liver tumours other than CLM.

Three case series allowed enrolment of patients with extrahepatic metastases, the proportion of whom ranged from 20 to 42 per cent (Gray et al. 2000; Lim et al. 2005a; Stubbs et al. 2001b). Seventeen to 88 per cent of patients were reported to have received chemotherapy for their liver metastases before treatment with SIR-Spheres in three case series (Gray et al. 1992; Gray et al. 2000; Lim et al. 2005a). Of the three studies that reported the proportion of liver involvement among included patients, Stubbs et al. (2001b) included the highest proportion of patients (40%) with more than 25 per cent liver involvement. Table 14 provides an overview of characteristics of patients in the included case series.

All the patients in the Gray et al. (2000) case series received SIR-Spheres in addition to HAC, and 7 per cent of those received two injections. Forty-one per cent of patients in the Gray et al. (1992) trial and 86 per cent of patients in the Stubbs et al. (2001b) trial received SIR-Spheres in addition to HAC, whereas in the unpublished series by Lim et al. (2005a), SIR-Spheres were evaluated as a standalone treatment.

The measurement of study outcomes was not uniform across the case series. Survival was reported in two of the studies (Gray et al. 2000; Stubbs et al. 2001b). All studies reported tumour response, however measurements were not made according to standard RECIST criteria. The effectiveness outcome measured by Lim et al. (2005a) was tumour response measured by tumour area change on CT scans at 2 months and bi-monthly thereafter. The two case series by Gray et al. (1992, 2000) reported on both tumour response by CEA (tumour marker) levels and tumour volume measurements. The study by Stubbs et al. (2001b) reported on CEA levels and tumour response by tumour size, without specifying whether measurements were made on tumour area or tumour volume.

Table 14 Patient characteristics in the included studies for the CLM indication

Study author and year	Total *n*	Treatment	Male (%)	Age (years)	Patients with extrahepatic metastases (%)	Patients with >25% liver involvement (%)	Patients treated with prior chemo for CLM (%)
Van Hazel et al. (2004), RCT	21	SIR-Spheres & systemic chemo	87%	65	24%	29%	0%
Gray et al. (2001), RCT	70 (of 74)	SIR-Spheres +HAC	77%	61	0%[1]	31%	14%
Gray et al. (1992), case series	29	SIR-Spheres (41% +HAC)	n.r.	n.r.	n.r.	n.r.	17%
Gray et al. (2000), case series	71	SIR-Spheres (7% ×2) & HAC	61%	33–76	42%	*n*.r.	37%
Lim et al. (2005a), case series	46 (32 with CRC)	SIR-Spheres	67%	64 (median)	20%	*n*.r.	88% (of CRC)
Stubbs et al. (2001b), case series	50	SIR-Spheres (86% +HAC)	62%	61 (median)	16%	40%	n.r.

n.r. = not reported
1. Study included patients with metastases to liver and lymph nodes in the porta hepatis only; 69% of patients reported lymph node involvement.

Quality of included studies: Colorectal metastases indication

Quality of RCTs

According to the quality assessment criteria outlined in Table 13, the two included RCTs can generally be considered of good quality. Appendix D includes a summary of the results of the quality assessment of the RCTs; a more detailed appraisal of the quality is given in the text below.

In both trials randomisation was conducted independently. In the van Hazel et al. (2004) trial, randomisation was performed by telephoning an independent site, which randomised patients using a computer program. Although the method of allocation concealment was not reported, it is assumed to be appropriate given that randomisation was conducted independently. Patients were stratified before randomisation by institution, presence or absence of extrahepatic metastases, and extent of liver involvement (<25% or >25%). Gray et al. (2001) reported using a blind-coded envelope method controlled by an independent person, but the method used to develop the randomisation sequence was not reported. Using blind-coded envelopes can be considered an appropriate method of allocation concealment. Patients in this trial were stratified before randomisation into three groups depending on the percentage of liver involved (<25%, 25%–50%, >50%).

In both studies, tumour response was measured independently using a standardised method, either by two medical practitioners in the Gray et al. (2001) study, or by one medical practitioner in the van Hazel et al. (2004) study, who evaluated all serial CT scans of all patients. However, the way tumour response was evaluated differed in the two trials. Van Hazel et al. (2004) used the standard RECIST criteria to determine response to

treatment by change in tumour area; Gray et al. (2001) used a different system (see characteristics of RCTs above), based on tumour area and tumour volume change. Outcome assessors were blinded to the patients' treatment allocation, but neither trial reported whether patients were blinded.

Patient follow-up was reported in both RCTs, with less than 15 per cent loss to follow-up in both trials. In van Hazel et al. (2004), two patients in the chemotherapy arm did not receive protocol treatment, as their condition deteriorated rapidly after trial entry. In Gray et al. (2001), four patients were deemed ineligible due to disseminated cancer at the time of randomisation, and one patient in the SIRT + HAC arm was unable to receive treatment. Excluding the four ineligible patients, all patients were followed up for a minimum period of 3.5 years in the Gray et al. (2001) trial. Minimum follow-up is not stated in van Hazel et al. (2004), but at the time of the report one patient was still alive 42.5 months after randomisation (information from application). Both studies report analysing outcome data on an intention to treat basis.

Both RCTs provided information on the calculation of required sample size. The trial by van Hazel et al. (2004) was designed to detect a 20 per cent difference in Grade 4 toxicity event rate, with a required sample size of 18 patients. Recruitment was closed after 21 patients. The trial by Gray et al. (2001) was originally designed to enter 95 patients to detect a 30 per cent increase in median survival, but was closed in 1997 after entering 74 patients. Reasons cited for the early closure included (1) increasing patient and physician reluctance to undergo randomisation; (2) a decision by the US Food and Drug Administration to accept treatment-related response and time to disease progression as acceptable criteria for premarket application approval; and (3) lack of funding to complete the study. After recruitment was stopped, the primary outcome measure was changed to tumour response. With tumour response as the primary outcome, 74 patients would allow:

- detection of an increase in response from 20% to 55% (difference of 35%) with 80% power and 95% confidence
- 70% power to detect an absolute 30% increase in survival at 6 months from 50% to 89% with a 95% confidence level.

The study also reports that 74 patients would enable detection of "an increase in median time to disease progression for control group patients of 4.5 months by 32% with 80% power and 95% confidence". It is unclear whether this statement refers to a 32 per cent increase in time to disease progression in SIR-Spheres patients assuming a median time to disease progression of 4.5 months in the control group.

Quality of case series

Overall, the quality of the four included case series was fair. Using the criteria in Table 13, a detailed quality assessment is provided in Appendix D, and summarised here.

All case series included patient populations that were applicable to the population under study. Thirty per cent of included patients in Lim et al. (2005a) had liver tumours other than from CRC, but results are available separately for CLM patients. For three of the case series, representativeness of the sample can be assumed, as patients entered the study consecutively (Gray et al. 2000; Lim et al. 2005a; Stubbs et al. 2001b). The same three studies had well-defined criteria for inclusion or exclusion of patients.

Three studies included patients with metastatic cancer in additional sites beyond the liver. At the time of recruitment, 16 per cent (Stubbs et al. 2001b) to 42 per cent (Gray et al. 2000) of patients had extrahepatic metastases.

The length of follow-up was variable. One study (Gray et al. 1992) reported outcomes after only 2 months, which is considered an inadequate length of follow-up. In Gray et al. (2000), all patients were followed until death, while Lim et al. (2005a) report that disease evaluation was performed at 2 months and bimonthly thereafter until disease progression, and Stubbs et al. (2001b) state a median follow-up for all patients of 25.5 months.

The study techniques are applicable to the research question and generally adequately described. However, Lim et al. (2005a) did not state the dosage of SIR-Spheres given to patients.

As described on page 32, the outcomes reported differed between studies. Two of the four studies reported on survival (Gray et al. 2000; Stubbs et al. 2001b). All studies reported tumour response as a change in tumour volume or tumour area assessed by CT scans, but the way these outcomes were reported and evaluated varied across studies, and no study used the standard RECIST criteria to evaluate treatment response. Two studies (Gray et al. 1992; Gray et al. 2000) reported on a decrease or percentage decrease in tumour volume, whereas another (Lim et al. 2005a) used tumour area measurements to determine partial and complete tumour response. From the information provided in Stubbs et al. (2001b), it remains unclear whether tumour volume, tumour area or both were used to assess tumour response. Three studies reported CEA levels (Gray et al. 1992; Gray et al. 2000; Stubbs et al. 2001b). None of the included case series report whether outcome assessors were blinded to treatment allocation.

Characteristics of included studies: Hepatocellular carcinoma indication

Characteristics of included studies

The evidence for SIR-Spheres in the HCC patient group comes from two case series (Lau et al. 1998; Lau et al. 1994). Lau et al. (1998) was the largest SIR-Spheres study of HCC patients, assessing 71 patients over 3 years. The Lau et al. (1994) study was smaller, with 18 patients, and investigated the optimum dose of SIR-Spheres as its primary outcome. Most patients in the Lau et al. (1998) study were hepatitis B carriers (91.5%). Lau et al. (1994) did not report on the viral hepatitis status of patients, but did report on the Child–Pugh classification (Appendix I), classifying 16 of the 18 patients as A and only two as B. As the recruitment period for this study overlaps the Lau et al. (1998) study by 7 months, there may be duplication of some patients.

Lau et al. (1998) measured survival, tumour response from tumour volume measurements from a CT scan before the procedure and then every 2 months following the procedure, and alpha-fetoprotein (AFP) serum marker levels. Lau et al. (1994) used serum AFP or ferritin levels combined with tumour volume measurements to assess response to treatment. Neither of the case studies reported on disease progression or quality of life.

Quality of included studies

The quality of the included case series was fair. Both studies reported clear inclusion and exclusion criteria, however it was not reported whether patients were recruited consecutively. Follow-up was appropriate in both studies, with patients in both studies being followed until death (or a minimum of 10.4 months for the three survivors in Lau et al. 1994, and an unknown minimum follow-up for survivors in Lau et al. 1998). In both studies, the outcomes of survival and serum markers were measured objectively, while the response measurement of tumour volume was subjective, although an independent radiologist calculated the measurements. The use of tumour volume as an outcome measurement rather than tumour area is not standard, as discussed above (see page 16). Further details of the quality assessment of the studies are provided in Appendix D.

Is it safe?

As described in the Background section of this report, patients with unresectable liver tumours have a very poor prognosis. The adverse events associated with SIR-Spheres and other treatments for these patients need to be balanced with the potential benefits of these treatments.

The assessment of the safety of SIR-Spheres is based on the included studies (n = 303 patients), additional case series included for the safety assessment (n = 200 patients SIR-Spheres, n = 142 patients other SIRT), TGA data and information from the applicant. Seven of the eight included studies provide data which enable assessment of the safety of SIR-Spheres for the CLM and HCC patient groups. The case series by Gray et al. (1992) did not report on safety outcomes. In addition to the included studies, a further eight case series were considered for the evaluation of safety. Of these, three were case series of SIR-Spheres (Ho et al. 1997; Leung et al. 1995; Stubbs & Wickremesekera 2004), while five were case series of other SIRT therapies (Andrews et al. 1994; Blanchard et al. 1989; Carr 2004; Dancey et al. 2000; Herba et al. 1988). As previously discussed, two of the additional case series report on the same group of patients (Ho et al. 1997; Leung et al. 1995), but both studies were considered because they both provide relevant safety information.

Both RCTs (van Hazel et al. 2004; Gray et al. 2001) and four of the SIR-Spheres case series (Gray et al. 2000; Lim et al. 2005a; Stubbs et al. 2001b; Lau et al. 1994) reported conducting CT scans and regular blood tests, including liver function tests, to monitor toxicities during follow-up. Both RCTs recorded toxicity using standard UICC criteria, which grades severity of symptoms from Grades 1 to 4, while the case series did not use standard criteria. Lim et al. (2005a) cited National Cancer Institute common toxicity criteria (NCI-CTC), but did not report adverse events accordingly (Lim et al. 2005a).

In addition to the included studies, safety information was available from the Incidence Reporting and Investigation Scheme of the TGA. Under this scheme, purchasers and users of medical devices such as SIR-Spheres are encouraged, and suppliers and manufactures are obliged, to report incidents that have caused or could cause injury to the patient or the device user (TGA 2000). In the case of SIR-Spheres, two reports were provided by the TGA that are included in the assessment of the safety of SIR-Spheres (TGA 2005).

Detailed information on safety is provided in the data extraction tables in Appendix D. The following paragraphs provide a summary of the safety issues involved with the use

of SIR-Spheres, a comparative assessment of Grades 3 and 4 toxicities observed in the two RCTs, an overview of the major adverse events reported in all of the included sources, and a summary of safety data from case series looking at SIRT technologies other then SIR-Spheres such as TheraSpheres or carbonised plastic. The latter case series were included to complement the safety information on SIR-Spheres, as similar safety issues might arise with these treatments. In addition, personnel safety issues associated with the use of SIR-Spheres are discussed. Information for this section was obtained from the Sirtex manual (Sirtex Medical 2002), the Westmead Private Hospital (2002) SIRT guidelines and the ARPANSA (2002) guidelines on discharge of patients from a hospital.

Safety issues involving the use of SIR-Spheres

According to information from the *Medical SIR-Spheres Users Manual* (Sirtex Medical 2002), common side-effects of treatment with SIR-Spheres include a transient decrease in haemoglobin, mild to moderate abnormalities of liver function tests (specifically, an increase in serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase and bilirubin) and gastrointestinal side-effects such as abdominal pain, nausea, vomiting and diarrhoea. It is further reported that almost all patients post-operatively develop a fever that can last up to a week (Sirtex Medical 2002). These side-effects represent the majority of adverse events generally occurring with SIR-Spheres and are Grade 1 and 2 toxicities according to UICC toxicity criteria.

In addition to the minor side-effects described above, there is a risk of acute or delayed serious adverse events with the use of SIR-Spheres. When SIR-Spheres microspheres inadvertently lodge in organs other than the liver (pancreas, stomach, duodenum), acute pancreatitis or peptic or duodenal ulceration can occur, which are characterised by an immediate, serious abdominal pain that will not abate after treatment with narcotic analgesia. High levels of radiation that may affect the normal liver parenchyma can lead to radiation hepatitis weeks after SIR-Spheres implantation (Sirtex Medical 2002). Excessive shunting to the lung may lead to radiation pneumonitis (Sirtex Medical 2002).

Given the serious adverse events that can occur when the microspheres are placed incorrectly, the safety of SIR-Spheres relies on the correct handling of the device. In preparation for the SIR-Spheres procedure, patients undergo a hepatic angiogram to determine the arterial anatomy of their liver. If a patient has a variable anatomy then additional vessels need to be occluded with coils or gel foam to prevent SIR-Spheres leakage. Patients are also required to have a technetium-99m scan with macroaggregated albumin (MAA) to measure lung-liver shunting. Patients with >20 per cent shunting are not eligible for SIR-Spheres, and patients with lung shunting of 10 to 20 per cent require dose reductions to minimise the risk of radiation pneumonitis (Sirtex Medical 2002). Some of the reported cases of radiation pneumonitis, hepatitis, gastritis and gastroduodenal ulceration may have occurred due to incorrect handling of SIR-Spheres and therefore may have been avoidable if the guidelines to determine patient eligibility and dose had been followed.

Safety issues for personnel working with this radioactive device are discussed in the section on Personnel Safety, the last safety section in this report.

Comparative assessment of treatment-related toxicities from RCTs

Comparing the toxicities occurring with SIR-Spheres and chemotherapy to those occurring with chemotherapy alone, the van Hazel et al. (2004) trial showed 13 Grade 3–4 toxicities in 11 patients treated with SIR-Spheres plus chemotherapy versus 5 Grade 3–4 toxicities in 8 patients treated with chemotherapy alone (2 patients assigned to this treatment did not receive treatment). As previously discussed, this trial used a systemic chemotherapy regimen that is no longer considered standard practice, although 5FU/LV is still included in the current regimens, with either irinotecan or oxaliplatin. In the Gray et al. (2001) trial, there were no differences in the treatment groups in the number of Grades 3 and 4 events reported—in both the SIR-spheres and HAC arm and the HAC-only arm, 23 Grades 3 and 4 events occurred. The details of the Grades 3 and 4 toxicity events in the two trials are listed in Table 15.

Table 15 Grades 3 and 4 toxicity and treatment-related death (Grade 5 toxicity) experienced during treatment in van Hazel et al. (2004) and Gray et al. (2001)

Event	Van Hazel et al. (2004)		Gray et al. (2001)	
	Number of events in systemic chemotherapy arm (*n* = 10)	Number of events in SIR-Spheres + chemotherapy arm (*n* = 11)	Number of events in HAC arm (*n* = 34)	Number of events in SIR-Spheres + HAC arm (*n* = 36)
Low blood count (granulocytopaenia, anaemia)	0	3	1	0
Gastrointestinal events (nausea, vomiting, gastritis, mucositis, diarrhoea, anorexia)	5	8	3	1
Radiation-induced cirrhosis	0	1	0	0
Liver abscess	0	1	0	0
Liver function test abnormalities	0	0	19	22
Total number of Grade 3–4 events	5	13	23	23
Treatment-related death	0	1	0	0

Generalisability of toxicity results from RCTs to current practice

As previously discussed, the van Hazel et al. (2004) trial uses a chemotherapy regimen that is no longer used in current clinical practice.

Due to the lack of trials comparing SIR-Spheres and current chemotherapy regimens with current chemotherapy regimens alone, the comparative treatment-related toxicities must be inferred. The toxicity spectrum of FOLFOX6 or FOLFIRI (current practice) relative to bolus 5FU/LV is distinct. The 5FU/LV regimen is associated with a greater incidence of mucositis, diarrhoea and neutropaenia relative to the current regimens. Characteristic of FOLFOX6 is cold-induced paraesthesia and cumulative peripheral neuropathy (Advisory Panel, May 2005). It has also been suggested that the addition of SIR-Spheres to current chemotherapy regimens (see Appendix G) may result in increased radiosensitisation, however no trials currently exist to enable the assessment of this possibility (Advisory Panel, April 2005).

Major adverse events summary

Death

Among the included information for the safety assessment of SIR-Spheres are reports of seven deaths. Of these, five were reported in the included studies, which evaluated a total of 503 patients. There was one treatment-related death in the combined SIR-Spheres and systemic chemotherapy arm in the van Hazel et al. (2004) trial. This patient died from sepsis associated with neutropaenia after a fourth cycle of chemotherapy (van Hazel et al. 2004). In two case series, four deaths occurred in a total of 171 patients treated with SIR-Spheres for CLM (Gray et al. 2000; Stubbs & Wickremesekera 2004). Two of these were cases of fatal radiation hepatitis, while two were due to severe radiation gastritis and acute hepatic necrosis. All three studies assessed patient eligibility or dosage using a Tc-MAA scan.

In the TGA documentation of adverse events, there are reports of two male patients with HCC and advanced cirrhosis who died approximately 4 months after treatment with SIR-Spheres. Liver failure secondary to radiation hepatitis was suggested as a provisional diagnosis, and no evidence of incorrect dosage or technical problems could be found. Following these incidents, the company issued safety alerts to advise physicians about precautions when using SIR-Spheres in patients with cirrhosis and other forms of impaired liver function (TGA 2005).

Radiation pneumonitis

Two cases of radiation pneumonitis were reported among 95 patients (2%) treated with SIRT using intra-arterial ^{90}Y-microspheres for either inoperable HCC or secondary hepatic tumours. In both patients, the percentage of lung shunting of Tc-MAA was at the level where dose reduction is advised (13.1% and 15.9%) (Ho et al. 1997; Leung et al. 1995). The investigators also reported on five additional patients with lung shunting above 15 per cent by Tc-MAA scan. All five patients underwent partial hepatic embolisation with inert hepatic particles, which reduced Tc-MAA lung shunting to below the 15 per cent eligiblity cutoff for SIRT. However, despite this intervention, three of these five patients were subsequently diagnosed with radiation pneumonitis.

Hepatic adverse events

Radiation hepatitis. In three case series with a total of 217 patients, two cases of radiation hepatitis and one case of likely radiation hepatitis were reported. All three studies assessed patient eligibility or dosage using a Tc-MAA scan. The two cases of radiation hepatitis occurred 7 and 15 weeks after SIR-Spheres administration, and both were fatal, as reported above (Gray et al. 2000; Stubbs & Wickremesekera 2004). In their case series of 46 CLM patients, Lim et al. (2005a) report one case of likely radiation hepatitis that settled with conservative management.

Radiation-induced cirrhosis. Van Hazel et al. (2004) reported on one patient who developed radiation-induced cirrhosis 1 year after treatment commenced. This patient responded well to conservative treatment. It was thought that the patient's low body weight was a contributing factor (van Hazel et al. 2004).

Other reported hepatic adverse events. Van Hazel et al. (2004) reported on a patient who developed a liver abscess in the site of a necrotic tumour mass who was treated with

SIR-Spheres and systemic chemotherapy. This patient recovered quickly following drainage of the abscess (van Hazel et al. 2004).

Stubbs and Wickremesekera (2004) reported one case of acute hepatic necrosis 5 days following the administration of SIR-Spheres in a patient with HCC who died, as reported above.

Gastrointestinal adverse effects

Radiation gastritis. Two cases of radiation gastritis are reported among the included safety information. One of these cases, which was fatal, occurred in the series of 100 patients with CLM reported by Stubbs and Wickremesekera (2004), as reported above.

In the TGA adverse events reports, one case of radiation gastritis is reported in a patient who subsequently developed cirrhosis of the liver. It appears that this patient is the patient with radiation-induced cirrhosis in the clinical trial by van Hazel et al. (2004) reported above. According to the TGA report, a technical error resulting in 'an inadvertent injection of some of the radioactive particles into the blood supply of the stomach' was responsible for the complication (TGA 2005).

Gastroduodenal ulceration. In three case series with a total of 196 patients treated with SIR-Spheres for CLM, ten patients are reported to have developed gastroduodenal ulceration, and eight patients developed peptic ulceration. In Stubbs et al. (2001b), six of 50 patients developed a duodenal ulcer within 2 months of treatment, which might have developed from misperfusion of the duodenum by SIR-Spheres or HAC, or both. Two of these patients had acute upper gastrointestinal bleeding, one of whom required surgery (Stubbs et al. 2001b). The case series by Lim et al. (2005a) identified four patients developing gastroduodenal ulceration confirmed on gastroscopy. Of the eight patients identified in Stubbs and Wickremesekera (2004), two had major bleeding and one required operation.

Other reported severe adverse events. Lim et al. (2005a) also reported a serious adverse event potentially related to SIR-Spheres: a patient presented with haematemesis 4 weeks after SIR-Sphere treatment and was found to have bleeding oesophageal varices due to portal hypertension (Lim et al. 2005a).

Adverse events reported for other SIRT techniques

Adverse events observed in studies using the SIRT techniques such as glass matrix or carbonised plastic microspheres were similar to the events observed with SIR-Spheres. Treatment-related deaths occurred in three of the 22 HCC patients treated with TheraSpheres reported on by Dancey et al. (2000): one death was due to hepatitis, one to liver failure and one to radiation pneumonitis.

Radiation gastritis was reported in five patients in an early study by Blanchard et al. (1989), which looked at 16 patients with liver tumours treated with 15-μm microspheres containing ^{90}Y. Radiation gastritis was accompanied by gastric ulceration in four of the five patients. One of the patients required antrectomy 6 months after treatment for a bleeding ulcer (Blanchard et al. 1989). In addition to the ulceration reported in Blanchard et al. (1989), gastroduodenal ulceration was observed in 11 out of 61 patients treated with TheraSpheres in three case series (Andrews et al. 1994; Dancey et al. 2000; Herba et al.

1988). One case of GI tract haemorrhage occurred in a patient with a history of bleeding duodenal ulcer (Herba et al. 1988).

Carr (2004) further reported on eight patients with worsening ascites and two patients with episodes of cholecystitis requiring cholecystectomy in his case series of 65 HCC patients treated with TheraSpheres.

Personnel safety

The radiation exposure resulting from SIR-Spheres is a safety issue for hospital staff involved in the preparation of the specific patient dose, the implantation procedure and clearing the room following the procedure. After implantation of the device, possible residual radiation from patients can require further safety precautions during after-care of the patient in the hospital and at discharge (Sirtex Medical 2002). A further issue relates to the storage of all of the equipment used with SIR-Spheres, as this equipment may be radioactive and needs to be safely stored until it is no longer radioactive.

In Australia, individual State regulations require that the effective dose to each exposed worker be less than 20 μSv per year (averaged over a period of 5 consecutive calendar years), and that the effective dose limit in a single year be 50 mSv, as defined by the NHMRC in its Radiation Health Series (National Occupational Health and Safety Commission 1995).

The applicant has indicated that SIR-Spheres are shielded with lead and Perspex throughout production, transport and delivery, and has provided sample radiation dose reports for selected staff members. Over a period of 6 months during which 15 patients were treated with SIR-Spheres, the applicant has indicated that each staff member received less than 0.15 μSv per 2-month period (MSAC 2002). This is confirmed in a study by (Shepherd et al. 1992), which found that radiation exposure to personnel was limited to less than 0.2 μSv per administration. A recent Australian review has suggested that the average effective background dose received by the Australian population is approximately 1.5 mSv per year (Webb, Solomon, and Thomson 1999).

As beta-emitting radioisotopes can deliver high doses of radiation only to objects close to the source, the whole-body exposure rates reported above would be expected to be low. The applicant has provided additional information based on doses measured on finger badges (Table 16).

Table 16 Radiation doses from finger badges (1 January to 31 December 2000)

Wearer	Dose (mSv)	Times worn	Average finger dose per implant (mSv)
Technologist (drawing up)	<0.02	5	0.004
Waste technician	0.82	8	0.1
Administering physician	1.67	2	0.84
Interventional radiologist	<0.02	2	<0.01

Another important consideration is that of residual radiation present at discharge of patients from hospital. In the previous MSAC review, the NHMRC recommendation on discharge of patients who have undergone treatment with radioactive substances speci-

fied that discharge should not occur until total activity remaining in the patient has dropped to 1200 MBq (National Health and Medical Research Council 1984). In the updated discharge recommendations from 2002, the maximum activity of ^{90}Y in the treated patient at discharge has been increased to 4000 MBq (ARPANSA 2002). As ^{90}Y doses delivered to patients by SIR-Spheres are between 2000 and 4000 MBq and as the half-life of ^{90}Y is around 3 days (64.1 hrs), a hospital stay of 1 day can be considered sufficient to ensure low residual radiation from the patient. SIR-Spheres should be performed in approved centres to ensure that these safety standards are met.

In contrast, the standard dose of ^{131}I-lipiodol is higher (approximately 2 GBq) and has a longer physical half-life of around 8 days (European Association of Nuclear Medicine 2002). Those administering treatment have a higher risk of radiation exposure than clinicians administering SIR-Spheres and must take precautions to minimise radiation exposure. Patients treated with ^{131}I-lipiodol need to stay in hospital for 7 to 10 days to meet radiation safety requirements and to follow instructions to reduce unnecessary radiation exposure to family members and the public for a period of time following discharge.

Is it effective?

The Advisory Panel agreed that the following efficacy endpoints should be used in the evaluation of data:

1. Survival
    - Overall survival
2. Disease progression
    - Progression-free survival
    - Hepatic progression-free survival
3. Tumour response
4. Quality of life

The following sections summarise the evidence relating to these efficacy endpoints. The evidence is presented separately for the CLM and HCC indications. Within the CLM indication, RCT evidence is reported before evidence from case series.

Colorectal metastases indication

Evidence from RCTs

This section provides data from the two included trials on the efficacy endpoints that have been determined to be most relevant by the Advisory Panel, as above.

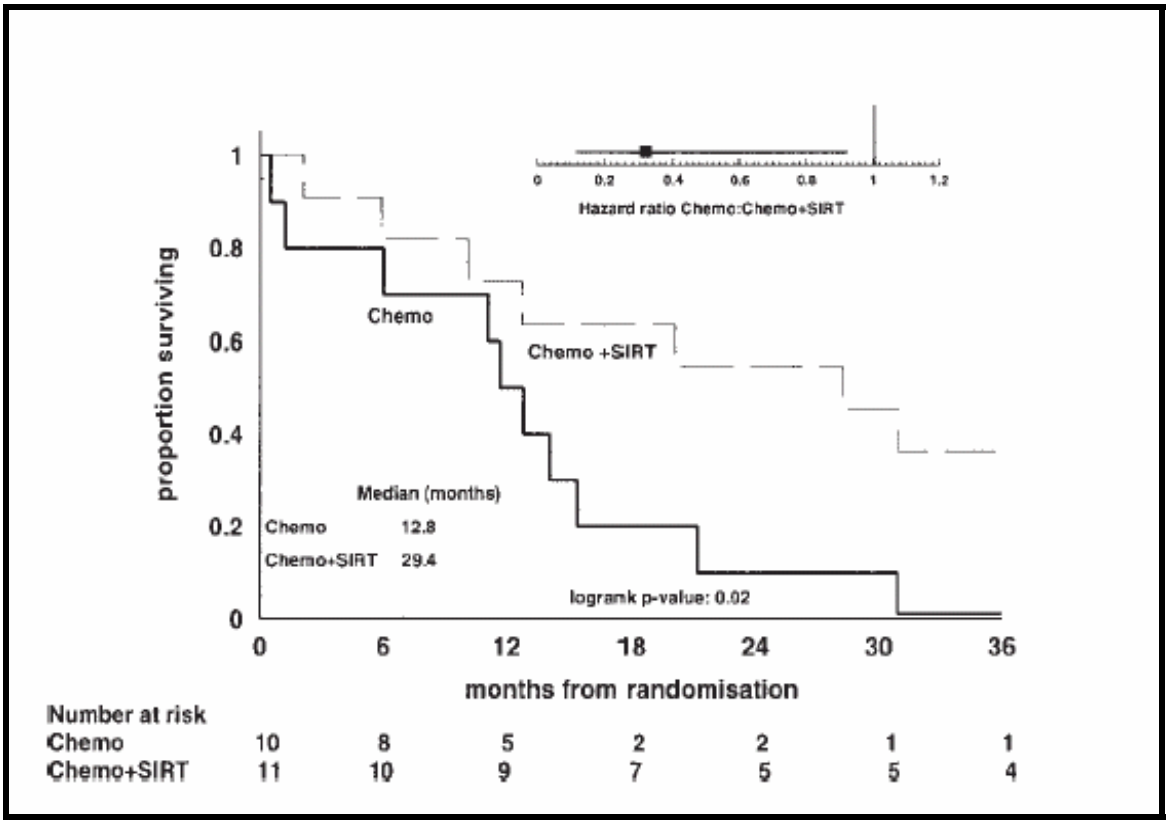
1. Overall survival

Van Hazel et al. 2004: systemic chemotherapy + SIR-Spheres. There was a statistically significant survival advantage in patients treated with SIR-Spheres and systemic chemotherapy compared to the systemic chemotherapy-only group. Patients treated with the combination of SIR-Spheres and systemic chemotherapy had a median survival of

29.4 months compared to 12.8 months for patients treated with chemotherapy alone (HR 0.33; 95% CI 0.12–0.91; $P = 0.025$). This difference is shown in Figure 3.

A second survival analysis was conducted because two patients randomised to the systemic chemotherapy group did not receive any chemotherapy. This analysis, which excluded the two patients, found the median survival of the SIR-Spheres and systemic chemotherapy group to be 29.4 months compared to 14.1 months for those receiving systemic chemotherapy only (HR 0.39; 95% CI 0.14–1.13; $P = 0.07$).

Figure 3 Patient survival by treatment from the van Hazel et al. (2004) trial



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Gray et al. 2001: hepatic arterial chemotherapy + SIR-Spheres. This trial found no statistically significant difference in survival between patients treated with SIR-Spheres plus HAC and patients treated with HAC alone. The Kaplan–Meier analysis suggested a trend towards increased survival after 12 months for patients treated with SIR-Spheres and HAC, but this difference was not statistically significant. The median survival in the HAC + SIR-Spheres arm was 17 months compared with 15.9 months in the HAC-only arm (HR = 0.71; 95% CI 0.43–1.16; $P = 0.18$) (Table 17). As discussed previously, this trial was not powered to detect an increase in survival as recruitment closed at 74 patients instead of the intended 95 patients.

An exploratory Cox regression analysis suggested that patients treated with SIR-Spheres plus HAC who survive more than 15 months experience a survival advantage compared with those treated with HAC alone. This survival advantage was not evident in patients surviving less than 15 months.

Table 17 Overall survival of all patients in Gray et al. (2001) trial

	HAC alone	HAC + SIR-Spheres
Number of patients	34	36
Mean survival (months)	18.4	23.5
Median survival (months)	15.9	17
Survival rates per year—at 1 year	68%	72%
Survival rates per year—at 2 years	29%	39%
Survival rates per year—at 3 years	6%	17%
Survival rates per year—at 4 years	0%	3.4%

Comparison between groups: log rank test $P = 0.18$

2. Disease progression

Disease progression was reported as progression-free survival in the van Hazel et al. (2004) trial, whereas Gray et al. (2001) report time to disease progression in the liver.

Progression-free survival (time to disease progression at any site). In the van Hazel et al. (2004) trial, the time to progressive disease (PD) was significantly longer for patients treated with SIR-Spheres plus systemic chemotherapy (median 18.6 months) than for patients in the systemic chemotherapy alone arm (3.6 months; $P < 0.0005$).

The site of first disease progression was recorded for all patients. In the SIR-Spheres and systemic chemotherapy arm, eight patients had first disease progression in the liver, one had PD in the liver and the lung, one had PD in the lung only, and another died from chemotherapy-related sepsis. In the control arm, eight patients had disease progression in the liver, one had PD in the liver and peritoneum, and one had PD in bone.

Hepatic progression-free survival (time to disease progression in the liver). Van Hazel et al. (2004) did not report time to progressive disease in the liver; however the liver was the site of first disease progression in most patients, as reported in the previous section.

Disease progression in the liver in the Gray et al. (2001) trial was reported by tumour area and tumour volume. Time to disease progression is presented as survival curves, measured by area (Figure 4) and by volume (Figure 5). The median hepatic progression-free survival of patients is not stated in the paper. Figure 4 indicates that when measured by tumour area, the median hepatic progression-free survival in the SIR-Spheres and HAC group was approximately 16 months, compared with approximately 10 months in the HAC-only group. Figure 5 indicates that when measured by tumour volume, the median hepatic progression-free survival in the SIR-Spheres and HAC group was approximately 12 months, compared with approximately 8 months in the HAC-only group. This advantage for patients being treated with SIR-Spheres was significant for both measures of disease progression, at $P < 0.01$ (log rank) for disease progression by tumour area and $P = 0.04$ (log rank) for disease progression by tumour volume.

Figure 4 Time to first disease progression measured by tumour area from the Gray et al. (2001) trial

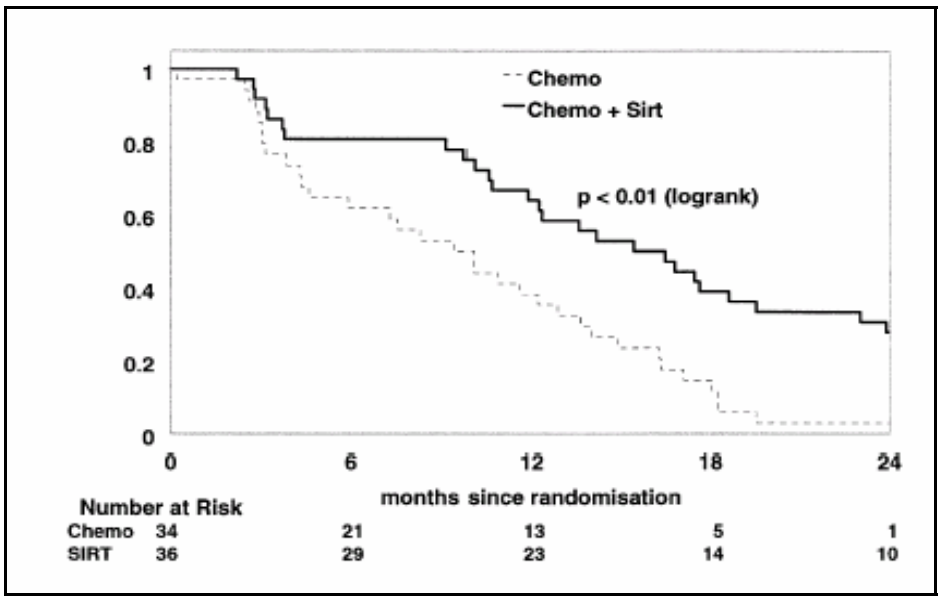

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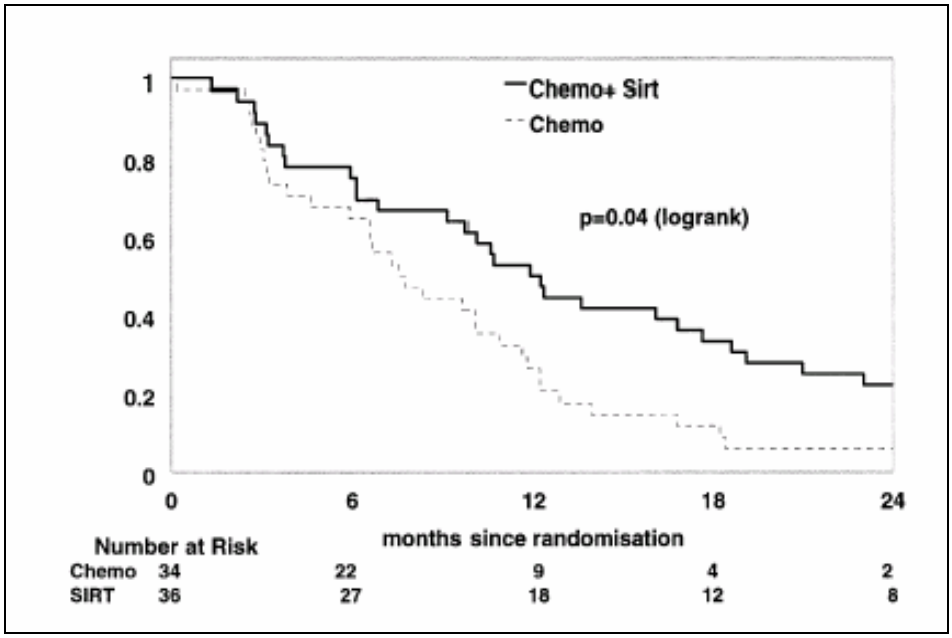
Figure 5 Time to first disease progression measured by tumour volume from the Gray et al. (2001) trial



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3. Tumour response

In the van Hazel et al. (2004) trial, tumour response was recorded using the RECIST criteria (Appendix H), and the results are summarised in Table 18. None of the patients in the chemotherapy-only arm showed a response to treatment. Ten out of the 11 SIR-Spheres plus systemic chemotherapy patients showed a partial response (PR) at first integrated response, and there were eight PRs in the best confirmed response. The differ-

ences in response were statistically significant at $P < 0.001$ according to Kruskal–Wallis tests.

Table 18 RECIST response data in van Hazel et al. (2004) trial

	CR	PR	SD	PD	*P* value[1]
First integrated response					
Chemotherapy (*n* = 10)	0	0	6	4	< 0.001
SIR-Spheres + chemotherapy (*n* = 11)	0	10	1	0	
Best confirmed response					
Chemotherapy (*n* = 10)	0	0	6	4	< 0.001
SIR-Spheres + chemotherapy (*n* = 11)	0	8	3	0	

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease
[1]P values from Kruskal–Wallis tests assessing differences in response between treatment groups

Gray et al. (2001) did not use RECIST criteria to categorise tumour response. Response to treatment was measured using three criteria: tumour area, tumour volume and CEA levels from 3-monthly CT scans and blood tests. As previously reported, these are not standard criteria to evaluate tumour response. Tumours in two patients, one in each study arm, responded to treatment to such an extent that metastases were subsequently surgically resectable. In all three criteria, tumour response rates were significantly better in the SIR-Spheres and HAC arm than in the HAC alone arm (see Table 19). In the tumour cross-sectional area response measurement, 44 per cent (16/36) of patients achieved either a CR or PR, compared to 18 per cent (6/34) in the HAC alone arm ($P = 0.01$). Similarly, tumour response in terms of changes in tumour volume and in CEA showed significantly better values of 50 per cent versus 24 per cent ($P = 0.03$) and 72 per cent versus 47 per cent ($P = 0.004$), respectively, in the SIR-Spheres plus HAC arm than in the HAC alone arm.

Table 19 Tumour response measurements in Gray et al. (2001) trial

Tumour area response	CR	PR	NC	PD	NA	*P* value[1]
HAC (*n* = 34)	0	6	13	8	7	0.01
HAC + SIR-Spheres (*n* = 36)	2	14	13	3	4	
Tumour volume response	CR	PR	NC	PD	NA	*P* value
HAC (*n* = 34)	1	7	12	9	5	0.03
HAC + SIR-Spheres (*n* = 36)	2	16	10	5	3	
CEA response	CR	PR	NC	PD	NA	*P* value
HAC (*n* = 34)	9	7	10	6	2	0.004
HAC + SIR-Spheres (*n* = 36)	15	11	2	1	7	

CR = complete response, PR = partial response, NC = no change, PD = progressive disease, NA = not assessable
[1]P values from Kruskal–Wallis tests assessing differences in CR, PR, NC and PD between treatment groups

4. Quality of life

Van Hazel et al. (2004) report on quality of life assessment using both a patient-based assessment (FLIC, Functional Living Index—Cancer) and a physician-based assessment (Spitzer index). Changes from baseline patient-rated quality of life for the first 3 months of treatment were analysed by *t*-test, and were found to be almost identical in both treatment groups ($P = 0.96$). This was also the case for physician-rated quality of life ($P = 0.98$).

Similarly, in the Gray et al. (2001) trial, no significant difference between the two study arms could be observed. The quality of life scores improved over the first 18 months in both treatment groups. Of the 11 measures used in the quality of life assessment, only sexual interest/ability deteriorated.

Evidence from case series

Evidence from four case series reporting on efficacy in CLM patients is presented in this following section. Effectiveness data are reported inconsistently across the papers and provide limited additional information.

1. Survival

The two case series reporting on survival showed a median survival of around 10 months (Gray et al. 2000; Stubbs et al. 2001b). Gray et al. (2000b) reported a median survival of 9.9 months (mean 12 months) from the administration of SIR-Spheres and of 17.3 months from the diagnosis of liver metastases in patients receiving SIR-Spheres and HAC. Similarly, Stubbs et al. (2001) found a median survival of 9.8 (range 1.0–30.3) months from the administration of SIR-Spheres (and HAC in 86% of patients) and 14.5 (range 1.9–91.4) months from the diagnosis of liver metastases.

Both case series also separately investigated patients who had liver metastases only. In Gray et al. (2000), survival was improved in this patient group, with a median survival of 13.5 months calculated from the time of administration of SIR-Spheres (Gray et al. 2000). Stubbs et al. (2001b) compared patients with extrahepatic liver disease within 6 months of treatment to those with liver metastases only. A statistically significant difference between survival was found between the groups, with a median survival of 6.9 (range 1.3–18.8) months in the group with extrahepatic metastases compared to 17.5 (range 1.0–30.3) months in the group with liver metastases only (Stubbs et al. 2001b).

2. Tumour response

The measurement of tumour response varied across papers, which variously used outcomes of tumour size, tumour area, tumour volume and changes in tumour markers.

Stubbs et al. (2001b) reported on tumour response as 'a definite reduction in lesion size, no enlarging or new lesions', with response present in 73 per cent (32/44) of patients at 3 months and in 82 per cent (23/28) of patients at 6 months of follow-up. In Lim et al. (2005a), 32 per cent (10/31) of patients with CLM had at least a 30 per cent decrease in the sum of target lesions at 2 months after treatment, which was defined as a partial response (Lim et al. 2005a).

A decrease in tumour volume was seen in 82 per cent (18/22) of patients in Gray et al. (1992) and 86 per cent (44/51) of patients in Gray et al. (2000), among whom 45 per cent (10/22) and 55 per cent (28/51) of patients showed a decrease in tumour volume of over 50 per cent.

A tumour response in terms of CEA level decrease was observed in three of the included case series. In Stubbs et al. (2001b), 94 per cent (32/34) of patients showed a decrease in CEA levels after 3 months. In the Gray et al. (1992; 2000) case series, a more than 50 per cent decrease in CEA was observed in 88 per cent (23/28) and 55 per cent (31/60) of patients. Normalisation of CEA levels in these series was found in 35 per cent (9/26) and 37 per cent (22/60) of patients (Gray et al. 1992; Gray et al. 2000).

Summary

The evidence for the efficacy of SIR-Spheres in CLM is based on two small RCTs (level II evidence), one comparing SIR-Spheres and systemic chemotherapy with systemic chemotherapy alone, and one comparing SIR-Spheres and hepatic arterial infusion with hepatic arterial infusion alone. These data are supplemented by four uncontrolled case series reports (level IV evidence), one which evaluated SIR-Spheres as a standalone treatment, and three which evaluated the efficacy of SIR-Spheres with HAC in all or a proportion of studied patients.

Survival improved when SIR-Spheres was used in combination with systemic chemotherapy (5-FU/LV) compared with chemotherapy alone. In the van Hazel et al. trial (2004) SIR-Spheres plus systemic chemotherapy gave a median survival time of 29.4 months, compared to 12.8 months in the systemic chemotherapy arm. This difference was statistically significant (HR 0.33; 95% CI 0.12–0.91; $P = 0.025$). This trial was of good quality, however the small sample size ($n = 21$) may limit the generalisability of its findings. Furthermore, in interpreting the results from the trial, it is important to recognise that SIR-Spheres was used in combination with systemic chemotherapy regimens which are no longer considered standard practice any more. The survival benefit of adding SIR-Spheres to current standard systemic chemotherapy regimens (FOLFOX/FOLFIRI) remains unknown.

There is a trend of improved overall survival in patients treated with SIR-Spheres and HAC. The Gray et al. trial (2001) showed a median survival of 17 months in the SIR-Spheres plus HAC arm compared to 15.9 months in the HAC-only arm, however this difference was not statistically significant (HR = 1.41; 95% CI 0.86–2.34; $P = 0.18$). The trial was insufficiently powered to detect a survival change, as recruitment closed early at 74 patients instead of the intended 95. Two case series report a median survival of around 10 months after SIR-Spheres and HAC treatment, but these studies are only of fair quality and provide only weak evidence (Gray et al. 2000; Stubbs et al. 2001b).

Progression-free survival (time to disease progression at any site) was significantly longer in patients treated with SIR-Spheres and systemic chemotherapy, with a median time to disease progression of 18.6 months compared with 3.6 months in the systemic chemotherapy arm only ($P < 0.0005$) (van Hazel et al. 2004). Gray et al. (2001) reported a statistically significantly delayed time to disease progression in the liver (hepatic progression-free survival) for SIR-Spheres and HAC, with a median time to disease progression of approximately 16 months, compared to 10 months in the HAC-only group, when measuring progression from tumour area, and 12 months compared to 8 months when measuring progression from tumour volume. Disease progression was not measured using standard RECIST criteria, which limits the interprability of these results.

Anti-tumour activity was demonstrated in both RCTs and in all four included case series. However, tumour response was measured and evaluated in various ways in the trials, with only the van Hazel et al. (2004) trial using the standard RECIST criteria. Under these criteria, a significant response could be observed in the SIR-Spheres and systemic chemotherapy arm compared to the systemic chemotherapy-only arm, in which no patients had a tumour response (van Hazel et al. 2004).

One case series (Lim et al. 2005a) indicates a tumour response when SIR-Spheres was administered as a standalone treatment. This evidence is insufficient to make any statement about any benefit from SIR-Spheres as a standalone treatment.

Hepatocellular carcinoma indication

No controlled trial evidence evaluating the use of SIR-Spheres for HCC was identified from the primary SIR-Spheres literature search. The evidence on which to assess SIR-Spheres in HCC is limited to two case-series (Lau et al. 1998; Lau et al. 1994).

1. Survival

The median survival was 9.4 months (range 1.8 to 46.4 months) in the Lau et al. (1998) case series and 7.1 months in the Lau et al. (1994) case series. The Lau et al. (1994) case series looked at effects of different radiation doses, and found that patients who received radiation doses greater than 120 Gy had a statistically significantly greater median survival (55.9 weeks) than the patients who received less than 120 Gy (26.2 weeks).

2. Tumour response

In the Lau et al. (1998) case series, a 50 per cent reduction in tumour volume (CT scan) was seen in 19 of 71 patients (26.7%). Four of these patients were able to undergo residual tumour resection, as their tumours responded to the SIR-Spheres therapy and their liver function was satisfactory. In the 46 patients who had an elevated pretreatment level of AFP (>100 ng/mL), the AFP showed a drop in 41 of these patients. Overall, 31 (67%) patients had a partial response and 10 (22%) had complete response in terms of AFP levels.

Lau et al. (1994) evaluated 16 of 18 patients for tumour volume on follow-up CT scans. Partial response occurred in eight patients. Patients who received a dose of greater than 120 Gy had a statistically significantly better response rate (7 out of 8 patients) than patients who received a dose less than 120 Gy (1 out of 8 patients). Ten of the 18 patients had raised AFP (>300 ng/mL) before treatment, and a drop of 80 per cent or more occurred in eight of those ten.

Summary

Two case series of fair quality (Level IV evidence) provide weak evidence to support the efficacy of SIR-Spheres in treating patients with HCC. Both case series evaluated survival, however as neither study was performed with a comparative population, it is not possible to draw conclusions about the effectiveness of SIR-Spheres in patients with HCC with regard to survival. Anti-tumour activity was evident in both case series, but standard methods for measuring tumour response were not used. Quality of life was not reported in either of the case series.

In contrast to the lack of evidence for the effectiveness of SIR-Spheres in patients with HCC, controlled trial evidence exists for the use of both TACE and ^{131}I-lipiodol in this patient population. As outlined in the Background section of this report, there are two recently published systematic reviews evaluating the use of TACE in patients with HCC. Llovet and Bruix (2003) conducted a meta-analysis which showed a significant improvement in 2-year survival in patients treated with TACE compared to patients treated conservatively (OR 0.53, 95% CI 0.32–0.89, $P = 0.017$). An RCT of TACE versus ^{131}I-lipiodol in patients with HCC found no statistically significant difference in survival between the two groups, but survival at 4 years was 10.2 per cent in the ^{131}I-lipiodol group and 0 per cent in the TACE group.

What are the economic considerations?

Economic evaluation of new health care technologies is particularly important where the new technology offers health benefits at additional cost. It is clear that there will always be a limit to the additional cost which would be paid for a given health gain. Economic evaluation is generally aimed at determining whether such incremental costs represent value for money.

The usual process for an economic evaluation is first to consider the additional benefits accrued with the new device or procedure relative to the comparator (ie the incremental effectiveness), and to then proceed with determining cost differences between the new procedure and the comparator (ie incremental costs). When both of these quantities are known, an incremental cost-effectiveness ratio can be determined. The calculation of an incremental cost-effectiveness ratio (ICER) is:

$$ICER = \frac{Cost_{NEW} - Cost_{COMPARATOR}}{Effectiveness_{NEW} - Effectiveness_{COMPARATOR}}$$

In cases where a new technology offers inferior or equal health benefits at a higher cost, it clearly does not provide value for money. This technology is "dominated" by the comparison technology. In cases where the new technology offers superior health benefits at a lower cost to the comparator, it is said to be "dominant".

Literature search

A literature search was conducted to identify published papers of economic evaluations of SIR-Spheres to the end of March 2005. The search of NHS and international HTA agencies' databases described in the Approach to Assessment section of this report did not find any economic evaluations of SIR-Spheres treatment for hepatic metastases secondary to CRC.

A broad search strategy was defined to search the databases Medline, Premedline, Embase and Current Contents. Table 20 outlines the search terms used for the Medline search. These terms were adjusted for searches in other databases according to the system of subject headings used.

Table 20 Medline search strategy for the economic evaluation

Number	Search string
1	exp microspheres/
2	exp Yttrium radioisotopes/
3	microsphere$.mp.
4	SIRT.mp.
5	(SIR-Sphere$ or (SIR adj Sphere$)).mp.
6	(select$ adj3 intern$ adj3 (radiat$ or radiother$)).mp.
7	or/ 1–6
8	Exp cost-benefit analysis/
9	Exp cost and cost analysis/
10	Exp economics, medical/
11	Exp economics, hospital/
12	Exp technology assessment, biomedical/
13	Exp health care costs/
14	Economic evaluation$.mp
15	Cost$.mp
16	Cost-utility analysis.tw
17	Cost-effectiveness analysis.tw
18	Or/ 8–17
19	7 and 18

These searches identified 273 non-duplicate references: 78 in Medline, 191 in Embase and 4 in Current Contents. None of the identified studies, however, provided relevant information on the cost-effectiveness of SIR-Spheres.

Economic evaluations—patients with hepatic metastases from colorectal cancer

A trial-based economic model supplied by the applicant and a exploratory economic evaluation were used to evaluate the cost-effectiveness of SIR-Spheres and systemic chemotherapy in patients with CLM. The comprehensive cost-effectiveness analysis provided by the applicant is based on the randomised trial comparing SIR-Spheres and 5-FU/LV to 5-FU/LV alone (van Hazel et al. 2004).

As 5-FU/LV alone is no longer used in current clinical practice (Advisory Panel, December 2004), an exploratory economic evaluation was conducted to determine the cost-effectiveness of SIR-Spheres when used in combination with current chemotherapy regimens compared to current chemotherapy regimens alone. These current chemotherapy regimens are:

1. FOLFOX6: oxaliplatin plus 5-FU/LV
2. FOLFIRI: irinotecan plus 5-FU/LV.

It is not clear exactly how SIR-Spheres will be used in combination with current chemotherapy regimens. Therefore, an assumption has been made that SIR-Spheres will be used in the same manner as in the van Hazel et al. (2004) trial where they were used with 5-FU/LV. How SIR-Spheres are used in clinical practice will dictate the type and magni-

tude of costs. As a result, the analyses presented here are estimates of one scenario of how SIR-Spheres may be administered.

Trial-based economic evaluation—SIR-Spheres plus 5-FU/LV vs 5-FU/LV alone

The applicant has provided a trial-based economic evaluation of SIR-Spheres plus 5-FU/LV versus 5-FU/LV alone, which is based on the van Hazel et al. (2004) trial. As this is the only direct comparison with a systemic chemotherapy regimen available, the analysis has been included here.

Clinical outcomes—survival

As at 7 January 2004, with a median follow-up time of 14.4 months, the applicant reports that the area under the survival curve for the 11 patients randomised to SIR-Spheres plus 5-FU/LV is 26.187 months, and the area under the curve for the 10 patients randomised to 5-FU/LV alone is 12.521 months.

The applicant indicated that to make comparisons of expected survival (area under the curve) of the two groups, a bootstrap procedure was required to obtain the distribution of the area under the curve. Five thousand random samples with replacement of size 11 and 10 were generated for each of the SIR-Spheres plus 5-FU/LV and 5-FU/LV alone groups. Distributions are provided in Appendix 6 of the application. The results are presented in Table 21.

Table 21 Overall survival—bootstrapped estimates (months)

	SIR-Spheres + 5-FU/LV	5-FU/LV alone
Median overall survival	24.37	12.49
Mean overall survival	24.41	12.58
Bootstrapped difference (mean and median)	11.84	
95% CI of difference	2.89–20.75	

Cost estimates

The cost component of this analysis has been divided into costs associated with the work-up required for treatment initiation, the treatment procedure itself, adverse events associated with the procedure and follow-up costs that are summarised in Table 26. The unit cost estimates have been updated to reflect updates in Pharmaceutical Benefits Scheme (PBS) and MBS prices, with the most recently available estimates used in the calculations presented here.

Work-up costs

The following assumptions have been made by the applicant in calculating costs associated with the work-up of patients (Table 22):

- All patients in both arms receive CT scan with contrast of lungs and abdomen to identify extrahepatic disease (divided equally between equipment <10 years old and >10 years old).

- SIR-Spheres patients undergo selective arteriography of >1 vessel.
- SIR-Spheres patients undergo hepatic angiography with digital subtraction angiography (DSA) (average number of runs per patient is 14–16)—two new MBS items requested by applicant.
- All patients in both arms undergo total body bone scan to determine extent of extrahepatic disease.
- SIR-Spheres patients undergo technetium scan with MAA to determine lung–liver shunting.

Table 22 Work-up costs

	5-FU/LV + SIR-Spheres (*n* = 11)		5-FU/LV alone (*n* = 10)	
	Total costs	Average per patient costs	Total costs	Average per patient costs
Work-up	$ 37 150	$ 3 377	$11 074	$1 107

Treatment procedure costs

The following assumptions have been made by the applicant in calculating costs associated with the treatment of patients (Table 23):

- SIR-Spheres patients undergo hepatic angiography with DSA (average number of runs per patient is 14–16)—two new MBS items requested by applicant.
- All SIR-Spheres patients require selective arteriography for placement of a microcatheter.
- All SIR-Spheres patients would require a new proposed MBS item for dosimetry, handling and injection of SIR-Spheres.
- SIR-Spheres currently costs $6800 per patient.
- All patients in SIR-Spheres arm require a single-photon emission computerized tomography (SPECT) scan to confirm placement of SIR-Spheres.
- All SIR-Spheres incur a theatre banding fee.
- Average length of stay of SIR-Spheres patients is 2.1 days.
- Total 5-FU administered in trial was 363 840 mg to SIR-Spheres patients and 137 093 mg to chemotherapy-only patients (costed at PBS item 2528C).
- Total leucovorin administered in trial was 23 565 mg to SIR-Spheres patients and 8 749 mg to chemotherapy-only patients (costed at PBS 8740B).
- Total chemotherapy administration calculated as the number of days per cycle (5) by total number of cycles for each arm: 115 for SIR-Spheres plus 5-FU/LV arm, 42 for chemotherapy-only (5-FU/LV) arm (MBS 13915).

Table 23 Treatment procedure costs

	SIR-Spheres + 5-FU/LV (*n* = 11)		5-FU/LV alone (*n* = 10)	
	Total costs	Average per patient costs	Total costs	Average per patient costs
Treatment	$186 415	$ 16 947	$ 19 833	$1 983

Adverse event costs

Adverse event (AE) rates are based upon data from the trial (van Hazel et al. 2004) and cover the time period patients were on protocol treatment (this implies until disease progression). Resource utilisation has been estimated by the applicant on the basis of expert opinion on the typical management for each type and grade of adverse event. The total adverse event treatment costs are shown in Table 24.

The applicant has included all AE types for which at least one patient in either arm experienced a Grade 3 or 4 event. The AEs included by the applicant were abdominal pain, granulocytopaenia, leukopaenia, nausea/vomiting, mucositis, gastritis, diarrhoea, anorexia, liver cirrhosis and liver abscess. The AEs not included by the applicant were changes in haemoglobin, bilirubin, Alanine aminotransferase (ALT), creatinine, alkaline phosphatase, aspartate aminotransferase (AST), tiredness and urinary frequency.

Table 24 Adverse event treatment costs

Trial	SIR-Spheres + 5-FU/LV (*n* = 11)		5-FU/LV alone (*n* = 8)	
	Total costs	Average per patient costs	Total costs	Average per patient costs
Adverse events	$ 32 605	$2 964	$ 17 092	$2 136

Follow-up costs

The following assumptions have been made by the applicant in calculating costs associated with the follow-up of patients:

- All SIR-Spheres patients receive an H2 receptor antagonist (PBS 1978D), 150 mg twice daily for 30 days.
- Administration of 5HT3 receptor antagonist (ondansetron): SIR-Spheres patients receive 8 mg twice daily for 6 days (3 packs of PBS 8225X); patients in chemotherapy-only arm receive one pack..
- All patients receive ongoing monitoring of disease
    - monthly blood tests
    - 3-monthly CT scans
    - attendance with consultant physician every 2 months.
- SIR-Spheres patients had a median survival of 24.4 months, during which time they would have undergone 24 blood tests, 8 CT scans and 12 attendances with a physician.
- Chemotherapy (5-FU/LV)-only patients had a median survival of 12.5 months, during which time they would have undergone 12 blood tests, 4 CT scans and 6 attendances with a physician.

The above assumptions may not accurately reflect current clinical practice, so the follow-up costs shown in Table 25 may overestimate the follow-up costs in clinical practice.

Table 25 Follow-up costs

Trial	SIR-Spheres + 5-FU/LV (*n* = 11)		5-FU/LV alone (*n* = 10)	
	Total costs	Average per patient costs	Total costs	Average per patient costs
Follow-up	$ 68 401	$ 6 219	$30 616	$ 3 062

Total costs per patient

Table 26 Average total cost per patient

Component	SIR-Spheres + 5-FU/LV	5-FU/LV alone
Work-up	$3 377	$1 107
Treatment	$16 947	$ 1 983
Adverse events	$2 964	$2 136
Follow up	$ 6 219	$3 062
Total average cost per patient	$ 29 507	$8 288

Incremental cost-effectiveness analysis

The base case analysis indicates a cost-effectiveness ratio of $21 938 per life year gained (LYG), based on bootstrapped estimates of survival difference, and estimates of resource utilisation discussed above (Table 27).

Table 27 Incremental cost-effectiveness estimates

Treatment	Average cost per patient	Average survival per patient (bootstrapped estimates)	Cost per LYG
SIR-Spheres + 5-FU/LV	$29 507	2.034	
5-FU/LV alone	$8 288	1.048	
Incremental difference	$21 219	0.987	$21 524

Sensitivity analyses

The applicant performed a series of sensitivity analyses around survival estimates and associated follow-up costs with increasing survival. The most pertinent results are presented in Tables 28 and 29.

1. Upper and lower confidence limits of survival difference only—not taking into account changes in follow-up costs with changing survival duration (Table 28).

Table 28 Sensitivity analysis estimates based on survival changes alone

Treatment	Average cost per patient	Average survival per patient (bootstrapped estimates)	Cost per LYG
SIR-Spheres + 5-FU/LV	$29 507		
5-FU/LV	$8 288		
Incremental difference in survival (base case)	$21 219	0.9867	$21 524
Incremental difference in survival (upper 95% CI)	$21 219	1.7292	$12 270
Incremental difference in survival (lower 95% CI)	$21 219	0.2408	$88 119

2. Upper and lower confidence limits of survival difference, also taking into account changes in follow-up costs with changing survival duration (Table 29).

a. Using the upper 95 per cent confidence limit of incremental efficacy (20.75 months), this gives a total survival duration of 12.521 months + 20.75 months = 33.271 months in the SIR-Spheres arm.

Follow-up costs will therefore reflect 33 blood tests, 11 CT scans and 16 consultations: Total follow-up costs of $8 427.68 for the SIRT plus 5-FU/LV arm.

b. Using the lower 95 per cent confidence limit of incremental efficacy (2.89 months), this gives a total survival duration of 12.521 months + 2.89 months = 15.411 months in the SIRT arm.

Follow-up costs will therefore reflect 15 blood tests, 5 CT scans and 7 consultations: Total follow-up costs of $3 945.83 for the SIR-Spheres plus 5-FU/LV arm.

Table 29 Sensitivity analysis estimates based on survival changes and associated change in follow-up costs

Treatment	Average cost per patient	Average survival per patient (bootstrapped estimates)	Cost per LYG
Incremental difference in survival (base case)	$21 219	0.9867	$21 524
Incremental difference in survival (upper 95% CI)	$23 855	1.7292	$13 795
Incremental difference in survival (lower 95% CI)	$19 373	0.2408	$80 440

Conclusions of trial-based economic evaluation

The incremental cost per LYG for SIR-Spheres and 5-FU/LV compared to 5-FU/LV alone is $21 524 in the base case analysis. The cost ranges from $12 270 per LYG to $88 440 per LYG in sensitivity analyses.

Exploratory economic evaluation—SIR-Spheres plus FOLFOX6/FOLFIRI vs FOLFOX6/FOLFIRI alone

Expert advice from the Advisory Panel indicates that 5-FU/LV alone is no longer used in current clinical practice. Patients are now commonly treated with the following alternative regimens (NCI 2005):

- **FOLFOX6 regimen** (oxaliplatin, leucovorin, 5-FU):
  Oxaliplatin (85–100 mg/m^2) as a 2-hour infusion day 1; leucovorin (400 mg/m^2) as a 2-hour infusion day 1; followed by a loading dose of 5-FU (400 mg/m^2) IV bolus on day 1, then 5-FU (2400–3000 mg/m^2) via ambulatory pump over 46 hours every 2 weeks.

- **FOLFIRI regimen** (leucovorin, 5-FU, irinotecan):
  Irinotecan (180 mg/m^2) as a 2-hour infusion day 1; leucovorin (400 mg/m^2) as a 2-hour infusion day 1; followed by a loading dose of 5-FU (400 mg/m^2) IV bolus on day 1, then 5-FU (2400–3000 mg/m^2) via ambulatory pump over 46 hours every 2 weeks.

An economic evaluation needs to compare the new service against current clinical practice. In this case SIR-Spheres are likely to be used in addition to current chemotherapy regimens, which include irinotecan or oxaliplatin in combination with 5-FU/LV. As indicated earlier, there are various possible clinical scenarios in which SIR-Spheres may be used in addition to current chemotherapy regimens. This evaluation represents one of these scenarios. The costs here should therefore be viewed as estimates of one possible clinical scenario, as other scenarios may result in different costs.

As there are no trials comparing current chemotherapy regimens with and without SIR-Spheres, we have attempted to quantify the range of likely cost-effectiveness by estimating costs and outcomes for SIR-Spheres plus FOLFOX6/FOLFIRI versus FOLFOX6/FOLFIRI alone.

Estimates of the treatment benefits and side-effects of newer chemotherapy regimens used in this evaluation were based on information and references provided by the Advisory Panel. Additional systematic reviews were not performed to inform these estimates. Estimates of the survival benefits of FOLFOX6 and FOLFIRI were extracted from a high-quality RCT reported by Tournigand et al. (2004), which best described the way these regimens are used in Australia.

Clinical outcomes—estimates of survival

Survival with FOLFOX6/FOLFIRI

In a study of sequential FOLFIRI/FOLFOX6 (A) versus FOLFOX6/FOLFIRI (B) Tournigand et al. (2004) estimated the median survival of arm A at 21.5 months and arm B at 20.6 months. The Advisory Panel has estimated that, in appropriate patients, the ratio of FOLFOX6 to FOLFIRI is approximately 80:20. This gives an overall weighted survival estimate of 20.78 months for FOLFOX6/FOLFIRI.

The following assumptions relating to the magnitude of the survival benefit of SIR-Spheres in addition to FOLFOX6/FOLFIRI have been made:

- Same absolute survival benefit in adding SIR-Spheres to FOLFOX6/FOLFIRI as reported for the combination of SIR-Spheres and 5-FU/LV
  —As the absolute survival benefit of adding SIR-Spheres to 5-FU/LV is 11.84 months, the survival in patients treated with SIR-Spheres + FOLFOX6/FOLFIRI is 32.62 months.

- Same relative benefit in adding SIR-Spheres to FOLFOX6 as reported for the combination of SIR-Spheres and 5-FU/LV.
  —As adding SIR-Spheres to 5-FU/LV led to a relative survival benefit of 24.37 months / 12.49 months = 1.95, the survival in patients treated with SIR-Spheres + FOLFOX6/FOLFIRI is 40.52 months.

- Same overall survival for SIR-Spheres and FOLFOX6/FOLFIRI as reported for the combination of SIR-Spheres and 5-FU/LV
  —Therefore, the survival in patients treated with SIR-Spheres + FOLFOX6/FOLFIRI is 24.37 months.

These assumptions are summarised in Table 30.

Table 30 Assumptions relating to magnitude of survival benefit for SIR-Spheres + FOLFOX6/FOLFIRI

Treatment	FOLFOX6/FOLFIRI + SIR-Spheres	FOLFOX6/FOLFIRI
Assumption 1		
Same absolute overall survival benefit as for adding SIR-Spheres to 5-FU/LV	32.62	20.78
Incremental difference in overall survival (months)	11.84	
Assumption 2		
Same relative overall survival benefit as for adding SIR-Spheres to 5-FU/LV	40.55	20.78
Ratio of survival in SIRT arm: chemo only	1.95	
Incremental difference in overall survival (months)	19.77	
Assumption 3		
Same overall survival for FOLFOX6/FOLFIRI + SIR-Spheres as for SIR-Spheres to 5-FU/LV	24.37	20.78
Incremental difference in overall survival (months)	3.59	

Cost estimates

The cost component of this analysis has been divided into costs associated with the work-up required for treatment initiation, the treatment procedure itself, adverse events associated with the procedure and follow-up costs.

Work-up costs

We have used a similar set of assumptions as the applicant in estimating the costs associated with the work-up of patients. The differences are as follows: the applicant included an additional 5 per cent of patients undergoing work-up (and therefore incurring work-up costs), but not receiving treatment; we have added an additional item of resource utilisation—the procedure costs for implantation of a drug delivery device for the delivery of chemotherapy.

The following assumptions have been made in calculating costs associated with the work-up of patients:

- All patients in both arms receive CT scan with contrast of lungs and abdomen to identify extrahepatic disease (divided equally between equipment <10 years old and >10 years old).
- SIR-Spheres patients undergo selective arteriography of >1 vessel.
- SIR-Spheres patients undergo hepatic angiography with DSA (average number of runs per patient is 14–16)—two new MBS items requested by applicant.
- All patients in both arms undergo total body bone scan to determine extent of extrahepatic disease.
- SIR-Spheres patients undergo technetium scan with MAA to determine lung–liver shunting.
- All patients undergo an inpatient procedure to implant drug delivery device for ambulatory chemotherapy.

The work-up costs are outlined in Table 31.

Table 31 Work-up costs

Services	Unit cost	Source	SIR-Spheres + FOLFOX6/FOLFIRI		FOLFOX6/FOLFIRI alone	
		MBS item No.	average units per pt	per pt cost[1]	average units per pt	per pt cost[1]
Attendances						
Initial consultation with consultant physician	$128.05	110	1.00	$128	1.00	$128
Pathology						
Full blood count	$17.20	65070	1.00	$17	1.00	$17
Liver function test	$19.80	66515	1.00	$20	1.00	$20
CEA and alpha-fetoprotein	$45.35	66653	1.00	$45	1.00	$45
Coagulation blood tests	$14.05	65120	1.00	$14		$0
Radiology						
CT scan with contrast (lung, abdo) (K)[2]	$560.00	56807	0.50	$280	0.50	$280
CT scan with contrast (lung, abdo) (NK)[3]	$283.85	56847	0.50	$142	0.50	$142
Selective arteriography by DSA technique—1 vessel (NR)[4]	$48.10	60072	0.25	$12	0.00	$0
Selective arteriography by DSA technique—2 vessel (NR)	$96.10	60075	0.25	$24	0.00	$0
Selective arteriography by DSA technique—3 vessel (NR)	$144.25	60078	0.50	$72	0.00	$0
Hepatic angiogram / DSA 1–9 runs (siting microcatheter during work-up)	$1 376.60	requested	0.25	$344	0.00	$0
Hepatic angiogram / DSA 10 + runs (siting microcatheter during work-up)	$1 867.30	requested	0.75	$1 400	0.00	$0
Tumour arterial embolisation / occlusion	$690.05	35321	0.10	$69	0.00	$0
Nuclear medicine						
Total body bone scan	$475.05	61421	1.00	$475	1.00	$475
Technetium 99m with MAA for lung/liver breakthrough (particle perfusion study)	$250.50	61499	1.00	$251	0.00	$0.00
Resources associated with preparation for ambulatory chemotherapy administration						
Theatre banding	$1 798.00		1.00	$1 798	1.00	$1 798
Days admitted to hospital	$390.00	NHCDC[5] (Round 6)	1.00	$390	1.00	$390
Insertion of implantable pump (open procedure)	$468.05	34527	0.50	$234	0.50	$234
Insertion of implantable pump (percutaneous procedure)	$231.10	34528	0.50	$116	0.50	$116
Total average work-up cost per patient				$5 831		$3 645

1. Costs were rounded to the nearest dollar for presentation
2. K - CT scan on equipment less than 10 years old
3. NK - CT scan on equipment 10 years or older
4. NR – no request requirements
5. NHCDC - National Hospital Cost Data Collection

Treatment procedure costs

Calculations of treatment procedure costs are displayed in tables 32-35. To simplify calculation of treatment costs, a fixed dosage regimen for FOLFOX6 and FOLFIRI was costed:

- No adjustment has been made for dosage reductions due to toxicity.
- No adjustment has been made for dosage increases (eg 5-FU—see Tournigand et al. 2004).

This means that the costs presented here are likely to be overestimates. In addition, the following assumptions have been made:

- Regimens are costed on the basis of patient mass 75 kg, height 1.75 m (estimates of average male height and weight), BSA 1.91 m^2 (Mosteller formula [Mosteller 1987]), SIR-Spheres trial 80 per cent male
- The cost of the filling pump for each cycle has been included.
- The cost of administering bolus dose and infusion for each cycle is included.
- Each patient receives two packs of ondansetron for each cycle of chemotherapy (8 mg twice daily for 4 days).
- The number of cycles of chemotherapy administered is based on median number of cycles from Tournigand et al. (2004) and van Hazel et al. (2004):
    - FOLFOX6/FOLFIRI arm: median number of cycles as per Tournigand et al. (2004):
      —FOLFIRI 1st line, 13 cycles; FOLFOX6 2nd line, 8 cycles
      —FOLFOX6 1st line, 12 cycles; FOLFIRI 2nd line, 6 cycles
    - SIR-Spheres + FOLFOX6/FOLFIRI arm:
      —Expert advice suggested the maximum number of first line cycles of FOLFOX6/FOLFIRI would be 10. Second line cycles have been kept as per Tournigand et al. (2004) (using 20 cycles has been tested in a sensitivity analysis)
    - It has been assumed that 2nd line cycles are as per Tournigand et al. (2004)
      —FOLFIRI 1st line, 10 cycles; FOLFOX6 2nd line, 8 cycles
      —FOLFOX6 1st line, 10 cycles; FOLFIRI 2nd line, 6 cycles.
- 80 per cent of patients receive FOLFOX6 as first line treatment; 20 per cent of patients receive FOLFIRI as first line treatment.
  —The total number of cycles of FOLFOX6 and FOLFIRI is weighted by these proportions.

The following assumptions were made by the applicant in calculating costs associated with the treatment of patients with SIRT, and are also applicable here:

- SIR-Spheres patients undergo hepatic angiography with DSA (average number of runs per patient is 14–16)—two new MBS items requested by applicant.

- All SIR-Spheres patients require selective arteriography for placement of a microcatheter.
- All SIR-Spheres patients would require a new proposed MBS item for dosimetry, handling and injection of SIR-Spheres.
- SIR-Spheres currently costs $6800 per patient.
- All patients in the SIR-Spheres arm require a SPECT scan to confirm placement of SIR-Spheres.
- All SIR-Spheres patients incur a theatre banding fee.
- Average length of stay of SIR-Spheres patients is 2.1 days.

Table 32 Resource use associated with SIR-Spheres treatment

			SIR-Spheres + FOLFOX6/FOLFIRI		FOLFOX6/FOLFIRI	
Service	Unit cost	MBS item No.	Average units per patient	Per pt cost[1]	Average units per patient	Per pt cost[1]
Hepatic angiogram / DSA 1–9 runs (siting microcatheter during work-up)	$1 376.60	requested (applicant)	0.25	$344	0	$0
Hepatic angiogram / DSA 10 + runs (siting microcatheter during work-up)	$1 867.30	requested (applicant)	0.75	$1 400	0	$0
Selective arteriography by DSA technique—1 vessel (NR)[2]	$48.10	60072	0.25	$12	0	$0
Selective arteriography by DSA technique—2 vessel (NR)	$96.10	60075	0.25	$24	0	$0
Selective arteriography by DSA technique—3 vessel (NR)	$144.25	60078	0.50	$72	0	$0
Tumour arterial embolisation / occlusion	$690.05	35321	0.10	$69	0	$0
Dosimetry, handling and injection of SIRT	$300.00	requested (applicant)	1.00	$300	0	$0
SIR-Spheres	$6 800.00	current price	1.00	$6 800	0	$0
SPECT study (liver and spleen)	$382.75	61353	1.00	$383	0	$0
Theatre costs	$1 798.00		1.00	$1 798	0	$0
Days admitted to hospital	$390.00	NHCDC[3] cost report round 6	2.10	$819	0	$0
Total costs associated with SIRT				$12 022		$0

1. Costs were rounded to the nearest dollar for presentation
2. NR – no request requirements
3. NHCDC - National Hospital Cost Data Collection

Table 33 Cost per cycle of chemotherapy

FOLFOX6	Unit cost	Source	Dose mg/m^2	BSA (70 kg; 1.75 m)	Average mg/cycle	Total $/cycle[1]
Oxaliplatin (2-h infusion day 1)	$ 8.4299	dispensed price/mg PBS 8540L	100.00	1.91	191.0	$1 610
5-FU loading dose	$0.01328	dispensed price / mg (PBS 2528C)	400.00	1.91	764.0	$10
5-FU ambulatory infusion (2400–3000 mg/m^2—median used)	$0.01328	dispensed price/mg (PBS 2528C)	2700.00	1.91	5157.0	$68
LV (2-h infusion day 1)	$ 0.7338	dispensed price/mg (PBS 8740B)	400.00	1.91	764.0	$561
Total cost per cycle FOLFOX6						$2 249
FOLFIRI						
Irinotecan (2-h infusion day 1)	$3.9235	dispensed price/mg PBS 8415X	180.00	1.91	343.8	$1 349
5-FU loading dose	$0.01328	dispensed price/mg (PBS 2528C)	400.00	1.91	764.0	$10
5-FU ambulatory infusion (2400–3000 mg/m^2—median used)	$0.01328	dispensed price/mg (PBS 2528C)	2700.00	1.91	5157.0	$68
LV (2-h infusion day 1)	$ 0.7338	dispensed price/mg (PBS 8740B)	400.00	1.91	764.0	$561
Total cost per cycle FOLFIRI						$1 988

1. Costs were rounded to nearest dollar for presentation

Table 34 Resource use associated with chemotherapy use

			SIR-Spheres + FOLFOX6/FOLFIRI		FOLFOX6/FOLFIRI	
	Unit cost	Source MBS item No.	Average units per patient	Total average per pt cost[1]	Average units per patient	Total average per pt cost[1]
			No. cycles		No. cycles	
Median number of cycles FOLFOX6 per patient (1st line and 2nd line) (1 cycle = 2 weeks)	$2 249.36		9.60	$21 594	11.20	$25 193
Median number of cycles FOLFIRI per patient (1st line and 2nd line) (1 cycle = 2 weeks)	$1 988.15		6.80	$13 519	7.40	$14 712
Injection of chemotherapy (<1 h) (5-FU bolus once per cycle)	$55.20	13915	16.400	$905	18.600	$1 026
Injection of chemotherapy (1–6 h) (2-h infusions)	$83.05	13918	16.400	$1 362	18.600	$1 545
Implantable device loading (once per cycle)	$83.05	13939	16.400	$1 362	18.600	$1 545
5HT3 receptor antagonist (ondansetron) (2 packs per cycle)	$73.68	PBS 8225X	32.800	$2 417	37.200	$2 741
Total chemotherapy treatment costs per patient				$41 159		$46 762
Sensitivity analysis—20 cycles—Total chemotherapy costs per patient				*$66 817*		

1. Costs were rounded to nearest dollar for presentation

Table 35 Total treatment costs

	SIR-Spheres + FOLFOX6/FOLFIRI	FOLFOX6/FOLFIRI
Total costs associated with SIR-Spheres	$12 022	$0
Total chemotherapy costs per patient	$41 159	$46 762
Total treatment costs (SIR-Spheres + chemotherapy) per patient	$53 181	$46 762
Sensitivity analysis 20 cycles first line	*$66 817*	
Sensitivity analysis 20 cycles first line (total treatment costs)	*$78 389*	

Adverse event costs

Adverse event rates are based on data from the Tournigand et al. (2004) trial of FOLFOX6/FOLFIRI, supplemented with data on likely SIR-Spheres-related AEs from the application and the van Hazel et al. (2004) trial. Adverse events were recorded for the time when patients were on protocol treatment (median number of cycles of chemotherapy, see table 36) that was calculated on the basis of assumptions discussed on page 61 and summarised here:

- FOLFOX6/FOLFIRI arm: median number of cycles as per Tournigand et al. (2004):
  —FOLFIRI 1st line, 13 cycles; FOLFOX 2nd line, 8 cycles
  —FOLFOX6 1st line, 12 cycles; FOLFIRI 2nd line, 6 cycles.

- SIRT + FOLFOX6/FOLFIRI arm:
  —FOLFIRI 1st line, 10 cycles; FOLFOX 2nd line, 8 cycles
  —FOLFOX6 1st line, 10 cycles; FOLFIRI 2nd line, 6 cycles.

- 80 per cent of patients receive FOLFOX as first line treatment; 20 per cent of patients receive FOLFIRI as first line treatment.

The Advisory Panel has indicated that FOLFOX6/FOLFIRI can lead to radiosensitisation. It is therefore possible that the use of SIR-Spheres with these new chemotherapy regimens may lead to increases in the number and seriousness of radiation-related adverse events. These events have not been costed here because the pattern of AEs with SIR-Spheres plus FOLFOX6/FOLFIRI is unclear at this stage. Costs here may therefore represent an underestimate of adverse event treatment costs.

We used the applicant's estimate of resource utilisation for management of each type and grade of adverse event (based on expert opinion), supplemented by advice from the Advisory Panel. Using 20 cycles instead of 10 cycles of chemotherapy as first line has been tested in a sensitivity analysis.

Where the applicant and Tournigand et al. (2004) have both reported the occurrence of particular AEs, rates from Tournigand et al. (2004) have been used. Adverse events reported by the applicant in the SIR-Spheres group, but not by Tournigand et al. (2004), were included for the SIR-Spheres plus FOLFOX6/FOLFIRI group in our analysis. These AEs were assumed to be related to SIR-Spheres administration.

The AEs assumed related to FOLFOX6/FOLFIRI administration (those reported by both the applicant and Tournigand et al. 2004), and included for both treatment groups

were neutropaenia, thrombocytopaenia, anaemia, febrile neutropaenia, nausea/vomiting, diarrhoea, mucositis, and cutaneous and neurological adverse events. In addition, patients were assumed to experience the following AEs at the rates reported by the applicant—abdominal pain, gastritis, anorexia, liver cirrhosis, liver abscess (Attachment E).

The mean costs for treating adverse events were $2968 in patients receiving SIR-Spheres plus chemotherapy and $2108 in the chemotherapy alone arm. A summary of the total per-patient cost for each type of adverse event is shown in table 37. Full details, including grade of AE, are available in Appendix J.

Table 36 Adverse event costs: median cycles of FOLFOX6/FOLFIRI for AE calculations

	SIR-Spheres + FOLFOX6/FOLFIRI	FOLFOX6/FOLFIRI alone
Median number of cycles FOLFOX6 per patient (1st line and 2nd line)	9.6	11.2
Median number of cycles FOLFIRI per patient (1st line and 2nd line)	6.8	7.4

Table 37 Adverse event costs

	SIR-Spheres + FOLFOX6/FOLFIRI		FOLFOX6/FOLFIRI alone	
Events (over all cycles, all grades)	Total No. events/pt	Cost $/pt	Total No. events/pt	Cost $ /pt
Neutropaenia	1.5191	$230.11	1.7039	$264.77
Thrombocytopaenia	1.2067	$8.73	1.3669	$10.19
Anaemia	1.3584	$66.61	1.5136	$74.54
Febrile neutropaenia	0.0258	$86.81	0.0285	$95.37
Nausea / vomiting	2.1450	$228.68	2.4077	$257.21
Diarrhoea	1.1686	$282.88	1.3033	$316.90
Mucositis	0.7607	$17.36	0.8575	$19.29
Cutaneous adverse events	0.4070	$1.50	0.4594	$1.74
Neurological adverse events	0.8757	$0.00	1.0188	$0.00
Abdominal pain	0.4545	$1 335.36	0.2000	$1.23
Gastritis	0.2727	$17.77	0.1000	$533.20
Anorexia	0.3636	$28.62	0.1000	$533.20
Cirrhosis	0.0909	$178.73	0.0000	$0.00
Liver abscess	0.0909	$484.73	0.0000	$0.00
Total average cost per patient		$2 968		$2 108
Sensitivity analyses (20 cycles)		*$3 486*		

Follow-up costs

The following assumptions have been made by the applicant in calculating costs associated with the follow-up of patients:

- All SIR-Spheres patients receive an H_2 receptor antagonist (PBS 1978D), 150 mg twice daily for 30 days.
- All patients receive ongoing monitoring of disease:
  - monthly blood tests

- 3-monthly CT scans
- attendance with consultant physician every 2 months.

The Advisory Panel indicated that this follow-up frequency was unlikely to occur in clinical practice and suggested an alternative follow-up schedule as outlined below. These estimates are used in the base case analysis, and are presented in Table 38:

- All SIR-Spheres patients receive an H_2 receptor antagonist (PBS 1978D), 150 mg twice daily for 30 days.
- All patients receive ongoing monitoring of disease:
  - 3-monthly blood tests
  - 6-monthly CT scans
  - attendance with consultant physician every 3 months.
- As there are three possible assumptions regarding survival duration in patients treated with SIR-Spheres (see Table 30), there are three possible follow-up costs for patients receiving SIR-Spheres, as follow-up depends on survival duration.

Costs of follow-up as reported by the applicant have been assessed in a sensitivity analysis (see Table 40 for results).

Table 38 Resource use associated with follow-up of patients

			SIR-Spheres + FOLFOX6 / FOLFIRI						FOLFOX6/FOLFIRI alone	
			Median survival (months) Assumption 1		Median survival (months) Assumption 2		Median survival (months) Assumption 3		Median survival (months)	
			32.62		40.55		24.37		20.78	
Services	Unit cost	Source	Average units per patient	Per pt cost[1]	Average units per patient	Per pt cost[1]	Average units per patient	Per pt cost[1]	Average units per patient	Per pt cost[1]
H2 receptor antagonist (Zantac generic)	$21.96	PBS 1978D	1.00	$22	1.00	$22	1.00	$22	0	$0
Full blood count	$17.20	MBS 65070	10.87	$187	13.52	$233	8.12	$140	6.93	$119
Liver function test × 3	$13.75	MBS 66506	10.87	$149	13.52	$186	8.12	$112	6.93	$95
CEA + alpha-fetoprotein	$45.35	MBS 66653	10.87	$493	13.52	$613	8.12	$368	6.93	$314
CT scan with contrast (lungs/abdo) (K)[2]	$560.00	MBS 56807	5.44	$3 045	6.76	$3 784	4.06	$2 274	3.46	$1 940
CT scan with contrast (lungs/abdo) (NK)[3]	$283.85	MBS 56847	5.44	$1 543	6.76	$1 918	4.06	$1 153	3.46	$983
Attendances with consultant physician	$64.10	MBS 116	10.87	$697	13.52	$866	8.12	$521	6.93	$444
Total follow-up costs per patient				$6 136		$7 622		$4 590		$3 895
Total follow-up costs per patient (sensitivity analysis)				*$12 732*		*$15 820*		*$9 517*		*$ 5 174*

1 costs were rounded to nearest dollar for presentation
2. K - CT scan on equipment less than 10 years old
3. NK - CT scan on equipment 10 years or older

Total costs per patient

The average total cost per patient (base case and sensitivity analyses) for SIR Spheres and FOLFOX6/FOLFIRI and for FOLFOX6/FOLFIRI alone are summarised in Table 39.

Table 39 Average total cost per patient

	SIR-Spheres + FOLFOX6/FOLFIRI			FOLFOX6/ FOLFIRI alone
	Assumption 1	Assumption 2	Assumption 3	
Median survival (months)	32.62	40.55	24.37	20.78
Work-up	$5 831	$5 831	$5 831	$3 645
Treatment	$53 181	$53 181	$53 181	$46 762
Adverse events	$2 968	$2 968	$2 968	$2 108
Follow-up	$6 136	$7 622	$4 590	$3 895
Total average cost per patient (base case)	$68 116	$69 602	$66 570	$56 410
Total average cost per patient (sensitivity analysis: more intensive follow-up)	*$74 712*	*$77 800*	*$71 497*	*$57 689*
Total average cost per patient (sensitivity analysis 20 cycles of FOLFOX/FOLFIRI as first line treatment)	*$94 293*	*$95 778*	*$92 746*	
Both sensitivity analyses	*$100 888*	*$103 976*	*$97 674*	*$57689*

Incremental cost-effectiveness analysis

The incremental cost-effectiveness analysis includes all three estimates of overall survival for SIR-Spheres plus FOLFOX6/FOLFIRI discussed on page 57.

The cost per life year gained (LYG) under the base case assumptions discussed above ranges from $8009 to $33 961. In a sensitivity analysis examining the effect of more intensive follow-up, the incremental cost-effectiveness ratio ranged from $12 210 to $46 157 per LYG. In a sensitivity analysis examining the effect of increasing the number of first line cycles of FOLFOX/FOLFIRI from 10 to 20, the cost per LYG ranged from $23 902 to $121 458 per LYG. These results are shown in Figures 6 and 7 and Table 40. As expected, there is considerable uncertainty surrounding these estimates, particularly associated with the magnitude of likely survival benefit gained by adding SIR-Spheres to FOLFOX6/FOLFIRI, which subsequently influences follow-up costs, and with the number of cycles of FOLFOX6/FOLFIRI that would be given in combination with SIR-Spheres.

Table 40 Incremental cost-effectiveness estimates

	Base case			Sensitivity analysis—more intensive follow-up		Sensitivity analysis—20 cycles first line chemotherapy		Both sensitivity analyses	
	Mean survival (years)	Average cost per patient ($)	Cost per LYG	Average cost per patient ($)	Cost per LYG	Average cost per patient ($)	Cost per LYG	Average cost per patient ($)	Cost per LYG
Survival assumption 1									
SIR-Spheres + FOLFOX6/FOLFIRI	2.7183	$68 116		$74 712		$94 293		$100 888	
FOLFOX6/FOLFIRI	1.7317	$56 410		$57 689		$56 410		$57 689	
Incremental difference	0.9867	$11 706	$11 865	$17 023	$17 253	$37 883	$38 395	$43 199	$43 783
Survival assumption 2									
SIRT-Spheres + FOLFOX6/FOLFIRI	3.3788	$69 602		$77 800		$95 778		$103 976	
FOLFOX6/FOLFIRI	1.7317	$56 410		$57 689		$56 410		$57 689	
Incremental difference	1.6471	$13 192	$8 009	$20 111	$12 210	$39 368	$23 902	$46 287	$28 102
Survival assumption 3									
SIR-Spheres + FOLFOX6/FOLFIRI	2.0308	$66 570		$71 497		$92 746		$97 674	
FOLFOX6/FOLFIRI	1.7317	$56 410		$57 689		$56 410		$57 689	
Incremental difference	0.2992	$10 160	$33 961	$13 809	$46 157	$36 336	$121 458	$39 985	$133 653

Figure 6 Incremental cost-effectiveness estimates for SIR-Spheres and FOLFOX6/FOLFIRI (base case)

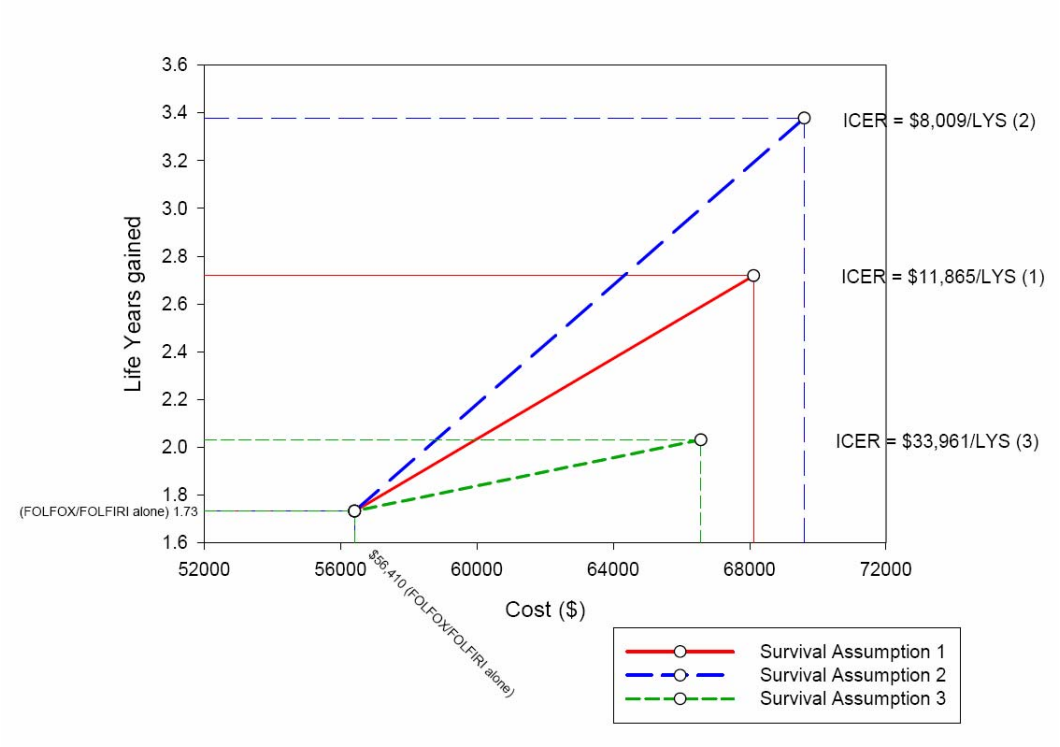
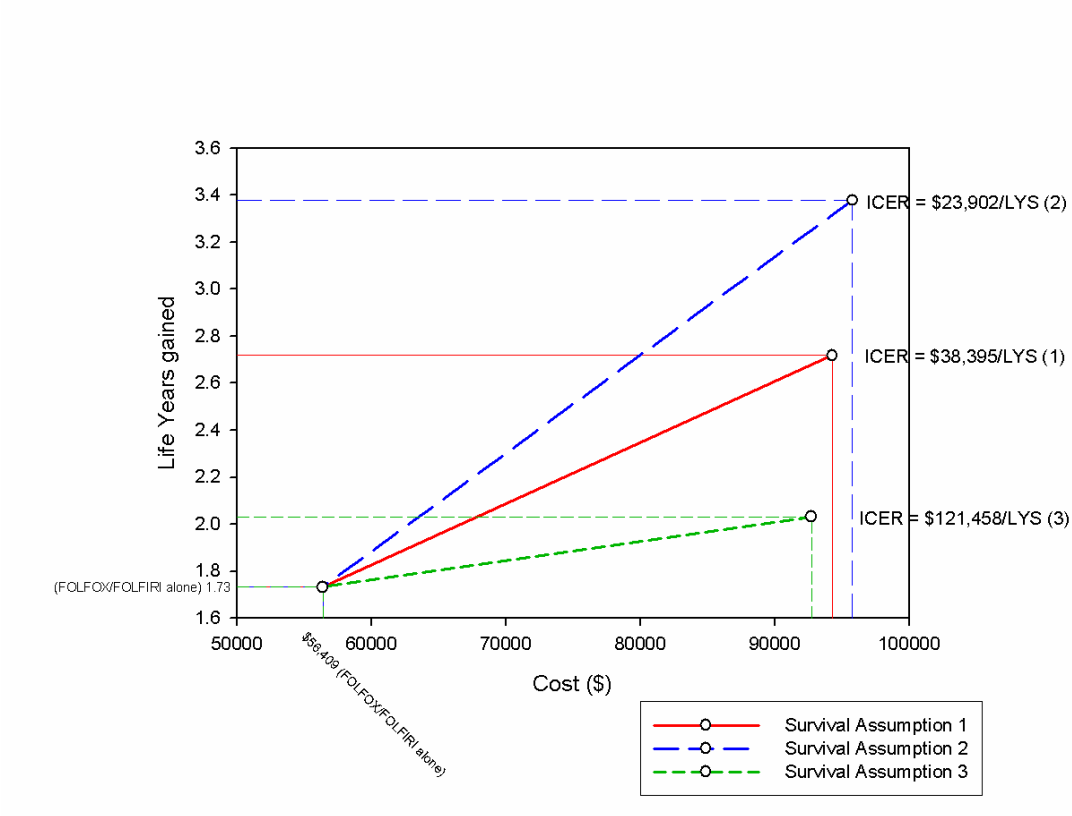


Figure 7 Incremental cost-effectiveness estimates for SIR-Spheres and FOLFOX6/FOLFIRI (sensitivity analysis—number of cycles of chemotherapy)



Limitations of these analyses

There are no trial data to indicate:

- how SIR-Spheres might be used in clinical practice with the new chemotherapy regimens, including the number of cycles of chemotherapy that would likely be used
- the magnitude of clinical benefit that might be achieved by adding SIR-Spheres to new regimens such as FOLFOX6/FOLFIRI
- the number and type of adverse events that might result from the combination of radiosensitisation caused by these chemotherapy regimens and the radiation delivered by SIR-Spheres.

Treatment costs are fixed, regardless of survival duration, and follow-up (eg monitoring) costs vary with survival. This method may overestimate or underestimate total true resource use in clinical practice depending on whether treatment duration and follow-up have fixed durations, or vary with survival.

As such, these analyses should be viewed as an exploration of the possible range of costs and benefits associated with SIR-Spheres when used in combination with FOLFOX6/FOLFIRI, over a plausible range of assumptions regarding survival magnitude. It *does not* represent a comprehensive cost-effectiveness analysis of SIR-Spheres because of the considerable uncertainties raised by the issues above. For this reason, the values presented here should not be taken as definitive.

Economic evaluation—patients with hepatocellular carcinoma

The 'Is it effective section?' of this report provides evidence of the effectiveness of SIR-Spheres as a treatment for patients with non-resectable, non-ablatable HCC. That section shows that the effectiveness of SIR-Spheres for this indication has not been well established. It is therefore inappropriate to conduct a full economic evaluation investigating the incremental costs and benefits of SIR-Spheres compared to TACE and ^{131}I-lipiodol.

In cases where effectiveness of an intervention is not established, a partial analysis examining the costs involved with the procedure and its comparators can help in getting a clearer picture about the economic aspects involved. In this case, however, costing of the comparators TACE and ^{131}I-lipiodol cannot be completed, as comprehensive information on the resource use associated with pretreatment work-up, treatment, follow-up and management of adverse events in these procedures is lacking.

Conclusions

Safety

The assessment of the safety of SIR-Spheres is based on information from seven of the eight included studies of SIR-Spheres in CLM and HCC patients, eight additional case series included for the safety assessment (3 evaluating SIR-Spheres and 5 evaluating other SIRTs), TGA data, and information provided by the applicant. Minor complications and side-effects associated with the use of SIR-Spheres include GI side-effects (abdominal pain, nausea, vomiting and diarrhoea), fever, a transient decrease in haemoglobin, and abnormal liver function tests. Major complications which have been reported include death, radiation hepatitis, radiation gastritis, radiation pneumonitis, radiation-induced cirrhosis, hepatic necrosis and gastrointestinal ulceration. Reports on the major complications from the included SIR-Spheres safety information contain seven deaths due to fatal radiation hepatitis, radiation gastritis, acute hepatic necrosis and sepsis associated with neutropaenia. Of these seven deaths, five were reported in the included studies, which evaluated a total of 503 patients. In addition, a small number of cases of radiation pneumonitis, radiation-induced cirrhosis, non-fatal radiation gastritis and gastrointestinal ulceration were found in the included studies.

- There is limited comparative evidence available to enable an assessment of the safety of SIR-Spheres compared to other therapies used in the treatment of liver tumours. Of the two comparative studies identified, one found no difference in the rate of Grades 3 and 4 toxicities between patients treated with SIR-Spheres plus HAC and patients treated with HAC alone (Gray et al. 2001). The other found 13 Grades 3 and 4 toxicities in patients treated with SIR-Spheres plus systemic chemotherapy compared to five Grades 3 and 4 toxicities in patients treated with systemic chemotherapy alone (van Hazel et al. 2004). This evidence, however, is based on older systemic chemotherapy regimens which are no longer current practice, and there was no information on the safety associated with the use of SIR-Spheres in combination with the new chemotherapy regimens.

- In addition to the safety of patients treated with SIR-Spheres, safety issues arise for personnel involved in implanting SIR-Spheres and handling the device. From the available information it appears that the doses of radiation delivered to personnel are reasonably low and are within ranges recommended by the National Occupational Health and Safety Commission (National Occupational Health and Safety Commission 1995). SIR-Spheres should be performed in approved centres to ensure that these safety standards are met.

Effectiveness

Effectiveness of SIR-Spheres for treatment of liver metastases of colorectal cancer

Six studies were identified for inclusion in the evaluation of the effectiveness of SIR-Spheres in CLM patients. These represent two small RCTs (level II evidence) and four

uncontrolled case series reports (level IV evidence). The two RCTs evaluated the use of SIR-Spheres plus HAC and SIR-Spheres plus systemic chemotherapy. In the trial comparing SIR-Spheres plus HAC to HAC alone, no statistically significant survival benefit was found, however the trial was underpowered to detect a survival difference (Gray et al. 2001). In the trial comparing SIR-Spheres plus systemic chemotherapy to chemotherapy alone, a statistically significant increase in survival was seen in patients treated with SIR-Spheres plus systemic chemotherapy (29.4 vs 12.8 months, HR 0.33; 95% CI 0.12–0.91; $P = 0.025$). This trial, however, used systemic chemotherapy regimens which no longer represent current practice. The survival advantage when SIR-Spheres are used in combination with current chemotherapy regimens is unknown. Due to the rapid evolution of chemotherapy regimens for the treatment of cancer, the feasibility of obtaining controlled trial evidence evaluating SIR-Spheres in conjunction with current chemotherapy regimens is likely to be low.

Improved tumour response rates were demonstrated for SIR-Spheres plus systemic chemotherapy and for SIR-Spheres plus HAC in both RCTs, and all four included case series indicate the anti-tumour activity of SIR-Spheres. However, tumour response was measured and evaluated in various ways, with only the van Hazel et al. (2004) trial using the standardised criteria. Using the RECIST criteria, van Hazel et al. (2004) found a statistically significant increase in tumour response rates in patients treated with SIR-Spheres plus systemic chemotherapy compared to those treated with systemic chemotherapy alone (van Hazel et al. 2004).

Effectiveness of SIR-Spheres for treatment of hepatocellular carcinoma

Two case series of fair quality were identified for inclusion in the evaluation of the effectiveness of SIR-Spheres in HCC. Both case series reported partial or complete tumour response in up to 50 per cent of patients, demonstrating that SIR-Spheres have anti-tumour activity. This provides weak evidence for the effectiveness of SIR-Spheres in patients with non-resectable, non-ablatable HCC. Without comparative studies, however, it is not possible to draw any conclusions about the relative effectiveness of SIR-Spheres compared to other existing treatments in patients with HCC.

Cost-effectiveness

Cost-effectiveness of SIR-Spheres for treatment of liver metastases of colorectal cancer

A trial-based economic model supplied by the applicant and an exploratory economic evaluation were used to evaluate the cost-effectiveness of SIR-Spheres and systemic chemotherapy in patients with CLM. The trial-based economic model is based on the van Hazel et al. (2004) trial, which compared SIR-Spheres and 5-fluorouracil plus leucovorin systemic chemotherapy (5-FU/LV) to 5-FU/LV systemic chemotherapy alone. This economic model showed that the addition of SIR-Spheres to 5-FU/LV results in an incremental cost per life year gained of $21 524 compared to 5-FU/LV alone. Sensitivity analyses show that this cost per life year gained may range from $12 270 to $88 119; the wide range indicates that the incremental cost-effectiveness ratio is particularly sensitive to changes in survival estimates.

As the van Hazel et al. (2004) trial used a systemic chemotherapy regimen that is no longer considered current practice, an economic model comparing SIR-Spheres plus current systemic regimens (FOLFOX6 and FOLFIRI) to current chemotherapy regimens alone was developed. Assuming 3 different scenarios for the magnitude of survival benefits, two alternative follow-up regimens associated with adding SIR-Spheres to current chemotherapy regimens and two different schedules of chemotherapy cycles (10 and 20 cycles), the cost per life year gained ranged from $8009 for the 'best case scenario' (incremental survival benefit of 1.65 years with less intensive follow-up and 10 cycles of FOLFOX/FOLFIRI) to $133 653 for the 'worst case scenario' (incremental survival benefit of 0.3 years with more intensive follow-up and 20 cycles of FOLFOX/FOLFIRI) when compared to the current chemotherapy regimens alone. These estimates are based on the assumption that SIR-Spheres will be used in the same manner with current chemotherapy regimens as they were used with 5-FU/LV in the van Hazel et al. (2004) trial. Due to the lack of trial data on the effectiveness of SIR-Spheres in combination with current chemotherapy regimens, the results of the exploratory economic evaluation should be viewed as an exploration of the possible costs and benefits associated with the use of SIR-Spheres alongside current chemotherapy regimens, over a plausible range of assumptions regarding the magnitude of the survival benefit associated with the use of SIR-Spheres.

Cost-effectiveness of SIR-Spheres for treatment of hepatocellular carcinoma

As the effectiveness of SIR-Spheres as a treatment for patients with HCC has not been established, cost-effectiveness could not be established, and an economic evaluation was not conducted.

Recommendations

1st indication

MSAC recommends that on the strength of evidence pertaining to the treatment of patients with hepatic metastases secondary to colorectal cancer which are not suitable for resection or ablation, interim public funding should be supported for first line treatment by administration of SIR-Spheres in combination with systemic chemotherapy using 5FU and leucovorin, with the collection of survival data. This data should be reported to MSAC within three years.

- The Minister for Health and Ageing endorsed this recommendation on 28 November 2005

2nd indication

As there is currently insufficient evidence pertaining to the treatment of non-resectable, non-ablatable hepatocellular carcinoma with SIR-Spheres, MSAC recommends that public funding should not be supported at this time.

- The Minister for Health and Ageing endorsed this recommendation on 28 November 2005

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness
- advise the Minister for Health and Ageing on references related to new or existing medical technologies and procedures
- assess health technologies referred by the Australian Health Ministers' Advisory Council and report its findings to the Council.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine, general practice, clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning.

Member	Expertise or affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Gerry FitzGerald	Australian Health Ministers' Advisory Council representative
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Professor Alan Lopez	medical statistics and population health

Member	Expertise or affiliation
Dr Ewa Piejko	general practice
Ms Sheila Rimmer	consumer health issues
Ms Samantha Robertson	department representative
Professor Jeffrey Robinson	obstetrics and gynaecology
Professor Michael Solomon	colorectal surgery, clinical epidemiology
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Advisory panel

Advisory Panel for MSAC application 1082
SIR-Spheres

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Evaluators for MSAC application 1082 SIR-Spheres

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Members from the Department of Health and Ageing for MSAC application 1082 SIR-Spheres

Ms Brenda Campe Project Manager	Health Technology Section Medicare Benefits Branch

Appendix C Details of studies of TACE and ^{131}I-Lipiodol

Tables 41 and 42 outline details of the studies identified by the scoping search for TACE and I^{131}-lipiodol in patients with HCC.

Table 41 RCTs comparing TACE with supportive care or non-beneficial systemic therapy

Author(s) and year	Intervention[1]	Liver disease[2]	Survival	Adverse events in TACE arm[3]
Lin et al. (1988)	TAE; *n* = 21 TAE + 5-FU; *n* = 21 5-FU; *n* = 21	80% HBV	1 yr: TAE = 42%; Control = 13%; *P* < 0.01 2 yr: TAE = 25%; Control = 13%; ns	3 patients had cholecystitis and gastric ulcer. Pain and fever in over 50% of patients.
Pelletier et al. (1990)	TACE (Gelfoam powder, doxorubicin 50 mg); *n* = 21 No therapy; *n* = 21	88% with cirrhosis Okuda Stage: I = 26; II = 52; III = 22	1 yr: TACE = 24% ; Control = 33%; ns	Side-effects include hepatitis, acute renal failure and GI haemorrhage. Pain and fever also common.
Group d'étude et de traitment du carcinome hépatocellulaire	TACE (cisplatin 70 mg + lipiodol); *n* = 47 No therapy; *n* = 45	91% with cirrhosis Okuda Stage: I = 90; II = 10; III = 0	1 yr: TACE = 62% ; Control = 43% 2 yr: TACE = 38% ; Control = 26%; ns	60% of the 50 pts who underwent TACE developed liver failure—encephalopathy, ascites or bilirubin elevation. 86% of TACE patients developed abdominal pain, fever or vomiting.
Bruix et al. (1998)	TAE ± steel coil; *n* = 40 No therapy; *n* = 40	HCV 75%	1 yr: TACE = 70% ; Control = 72% 2 yr: TACE = 49% ; Control = 50%; ns	No difference in complications between the two arms.
Pelletier et al. (1998)	TACE (cisplatin 2 mg/kg, lipiodol, lecithin, gelatine sponge); *n* = 37 Tamoxifen (40 mg); *n* = 36	Alcoholic 53% HCV 15% HBV 16% Other 16%	1 yr: TACE 51% ; Control 24% 2 yr: TACE 55% ; Control 26%	2 treatment-related deaths—acute liver failure and gastric perforation. Fever and abdominal pain were the most common side-effects of TACE. Liver decompensation occurred in 50% of TACE patients.
Lo et al. (2002)	TACE;N = 40 (cisplatin 30 mg + lipiodol) No therapy; *n* = 39	HBV 80% Okuda Stage: I = 37; II = 42	1 yr : TACE = 57% ; Control = 32% 2 yr : TACE = 31% ; Control = 11% ; *P* = 0.002	5 pts—liver failure 4 pts—GI bleeding 2 pts—rupture of tumour
Llovet et al. (2002)	TAE; *n* = 37 TACE (lipiodol + doxorubicin 25–75 mg/m^2); *n* = 40 No therapy; *n* = 35.	HCV 85% HBV 6% Alcohol 7% Other 2% Okuda stage: I = 65%; II = 35A% Child-Pugh class: A 70%; B 30%	1 yr: TAE = 75%; TACE = 82%; Control = 63% 2 yr: TAE = 50%; TACE = 63%; Control = 27%; *P* = 0.025	Embolisation group: cholecystitis, ischaemic hepatitis, liver abscess, pulmonary thromboembolism, liver failure and GI haemorrhage. TACE group: cholecystitis, leucopaenia, ischaemic biliary stricture, hepatic infarct, bacterial peritonitis, bacteraemia, septic shock.

[1] TAE—transarterial embolisation; 5-FU—5-fluorouracil
[2] HBV—Hepatitis B Virus; HCV—Hepatitis C Virus
[2] GI—gastrointestinal

Table 42 Summary of ^{131}I-lipiodol studies

Author(s) and year	Intervention	Liver disease	Survival	Adverse events
Raoul et al. (1997)	^{131}I-lipiodol *n* = 73 TACE (Cisplatinum 70 mg mixed with lipiodol and gelatine sponge fragments) *n* = 69	Okuda classification I or II Child–Pugh classification ^{131}I-lipiodol: A = 53; B = 11; C = 1 TACE: A = 44; B = 19; C = 1 Most pts had alcoholic cirrhosis	No significant difference in survival between the groups. 1-yr survival: ^{131}I-lipiodol 38%, TACE 42% 2-yr survival: ^{131}I-lipiodol 22%, TACE 22%	Fewer adverse events in ^{131}I-lipiodol group: 3 events (4.6%) vs 29 events (45%) in TACE group . ^{131}I lipiodol—3 events (pneumonitis, persistent high-grade fever, liver failure) TACE—29 events (7 pts post-embolisation pain, 9 GI haemorrhages, 1 ischaemic cholecystitis, 9 severe liver failure, 2 haemoperitoneum, 1 bronchial spasm)
Leung et al. (1994)	^{131}I-lipiodol *n* = 26	Okuda classification: I = 12; II = 14 Only 8 pts had received no previous treatment	Minimum median survival of 6 months (range 1.2–16.6 months). 50% survival at 7 months after treatment	No significant toxicities reported. 1 pt developed possible radiation hepatitis.
Rindani et al. (2002)	^{131}I-lipiodol *n* = 12	Unresectable HCC 3 pts—alcohol cirrhosis 2 pts—HBV 1 pt—HCV Child–Pugh: A = 9; B = 3	Median survival of 14.5 months (range 2–50 months).	Treatment well tolerated 1 pt developed transient upper-right quadrant pain. 1 pt required wound debridement from following extravasation of lipiodol into subcutaneous tissues.

Appendix D Studies included in the review

The references included in the report are listed below. Details of the characteristics of each of these studies are presented in Tables 43 to 46.

CLM indication

RCTs

Gray, B., van Hazel, G., Hope, M., Burton, M., Moroz, P., Anderson, J. & Gebski, V., 2001, 'Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from large bowel cancer', *Annals of Oncology,* 12, 1711–1720.

van Hazel, G., Blackwell, A., Anderson, J., Price, D., Moroz, P., Bower, G., Cardaci, G. & Gray, B., 2004, 'Randomised phase 2 trial of SIR-Spheres plus Fluorouracil/ Leucovorin chemotherapy versus Fluorouracil/Leucovorin chemotherapy alone in advanced colorectal cancer', *Journal of Surgical Oncology,* 88, 78–85.

Case series

Gray, B.N., Anderson, J. E., Burton, M.A., van Hazel, G., Codde, J., Morgan, C., Klemp, P, 1992, 'Regression of liver metastases following treatment with yttrium-90 microspheres', *Australian* & *New Zealand Journal of Surgery*, 62 (2), 105–110.

Gray, B.N., van Hazel, G., Buck, M., Paton, G., Burton, M.A., & Anderson, J., 2000, 'Treatment of colorectal liver metastases with SIR-Spheres plus chemotherapy', *GI Cancer*, 3 (4), 249–257.

Lim, L., Gibbs, P., Yip, D., Shapiro, J.D., Dowling, R., Smith, D., Little, A., Bailey, W., Liechtenstein, M., 2005a, 'A prospective study of treatment with Selective Internal Radiation therapy (SIR-spheres) in patients with unresectable primary or secondary hepatic malignancies', *Internal Medicine Journal*, 35, 222–227.

Stubbs, R.S., Cannan, R.J. & Mitchell, A.W, 2001b, 'Selective internal radiation therapy with 90Yttrium microspheres for extensive colorectal liver metastases', *Journal of Gastrointestinal Surgery*, 5(3), 294–302.

HCC indication

Case series

Lau, W.Y., Ho, S., Leung, T.W.T., Chan, M., Ho, R., Johnson, P.J., & Li, A.K.C., 1998, 'Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of 90yttrium microspheres', *International Journal of Radiation Oncology, Biology and Physics*, 40 (3), 583–592.

Lau, W.Y., Leung, T.W.T., Ho, S., Leung, N.W.Y., Chan, M., Lin, J., Metreweli, C., Johnson, P. & Li, A.K.C., 1994, 'Treatment of inoperable hepatocellular carcinoma with intrahepatic arterial yttrium-90 microspheres: A phase I and II study', *British Journal of Cancer,* 70 (5), 994–999.

Additional case series included for safety evaluation

Andrews, J.C., Walker, S.C., Ackermann, R.J., Cotton, L.A., Ensminger, W.D., & Shapiro, B., 1994, 'Hepatic radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical follow-up', *Journal of Nuclear Medicine*, 35 (10), 1637–1644.

Blanchard, R.J., Morrow, I. ., & Sutherland, J.B., 1989, 'Treatment of liver tumors with yttrium-90 microspheres alone', *Canadian Association of Radiologists Journal*, 40 (4), 206–210.

Carr, B.I., 2004, 'Hepatic arterial ^{90}yttrium glass microspheres (Therasphere) for unresectable hepatocellular carcinoma: interim safety and survival data on 65 patients', *Liver Transplantation*, 10 (2) Supp 1, S107–S110.

Dancey, J.E., Shepherd, F.A., Paul, K., Sniderman, K.W., Houle, S., Gabrys, J., Hendler, A.L. & Goin, J.E., 2000, 'Treatment of nonresectable hepatocellular carcinoma with intrahepatic ^{90}Y-microspheres', *Journal of Nuclear Medicine,* 41, 1673–1681.

Herba, M.J., Illescas, F.F., Thirlwell, M.P., Boos, G.J., Rosenthall, L., Atri, M., & Bret, P.M., 1988, 'Hepatic malignancies: improved treatment with intraarterial Y-90', *Radiology*, 169 (2), 311–314.

Ho, S., Lau, W.Y., Leung, T.W., Chan, M., Johnson, P.J. & Li, A.K., 1997, 'Clinical evaluation of the partition model for estimating radiation doses from yttrium-90 microspheres in the treatment of hepatic cancer', *European Journal of Nuclear Medicine*, 24 (3), 293–298.

Leung, T.W.T., Lau, W.Y., Ho, S.K.W., Phil, M., Ward, S.C., Chow, J.H.S., Chan, M. S.Y., Metreweli, C., Johnson, P.J. & Li, A.K.C., 1995, 'Radiation pneumonitis after selective internal radiation treatment with intraarterial ^{90}yttrium-microspheres for inoperable hepatic tumors', *International Journal Radiation Oncology*, 33 (4), 919–924.

Stubbs, R.S. & Wickremesekera, S.K., 2004, 'Selective internal radiation therapy (SIRT): a new modality for treating patients with colorectal liver metastases', *HBP*, 6 (3), 133–139.

Table 43 Colorectal liver metastases—Characteristics of RCTs

Study	Study design	*N*	Treatment	Patient characteristics	Outcomes	Quality assessment
Van Hazel et al. (2004)	Prospective phase 2 RCT of SIR-Spheres + systemic chemotherapy vs systemic chemotherapy Patients were stratified before randomisation by institution, presence or absence of extra-hepatic metastases, and extent of liver involvement by tumour Setting: 3 Australian hospitals Inclusion criteria: • Older than 18 years of age • Histologically proven adenocarcinoma of the colorectum • CT scan evidence of non-resectable, non-ablatable liver metastases • Adequate haematologic, hepatic, renal function • No central nervous system metastases • No evidence of ascites, cirrhosis or portal hypertension • WHO performance status < 3 • Not previously received chemotherapy or radiotherapy for liver metastases Follow-up: Maximum 42.5 months after randomisation (patient still alive at time of report)	Total *n* = 21 *n* = 11 in SIR-Spheres + systemic chemotherapy group *n* = 10 in systemic chemotherapy group At the time of the report, all patients have died except one patient in combination therapy group	Systemic chemotherapy[1]: 5-FU/LV for 5 consecutive days and repeated at 4-weekly intervals SIR-Spheres: single dose on 3rd/4th day of second cycle of chemotherapy Dose of SIR-Spheres: • In first five patients: 2.5 GBq • In subsequent patients according to formula: Dose (GBq) = (body surface area (m^2) – 0.2) + (% tumour involvement/100) Protocol treatment: • SIR-Spheres and systemic chemotherapy: *n* = 11 • Systemic chemotherapy: *n* = 8 (2 did not receive protocol treatment owing to rapid deterioration and death) Protocol treatment until unacceptable toxicity, patient request or disease progression After protocol treatment: non-protocol chemotherapy and supportive treatment allowed and recorded	SIR-Spheres + systemic chemotherapy (*n* = 11): • Extrahepatic metastases: 2 (lung) • Mean age (years): 64 • Male/female: 10/1 • Histologic differentiation of primary bowel cancer (poor/moderate/well): 1/10/0 • Size of liver metastases (<25%/>25%): 8/3 • Elevated CEA before treatment: 8 Systemic chemotherapy (*n* = 10): • Extrahepatic metastases: 3 (2 in lung, 1 in peritoneal cavity) • Mean age (years): 65 • Male/female: 8/2 • Histologic differentiation of primary bowel cancer (poor/moderate/well): 2/6/2 • Size of liver metastases (<25%/>25%): 7/3 • Elevated CEA before treatment: 7	SIR-Spheres + systemic chemotherapy (*n* = 11): Median survival: 29.4 months Time to progressive disease: 18.6 months Site of first disease progression: liver (8), liver and lung (1), lung(1), (1 died without progression) Tumour response (RECIST criteria): • First integrated response: *n* = 10 w partial response; *n* = 1 w stable disease, • Best confirmed response: *n* = 8 w partial response; *n* = 3 w stable disease Systemic chemotherapy (*n* = 10): Median survival: 12.8 months Median survival (*n* = 8 receiving treatment): 14.1 months Progression-free survival: 3.6 months Site of first disease progression: liver (8), liver and peritoneum (1), bone (1) Response (RECIST): • First integrated response: *n* = 6 w stable disease, *n* = 4 w disease progression • Best confirmed response: *n* = 6 w stable disease; *n* = 4 w disease progression SIR-Spheres + FU/LV vs FU/LV: • Survival HR: 0.33 (95% CI: 0.12–0.91; P = 0.025) • Changes in patient-reported quality of life: P = 0.96 • There were more Grades 3 and 4 toxicity events in patients receiving the combination treatment	Randomisation: • computer-based randomisation sequence • allocation concealment assumed appropriate (independent centre randomisation) Outcome assessment: Standardised assessment Blinding: • Outcome assessors: blinded • Patient: unknown Follow-up: • Intention to treat • <15% (2/21) loss to follow-up

[1] 5-FU/LV—5-fluoruracil 425 mg/m^2/day plus leucovorin 20 mg/m^2/day; floxuridine—continuous infusion floxuridine at 0.3 mg/kg of body weight/day

Study	Study design	*N*	Treatment	Patient characteristics	Outcomes	Quality assessment
Gray et al. (2001)	Prospective phase 3 RCT of SIR-Spheres and regional HAC vs regional HAC run from 1991–1997 Patients were stratified into three groups before randomisation by percentage of liver involved with tumour (<25%, 25%–50%, >50%) Inclusion criteria: • CT scan evidence of non-resectable, non-ablatable liver metastases • Metastases limited to the liver and lymph nodes in the porta hepatis • Adequate haematologic and hepatic function • No evidence of ascites or cirrhosis • WHO performance status 0–2 • Not previously received radiotherapy to the liver Trial designed to enter 95 patients, but closed for accrual in 1997 (*n* = 74) Follow-up: At least 3.5 years after randomisation	Total *n* = 70 *n* = 36 in Sir-Spheres + HAC group (3 excluded) *n* = 34 in HAC group (1 excluded) Exclusions due to presence of unconfirmed disseminated cancer at time of randomisation	HAC: floxuridine for 12 days and repeated at 4-weekly intervals SIR-Spheres: single injection • In first patient: at time of insertion of access port • In subsequent patients: after recovery from surgery, within 4 weeks of insertion of access port • Dose of SIR-Spheres: According to tumour size (<25%/25%–50%/>50%): 2 GBq / 2.5 GBq / 3 GBq Protocol treatment: • SIR-Spheres and HAC: *n* = 35 (1 did not receive protocol treatment owing to rapid deterioration and death) • HAC: *n* = 36 Protocol treatment for 18 cycles or until evidence of tumour progression, development of extrahepatic metastases, unacceptable toxicity, port failure or patient request After protocol treatment: non-protocol chemotherapy and supportive treatment allowed and recorded	All patients had undergone complete surgical resection of a primary adenocarcinoma of the large bowel SIR-Spheres + HAC (*n* = 36): • Mean age (years): 59 • Male/female: 28/8 • Primary bowel cancer: colon/rectum: 29/7 involved lymph nodes: 24 poorly differentiated: 5 • Lead time from bowel cancer resection to randomisation (mean/median days): 137/56 • Patients treated with prior chemotherapy for liver metastases: 5 • Amount of protocol chemotherapy used/patient (mean/median): 1863/1445 mg • Number of cycles of protocol chemotherapy (mean): 8.7 • Tumour size (<25%/25%–50%/>50%): 24/9/3 SIR-Spheres + HAC (*n* = 34): • Mean age (years): 62 • Male/female: 26/8 • Primary bowel cancer: colon/rectum: 31/3 involved lymph nodes: 24 poorly differentiated: 5 • Lead time from bowel cancer resection to randomisation (mean/median days): 135/57 • Patients treated with prior chemotherapy for liver metastases: 5 • Amount of protocol chemotherapy used/patient (mean/median): 1822/1349 mg • Number of cycles of protocol chemotherapy (mean): 8 • Tumour size (<25%/25%–50%/>50%): 24/8/2	SIR-Spheres + HAC (*n* = 36): Survival: (5- / 3- / 2- / 1-year): 3.5% / 17% / 39% / 72% Hepatic progression-free survival (median): • by tumour area: ~16 months (read off graph) • by tumour volume: ~12 months (read off graph) Tumour response[1]: • Change in tumour area: 44% (16/36) CR or PR • Change in tumour volume: 50% (18/36) • Change in CEA levels: 72% (26/36) HAC (*n* = 34): Survival: (5- / 3- / 2- / 1-year): 0% / 6.5% / 29% / 68% Hepatic progression-free survival (median): • By tumour area: ~10 months (read off graph) • By tumour volume: ~ 8 months (read off graph) Tumour response: • Change in tumour area: 18% (6/34) CR or PR • Change in tumour volume: 24% (8/34) CR or PR • Change in CEA levels: 47% (16/34) CR or PR Tumours in one patient in each arm responded to treatment to such an extent that metastases were subsequently surgically resectable. SIR-Spheres + HAC vs HAC: • Survival HR: 1.41, 95% CI 0.86–2.34; *P* = 0.18) • Hepatic progression-free survival by tumour area/tumour volume: *P* < 0.01 (log rank) / *P* = 0.04 (log rank) • Cox regression in patients surviving >15 months suggests survival advantage in SIR-Spheres + HAC patients (*P* = 0.06) • Tumour response differences significant w *P* = 0.001 / 0.04 / 0.06 for tumour area, tumour volume, CEA level change There was no increase in Grades 3 and 4 toxicity events and no loss in quality of life in patients receiving the combination treatment compared to HAC alone	Randomisation: • Randomisation performed by independent person; method of sequence generation not reported • Allocation concealment appropriate (blind-coded envelope) Outcome assessment: Standardised measurement, but non-standard criteria Blinding: • Outcome assessors: blinded • Patient: unknown Follow-up: • Intention to treat • <15% (4/70) loss to follow-up

[1]CEA—serum carcinoembryonic antigen

Table 44 Colorectal liver metastases—characteristics of case series

Study	Study characteristics[1]	*N*	Patient characteristics[2]	Efficacy data	Safety data	Quality assessment
(Gray et al. 1992f)	Objective: To evaluate patients with proven liver metastases from primary tumours in the large bowel undergoing SIR-Spheres therapy Setting: • Royal Perth Hospital, Perth, Western Australia, Australia • Recruitment period not reported Inclusion criteria: Not reported Intervention: SIR-Spheres: ^{90}Y activity administered (range): 755–4240 MBq HAC • *n* = 12 (patients 18–29) also received continuous infusion of 5-fluorouracil (600 mg/m^2/day) for 10-days starting 1 day after SIR-Spheres administration • *n* = 6 of these repeated cycles Follow-up: CT scans 3-monthly (6 months for *n* = 1, 9 months for *n* = 1), CEA monthly Comments: Unclear whether prospective or retrospective	*n* = 29 *n* = 20 evaluable *n* = 9 not evaluable by CT scans owing to: • metastases not detected on CT scans (1) • CT scans not available for 7: deterioration from progression of extrahepatic disease (3), deterioration from progression in liver (2), referral to outside WA (2) • *n* = 1 unknown *n* = 3 not evaluable by CEA because CEA levels within normal range	Previous treatment: • *n* = 24 no prior therapy for LM • *n* = 4 w prior hepatic perfusion chemotherapy only • *n* = 1 w prior hepatic perfusion chemotherapy + systemic treatment *n* = 3, primary large bowel removed at the same time as SIR-Spheres administration	Tumour response: Tumour volume (22/29): • Mean decrease (range): 48% (12%–83%) • 82% (*n* = 18) w decrease • 45% (*n* = 10) w >50% decrease CEA (26/29) • 100% w decrease of CEA • 88% (*n* = 23) w >50% decrease in CEA • 35% (*n* = 9) CEA normalised	Not reported	Sample: • Unclear if consecutive sample • Relevant population Eligibility criteria Not explicit Study entry: Not clear if all subjects entered the survey at a similar point in their disease progression Follow-up 3 months for most patients—adequate Intervention: Adequately described and applicable Outcome assessment: • Objective (CEA levels) and subjective (tumour volume) measures • Blinding unclear Comparative subseries: n.a.

[1] HAC—hepatic arterial chemotherapy; CT—computed tomography; CEA—serum carcinoembryonic antigen
[2] LM—liver metastases

Study	Study characteristics[1]	*N*	Patient characteristics	Efficacy data	Safety data	Quality assessment

(Gray et al. 2000b)	Objective:
	To evaluate patients with non-resectable, non-ablatable liver metastases from primary adenocarcinoma of the large bowel treated with SIRT followed by HAC (floxuridine)
	Setting:
	• Hepatobiliary surgical oncology centre, Royal Perth Hospital, Perth, WA, Australia
	• Recruitment period not reported
	Exclusion criteria:
	• life expectancy considered <1 month
	• in end-stage liver failure
	• extrahepatic metastases rather than liver metastases are likely to be life-limiting event
	Intervention:
	Sir-Spheres:
	n = 66 w 1 injection
	n = 5 w 2 injection
	^{90}Y activity (mean): 2.13 GBq ± 0.73
	HAC:
	All patients received at least one 12-day cycle of floxuridine (0.3 mg/kg body weight), repeated every 28 days until disease progression, within 24 h of SIRT administration
	Follow-up:
	Until death in all patients, monthly CEA levels, 3-monthly CT scans
	Comments:
	Unclear whether prospective or retrospective
		n = 71
		n = 48 evaluable for tumour volume
		n = 60 evaluable for CEA
		
		n = 23 not evaluable for tumour volume due to:
		• pretreatment scan not available *n* = 7
		• follow-up scan not available in *n* = 16 due to: residence outside WA (11), death within 3 months (3), not reported (2)
		
		n = 11 not evaluable for CEA due to:
		• CEA not elevated before in *n* = 4
		• CEA not measured before in *n* = 2
		• Early death *n* = 1
		• Results not available due to residence outside WA *n* = 4
			• Male/female: 43/28
			• Age (range): 33–76 yrs
			
			Previous treatment:
			• In all patients, large bowel had previously been surgically removed
			• *n* = 26 treated w systemic chemotherapy (5-fluorouracil) before referral to SIR-Spheres
			
			Tumour characteristics:
			• *n* = 30 w extrahepatic metastases besides liver metastases
			• Tumour size varied
			• Tumour volume (mean/median): 744 mL ± 744 / 476
				Survival:
				In all patients (71)
				• Median / mean survival from SIRT administration: 9.9 / 12 months
				• Median survival from diagnosis of LM: 17.3 months
				In patients with LM only (41/71):
				• Median survival from SIRT administration: 13.5 months
				• Median survival from diagnosis of liver metastases: 18.5 months
				
				Tumour response:
				Tumour volume (51/71)
				• 86% (44/51) w decrease in tumour volume; of these:
				  • mean decrease: 58%
				  • 12% (*n* = 6) w <30% volume decrease
				  • 75% (*n* = 38) w >30% volume decrease
				  • 55% (*n* = 28) had >50% volume decrease
				CEA (60/71):
				• *n* = 3 CEA increased
				• *n* = 4 decrease <50% (PR)
				• 37% (*n* = 22) CEA decreased to normal (CR)
				• 55% (*n* = 31) CEA decrease ≥ 50%, but not normalised (PR)
					• *n* = 1 w fatal radiation hepatitis
					• No cases of biliary sclerosis
					• Transient abdominal pain and nausea common after injection, subsided with mediation
						Sample:
						• Consecutive patients
						• Relevant population
						Eligibility criteria:
						Explicit exclusion criteria
						Study entry:
						Subjects entered the survey at varying stages of disease progression (42% w extrahepatic metastases)
						Follow-up:
						Adequate
						Intervention:
						Adequately described
						Outcome assessment:
						• Objective (CEA levels, survival) and subjective (tumour volume) measures
						• Blinding unclear
						Comparative subseries: n.a.

[1] HAC—hepatic arterial chemotherapy ; CT—computed tomography; CEA—serum carcinoembryonic antigen

Study	Study characteristics[1]	*N*	Patient characteristics[1]	Efficacy data[2]	Safety data	Quality assessment
Lim et al. (2005a)	Objective: To prospectively evaluate SIR-Spheres in patients w unresectable primary or secondary hepatic malignancies Setting: • 3 Australian centres: Royal Melbourne Hospital, Cabrini Hospital Malvern, Canberra Hospital • Recruitment period: Jan 2002 – June 2003 Inclusion/exclusion criteria: Inclusion: • Liver metastases from CRC or other primary tumour • Extrahepatic disease allowed if liver is dominant site of disease • Adequate hepatic, liver and renal function Exclusion: • Excluded if ascites, portal hypertension, portal vein thrombosis, survival < 3 months, brain metastases, poor performance (ECOG > 2). Intervention: • SIR-Spheres: dosage calculated according to patient's body surface area and % tumour involvement of liver • No details of dosages administered given Follow-up: Until disease progression (median: 9.8 months), disease evaluation at 2 months and bimonthly thereafter	*n* = 46 *n* = 43 evaluable *n* = 3 not evaluable due to: • *n* = 1 residence outside Australia • *n* = 2 death before evaluation	• Male/female: 31/15 • Median age (range): 64 (46–78) • 88% w ECOG performance of 0 or 1 Previous treatment: Of patients w CRC (*n* = 32): • *n* = 28 w prior chemo (>2 months prior SIR-Spheres) Tumour characteristics: • *n* = 32 w CRC • *n* = 5 w HCC • *n* = 2 w ACUP • *n* = 7 w other primary tumours • 20% w low-volume extra-hepatic disease	Tumour response (*n* = 43): CT at 2 months: • 26% (*n* = 12) w PR (>30% decrease in the sum of longest dimension of target lesions) • 27% (*n* = 12) w SD • 44% (*n* = 19) w disease progression or not evaluable At 6 months: • *n* = 1 complete response at 6 months Patients w CRC (*n* = 31), at 2 months: • 32% (*n* = 10) w PR • 29% (*n* = 9) w SD • 39% (*n* = 12) w PD All responses (*n* = 37) in patients with disease confined to the liver	• *n* = 1 w likely radiation hepatitis that settled with conservative management • 8% (*n* = 4) w severe gastric/duodenal ulceration • *n* = 1 w haematemesis (bleeding of oesophageal varices due to portal hypertension) • Lethargy, anorexia, nausea observed in most patients to variable extent • *n* = 3 w severe nausea and lethargy for 2 weeks	Sample: • Consecutive patients • Relevant population Eligibility criteria: Explicit inclusion/exclusion criteria Study entry: Subjects entered the survey at varying stages of disease progression (20% w extrahepatic metastases) Follow-up: Results mainly on 2 months follow-up, inadequate length Intervention: Adequately described and applicable; no details of dosage given Outcome assessment: • Subjective (tumour area) measures, confirmed on repeat imaging • Blinding unclear Comparative subseries: *n*.a.

[1] CRC—colorectal cancer; HCC—hepatocellular carcinoma; ACUP—adenocarcinoma of unknown primary site; ECOG—Eastern Cooperative Oncology Group

[2] Response criteria: CR—complete response; PR—partial response; SD—stable disease; PD—progressive disease

Study	Study characteristics[1]	*N*	Patient characteristics	Efficacy data	Safety data	Quality assessment
(Stubbs, Cannan, and Mitchell 2001)	Objective: To assess Sir-Spheres in patients w CLM that is non-resectable and not suitable for cryotherapy Setting: • Wakefield Hospital, Wellington, New Zealand • Recruitment period: Feb 1997 – June 1999 Inclusion/exclusion criteria: Inclusion: • patients with extensive CLM not suitable for resection or cryotherapy • considered fit for laparotomy • extrahepatic disease contraindicated unless only minor intra-abdominal lymphadenopathy or minor lung metastases Exclusion: • life expectancy < 6 weeks Intervention: SIR-Spheres: • in *n* = 43 through port, in *n* = 7 through hepatic artery catheter • ^{90}Y dosage according to tumour size (<25%/25%–50%/>50%): 2 / 2.5 / 3 GBq • SIRT administered 0.5 to 71.6 (median: 3.2) months after diagnosis of liver metastases HAC *n* = 43 (patients 18–29) also received continuous infusion of 5-fluorouracil (1 g/day) for 4 days every 4 weeks, around time of SIR-Spheres administration Follow-up: CEA monthly, CT scan 3-monthly	*n* = 50 *n* = 3 excluded for CEA response evaluation: normal CEA levels before treatment Other reasons for exclusions (CT scan and CEA) are not reported	• Male/female: 31/19 • Median age (range): 61.4 (33–76) Previous treatment: Not reported Tumour characteristics: • *n* = 30 w <25% liver involvement • *n* = 13 w 25%–50% liver involvement • *n* = 7 w >50% liver involvement • *n* = 8 with evidence of extrahepatic disease	Survival In all patients (50) • Median survival from SIR-Spheres administration: 9.8 months (1–30.3) • Median survival from diagnosis of LM 14.5 months (1.9–91.4) In patients with LM only (24/50): • Median survival from SIRT administration: 17.5 months (1–30.3) • Median survival from diagnosis of LM: 24.7 months Tumour response: Tumour response as 'definite reduction in size of index lesions; no enlarging or new lesions' (unclear whether tumour volume, tumour area or one dimension only) CT at 3 months (*n* = 44) • *n* = 32 decrease in tumour size or new lesion • *n* = 8 no change SD • *n* = 4 increase in tumour size or new lesion CT at 6 months (*n* = 28) • *n* = 23 decrease in tumour size or new lesion • *n* = 4 no change (SD) • *n* = 1 increase in tumour size or new lesion CEA at 3 months (*n* = 34): • 5.9% (*n* = 2) increased CEA at 6 months (*n* = 25): • 20% (*n* = 5) increased CEA at 12 months (*n* = 16): • 37.5% (*n* = 6) increased	• 28% (*n* = 14) w acute pain and nausea requiring treatment with narcotic and antiemetics • 12% (*n* = 6) w duodenal ulcer within 2 mo of treatment (may have been from misperfusion of SIR-Spheres of the duodenum); 2 of these 6 patients had a GI bleed (1 requiring surgery) • All patients had lethargy and some anorexia for up to 6 weeks	Sample: • Consecutive patients • Relevant population Eligibility criteria: Explicit inclusion/exclusion criteria Study entry: Subjects entered the survey at varying stages of disease progression (*n* = 8 w extrahepatic metastases) Follow-up: Adequate length follow-up Intervention: Adequately described Outcome assessment: • Objective for tumour marker (CEA levels) and survival, and subjective for CT measurements • Blinding unclear Comparative Subseries: n.a. Comment: • Reasons for loss to follow-up not reported

[1] HAC—hepatic arterial chemotherapy ; CT—computed tomography; CEA—serum carcinoembryonic antigen

Table 45 Hepatocellular carcinoma—characteristics of case series

Study	Study characteristics[1]	*n*	Patient characteristics[2]	Efficacy data[3]	Safety data	Quality assessment
(Lau et al. 1998j))	Objective: To evaluate efficacy of SIR-Spheres in non-resectable HCC Setting: • Prince of Wales Hospital, Shatin, Hong Kong • Recruitment period October 1992 – December 1995 Inclusion criteria: • Considered non-resectable on basis of ultrasound, AFP levels , CT and hepatic angiography levels • No extrahepatic spread of disease • Karnofsky performance score of >70% • Adequate liver function with total bilirubin < 2.94 mg/dL • No tumour invasion into portal vein, hepatic artery, hepatic vein, or inferior vena cava • Lung shunting <15% • Average T/N ratio ≥2 Intervention: SIR-Spheres: • Initial median ^{90}Y activity (range): 3.0 GBq (0.8–5.0 GBq) • Repeated treatments in *n* = 15 (10 w 2 treatments; 3 w 4 treatments, 1 w 5 treatments) • Median ^{90}Y activity (range) in repeated treatments: 3.0 GBq (1–4 GBq) Follow-up: Tumour marker at 1–4-week intervals; ultrasound and CT scan every 2 months	*n* = 71 *n* = 25 excluded for AFP response evaluation: pretreatment level < 100 ng/mL	• Male/female: 62/9 • Median age (range): 65 years (24–85 years) • *n* = 65 (91.5%) were HBsAg carriers • *n* = 43 (60.1%) w cirrhosis Previous treatment: • *n* = 20 w SIR-Spheres after postoperative recurrence Tumour characteristics: • Median size of biggest tumour nodule (range): 8.5 cm (1.0–22.6 cm) in diameter	Survival: • Median survival (range): 9.4 months (1.8–46.4) Tumour response: CT at 2 months (*n* = 71): • No decrease in tumour volume CT at 4–10 months (*n* = 71): • 26.7% (*n* = 19) w partial response (PR > 50% decrease in tumour volume) • 8.5% (*n* = 6) w progressive disease after first treatment due to new lesions (*n* = 3) or distant metastases (*n* = 3) AFP level response (*n* = 46) (after median of 50 days after treatment): • 67% (*n* = 31) w >50% drop in AFP levels (PR) • 22% (*n* = 10) w normalisation of AFP levels (CR)	• *n* = 10 w transient, low-grade fever • *n* = 12 w abdominal distension, discomfort, nausea and vomiting	Sample: • Consecutive patients not reported • Relevant population Eligibility criteria: Explicit inclusion criteria Study entry: Patients entered the study at a similar point in their disease progression Follow-up: Adequate length follow-up Intervention: Adequately described Outcome assessment: • Objective for tumour marker (AFP levels) and survival, and subjective for tumour response (tumour volume) • Blinding unclear Comparative Subseries: n.a.

[1]HCC—hepatocellular carcinoma; AFP—alpha-fetoprotein
[2]HBsAg—Hepatitis B surface Antigen
[3]Response criteria: CR—complete response; PR: partial response; SD: stable disease; PD: progressive disease

Study	Study characteristics[1]	*N*	Patient characteristics	Efficacy data[2]	Safety data	Quality assessment
Lau et al. (1994)	Objective: Phase I and II study to determine optimum dose of radiation and response of SIR-Spheres in non-operable HCC Setting: • Prince of Wales Hospital, Shatin, Hong Kong • Recruitment period November 1990 – May 1993. Inclusion criteria: • Age < 75 years • No extrahepatic spread of disease • Karnofsky performance score of >70% • Adequate liver function with bilirubin < 50 mmol L^{-1} • No medical illness that precluded patient from laparotomy • No tumour invasion into portal vein, hepatic artery, hepatic vein or inferior vena cava • Lung shunting <15% • Average T/N ratio >2 Intervention: SIR-Spheres: • Total ^{90}Y activity (range): 2.0–7.0 GBq Follow-up: Tumour marker at 2–4-week intervals; CT scans at 2, 4, 6 months and 1 year. Comment: Patients in this study may be included in Lau et al. 1998 case series, as recruitment period overlaps	*n* = 18 *n* = 2 excluded for tumour response due to death 2 and 4 months after treatment *n* = 8 excluded for AFP response evaluation: pretreatment level < 300 ng/mL	• Male/female: 17/1 • Median age (range): 52 years (18–74) • *n* = 2 w extrahepatic spread	Survival: *n* = 2 w extrahepatic spread died 2 and 4 months after treatment In *n* = 18: • median survival: 30.6 weeks In *n* = 16 (excluding 2 patients w extrahepatic spread): • median survival: 35 weeks Tumour response: CT at 2 months (*n* = 16): • 50% (*n* = 8) w partial response (PR > 50% decrease in tumour volume) AFP level response (*n* = 10): • 80% (*n* = 8) w drop of 80% or more	Treatment well tolerated; no major complications	Sample: • Consecutive patients not reported • Relevant population Eligibility criteria: Explicit inclusion criteria Study entry: Patients entered the study at a similar point in their disease progression (*n* = 2 w extrahepatic spread) Follow-up: Adequate length follow-up Intervention: Adequately described Outcome assessment: • Objective for tumour marker (AFP levels) and survival, and subjective for tumour response (tumour volume) • Blinding unclear Comparative Subseries: n.a.

[1]HCC—hepatocellular carcinoma

[2]Response criteria: CR—complete response; PR: partial response; PD: progressive disease

Table 46 Additional case series included for the safety evaluation (by type of microsphere)

Study	LM or HCC	*N*	Setting	Study characteristics	Patient characteristics	Safety data
Type of microspheres: SIR-Spheres						

(Ho et al. 1997i)), Leung et al. (1995)[1]	HCC	*n* = 100
		
		n = 94 HCC
		n = 6 CLM
			Prince of Wales Hospital, Shatin, Hong Kong	• No date range reported
				• Unclear whether consecutive or selected patients
				• Unclear whether retrospective or prospective
				• 21 patients had multiple treatments
					Not reported	• *n* = 5 w radiation pneumonitis:
						  • *n* = 1 after 2nd dose
						  • *n* = 3 with >20% lung shunting (reduced to <15% with hepatic embolisation before treatment)

Stubbs and Wickremesekera (2004)	CLM	*n* = 100	Wakefield Gastroenterology Centre, New Zealand	Review article	Not reported	• *n* = 28 w acute pain and nausea
						• *n* = 8 w peptic ulceration (2 w major bleeding and 1 requiring operation)
						• *n* = 3 treatment-related deaths:
						  • *n* = 1 due to severe radiation gastritis
						  • *n* = 1 due to progressive radiation hepatitis
						  • *n* = 1 due to acute hepatic necrosis

Type of microspheres: glass matrix TheraSpheres						
(Andrews et al. 1994a))	LM + HCC	*n* = 24 *n* = 17 LM from CRC *n* = 6 LM from neuroendocrine tumours *n* = 1 HCC	University of Michigan Medical Centre, Ann Arbor, MI, USA	• Prospective phase I study • Dose ranging study to determine hepatic tolerance • Inclusion criteria clearly defined • Not used in combination with any other treatment	• Failed conventional therapy, no prior radiotherapy; CT evidence of PD • Estimated whole SIRT dose: 5000 cGy (2pts); 7500cGy (6pts); 10 000 cGy (7pts); 12 500 cGy (6pts); 15 000 cGy (3 pts)	• *n* = 24 w mild transient increases in transaminase levels • *n* = 4 w transient fever • *n* = 18 w fatigue • *n* = 4 w gastritis • No pulmonary fibrosis noted with 53 months follow-up • No hepatic or haematological toxicity
Carr (2004)	HCC	*n* = 65	Liver Cancer Centre, Pittsburgh, PA, USA.	• Retrospective: 8/2000 to 8/2003 with historical controls • All patients had additional TACE treatment concurrently	• Male/female: 47/18 • Underlying liver disease: *n* = 48 w cirrhosis, *n* = 27 w HCV, *n* = 15 w HBV, *n* = 28 alcohol, *n* = 28 IV drug abuse, *n* = 2 w HIV • Okuda cirrhosis staging: *n* = 42 stage I, *n* = 21 stage II, *n* = 3 stage III • SIRT dose (mean/median): 145.7Gy / 134.3 Gy	• Elevated bilirubin and lymphopaenia common • Several patients with transient nausea and ankle oedema • *n* = 9 w abdominal pain • *n* = 8 w worsening ascites • *n* = 2 w episodes of cholecystitis requiring cholecystectomy • 1 episode each of generalised pain and urinary electrolyte wasting

Study	LM or HCC	*N*	Setting	Study characteristics	Patient characteristics	Safety data
Dancey et al. (2000)	HCC	*n* = 22	University of Toronto, Ontario, Canada	• Prospective: March 1992 – March 1996. N = 2 w second treatment	• *n* = 2 ineligible due to unconfirmed HCC • Male/female: 14/6 • *n* = 3 w prior hepatic surgery • Okuda cirrhosis staging: *n* = 9 stage I, *n* = 11 stage II • Estimated SIRT liver dose: 100 Gy (11pts), 80–100 Gy (5pts), <80 (4 pts)	• Elevated liver enzymes and bilirubin • Gastroduodenal ulcers: *n* = 3 pts • Severe GI pain: *n* = 1 • Severe nausea: *n* = 1 • *n* = 3 deaths due to hepatitis, liver failure and radiation pneumonitis
(Herba et al. 1988h))	LM	*n* = 15 *n* = 12 LM from CRC *n* = 1 LM from carcinoid *n* = 1 LM from islet cell *n* = 1 primary liver cancer	Montreal General Hospital, Montreal, Quebec, Canada	• Prospective Phase I/II study • To assess toxicity and any preliminary therapeutic response • Clear protocol defined inclusion criteria • not used in combination with any other treatment	• Male/female: 12/3 • Mean age (range): 62 (50–74) years • Three SIRT dose levels: 5000 cGy (10 pts), 7500 cGy (3 pts), 10 000 cGy (2 pts)	• *n* = 14 w increased liver enzymes • *n* = 1 w white blood cell fluctuations (few weeks) • *n* = 2 w mild, temporarilyy increased serum bilirubin • *n* = 3 w antral and pyloric ulceration / duodenitis 6–8 weeks after treatment • *n* = 1 w GI tract haemorrhage with history of bleeding duodenal ulcer (2–3 yrs previously)
Type of Microspheres: Carbonised Plastic						
(Blanchard, Morrow, and Sutherland 1989b))	LM + HCC	*n* = 16 *n* = 8 LM from CRC *n* = 3 LM from carcinoid *n* = 4 LM from other tumours *n* = 1 HCC *n* = 20 controls	University of Manitoba, Health Sciences Centre, Winnipeg, Manitoba, Canada	• Prospective: 09/1976 to 09/1978 • 40 patients screened clinically, 36 with angiography • 20 patients not eligible acted as 'control group' • Not used in combination with any other treatment	Male/female: 9/7 No other information	• *n* = 3 w transient hepatic enzyme elevation • *n* = 10 w transient, low-grade fever • *n* = 12 w abdominal distension, discomfort, nausea and vomiting • *n* = 4 w radiation gastritis with ulceration, one of which required surgery • *n* = 1 w radiation gastritis no ulceration • *n* = 5 w nausea and anorexia • No cholecystitis or pancreatitis

[1]Leung et al. (1995) is a substudy of the 5 cases of radiation pneumonitis reported in Ho et al. (1997).

Appendix E Excluded studies

The following is a list of publications which were retrieved in full text for possible inclusion in the review and found to meet one of the exclusion criteria outlined in Table 7.

Ho, S., Lau, W.Y., Leung, T.W., Chan, M., Chan, K.W., Lee, W.Y., Johnson, P.J. & Li, A.K., 1997, 'Tumour-to-normal uptake ratio f ^{90}Y microspheres in hepatic cancer assessed with ^{99m}Tc macroaggregated albumin', *The British Journal of Radiology*, 70, 823–828.

Lim, L., Yip, D., Shapiro, J.D., Dowling, R., Smith, D., Little, A., Bailey, W., Liechtenstein, M. & Gibbs, P., 2005b, 'A prospective study of treatment with Selective Internal Radiation therapy (SIR-spheres) in patients with unresectable liver metastases from colorectal cancer previously treated with 5-FU based chemotherapy' (*unpublished article supplied by applicant).*

Medical Services Advisory Committee, 2003. 'Selective Internal Radiation Therapy for hepatic metastases using SIR-Spheres, MSAC application 1034, assessment report.' Canberra: Commonwealth of Australia.

Moroz, P., Anderson, J.E.M., van Hazel, G. & Gray, B.N., 2001, 'Effect of selective internal radiation therapy and hepatic arterial chemotherapy on normal liver volume and spleen volume', *Journal of Surgical Oncology*, 78, 248–252.

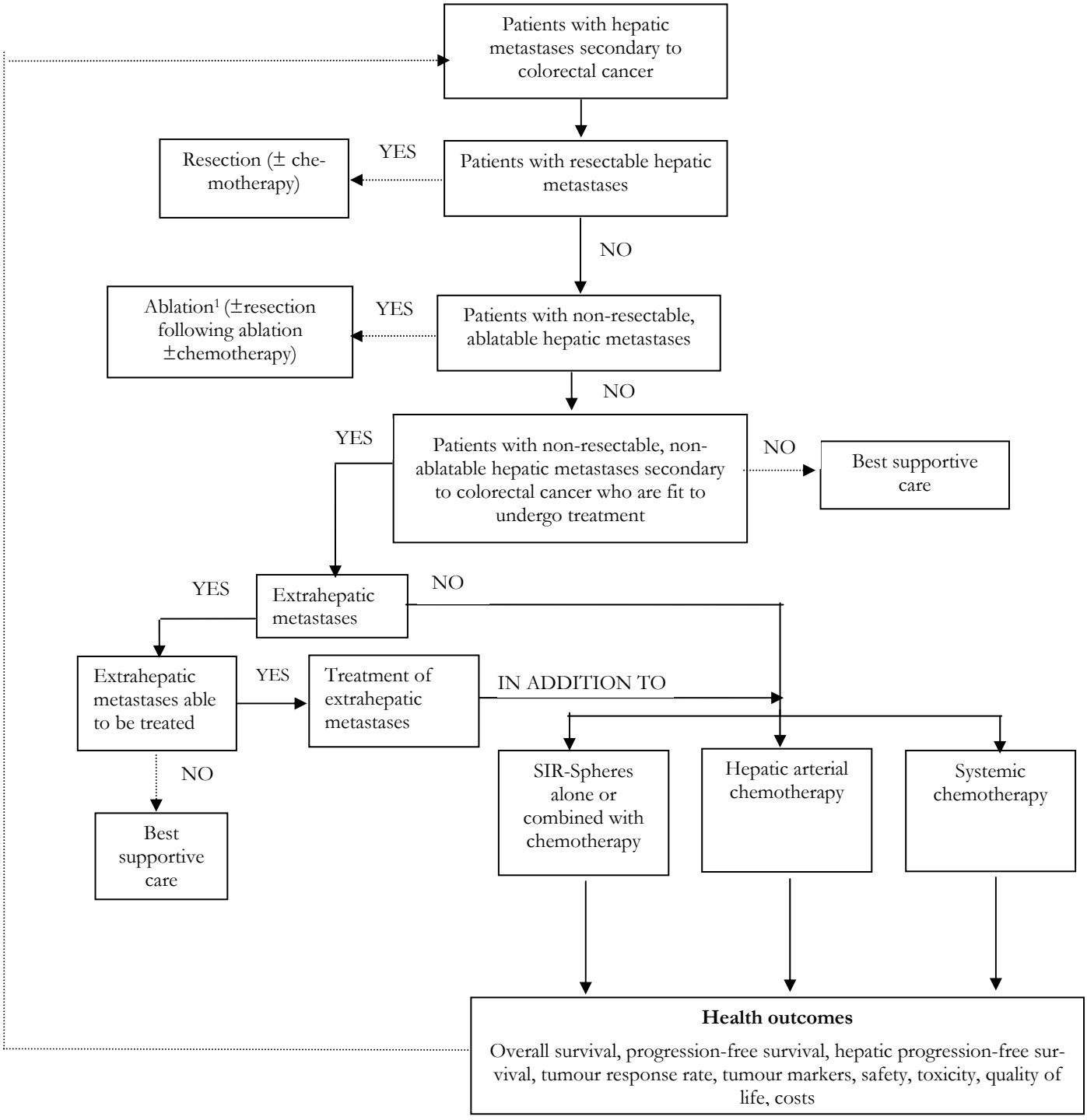
Shepherd, F.A., Rotstein, L.E., Houle, S., Yip, T-C.K., Paul, K. & Sniderman, K.W., 1992, 'A phase I dose escalation trial of yttrium-90 microspheres in the treatment of primary hepatocellular carcinoma', *Cancer*, 70, 2250–2254.

Stubbs, R.S., Cannan, R.J. & Mitchell, A.W., 2001a, 'Selective internal radiation therapy (SIRT) with ^{90}yttrium microspheres for extensive colorectal liver metastases', *Hepato-Gastroenterology*, 48, 333–337.

Wickremesekera, J.K., Chen, W., Cannan, R.J. & Stubbs, R.S., 2001, 'Serum proinflammatory cytokine response in patients with advanced liver tumors following selective internal radiation therapy (SIRT) with ^{90}yttrium microspheres', *International Journal of Radiation Oncology, Biology and Physics*, 49 (4), 1015–1021.

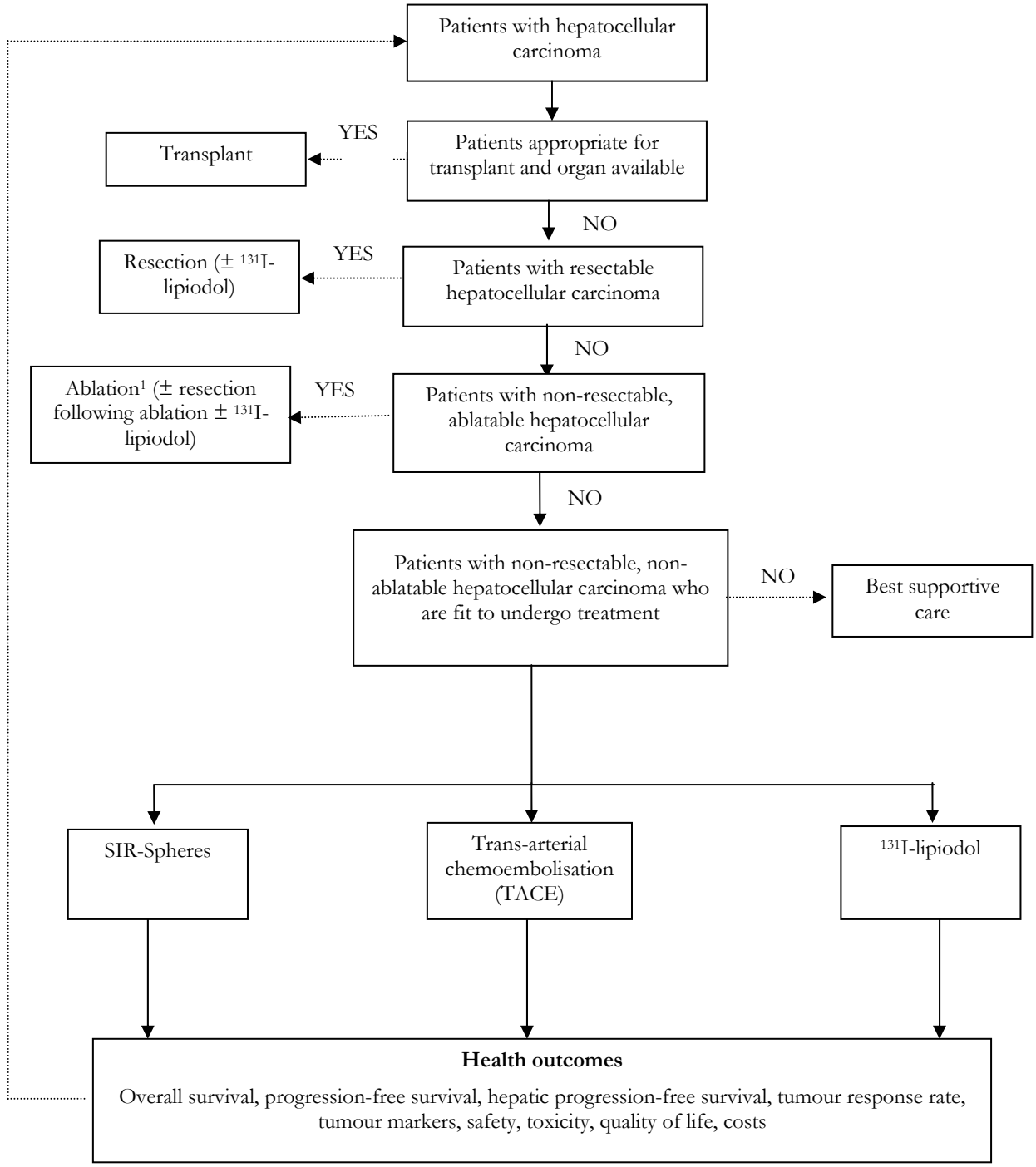
Appendix F Clinical flow charts

Figure 8 Flow chart of SIR-Spheres treatment for hepatic metastases secondary to colorectal cancer



[1]Ablation: Radiofrequency ablation (RFA), cryoablation, microwave ablation or laser ablation

Figure 9 Flow chart of SIR-Spheres for patients with non-resectable hepatocellular carcinoma



[1]Ablation: Radiofrequency ablation (RFA), percutaneous ethanol injection, cryoablation, microwave ablation or laser ablation

Appendix G Systemic chemotherapy regimens

These are the most common first line systemic chemotherapy regimens used for advanced colorectal cancer. This information was sourced from the US National Cancer Institute website (http://www.nci.nih.gov/cancertopics).

FOLFOX4 regimen (oxaliplatin, leucovorin, 5-FU)

Oxaliplatin (85 mg/m^2) as a 2-hour infusion day 1; leucovorin (200 mg/m^2) as a 2-hour infusion days 1 and 2; followed by a loading dose of 5-FU (400 mg/m^2) IV bolus, then 5-FU (600 mg/m^2) via ambulatory pump over 22 hours days 1 and 2 every 2 weeks.

FOLFOX6 regimen (oxaliplatin, leucovorin, 5-FU)

Oxaliplatin (85–100 mg/m^2) as a 2-hour infusion day 1; leucovorin (400 mg/m^2) as a 2-hour infusion day 1; followed by a loading dose of 5-FU (400 mg/m^2) IV bolus on day 1, then 5-FU (2400–3000 mg/m^2) via ambulatory pump over 46 hours every 2 weeks.

FOLFIRI regimen (leucovorin, 5-FU, irinotecan)

Irinotecan (180 mg/m^2) as a 2-hour infusion day 1; leucovorin (400 mg/m^2) as a 2-hour infusion day 1; followed by a loading dose of 5-FU (400 mg/m^2) IV bolus on day 1, then 5-FU (2400–3000 mg/m^2) via ambulatory pump over 46 hours every 2 weeks.

IFL (or Saltz) regimen (irinotecan, 5-FU, leucovorin)

Irinotecan (125 mg/m^2), 5-FU (500 mg/m^2) IV bolus and leucovorin (20 mg/m^2) IV bolus weekly for 4 out of 6 weeks.

Appendix H RECIST criteria

The RECIST criteria (Response Evaluation Criteria In Solid Tumours) have been developed as a result of a large international collaboration of the European Organization for Research and Treatment of Cancer, the National Cancer Institute (NCI) of the United States and the National Cancer Institute of Canada Clinical Trials Group.

The RECIST process and recommendations are reported extensively in Therasse et al. (2000) and are summarised in Table 48. They include comments on the following areas:

- Measurability of tumour lesions at baseline, including definitions and specifications by different types of measurement (including clinical examination, imaging, tumour markers and histology).
- Tumour response evaluation, including baseline evaluation, response criteria (target lesions, non-target lesions, best overall response, frequency of re-evaluation, confirmation, duration of overall response or stable disease) and progression-free survival or time to progression.
- Response review.
- Reporting of results.
- Response evaluation in randomised phase III trials.

The specific areas of the document (Therasse et al 2000) that are applicable to results reported for SIRT are described next.

Evaluation of best overall response: Tumour evaluation includes the evaluation of the best overall response, which is defined 'as the best response recorded from the start of treatment until disease progression/recurrence'. Responses of measurable disease in target and non-target lesions with or without new lesions are considered in the definition of the overall response. Progressive disease is referred to as ≥20 per cent increase in tumour size over the smallest sum observed. In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Table 47).

Table 47 Overall responses for all possible combinations of tumour responses in target and non-target lesions with or without the appearance of new lesions

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	no	CR
CR	incomplete response / SD	no	PR
PR	non-PD	no	PR
SD	non-PD	no	SD
PD	any	yes or no	PD
any	PD	yes or no	PD
any	any	yes	PD

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease

Confirmation: Confirmation of objective response is an important response criterion, which is considered to "avoid overestimating the response rate observed," which "is particularly important in non-randomised trials where response is the primary end point." Only if tumour response measurements are confirmed can patients be assigned the response status. A partial or complete response is confirmed by a repeat assessment "no less than 4 weeks after the criteria for these response measurements are first met." To confirm stable disease, the guidelines state that "measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol." In cases when repeat assessments to confirm changes in tumour size are not feasible or not part of standard protocol practice, this needs to be made explicit when reporting the outcome of such studies.

Table 48 RECIST guidelines

Characteristic	RECIST
Measurability of lesions at baseline	Measurable disease Unidimensional (LD only, size with conventional techniques >20 mm; spiral CT > 10 mm)
	Unmeasurable disease All other lesions, including small lesions.
Objective response	Target lesions Change in sum of LDs, maximum of 5 per organ up to 10 total [more than one organ]) CR: disappearance of all target lesions, confirmed at ≥4 weeks PR: ≥30% decrease from baseline, confirmed at ≥4 weeks PD: ≥20% increase over smallest sum observed, or appearance of new lesions SD: neither PR or PD criteria met
	Non-target lesions CR: disappearance of all target lesions and normalisation of tumour markers, confirmed at ≥4 weeks PD: unequivocal progression of non-target lesions, or appearance of new lesions Non-PD: persistence of one or more non-target lesions or tumour markers above normal limits or both
Overall response	Best response recorded in measurable disease from treatment start to disease progression or recurrence Non-PD in non-target lesion(s) will reduce a CR in target lesions(s) to an overall PR Non-PD in non-target lesion(s) will not reduce a PR in target lesion(s)
Duration of response	Overall CR From: date CR criteria first met To: date recurrent disease first noted Overall response From: date CR or PR criteria first met (whichever status cane first) To: date recurrent disease or PD first noted SD From: date of treatment start To: date PD first noted

Source: (Gehan and Tefft 2000)
LD = longest diameter, CR = complete response, PR = partial response, PD = progressive disease, NC = no change, SD = stable disease
§ lesions that can be measured only unidimensionally are considered to be measurable (eg mediastinal adenopathy, malignant hepatomegaly)

Appendix I HCC classification systems

The Okuda staging system for hepatocellular carcinoma

Parameter	Points	
	0	1
Tumour size	<50% of liver	>50% of liver
Ascites	no	yes
Albumin (g/dL)	≥3	<3
Bilirubin (mg/dL)	<3	≥3
Okuda stage I: 0 points; Okuda stage II: 1 or 2 points; Okuda stage III: 3 or 4 points		

Adapted from Grieco et al. (2005).

The Child–Pugh liver function classification system

Clinical or biochemical measurement	Points scored		
	1	2	3
Encephalopathy grade	None	1–2	3–4
Ascites	absent	mild	moderate to severe
Bilirubin (µmol/L)	<35 µmol/L	36–60 µmol/L	>60 µmol/L
Albumin	>35 g/L	28–35 g/L	<28 g/L
Prothrombin time score (s prolonged)	1–4 s	4–6 s	>6 s
International normalised ratio	[<1–7]	[1.7–2.3]	[>2.3]
Child–Pugh A: score ≤ 6; Child–Pugh B: score 7–9; Child–Pugh C: score ≥10			

Adapted from Ginsburg (2003)

TNM staging system for liver cancer

Primary tumour (T)		Regional lymph nodes (N)		Distant metastasis (M)	
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed	MX	Distant metastasis cannot be assessed
T0	No evidence of primary tumour	N0	No regional lymph node metastasis	M0	No distant metastasis
T1	Solitary tumour without vascular invasion	N1	Regional lymph node metastasis	M1	Distant metastasis
T2	Solitary tumour with vascular invasion or multiple tumours, none >5 cm				
T3	Multiple tumours >5 cm or tumour involving a major branch of the portal or hepatic vein(s)				
T4	Tumour(s) with direct invasion of adjacent organs other than the gall bladder or with perforation of the visceral peritoneum				

Stage	Primary tumour classification	Regional lymph nodes classification	Distant metastasis classification
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIa	T3	N0	M0
Stage IIIb	T4	N0	M0
Stage IIIc	Any T	N1	M0
Stage IV	Any T	Any N	M1

Adapted from Greene et al. (2002)

Appendix J Adverse events costs

Table 49 Economic evaluation of adverse event costs

		Weighted avg for 1st and 2nd line tTX(from Tournigand et al. 2004 Table 3)					
		FOLFOX	FOLFIRI	SIRT + FOLFOX/FOLFIRI		FOLFOX/FOLFIRI alone	
Events (over all cycles)	Unit cost	No. events /pt / cycle	No. events /pt / cycle	Total No. events/pt	Cost $ /pt	Total No. events/pt	Cost $ /pt
Neutropaenia				1.5191	$230.11	1.7039	$264.77
Grade 1	$0.00	0.0161	0.0438	0.4526	$0.00	0.5046	$0.00
Grade 2	$0.00	0.0194	0.0399	0.4580	$0.00	0.5130	$0.00
Grade 3	$102.34	0.0234	0.0433	0.5185	$53.07	0.5819	$59.55
Grade 4	$1 966.00	0.0085	0.0013	0.0900	$177.04	0.1044	$205.22
Thrombocytopaenia				1.2067	$8.73	1.3669	$10.19
Grade 1	$0.00	0.0525	0.0688	0.9719	$0.00	1.0972	$0.00
Grade 2	$0.00	0.0155	0.0080	0.2028	$0.00	0.2324	$0.00
Grade 3	$102.34	0.0030	0.0000	0.0291	$2.98	0.0339	$3.47
Grade 4	$1 966.00	0.0003	0.0000	0.0029	$5.75	0.0034	$6.71
Anaemia				1.3584	$66.61	1.5136	$74.54
Grade 1	$0.00	0.0343	0.0999	1.0084	$0.00	1.1232	$0.00
Grade 2	$143.40	0.0100	0.0272	0.2809	$40.28	0.3132	$44.92
Grade 3	$286.80	0.0024	0.0062	0.0652	$18.70	0.0728	$20.88
Grade 4	$1 966.00	0.0003	0.0001	0.0039	$7.62	0.0044	$8.75
Febrile neutropaenia				0.0258	$86.81	0.0285	$95.37
Grade 1	$0.00	0.0000	0.0000	0.0000	$0.00	0.0000	$0.00
Grade 2	$1 966.00	0.0006	0.0000	0.0058	$11.44	0.0068	$13.34
Grade 3	$3 419.13	0.0000	0.0025	0.0171	$58.60	0.0186	$63.77
Grade 4	$5 880.88	0.0000	0.0004	0.0029	$16.78	0.0031	$18.26
Nausea, vomiting				2.1450	$228.68	2.4077	$257.21
Grade 1	$77.14	0.0534	0.0888	1.1167	$86.15	1.2555	$96.85
Grade 2	$83.38	0.0370	0.0800	0.8993	$74.98	1.0066	$83.92
Grade 3	$336.71	0.0067	0.0088	0.1241	$41.80	0.1401	$47.19
Grade 4	$5 332.00	0.0003	0.0003	0.0048	$25.75	0.0055	$29.24
Diarrhoea				1.1686	$282.88	1.3033	$316.90
Grade 1	$75.93	0.0237	0.0605	0.6387	$48.49	0.7129	$54.13
Grade 2	$82.21	0.0100	0.0346	0.3313	$27.24	0.3681	$30.26
Grade 3	$199.12	0.0067	0.0150	0.1660	$33.05	0.1856	$36.96
Grade 4	$5 332.00	0.0015	0.0027	0.0327	$174.10	0.0367	$195.55
Mucositis				0.7607	$17.36	0.8575	$19.29
Grade 1	$0.00	0.0285	0.0330	0.4986	$0.00	0.5641	$0.00
Grade 2	$13.31	0.0091	0.0158	0.1950	$2.60	0.2191	$2.92

Grade 3	$220.26	0.0018	0.0073	0.0670	$14.77	0.0743	$16.37
Grade 4	$5 332.00	0.0000	0.0000	0.0000	$0.00	0.0000	$0.00
Cutaneous Adverse Events				*0.4070*	*$1.50*	*0.4594*	*$1.74*
Grade 1	$0.00	0.0167	0.0260	0.3375	$0.00	0.3798	$0.00
Grade 2	$0.00	0.0036	0.0027	0.0530	$0.00	0.0605	$0.00
Grade 3	$91.17	0.0015	0.0003	0.0165	$1.50	0.0191	$1.74
Grade 4	$1 966.00	0.0000	0.0000	0.0000	$0.00	0.0000	$0.00
Neurological Adverse Events				*0.8757*	*$0.00*	*1.0188*	*$0.00*
Grade 1	$0.00	0.0295	0.0034	0.3058	$0.00	0.3550	$0.00
Grade 2	$0.00	0.0313	0.0000	0.3002	$0.00	0.3502	$0.00
Grade 3	$0.00	0.0267	0.0020	0.2697	$0.00	0.3136	$0.00
Grade 4	$0.00	0.0000	0.0000	0.0000	$0.00	0.0000	$0.00
Abdominal pain				*0.4545*	*$1 335.36*	*0.2000*	*$1.23*
Grade 1	$6.17			0.0000	$0.00	0.2000	$1.23
Grade 2	$92.97			0.0909	$8.45	0.0000	$0.00
Grade 3	$1 966.00			0.1818	$357.45	0.0000	$0.00
Grade 4	$5 332.00			0.1818	$969.45	0.0000	$0.00
Gastritis				*0.2727*	*$17.77*	*0.1000*	*$533.20*
Grade 1	$7.08			0.0000	$0.00	0.0000	$0.00
Grade 2	$10.01			0.1818	$1.82	0.0000	$0.00
Grade 3	$175.47			0.0909	$15.95	0.0000	$0.00
Grade 4	$5 332.00			0.0000	$0.00	0.1000	$533.20
Anorexia				*0.3636*	*$28.62*	*0.1000*	*$533.20*
Grade 1	$77.14			0.2727	$21.04	0.0000	$0.00
Grade 2	$83.38			0.0909	$7.58	0.0000	$0.00
Grade 3	$1 966.00			0.0000	$0.00	0.0000	$0.00
Grade 4	$5 332.00			0.0000	$0.00	0.1000	$533.20
Cirrhosis				*0.0909*	*$178.73*	*0.0000*	*$0.00*
Grade 1	$0.00			0.0000	$0.00	0.0000	$0.00
Grade 2	$0.00			0.0000	$0.00	0.0000	$0.00
Grade 3	$1 966.00			0.0909	$178.73	0.0000	$0.00
Grade 4	$5 332.00			0.0000	$0.00	0.0000	$0.00
Liver Abscess				*0.0909*	*$484.73*	*0.0000*	*$0.00*
Grade 1	$1 966.00			0.0000	$0.00	0.0000	$0.00
Grade 2	$1 966.00			0.0000	$0.00	0.0000	$0.00
Grade 3	$5 332.00			0.0000	$0.00	0.0000	$0.00
Grade 4	$5 332.00			0.0909	$484.73	0.0000	$0.00
Total average cost per patient					$2 968		$2 108

Abbreviations

AACR	Australasian Association of Cancer Registries
ACN	Australian Cancer Network
AE	adverse event
AFP	alpha-fetoprotein
AIHW	Australian Institute of Health and Welfare
ARPANSA	Australian Radiation Protection and Nuclear Safety Agency
CEA	carcinoembryonic antigen
CI	confidence interval
CLM	colorectal liver metastases
COSA	Clinical Oncological Society of Australia
CR	complete response
CRC	colorectal cancer
CT	computed tomography
DSA	digital subtraction angiography
FOLFIRI	fluorouracil, leucovorin and irinotecan
FOLFOX	fluorouracil, leucovorin and oxaliplatin
5-FU	5-fluorouracil
GI	gastrointestinal
HAC	hepatic arterial chemotherapy
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HTA	Heath Technology Assessment
ICD-10-AM	The International Statistical Classification of Diseases and Related Health Problems Tenth Revision, Australian Modification
ICER	incremental cost effectiveness ratio
IFL	irinotecan, 5-FU, leucovorin
LM	liver metastases
LV	leucovorin
LYG	life year gained
MAA	macroaggregated albumin
MBS	Medicare benefits schedule

MSAC	Medical Services Advisory Committee
N or *n*	number of patients (in population; in study)
n/a	not applicable
NA	not assessable
NC	no change
NCI	National Cancer Institute
NHMRC	National Health and Medical Research Council
NHS	UK National Health Service
NOHSC	National Occupational Health and Safety Commission
n/r	not reported
ns	not significant
OR	odds ratio
PBS	Pharmaceutical Benefits Scheme
PD	progressive disease
PEI	percutaneous ethanol injection
PR	partial response
pts	patients
RCT	randomised controlled trial
RECIST	response evaluation criteria in solid tumours
RFA	radiofrequency ablation
SD	stable disease
SIR-Spheres	Selective Internal Radiotherapy Spheres
SIRT	Selective Internal Radiation Therapy
SPECT	single-photon emission computerized tomography
TACE	transarterial chemoembolisation
TAE	transarterial embolisation
TGA	Therapeutic Goods Administration
TNM	tumour, node, metastasis
UICC	Union internationale contre le cancer

Glossary

Arteriography	An investigational procedure involving the use of roentgenography of arteries after injection of radiopaque material into the bloodstream.
Ascites	An effusion and accumulation of serous fluid in the abdominal cavity.
Cholecystitis	An acute or chronic inflammation of the gall bladder.
Cholecystectomy	A term describing the surgical removal of the gall bladder, which may be performed through an open incision or via laparoscopy.
Encephalopathy	Any degenerative disease of the brain.
FOLFIRI	An abbreviation for a type of combination chemotherapy that is used to treat colorectal cancer. It includes fluorouracil, leucovorin and irinotecan.
FOLFOX	An abbreviation for a type of combination chemotherapy that is used to treat colorectal cancer. It includes fluorouracil, leucovorin and oxaliplatin.
Haemoperitoneum	An effusion of blood in the peritoneal cavity.
Hepatoma	A term for carcinoma derived from liver cells. A better term to use is hepatocarcinoma or hepatocellular carcinoma.
Lymphopaenia	Reduction in the number of lymphocytes, the white blood cells that fight infection and disease.
Metastases	Cancer that started from cancer cells from another part of the body. For example: cancer that starts in the colon develops metastases in the liver.
Peritonitis	An inflammation of the peritoneum, the serous membrane which lines the cavity of the abdomen, which is marked by exudations in the peritoneum of serum, fibrin, cells and pus and attended by abdominal pain and tenderness, constipation, vomiting and moderate fever.
Pneumonitis	Inflammation of the lung secondary to viral or bacterial infection. Common symptoms include a productive cough, fever, chills and shortness of breath.
Radioisotopes	Isotopes (atomic species differing in mass number but having the same atomic number) that exhibit radioactivity and undergo radioactive decay, which is accompanied by the emission of energy.
Superior mesenteric portovenography	Portovenography of the superior mesenteric vein (vein from the small intestines). Portovenography = portography, an examination of the portal circulation by the use of x-ray films after injection of radiopaque material.
Transarterial embolisation	A treatment designed to inhibit tumour growth by the occlusion of arterial flow by synthetic (Gelfoam, Ivalon or others) or natural particles (blood clots).
Transarterial chemoembolisation	A treatment designed to inhibit tumour growth by the occlusion of arterial flow by synthetic (Gelfoam, Ivalon or others) or natural particles (blood clots) preceded by the administration of chemotherapy with or without ^{131}I-lipiodol.

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