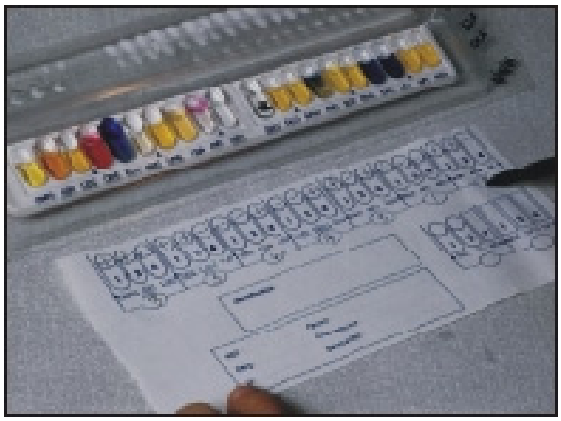
Health Technology Assessment
HTA-rapport 2010:27

^{90}YTTRIUM RADIOEMBOLISATION FOR HEPATOCELLULAR CARCINOMA AND COLORECTAL LIVER METASTASES

M Rizell, R Hultborn, P Bernhardt, J Svensson,
M Sternby Eilard, O Samuelsson, A Strandell,
T Svanberg, U Wikberg-Adania

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

HTA-centrum



HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	⊕⊕⊕⊕	(Previously Level of evidence 1)
Moderate quality of evidence	⊕⊕⊕	(Previously Level of evidence 2)
Low quality of evidence	⊕⊕	(Previously Level of evidence 3)
Very low quality of evidence	⊕	(Previously Level of evidence 4)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work. (GRADE 2004, GRADE List of publications)

Christina Bergh, Professor, MD.
Head of HTA-center

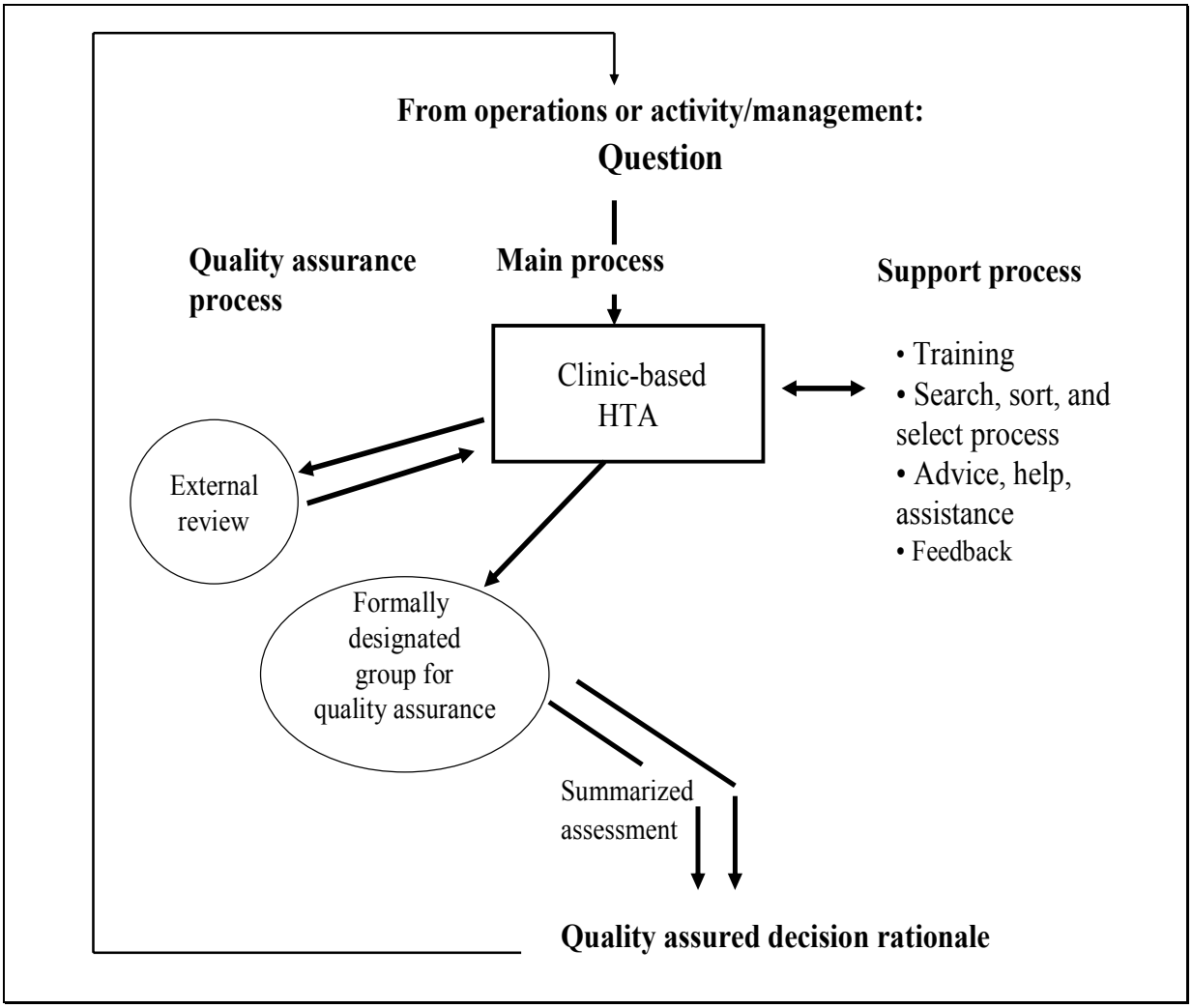

From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

Table of content

Utlåtande och sammanfattande bedömning från Kvalitetssäkringsgruppen

BEHANDLING AV PRIMÄR LEVERCANCER ELLER LEVERMETASTASER FRÅN KOLOREKTAL CANCER MED SELEKTIV TILLFÖRSEL AV RADIOAKTIVA ^{90}YTTRIUM MIKROSFÄRER

HTA-kvalitetssäkringsgruppen har ett uppdrag att yttra sig över genomförda HTA i Västra Götalandsregionen. Yttrandet skall innefatta sammanfattning av frågeställning, samlat evidensläge, patientnytta, risker samt ekonomiska och etiska aspekter för den studerande teknologin.

Denna HTA har genomförts på begäran av verksamhetschef Michael Olausson, Transplantationscentrum, Sahlgrenska Universitetssjukhuset (SU).
En arbetsgrupp bestående av Ragnar Hultborn, professor, Onkologi (SU), Peter Bernhardt, docent, Avdelningen för radiofysik (SU), Magnus Rizell, överläkare, Transplantationscentrum (SU), Johanna Svensson, specialistläkare, Onkologi (SU), och Malin Sternby Eilard, specialistläkare, Transplantationscentrum (SU) har tillsammans med HTA-centrum tagit fram HTA rapporten.

Resurspersoner från HTA-centrum har varit Ola Samuelsson, docent, Annika Strandell, docent, Therese Svanberg, bibliotekarie, Ulla Wikberg-Adania, bibliotekarie.

HTA-rapporten samt åberopad och förtecknad litteratur har granskats av Christian Rylander, med.dr, Anestesi (SU/Sahlgrenska).

Slutsatser har diskuterats vid möten mellan HTA-centrum och HTA-projektgruppen. Ett utlåtande har tagits fram, diskuterats och fastställts vid Kvalitetssäkringsgruppens möte 2010-06-02.

Projektet har pågått under perioden 2009-11-30—2010-06-02.

Den systematiska litteratursökningen sträckte sig fram till och med 2010-01-22.

Kvalitetssäkringsgruppen

Christina Bergh
Professor
Magnus Hakeberg,
Professor
Hans Hedelin,
Professor
Peter Johansson
Med.dr, Överläkare

Lennart Jivegård,
Universitetslektor
Anders Larsson
Överläkare
Ola Samuelson,
Docent
Henrik Sjövall
Professor

Maria Skogby
M.dr, Vårdenhetschef
Annika Strandell
Docent
Therese Svanberg
HTA-bibliotekarie

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset
HTA-centrum
Röda Stråket 8, 413 45 Göteborg
TELEFON växel 031-342 00 00, direkt 031-342 15 56

Frågeställning:
Ger brakyterapi med ^{90}Yttriummärkta mikrosfärer förlängd överlevnad i jämförelse med konventionell ”salvage”-behandling alternativet kemoembolisering eller annan palliativ behandling för patienter med primär hepatocellulär cancer respektive levermetastaserad kolorektalcancer?

PICO: (Patient, Intervention, Comparison, Outcome)

PICO I:
- P = Patienter över 18 år med primär hepatocellular cancer (HCC)
- I = ^{90}Yttrium-mikrosfärer (glas eller resin-sfärer) givet via arteria hepatica
- C = Kemoemboliseringor eller palliativ behandling
- O = 1. Överlevnad
  2. Tumörreduktion, tid till progress, livskvalitet och toxicitet

PICO II:
- P = Patienter över 18 år med levermetastaser från kolorektal cancer (CRC)
- I = ^{90}Yttrium-mikrosfärer (glas eller resin-sfärer) givet via arteria hepatica
- C = Konventional “salvage” behandling
- O = 1. Överlevnad
  2. Tumörreduktion, tid till progress, livskvalitet och toxicitet

Resultatet av HTA-processen:

Metod och målgrupp:
Primär levercancer och kolorektal cancer är två mycket vanliga cancerformer.
De kurativa behandlingsalternativ som är tänkbara för patienter med primär levercancer är levertransplantation, leverresektion eller ”radiofrequency ablation”. En del patienter är emellertid inte lämpliga för kirurgiska åtgärder och de har en mycket hög mortalitet. Radioembolisering med ^{90}Yttrium-mikrosfärer är en teknologi som dels har potential att kunna minska tumörvävnadens utbredning och därmed möjliggöra kurativ levertransplantation, och dels kan ges i palliativt syfte för att eventuellt förbättra överlevnad och livskvalitet.
Patienter med primär kolorektal cancer med metastaser i levern har en mycket dålig prognos. Idag behandlas dessa patienter palliativt med systemisk kemoterapi som i många fall är förenad med allvarliga biverkningar med bl.a. toxisk påverkan på framförallt benmärg. Även hos dessa patienter har lokal brakyterapi med ^{90}Yttrium-mikrosfärer potential att förbättra överlevnad och livskvalitet, och reducera behovet av kemoterapi.

Evidensläge för studerad patientnytta:

Hepatocellulär cancer

Den systematiska litteratursökningen fann 16 studier som rapporterat behandlingsresultat av radioembolisering med ^{90}Yttrium-märkta mikrosfärer hos patienter med HCC som inte varit åtkomlig för kirurgi. Fyra studier var kontrollerade studier men ingen var randomiserad. Övriga 12 studier var fallserier. Av de kontrollerade studierna var två av medelhög och två av låg vetenskaplig kvalitet.

- *Överlevnad*. I jämförelse med kemoembolisering förlängdes överlevnaden med 3 respektive 17 månader i de två studierna som bedömdes ha medelhög vetenskaplig kvalitet. Evidensgraden för effekten på överlevnad är otillräcklig (Grade ⊕).
- *Behandlingssvar på tumörvävnad.* Andelen patienter som fick ett komplett eller partiell tumörsvar, dvs. helt försvunnen eller avsevärt reducerad tumörmassa, varierade mellan 26 – 61 %. Evidensgraden för effekten på tumörsvar är otillräcklig (Grade ⊕).
- *Komplikationer.* De flesta patienter erfor illamående och uttalad trötthet. Lymfopeni observerades hos majoriteten av patienterna. Allvarlig biverkan förekom hos 22 – 42 % avseende levertoxicitet och 7 -39 % avseende bilirubin-toxicitet

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET
Sahlgrenska Universitetssjukhuset
HTA-centrum
Röda Stråket 8, 413 45 Göteborg
TELEFON växel 031-342 00 00, direkt 031-342 15 56

Levermetastaser från kolorektal cancer

Den systematiska litteratursökningen fann åtta studier som rapporterat behandlingsresultat av radioembolisering med ^{90}Yttrium-märkta mikrosfärer hos patienter med levermetastaser från kolorektal cancer som inte varit åtkomliga för kirurgi. Tre studier var kontrollerade, varav två randomiserade. Övriga fem studier var fallserier. Av de randomiserade studierna var en av medelhög och en av låg vetenskaplig kvalitet. Även den icke-randomiserade, kontrollerade studien hade låg vetenskaplig kvalitet.

- *Överlevnad.* Ingen skillnad i överlevnad observerades i den något större randomiserade studien som bedömdes ha medelhög kvalitet eller i den icke-randomiserade studien. I den mindre kontrollerade studien av låg kvalitet rapporterades en förlängd överlevnad hos gruppen som behandlades med radioembolisering. Evidensgraden för effekten på överlevnad är otillräcklig (Grade ⊕).
- *Behandlingssvar på tumövävnad.* Andelen patienter som fick ett komplett eller partiell tumörsvar varierade mellan 34 – 75 %. Evidensgraden för en positiv effekt avseende tumörsvar är enligt begränsad (Grade ⊕⊕).
- *Komplikationer.* De flesta patienter erfor illamående, buksmärta och uttalad trötthet. Allvarlig biverkan förekom hos 2 – 4 % avseende levertoxicitet, 12 % avseende bilirubin-toxicitet och 5 – 8 % avseende ”gastrointestinal” toxicitet.

Risker

Levertoxiciteten till följd av radioembolisering med ^{90}Yttrium-mikrosfärer har rapporterats vara relativt hög. Enstaka dödsfall som en direkt följd av behandlingen har rapporterats

Etiska aspekter:

De etiska aspekterna kan delas upp i individuella och i samhällsaspekter. För den enskilde patienten ger den nya behandlingen ett visst hopp om en ökad överlevnad, vilket kan vara mycket betydelsfullt i enskilda fall. För samhället innebär behandlingen att en omfördelning av resurser måste ges till en behandling som saknar tillräcklig dokumentation av patientnytta.

Ekonomiska aspekter

Om behandling av primär hepatocellulär cancer med kemoembolisering eller annan ”salvage” behandling ersätts av brakyterapi med ^{90}Yttriummärkta mikrosfärer innebär detta en måttlig årlig kostnadsökning på ca 0,5 miljoner kronor. Om den adderas till nuvarande palliativ behandling av levermetastaser från kolorektal cancer ökar den årliga kostnaden med ca 8 miljoner kronor.

Sammanfattning och slutsats

Brachyterapi med ^{90}Yttriummärkta mikrosfärer har studerats i två olika patientgrupper med diagnoserna primär hepatocellulär cancer och levermetatstaser från kolorektal cancer. Behandlingen har en positiv effekt på tumörsvar (GRADE ⊕ för primär levercancer och GRADE ⊕⊕ för levermetastaser från koleraktal cancer). Dokumentationen om dess effekter på överlevnad är otillräcklig (GRADE ⊕). Levertoxicitet är en allvarlig biverkan. Kostnadsökningen är måttlig om metoden ersätter annan behandling (vid primär levercancer) och betydande om den ges som tillägg till annan palliativ behandling.

För HTA-kvalitetssäkringsgruppen 2010-06-02

Christina Bergh
Ordförande
HTA-kvalitetssäkringsgruppen

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset
HTA-centrum
Röda Stråket 8, 413 45 Göteborg
TELEFON växel 031-342 00 00, direkt 031-342 15 56

Statement from the Regional HTA Centre of the Region Västra Götaland in Sweden

^{90}YTTRIUM RADIOEMBOLISATION FOR HEPATOCELLULAR CARCINOMA AND COLORECTAL LIVER METASTASES

The Regional Health Technology Assessment Centre (HTA-centrum) of the Region Västra Götaland, VGR, in Sweden has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, level of evidence, efficacy, risks, and economical and ethical aspects of the particular health technology that has been assessed in the report.

Michael Olausson, Head of the Department of Transplantation and Liver Surgery, Sahlgrenska University Hospital, Göteborg, Sweden, requested the present HTA.

A working group under the chairmanship of Magnus Rzell, MD, PhD, the Department of Transplantation and Liver Surgery, Sahlgrenska University Hospital, Göteborg, Sweden produced the HTA report. The other members of the working group were Peter Bernhardt, professor, Department of Medical Physics and Bioengineering, Ragnar Hultborn, professor, Department of Oncology, Malin Sternby Eilard, MD, Department of Transplantation and Liver Surgery, and Johanna Svensson, MD, Department of Oncology. All at the Sahlgrenska University Hospital, Göteborg, Sweden.

The participants from the HTA centre were Ola Samuelsson, MD, PhD, Annika Strandell, MD, PhD, Therese Svanberg, librarian, and Ulla Wikberg-Adania, librarian.

Christian Rylander, PhD, Department of Anaesthesiology, Sahlgrenska University Hospital, Göteborg, Sweden, has critically appraised the report.

The project lasted during the time period 2009-11-30 – 2010-06-02.
The literature search covered the time up to January 2010.

The HTA-centre:

Christina Bergh Professor	LennartJivegård, PhD, MD	Maria Skogby PhD, RN
Magnus Hakeberg, Professor, OD	Anders Larsson PhD, MD	Annika Strandell PhD, MD
Hans Hedelin, Professor, MD	Ola Samuelson, PhD, MD	Therese Svanberg HTA-librarian
Peter Johansson PhD, MD	Henrik Sjövall Professor, MD	

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset
HTA-centrum
Röda Stråket 8, 413 45 Göteborg
TELEFON växel 031-342 00 00, direkt 031-342 15 56

Question at issue:

Does treatment with ^{90}Yttrium microspheres prolong life in comparison with conventional salvage treatment, such as chemoembolisation or other palliative treatments, in patients with primary liver cancer or liver metastases from colorectal cancer?

Patients, Intervention, Comparison, and Outcome (PICO

PICO I:

P = Patients over 18 years with primary hepatocellular carcinoma
I = ^{90}Yttrium-coated microspheres (glass or resin), administered via the hepatic artery.
C = Chemoembolisation or other palliative treatment
O = 1. Survival
2. Response rate, Time to progression, Quality of Life and Toxicity

PICO II:

P = Patients over 18 years with liver metastases from colorectal cancer
I = ^{90}Yttrium-coated microspheres (glass or resin), administered via the hepatic artery
C = Conventional "salvage" therapy

O = 1. Survival
2. Response rate, Time to progression, Quality of Life and Toxicity

Summary of the health technology assessment:

Method and patient category:

Hepatocellular cancer (HCC) and colorectal cancer (CRC) are common cancer forms.

The present treatment of HCC includes orthotopic liver transplantation, liver resection and radiofrequency ablation. The aim of these treatments is curative. However, not all patients are suitable for surgery or radiofrequency ablation. These patients have a very poor prognosis. For palliative treatment and for patients on the waiting list for liver transplantation radioembolisation with ^{90}Yttrium-labeled microspheres may be an alternative treatment strategy.

Patients with unresectable hepatic metastases from CRC also have a very poor prognosis. These patients are predominantly considered for systemic chemotherapy to diminish the tumour burden. Surgery has not been shown to prolong life, if tumor excision is not radical. External irradiation of liver tumours for multifocal disease is seldom feasible, since the risk of acute or late damage to the normal liver tissue is overwhelming. A local and selective tumour treatment of a disseminated tumour may improve the quality of life and prolong survival.

Level of evidence:

Hepatocellular carcinoma

The systematic literature search identified 16 studies that have reported the therapeutic outcome of radioembolisation with ^{90}Yttrium-labeled microspheres in patients with unresectable HCC. Four studies were non-randomized controlled studies, and 14 case series. There was no randomized, controlled trial. Two of the controlled studies were of moderate scientific quality, and two were of low scientific quality.

- *Survival*. In comparison with chemoembolisation the survival was 3 and 17 months longer, respectively, in the two studies of moderate scientific quality. The level of evidence with regard to the effect on survival is very low according to the GRADE system (Grade ⊕).
- *Tumour response.* The frequency of patients with a complete or partial tumour response varied between 26-61 %. The level of evidence with regard to tumour response is very low according to the GRADE system (Grade ⊕).
- *Complications.* Most patients experienced nausea and extreme fatigue. Lymfopenia was observed in the majority of the patients. A serious adverse effect occurred in 22 – 42 % with regard to liver toxicity, and in 7 -39 % with regard to bilirubin-toxicity.

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset
HTA-centrum
Röda Stråket 8, 413 45 Göteborg
TELEFON växel 031-342 00 00, direkt 031-342 15 56

Liver metastases from colorectal cancer

The systematic literature search identified eight studies that have reported the therapeutic outcome of radioembolisation with ^{90}Yttrium-labeled microspheres in patients with unresectable liver metastases from CRC. Three studies were controlled studies, two of which being randomised (RCT). The other five studies were case series. One of the RCTs was of moderate and the other of low scientific quality. The non-randomised, controlled study was also of low scientific quality.

- *Survival.* There was no difference in survival between radioembolisation with ^{90}Yttrium and the control therapy in the RCT of moderate scientific quality or in the non-randomised, controlled study of low scientific quality. The level of evidence with regard to the effect on survival is very low according to the GRADE system (Grade ⊕).
- *Tumour response.* The frequency of patients with a complete or partial tumour response varied between 34 – 75 %. The level of evidence with regard to tumour response is very low according to the GRADE system (Grade ⊕⊕).
- *Complications.* Most patients experienced nausea, abdominal pain and extreme fatigue. A serious adverse effect occurred in 2 – 4 % with regard to liver toxicity, in 12 % with regard to bilirubin-toxicity, and in 5 – 8 % with regard to gastrointestinal toxicity.

Risks

The liver toxicity of radioembolisation with ^{90}Yttrium-labeled microspheres is relative high. A few fatal cases have been reported as the direct consequence of this treatment.

Ethical aspects:

Ethical issues may be separated into those concerning the patients being candidates for this treatment in terms of suffering in relation to potential benefits, and those concerning what should be prioritized based on cost-effectiveness calculations.

Economical aspects

The use of with radioembolization with ^{90}Yttrium in HCC instead of TACE and in CRC as additional palliative therapy is estimated to increase the annual cost between 8-10 million SEK (800 000 – 1 000 000 €).

.

Concluding remarks

Brachytherapy using radioembolisation with ^{90}Yttrium-labeled microspheres has been assessed in two categories of patients; in patients with unresectable primary hepatocellular carcinoma and in patients with liver metastases from colorectal cancer.

The level of evidence of the effects on survival is very low for both these cancer forms (Grade ⊕). The level of evidence of a positive effect on tumour response in liver metastases from colorectal cancer is low (Grade ⊕⊕), whereas the level of evidence of tumour response in hepatocellular carcinoma is very low (Grade ⊕).

The increase in cost is moderate if the method is used instead of chemoembolisation in HCC patients. If it is used as an additive treatment in CRC patients the increase in cost is significant.

On behalf of HTA-centrum Göteborg, Sweden, 2010-06-02

Christina Bergh, Professor, MD.
Head of HTA-centre

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset
HTA-centrum
Röda Stråket 8, 413 45 Göteborg
TELEFON växel 031-342 00 00, direkt 031-342 15 56

Which health technology or method will be assessed?

^{90}YTTRIUM RADIOEMBOLISATION FOR HEPATOCELLULAR CARCINOMA AND COLORECTAL LIVER METASTASES

1a. Who will lead the project?

Magnus Rizell, MD, PhD, Senior consultant Department of Transplantation and Liver Surgery, Sahlgrenska University Hospital

Co-workers:
Ragnar Hultborn, MD, PhD, Professor, Department of Oncology, Sahlgrenska University Hospital
Peter Bernhardt, Physicist, PhD, Professor, Department of Medical Physics and Bioengineering, Sahlgrenska University Hospital
Johanna Svensson, MD, Department of Oncology, Sahlgrenska University Hospital
Malin Sternby Eilard, MD, Department of Transplantation and Liver Surgery, Sahlgrenska University Hospital

1b. Who posed the question?

Michael Olausson, MD, Professor, Head of Department of Transplantation and Liver Surgery, Sahlgrenska University Hospital.

1c. Additional parties who posed the question

Per Karlsson, MD, Associate Professor, Head of Department of Oncology, Sahlgrenska University Hospital

1d. Other participants, from the HTA centre and external reviewers

Ola Samuelsson, MD, PhD, Annika Strandell, MD, PhD, Therese Svanberg, librarian, Ulla Wikberg-Adania, librarian

External reviewers
Christian Rylander, MD, PhD

1e. Are there any conflicts of interest for the proposer or any of the participants in the work group?

No.

Disease/disorder of Interest and Present Treatment

2a. Disease/disorder of interest and its degree of severity

Hepatocellular cancer (HCC) and colorectal cancer (CRC) are among the most common cancer forms.

Patients with unresectable HCC have a short life expectancy with a median survival of 3-6 months and a 5-year survival of less than 10 %. Patients with resectable liver metastases from CRC have a 5-year survival of 20 - 40 %. Patients with unresectable metastases from CRC confined to the liver have a median survival of 6 -10 months without treatment. With current chemotherapy it may be prolonged to 18-21 months (Wagner et al., 2009).

2b. Prevalence and incidence of the disease/disorder

The population of the Region Västra Götaland of Sweden (VGR) is 1,55 million people.

During 2000 - 2008 there were 388 patients diagnosed with HCC. This corresponds to an average annual incidence of about 50 patients, of which around 40 would be unresectable.

In 2007 the incidence of CRC was 1054 patients in this population. The annual incidence of patients with isolated, unresectable hepatic metastases is estimated to be around 35 (The Regional Oncological Center; National Board of Health and Sjövall et al., 2004).

2c. Present treatment of the disease/disorder in the outpatient setting/ in-patient setting

The present treatment of HCC includes orthotopic liver transplantation, liver resection and radiofrequency ablation. The aim of all these three treatments is curative. For palliative treatment and for patients on the waiting list for liver transplantation there are two main alternative treatment strategies.

1. ***Regional chemotherapy*** together with embolization products that give a stagnant blood flow in the vasculature of the tumour. This is administered via the hepartic artery, and the treatment is called trans-arterial chemoembolization (TACE). TACE is administered as an in-hospital procedure, and the patients stay overnight. Results in recent reported case series, and in randomized, controlled trials have indicated an increased survival by about one year, and the median survival time for patients suitable for TACE is around 20 months (Forner et al., 2009). However, the selection of patients is crucial (Llovet et al., 2002). According to current international guidelines TACE is indicated in patients with no extrahepatic metastases, without portal thrombosis and with a good liver function (Forner et al., 2010)

2. ***Systemic therapy*** with the tyrosine kinase inhibitor sorafenib (Nexavar®).
   This treatment is given in an outpatient setting. Two randomized, controlled trials have shown an increased survival time in patients with good liver function by about 3 months, from a median of 7 months to 10 months (Llovet et al., 2008).

Both of these treatments for HCC have been accepted in the regional treatment program of VGR (www.oc.gu.se).

Patients with unresectable hepatic metastases from CRC are predominantly considered for systemic chemotherapy. This is normally administered in the outpatient setting. In case of tumour progression the patient may be considered for second-line chemotherapy or liver-directed treatment, provided there is no extrahepatic metastases. The present alternatives are:

1. ***Regional chemotherapy*** such as TACE or hepatic artery chemotherapy (HAC). These alternatives are presently not used in the Western Region.

2. ***Systemic chemotherapy*** including oxaliplatin or irinotecan combined with 5-FU, and sometimes a biological compound (Avastin®, Vectibix® or Erbitux®).

2d. Number of patients per year who undergo the current treatment regimen?

Based on the incidence of HCC we estimate that around 15 - 20 patients can be treated annually with either TACE or with the new treatment technology ^{90}Yttrium-radioembolization. In addition, some patients are referred from other regions.

The number of patients with CRC and isolated, unresectable hepatic metastases who may be considered for systemic chemotherapy, possibly in combination with or followed by liver-directed therapy such as ^{90}Yttrium-radioembolization is estimated to be around 35 patients annually.

2e. The normal pathway of a patient through the health care system

Patients in the Western Region of Sweden who are diagnosed with HCC are referred to the Department of Transplantation and Liver Surgery at Sahlgrenska University Hospital. After a thorough work-up a multidisciplinary board proposes a treatment. In case of anti-tumoral palliative treatment the Department of Transplantation and Liver Surgery will administer this. In case of symptomatic palliative measures the palliative treatment teams in the region will take the responsibility and provide this treatment.

Patients who are considered for systemic chemotherapy for CRC are taken care of by oncologists at Sahlgrenska University Hospital or at the local hospitals in the region. Locoregional treatment to the liver is only available at Sahlgrenska University Hospital.

2f. Actual waiting in days for medical assessment /treatment

Both categories of patients with HCC and CRC are normally assessed within two weeks after referral. The waiting time between board decision and start of chemotherapy is usually another one to two weeks. The waiting time for the first TACE is usually slightly longer, between 1 to 6 weeks (median 4 weeks).

Present Health Technology

3a. Name of the health technology at issue

Radioembolization with ^{90}Yttrium-coated microspheres administered in the hepatic artery.

3b. Description of the new technology

Radioembolization with ^{90}Yttrium-labeled microspheres is a local therapy where the liver is the target organ. A 2 to 8 fold higher uptake of locally irradiating spheres can be achieved in the tumor tissue compared to in the normal liver tissue. This is due to the fact that tumors mainly are supplied by arterial blood, whereas the normal liver tissue mainly is supplied by venous blood. Infusion of the microspheres, via an injection in the hepatic artery, will trap the microspheres in the capillary bed. This enables the delivery of high doses to the tumor tissue.

3c. The work group's understanding of the potential value of the health technology

Radioembolization with ^{90}Yttrium may be used for neo-adjuvant treatment in patients considered for curative treatments such as orthotopic liver transplantation, resection, or radiofrequency ablation, aiming to decrease the risk for recurrence. ^{90}Y-treatment may also reduce the tumour mass to increase the number of HCC-patients eligible for curative interventions, so called, downstaging. Furthermore, in the case of resection the administration of ^{90}Yttrium to the part of the liver which is supposed to be resected, may add a stimulus for contralateral growth of the liver. Also, ^{90}Yttrium administered in the part of the liver that is left has the potential to destroy microscopic foci of tumour, not visible at usual staging radiography.

This treatment may be valuable also in the palliative setting for HCC, enabling prolonged survival. It may be a better alternative than TACE, which is the first treatment option today, since it has the potential to be more selective and has a rather low complication rate. Moreover, since fewer treatment procedures are normally needed for ^{90}Yttrium than for TACE, ^{90}Yttrium may improve the quality of life.

The primary aim of treatment of liver metastases from CRC is to diminish the tumour burden. A local treatment of a disseminated tumour may also prolong life. However, local treatment of liver dominated disease is complicated. Surgery has not been shown to prolong life, if tumor excision is not radical. External irradiation of liver tumours for multifocal disease is seldom feasible, since the risk of acute or late damage to the normal liver tissue is overwhelming.

For CRC radioembolization with ^{90}Yttrium could be especially valuable for those with metastatic spread confined only to the liver. It should be supplemented by systemic "adjuvant" chemotherapy, either at time of the diagnosis of liver metastases as subclinical disease often is present elsewhere at this time, or at the time of manifest extrahepatic disease.The effects of radioembolization with ^{90}Yttrium combined with systemic chemotherapy may be additive or synergistic. The addition of systemic treatment may inhibit further systemic spread (treatment of subclinical disease). One clear benefit of a

locally administered treatment is that it will reduce the toxicity to other organs such as the bone marrow.

In summary, therapy by radioembolization with ^{90}Yttrium-labeled microspheres is a theoretically interesting, selective treatment with potential advantages;

- It may improve the anti-tumor effect, as described above.
- It is a rather tumour selective treatment.
- It may improve quality of life, being a treatment with a possibly favourable toxicity profile.
- It is expected to require less resource since it is a low intensity treatment, which normally is not repeated with shorter intervals than 6-12 months.

The treatment is based on a multidisciplinary teamwork. This is at present available at Sahlgrenska University Hospital, which has the task to be the leading centre in the Western Region of Sweden for liver transplantation and other locoregional liver treatments in advanced diseases.

3d. The central question for the current HTA project in one sentence

Does treatment with ^{90}Yttrium microspheres prolong life in comparison with conventional salvage treatment, such as chemoembolization or other palliative treatments, in patients with primary liver cancer or liver metastases from colorectal cancer?

PICO I:
P = Patients over 18 years with primary hepatocellular carcinoma (HCC)
I = ^{90}Yttrium-coated microspheres (glass or resin), administered via the hepatic artery.
C = Chemoembolization or other palliative treatment
O = 1. Survival
2. Response rate, Time to progression, Quality of Life and Toxicity

PICO II;
P = Patients over 18 years with liver metastases from colorectal cancer (CRC)
I = ^{90}Yttrium-coated microspheres (glass or resin), administered via the hepatic artery
C = Conventional “salvage” therapy
O = 1. Survival
2. Response rate, Time to progression, Quality of Life and Toxicity

3e. Key words

hepatocellular carcinoma, colorectal cancer, hepatic metastasis, locoregional therapy, ^{90}Yttrium microspheres

Review of the Level of Evidence

4. Search strategy, study selection and references – appendix 1

During December 2009 – January 2010, the library performed literature searches in PubMed, the Cochrane Library, EMBASE and a number of HTA- databases. (See appendix 1 for details.) Reference lists of relevant articles were also scanned for additional references.

A total of 1334 articles were identified, of which 1261 abstracts were excluded by the library. Another 25 articles were excluded by the library after having been read in full text. 48 articles were sent to the work group for assessment. 24 of these articles are included in the report, 7 are controlled studies and have been critically appraised. The appraisal of articles is based on checklists from SBU (2008), which were developed by Olle Nyrén, professor, Karolinska Institutet, Stockholm.

Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in appendix 1. The literature search and exclusion of abstracts were made by two librarians (TS, UWA) in consultation with the HTA-centre and the project group.

5a. Describe briefly the present knowledge of the health technology

Hepatocellular carcinoma

The systematic literature search identified 16 studies, which have reported treatment effects of radioembolization with ^{90}Yttrium microspheres in patients with unresectable HCC. Four were non-randomized, controlled studies and 12 were case series including 41 up to 291 patients. Of the non-randomized, controlled studies two were of moderate scientific quality and two of low scientific quality. There was no randomized, controlled trial.

The controlled studies of moderate quality compared radioembolization with TACE. They reported average survival rates of 8.5 and 11.5, and 18.7 and 35.7 months, respectively, in the different treatment groups. Thus, in comparison to TACE treatment the use of radioembolization with ^{90}Yttrium microspheres significantly prolonged survival by an average of 3 and 17 months in these two different trials.

The 16 studies were heterogeneous with regard to baseline patient characteristics in terms of stage of cancer disease, liver function, and previously administered therapy.

The response rate (i.e. complete or partial response) varied between 26 - 61% according to the WHO criteria, 34 - 86% according to the EASL criteria, and 8 - 23% according to the RECIST criteria. These three different criteria were analyzed in parallel in only one study.

The quality of evidence for radioembolization with ^{90}Yttrium microspheres on the effects on survival as well as on tumor response is very low (⊕) according to the GRADE system.

The reporting of adverse effects and toxicity was inconsistent between studies, varying in type of toxicity, grade of toxicity, time of occurence after treatment and the possible relation to treatment. Most patients reported nausea and fatigue. Lymphopenia also occurred in the majority of cases. Grade 3 - 4 liver toxicity was reported in 22 - 42 % of the patients and grade 3 - 4 bilirubin toxicity in 7 - 39 % of patients. Other occasionally reported severe complications were cholecystitis, gastric ulcers and pneumonitis. The treatment related mortality ranged from 0 to 9%.

Colorectal cancer

The systematic literature search identified eight studies, which have reported treatment effects of radioembolization with ^{90}Yttrium microspheres in patients with unresectable liver metastases from CRC. Two were randomized, controlled trials, and one was a non-randomized controlled study. The remaining five studies were case series including 41 to 208 patients.

One of the RCTs was of moderate scientific quality. The other RCT was a small trial of low scientific quality. Also the non-randomized controlled study was of low quality. Only the small RCT reported a significantly prolonged survival in radioembolized patients in comparison with alternative treatment, whereas there was no differences in survival rate in the other two controlled trials.Including the five case series the reported median survival varied from 7 up to 29 months.

The response rate (i.e. complete or partial response) varied from 41 – 73 %. The methods used to measure reduction of tumour and the criteria for complete response, partial response, stable disease and progressive disease varied between studies. In the randomized, controlled study the volume of the tumour mass was calculated. According to this criterion there were 2.1 times as many patients in the group treated with radioembolization with ^{90}Yttrium microspheres that had a complete or partial response in comparison with those who were treated with locoregional chemotherapy (HAC).

The eight studies of CRC were also heterogeneous with regard to baseline patient characteristics, i.e. in terms of the stage of the disease, liver function, and previously administered therapy. Generally the patients had already received intensive treatments prior to start of the studies, often with two or three different lines of systemic chemotherapy.

The quality of evidence for radioembolization with ^{90}Yttrium microspheres with regard to tumour response rate is low (⊕⊕), and with regard to the effects on survival very low (⊕) according to the GRADE system.

As in HCC patients the dominating adverse effects of radioembiolization were nausea, mild abdominal pain and fatigue. Almost all patients experienced this. More serious toxicity (Grade 3 - 4) was observed in 6 of 8 studies. Grade 3 - 4 liver toxicity was reported in 2 - 4 % of patients, grade 3 - 4 gastrointestinal toxicity in 5 - 8 %, and grade 3 - 4 bilirubin toxicity in 12 % of patients. Among the total of 554 patients followed in these studies there were three fatal cases of potentially treatment-related toxicity; two radiation hepatitis and one pancreatitis.

5b. Outcome tables – appendix 2

Table 1 a – c: Hepatocellular carcinoma
Table 2 a – c: Liver metastases from colorectal cancer

5c. Excluded articles – appendix 3

5d. Ongoing research

Hepatocellular carcinoma
In www.clinicaltrials.gov. there are 19 reported ongoing studies. Four of these are randomised, controlled trials.

Two of the RCTs compare ^{90}Yttrium microspheres to TACE in patients with unresectable HCC. One RCT compare ^{90}Yttrium microspheres to radiofrequency ablation in ablatable patients, and to either TACE alone or in combination with radiofrequency ablation in unablatable patients with unresectable HCC. The fourth RCT compares sorafenib combined with ^{90}Yttrium microspheres with sorafenib alone as a bridge/down-staging prior to orthotopic liver transplantation in HCC patients.

The other 15 studies are observational cohort studies, mainly focusing on safety/toxicity and response/survival. Seven of them will also study quality of life.

Colorectal cancer
In www.clinicaltrials.gov. there are six reported ongoing studies. Five of them are RCTs.

The two largest are both multicentre Phase III RCTs with the intention to recruit 450 and 490 patients, respectively. The first one evaluates the efficacy of ^{90}Yttrium-microspheres in combination with Oxaliplatin + 5-FU chemotherapy as first line treatment of unresectable liver dominant colorectal metastases compared to Oxaliplatin + 5-FU chemotherapy alone. The other will evaluate the efficacy and safety of adding ^{90}Yttrium - microspheres to a systemic chemotherapy regimen of Oxaliplatin + 5-FU for 6 months (with or without Bevacizumab) compared to Oxaliplatin + 5-FU for 6 months (with or without Bevacizumab) alone as first-line therapy in patients with unresectable liver metastases from colorectal cancer.

6 Which medical societies or health authorities recommend the new health technology?

Resin-based treatment with ^{90}Yttrium microspheres has Federal Drug Administration (FDA) approval for use in patients with liver metastases from colorectal cancer, and treatment with glass microspheres has FDA approval for use in patients with unresectable hepatocellular cancer.

Presently there are no national treatment recommendations.

Ethical aspects

7a. Ethical consequences

Ethical issues may be separated into those concerning the patients being candidates for this treatment in terms of suffering in relation to potential benefits, and those concerning what should be prioritized based on cost-effectiveness calculations.

For HCC this treatment may become a tool to reduce the tumour size, and, thereby, allow more tumours to become resectable, and possibly cured. For most of the patients it may become a valuable complement to existing treatment options, with a possibly greater anti-tumour effect. Furthermore, it may provide a favourable toxicity profile, a better quality of life with less hospital contacts having a long-term effect, and being cost effective, not being more expensive than pre-existing therapies.

For CRC these issues may be differently addressed depending on whether this treatment is offered already initially at the time of diagnosis, or if it is used as additional salvage therapy when other treatments have failed. The latter scenario may be important for the individual but not favourable for the health care system. However, administration of ^{90}Yttrium microspheres in an early phase of therapy has the possibility to have an impact on response and survival. This must be balanced against more complications for the individual and additional expenses for the health care system since this new technology most probably will be used as additional therapy.

7b. Will other patient groups or other treatments be adversely affected (pushed aside) due to an introduction of the new health technology?

For HCC radioembolization with ^{90}Yttrium microspheres may substitute TACE. Therefore, there will be no competition of resources.

.

For CRC radioembolization with ^{90}Yttrium microspheres will be added to the present treatments for CRC. Thus, the absolute costs and the cost-effectiveness must be considered in competition with other treatment modalities, see section 9.

Organisation

8a. When can this new health technology be put into practice?

Radioembolization with ^{90}Yttrium microspheres of liver tumours is already used in selected patients at Sahlgrenska University Hospital.

8b. Is this technology used in other hospitals in Region Västra Götaland or in other parts of Sweden?

No.

8c. According to the work group, will there be any consequences of the new health technology for personnel?

For ***palliative treatment*** of HCC there will be no negative consequences for the personnel at the Department of Transplantation and Liver Surgery since ^{90}Yttrium treatment will be administered less frequently than the present alternative, i.e. chemoembolization (TACE). For the Department of Radiophysics and the Department of Oncology there will be an increased work load.

If radioembolization with ^{90}Yttrium will be used for HCC in a potentially curative setting to ***downstage*** patients prior to surgery this will require more resources to the Department of Transplantation and Liver Surgery, the Department of Radiophysics and the Department of Oncology.

For ***palliative treatment*** of metastases from CRC confined only to the liver, but unresectable, the introduction of radioembolization with ^{90}Yttrium microspheres will increase the work load by about 35 new patients each at the Department of Transplantation & Liver Surgery, the Department of Radiophysics and the Department of Oncology.

The workload at the local hospitals will remain unchanged since the ^{90}Y treatment will be added to present treatments.

8d. Will there be any consequences for other clinics or supporting functions at the hospital or in the whole Western Region of Sweden?

See above, 8c.

Economy

9a. Present costs of currently used technologies and the new technology.

Treatment of unresectable HCC

^{90}Yttrium microspheres are injected in the hepatic artery by an interventional radiologist in the Department of Radiology. Prior to this administration of the irradiating microspheres several investigations have been evaluated by physicians from the Department of Oncology, Department of Radiophysics, Department of Radiology and the Department of Transplantation and Liver Surgery. A physicist at the Department of Radiophysics is responsible for the dose calculations.

The hospital stay for the five patients who were treated in 2009 ranged from 1-3 occasions, with a total length of stay at the ward ranging from 2 to 7 days.

The cost of radioembolization with ^{90}Yttrium microspheres presented below is based on the costs of these five patients in 2009.

Treatment	Dose	Pharmaceutical/ interventional costs (historical data)	Ward and laboratory/ additional x-ray	Cost
SIR-spheres (Y^{90}) (n=5)	One treatment	160 000 SEK	63 000 SEK 150 000 SEK	223 000 SEK
Chemo-embolization (n=23)	150mg Doxorubicin intraarterial treatment. Median: 2,5 treatments	53 000 SEK		203 000 SEK
Sorafenib (Nexavar®)	400mg x 2 orally b.i.d. Median: 6 months therapy	210 000 SEK		210 000 SEK

Footnote: 1 Euro ≈ 10 SEK

Treatment of liver metastases from CRC

The cost for systemic chemotherapy including irinotecan or oxaliplatin together with 5-FU is about 100 000 SEK (10 000 €) for 6 months therapy. If a targeting agent is included (Avastin®, Vectibix® or Erbitux®) the total cost is about 300 000 SEK (30 000 €). The additional cost for ^{90}Yttrium microshperes would be the same as presented in the table above, i.e. 223 000 SEK (22 300 €).

9b. Total change of cost

Treatment of unresectable HCC
Since radioembolization with ^{90}Yttrium microspheres will replace local chemoembolization the annual increase will be about 400 000 SEK (40 000 €), (20 x (223 000 - 203 000) SEK = 400 000 SEK).

Treatment of liver metastases from CRC
Since radioembolization with ^{90}Yttrium microspheres will be added to systematic chemotherapy the annual increase in cost for Sahlgrenska University Hospital will be almost 8 million SEK (800 000 €), (35 x 223 000 SEK = 7 805 000 SEK).

9c. Can the new technology be adopted and used within the present budget (clinic budget/hospital budget)?

No.

9d. Are there any available analyses of health economy? Cost advantages or disadvantages?

The impact on economy can be looked upon from different points of view as suggested below:

1. are the procedures to be ***added*** to the present day treatments or are they aimed to ***substitute*** for some present day treatments?

2. should the expenses be calculated as a ***fixed sum*** irrespective of what is gained in time of survival, or should we express the ***costs per gained survival time***?

In the case of HCC radioembolization with ^{90}Yttrium in the palliative setting will most probably substitute TACE, but not sorafenib, see 9b.

In the case of CRC with unresectable hepatic metastases radioembolization with ^{90}Yttrium treatment will most probably be added to current treatments, and not be a substitute for them. Thus, there will be an additional cost for this procedure, which should be related to the possible gain in survival, see 9b.

The following calculations of cost-effectiveness are based on assumptions and not on solid data, and should therefore be looked upon as a basis for discussion.

For CRC there are only two RCTs, see Table 1a. The weighted median survival in these two RCTs added together for the patients receiving ^{90}Yttrium treatment were 19.9 months [((36 x 17) + (11 x 29.4))/(36 +11)] versus 15.2 months [((34 x 15.9) + (10 x 12.8))/(34 +10)] for the chemotherapy-only group. The weighted median survival for all ^{90}Yttrium treated patients added together in the eight studies (Table 1a) was 12.6 months. Assuming the same fractional improvement as in the RCTs (19.9 -15.2/15.2 = 0.31), the theoreticalsurvival in a “control group” of all eight studies would be 9.6 months (=12.6/1.31). This will then imply a gain of 3.0 months. With a cost for the procedure of 223 000 SEK the cost per gained year would be 892 000 SEK (= 12 x (223 000/3) SEK). If

assumed that this treatment would be done up front at diagnoses of metastases, like in the randomized studies, the cost per gained year would be 572 000 SEK (57 200 €), (nb. cost per gained year is not the same as QALY).

Are the survival data in the published studies representative of Swedish conditions? A recent Swedish population based study reported a median survival of 18 months in patients with metastatic cancer confined to the liver only and treated by chemotherapy (Sjövall et al., 2004), i.e. similar to the data in the randomized trials in which treatment was started at the time of diagnosis of hepatic metastates. The case series had a shorter survival of 12.7 months (simulated control 9.6 months), which is reasonable or rather high with regard to the late stage of these patients.

How does the cost of gained year of radioembolization with ^{90}Yttrium compare with currently used chemotherapy?

The incremental cost of oxaliplatin added to 5-FU and folinic acid in the first line treatment of metastatic colon cancer is approximately 500 000 SEK (50 000 €) per gained year: More recently the incremental cost of the anti-angiogenic monoclonal antibody bevacizumab or the epidermal growth factor receptor-antibody cetuximab added to 5-FU and oxaliplatin or irinotecan is in the range of 1-2 million SEK (100 000 – 200 000 €).

Unanswered Questions

10a. Important gaps in scientific knowledge?

In the included studies there have been no reports of dose-response relationship, possibly due to the imperfect methods used for absorbed dose estimates. Most methods used to calculate the amounts of ^{90}Yttrium-microspheres administrated to patients are probably suboptimal. The radioactivity administrated to the patients are based on three different approaches: the empirical method, the body surface area (BSA) method and the partition model. Most of the studies presented in the literature have used either the empirical or the BSA method. However, both methods calculate the absorbed dose to the liver tissue indirectly, and, consequently, the obtained absorbed doses to the liver tissue will vary widely between patients. A retrospective analysis of the BSA method applied to the first 16 patients treated at the Sahlgrenska University Hospital showed that the mean absorbed doses to the liver tissue ranged from 15 to 60 Gy.

The partition model is a direct dosimetric model. The calculation of the absorbed dose to the liver is based on CT measurement of the liver and tumour volumes. This method clearly increases the precision in the estimation of the absorbed dose to the liver. A higher precision may yield an increased knowledge in the dose-response relationship, and minimise the risk of administrating too low activity amount- thereby lowering the therapeutic effect, as well as it might enlarge patient safety. Furthermore, a study based on accurate dosimetry may improve the selection of good tumour responders. Patients with good tumour response to treatment may also be suitable candidates for additional treatments, which further could increase their lifespan.

10b. Is there any interest in your own clinic/research group/organisation to start studies/trials within the research field at issue?

Yes, in the specific areas of research listed below:

1. A study with the aim to develop a better method to calculate the absorbed dose in the liver (see 10a)

2. A Phase I-study of the feasibility and safety of ^{90}Yttrium treatment of HCC as neo-adjuvant therapy one to two weeks before liver surgery in patients with tumours with a high risk for recurrence and/or in patients with tumours located in areas where there are difficulties to achieve negative tumour margins in specimens.

3. An RCT in patients with hepatic metastases from CRC to analyse the possible benefit in survival when ^{90}Yttrium is added as first-line treatment to conventional chemotherapy in inoperable CRC without extrahepatic metastases. Secondary endpoints would be time to progression, frequency of patients that undergo curative liver surgery after downstaging of the tumour, and cost-benefit.

4. A mulitcentreRCT phase-II study in HCC comparing TACE and ^{90}Y treatment.

5. A mulitcentre RCT phase-II study of the feasibility and safety of ^{90}Yttrium treatment in comparison to TACE of cancer from the intrahepatic bile ducts. These tumours respond poorly to chemotherapy, but may be possible to treat with ^{90}Yttrium. In small phase I studys, promising results for TACE have been shown. The study would be a multicentre study together with the other Swedish centres.

6. A Phase I-study of the feasibility and safety of ^{90}Yttrium treatment of patients with ocular malignant melanoma, who do not respond to hyperthermic liver perfusion with melfalan chemotherapy.

Summary of the Health Technology Assessment

- **Method and patient group**
  Patients with unresectable hepatocellular carcinoma and patients with unresectable metastases from colorectal cancer, confined only to the liver, have a short life expectancy with a median survival of 3 - 6 months and 6 -10 months, respectively

  Radioembolization with ^{90}Yttrium-labeled microspheres is a local therapy where the liver is the target organ. It is a new technology with theoretically interesting and potential advantages in comparison to other treatment modalities.

- **Question at issue**
  Does treatment with ^{90}Yttrium microspheres prolong life in comparison with conventional salvage treatment, such as chemoembolization or other palliative treatments, in patients with primary liver cancer or liver metastases from colorectal cancer?

- **Patients, Intervention, Comparison, and Outcome (PICO)**

PICO I:	PICO II:
P = Patients over 18 years with primary hepatocellular carcinoma	P = Patients over 18 years with liver metastases from colorectal cancer
I = ^{90}Yttrium-coated microspheres (glass or resin), administered via the hepatic artery.	I = ^{90}Yttrium-coated microspheres (glass or resin), administered via the hepatic artery
C = Chemoembolization or other palliative treatment	C = Conventional "salvage" therapy
O = 1. Survival 2. Response rate, Time to progression, Quality of Life and Toxicity	O = 1. Survival 2. Response rate, Time to progression, Quality of Life and Toxicity

- **Studied risks and benefits for patients of the new health technology**
  <u>Hepatocellular carcinoma</u>
  The systematic literature search identified 16 studies, which have reported treatment effects of radioembolization with ^{90}Yttrium microspheres in patients with unresectable HCC. No study was a randomized, controlled trial. Four were non-randomized, controlled studies and 12 were case series. Of the non-randomized, controlled studies two were of moderate scientific quality and two of low scientific quality. In comparison to TACE treatment the use of radioembolization with ^{90}Yttrium microspheres prolonged survival by an average of 3 and 17 months in the two trials of moderate quality.

  The response rate (i.e. complete or partial response) varied between 26 - 61% according to the WHO criteria.

  The quality of evidence for radioembolization with ^{90}Yttrium microspheres on the effects on survival, as well as on tumor response is very low (⊕) according to the GRADE system.

  Most patients experienced nausea and fatigue. Lymphopenia also occurred in the majority of cases. Grade 3 - 4 liver toxicity was reported in 22 - 42 % of the patients and grade 3 - 4 bilirubin toxicity in 7 - 39 % of patients.

Colorectal cancer

The systematic literature search identified eight studies, which have reported treatment effects of radioembolization with ^{90}Yttrium microspheres in patients with unresectable liver metastases from CRC. Two were randomized, controlled trials, and one was a non-randomized controlled study. The remaining five studies were case series. One of the RCTs was of moderate scientific quality. The other RCT and the non-randomized controlled study were of low quality. Only the small RCT reported a significantly prolonged survival in radioembolized patients in comparison to alternative treatment, but both randomized trials showed significantly higher response rates for patients treated with ^{90}Yttrium microspheres.

The response rate (complete or partial) in the eight studies varied from 34 % to 75 %.

The quality of evidence for radioembolization with ^{90}Yttrium microspheres with regard to tumour response rate is low (⊕⊕), and with regard to the effects on survival it is very low (⊕) according to the GRADE system.

As for HCC patients the dominating adverse effects of radioembiolization were nausea, mild abdominal pain and fatigue. Grade 3 - 4 liver toxicity was reported in 2 - 4 % of patients, grade 3 - 4 gastrointestinal toxicity in 5 - 8 %, and grade 3 - 4 bilirubin toxicity in 12 % of patients.

- **Ethical questions**

  Ethical issues may be separated into those concerning the patients being candidates for this treatment in terms of suffering in relation to potential benefits, and those concerning what should be prioritized based on cost-effectiveness calculations.

- **Economical aspects**

  The use of with radioembolization with ^{90}Yttrium in HCC instead of TACE and in CRC as additional palliative therapy is estimated to increase the annual cost between 8-10 million SEK (800 000 -1 000 000 €).

APPENDIX 1 - SEARCH STRATEGY, STUDY SELECTION AND REFERENCES

Question(s) at issue:

Does treatment with ^{90}Yttrium microspheres prolong life in comparison with conventional salvage treatment, such as chemoembolization or other palliative treatments, in patients with primary liver cancer or liver metastases from colorectal cancer?

P = Patients I = Intervention C = Comparison O = Outcome

PICO 1

P	Patients over 18 years with primary hepatocellular carcinoma (HCC)
I	^{90}Yttrium -coated microspheres (glass or resin), administrated via the hepatic artery
C	Chemoembolization or other palliative treatment
O	1) Survival 2) Response rate Time to progression Quality of life Toxicity

PICO 2

P	Patients over 18 years with liver metastases from colorectal cancer (CRC)
I	^{90}Yttrium -coated microspheres (glass or resin-beads), administrated via the hepatic artery
C	Conventional ”salvage” therapy
O	1) Survival 2) Response rate Time to progression Quality of life Toxicity

Search strategy

PubMed search 1, 2009-12-11, updated 2010-01-22

HCC OR hepatocellular cancer OR hepatocellular carcionoma OR ”primary liver cancer” OR liver metastasis OR liver metastases OR colorectal cancer OR colorectal neoplsms OR colorectal carcionoma OR colorectal tumor OR colorectal tumors
AND
“Yttrium Radioisotopes” OR SIR-sphere* OR therasphere* OR selective internal radiation therapy OR SIRT OR selective internal radiotherapy OR radioembolisation OR radio embolisation OR radioembolization OR radio embolization OR “yttrium 90” OR yttrium-90 OR yttrium90 OR 90-yttrium OR “90 yttrium” OR 90yttrium OR 90y OR ”90 y” OR 90-y OR y-90 OR y90 OR ”y 90”
481 results

PubMed search 2, 2010-01-15

"Yttrium Radioisotopes" OR SIR-sphere* OR therasphere* OR selective internal radiation therapy OR SIRT OR selective internal radiotherapy OR radioembolisation OR radio embolisation OR radioembolization OR radio embolization OR "yttrium 90" OR yttrium-90 OR yttrium90 OR 90-yttrium OR "90 yttrium" OR 90yttrium OR 90y OR "90 y" OR 90-y OR y-90 OR y90 OR "y 90"
AND
Liver tumor OR liver tumors OR hepatic tumors OR hepatic tumors OR liver cancer OR hepatic malignancies OR liver malignancies
622 results

Search 2 NOT search 1: **243**

Total PubMed search results:
724 results

Cochrane 2009-12-11

Yttrium OR SIR-sphere* OR therasphere* OR selective internal radiation therapy OR SIRT OR selective internal radiotherapy OR radioembolisation OR radio embolisation OR radioembolization OR radio embolization OR "yttrium 90" OR yttrium-90 OR yttrium90 OR 90-yttrium OR "90 yttrium" OR 90yttrium OR 90y OR "90 y" OR 90-y OR y-90 OR y90 OR "y 90"
AND
HCC OR hepatocellular cancer OR hepatocellular carcinoma OR "primary liver cancer" OR liver metastasis OR liver metastases OR colorectal cancer OR colorectal neoplasms OR colorectal carcinoma OR colorectal tumor OR colorectal tumors

Cochrane reviews: 20
Other reviews: 1
Cochrane clinical trials: 8
Technology assessment: 3
Economic evaluations: 1

33 results

CRD 2009-12-16

Yttrium OR SIR-sphere* OR therasphere* OR selective internal radiation therapy OR SIRT OR selective internal radiotherapy OR radioembolisation OR radioembolization OR "yttrium 90" OR yttrium-90 OR yttrium90 OR 90-yttrium OR "90 yttrium" OR 90yttrium
AND
Liver tumor OR liver tumors OR hepatic tumors OR hepatic tumors OR liver cancer OR hepatic malignancies OR liver malignancies

DARE 8
NHS EED 7
HTA 3

18 results

EMBASE 2009-12-15

exp yttrium **or** exp yttrium 90 **or** exp radioisotope therapy **or** sir-sphere*.af. **or** therasphere*af. **or** selective internal radiation therapy **or** SIRT **or** selective internal radiation.af **or** radioembolisation **or** radio embolisation **or** radioembolization **or** radio embolization .af **or** yttrium 90 af **or** yttrium-90 or yttrium90 **or** 90-yttrium **or** 90 yttrium **or** 90yttrium.af.**or** 90y or 90 y or 90-y or y90 or y 90 or y-90.af.
AND
exp liver cell carcionoma **or** (HCC or hepatocellular carcionoma or hepatocellular cancer **or** "primary liver cancer" **or** liver metastasis **or** liver metastases.af. **or** exp colorectal cancer or exp colorectal carcionoma **or** (colorectal cancer **or** colorectal neoplasms **or** colorectal carcionoma **or** colorectal tumor* **or** colorectal tumour*af. **or** exp colorectal tumor

559 results

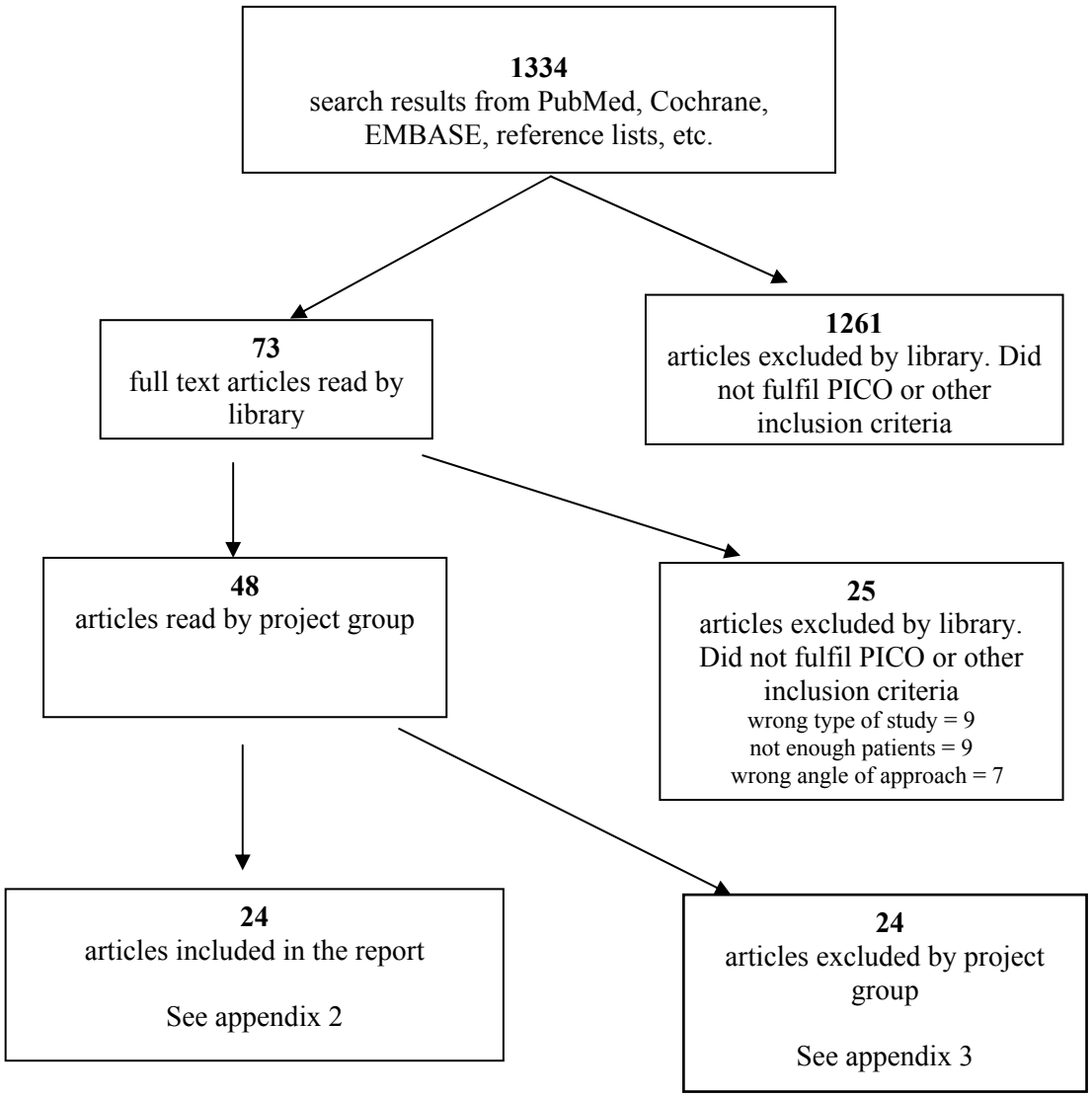
Eligibility criteria

Study design:
Randomised controlled trials, studies with some kind of control group, cohort studies, etc.; case series if > 40 patients
Not: case reports or "non-systematic" reviews

Language:
English, Swedish, Norwegian, Danish

Publication date: 1990-

Selection process – flow diagram



References

Included studies:

Hepatocellular carcinoma

Atassi B, Bangash AK, Lewandowski RJ, Ibrahim S, Kulik L, Mulcahy MF, Murthy R, Ryu RK, Sato KT, Miller FH, Omary RA, Salem R. Biliary sequelae following radioembolization with Yttrium-90 microspheres.
J Vasc Interv Radiol. 2008 May;19(5):691-7.

Carr BI, Kondragunta V, Buch SC, Branch RA. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a Two-Cohort Study.
Cancer. 2010 Mar 1;116(5):1305-14.

Carr BI. Hepatic arterial 90Yttrium glass microspheres (Therasphere) for unresectable hepatocellular carcinoma: interim safety and survival data on 65 patients.
Liver Transpl. 2004 Feb;10(2 Suppl 1):S107-10.

Geschwind JF, Salem R, Carr BI, Soulen MC, Thurston KG, Goin KA, Van Buskirk M, Roberts CA, Goin JE. Yttrium-90 microspheres for the treatment of hepatocellular carcinoma.
Gastroenterology. 2004 Nov;127(5 Suppl 1):S194-205.

Goin JE, Salem R, Carr BI, Dancey JE, Soulen MC, Geschwind JF, Goin K, Van Buskirk M, Thurston K. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: factors associated with liver toxicities.
J Vasc Interv Radiol. 2005 Feb;16(2 Pt 1):205-13.

Goin JE, Salem R, Carr BI, Dancey JE, Soulen MC, Geschwind JF, Goin K, Van Buskirk M, Thurston K. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: a risk-stratification analysis.
J Vasc Interv Radiol. 2005 Feb;16(2 Pt 1):195-203.

Iñarrairaegui M, Martinez-Cuesta A, Rodríguez M, Bilbao JI, Arbizu J, Benito A, Alegre F, D'Avola D, Ignacio Herrero J, Quiroga J, Prieto J, Sangro B. Analysis of Prognostic Factors After Yttrium-90 Radioembolization of Advanced Hepatocellular Carcinoma.
Int J Radiat Oncol Biol Phys. 2010 Jan 5. [Epub ahead of print]

Keppke AL, Salem R, Reddy D, Huang J, Jin J, Larson AC, Miller FH. Imaging of hepatocellular carcinoma after treatment with yttrium-90 microspheres.
AJR Am J Roentgenol. 2007 Mar;188(3):768-75.

Kooby DA, Egnatashvili V, Srinivasan S, Chamsuddin A, Delman KA, Kauh J, Staley CA 3rd, Kim HS. Comparison of Yttrium-90 Radioembolization and Transcatheter Arteria Chemoembolization for the Treatment of Unresectable Hepatocellular Carcinoma.
J Vasc Interv Radiol. 2010; 21:224-230.

Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, Sato KT, Benson A 3rd, Nemcek AA Jr, Gates VL, Abecassis M, Omary RA, Salem R. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis.
Hepatology. 2008 Jan;47(1):71-81.

Lau WY, Ho S, Leung TW, Chan M, Ho R, Johnson PJ, Li AK. Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of 90yttrium microspheres. *Int J Radiat Oncol Biol Phys.* 1998 Feb 1;40(3):583-92.

Lewandowski RJ, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, Ibrahim SM, Sato KT, Baker T, Miller FH, Omary R, Abecassis M, Salem R. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. *Am J Transplant.* 2009 Aug;9(8):1920-8.

Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, Atassi B, Baker T, Gates V, Miller FH, Sato KT, Wang E, Gupta R, Benson AB, Newman SB, Omary RA, Abecassis M, Kulik L. Radioembolization for Hepatocellular Carcinoma Using Yttrium-90 Microspheres: A Comprehensive Report of Long-term Outcomes. *Gastroenterology.* 2010 Jan; 138(1):52-64.

Salem R, Lewandowski RJ, Atassi B, Gordon SC, Gates VL, Barakat O, Sergie Z, Wong CY, Thurston KG. Treatment of unresectable hepatocellular carcinoma with use of 90Y microspheres (TheraSphere): safety, tumor response, and survival. *J Vasc Interv Radiol.* 2005 Dec;16(12):1627-39.

Steel J, Baum A, Carr B. Quality of life in patients diagnosed with primary hepatocellular carcinoma: hepatic arterial infusion of Cisplatin versus 90-Yttrium microspheres (Therasphere). *Psychooncology.* 2004 Feb;13(2):73-9.

Young JY, Rhee TK, Atassi B, Gates VL, Kulik L, Mulcahy MF, Larson AC, Ryu RK, Sato KT, Lewandowski RJ, Omary RA, Salem R.
Radiation dose limits and liver toxicities resulting from multiple yttrium-90 radioembolization treatments for hepatocellular carcinoma.
J Vasc Interv Radiol. 2007 Nov;18(11):1375-82.

Colorectal cancer:

Cianni R, Urigo C, Notarianni E, Saltarelli A, Salvatori R, Pasqualini V, Dornbusch T, Cortesi E. Selective internal radiation therapy with SIR-spheres for the treatment of unresectable colorectal hepatic metastases.
Cardiovasc Intervent Radiol. 2009 Nov;32(6):1179-86.

Gray B, Van Hazel G, Hope M, Burton M, Moroz P, Anderson J, Gebski V. Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer.
Ann Oncol. 2001 Dec;12(12):1711-20.

Gray B, Van Hazel G, Buck M, Paton G, Burton M, Anderson J. Treatment of colorectal liver metastases with SIR-Spheres plus chemotherapy.
GI Cancer. 2000, 3(4):249-257.

Hong K, McBride JD, Georgiades CS, Reyes DK, Herman JM, Kamel IR, Geschwind JF. Salvage therapy for liver-dominant colorectal metastatic adenocarcinoma: comparison between transcatheter arterial chemoembolization versus yttrium-90 radioembolization.
J Vasc Interv Radiol. 2009 Mar;20(3):360-7.

Kennedy AS, Coldwell D, Nutting C, Murthy R, Wertman DE Jr, Loehr SP, Overton C, Meranze S, Niedzwiecki J, Sailer S. Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience.
Int J Radiat Oncol Biol Phys. 2006 Jun 1;65(2):412-25.

Mulcahy MF, Lewandowski RJ, Ibrahim SM, Sato KT, Ryu RK, Atassi B, Newman S, Talamonti M, Omary RA, Benson A 3rd, Salem R. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres.
Cancer. 2009 May 1;115(9):1849-58.

Stubbs RS, O'Brien I, Correia MM. Selective internal radiation therapy with 90Y microspheres for colorectal liver metastases: single-centre experience with 100 patients.
ANZ J Surg. 2006 Aug;76(8):696-703.

Van Hazel G, Blackwell A, Anderson J, Price D, Moroz P, Bower G, Cardaci G, Gray B. Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer.
J Surg Oncol. 2004 Nov 1;88(2):78-85.

Excluded studies:

Ariel IM, Padula G. Treatment of symptomatic metastatic cancer to the liver from primary colon and rectal cancer by the intraarterial administration of chemotherapy and radioactive isotopes.
J Surg Oncol. 1978;10(4):327-36.

Ariel IM, Pack GT. Treatment of inoperable cancer of the liver by intra-arterial radioactive isotopes and chemotherapy.
Cancer. 1967 May;20(5):793-804.

Boppudi S, Wickremesekera SK, Nowitz M, Stubbs R. Evaluation of the role of CT in the assessment of response to selective internal radiation therapy in patients with colorectal liver metastases.
Australas Radiol. 2006 Dec;50(6):570-7.

Carretero C, Munoz-Navas M, Betes M, Angos R, Subtil JC, Fernandez-Urien I, De la Riva S, Sola J, Bilbao JI, de Luis E, Sangro B. Gastroduodenal injury after radioembolization of hepatic tumors.
Am J Gastroenterol. 2007 Jun;102(6):1216-20.

Cianni R, Urigo C, Notarianni E, Saltarelli A, D'Agostini A, Iozzino M, Dornbusch T, Cortesi E. Radioembolisation using yttrium 90 (Y-90) in patients affected by unresectable hepatic metastases.
Radiol Med. 2010 Jan 20. [Epub ahead of print]

Dhabuwala A, Lamerton P, Stubbs RS. Relationship of 99mtechnetium labelled macroaggregated albumin (99mTc-MAA) uptake by colorectal liver metastases to response following Selective Internal Radiation Therapy (SIRT).
BMC Nucl Med. 2005 Dec 23;5:7.

Dunfee BL, Riaz A, Lewandowski RJ, Ibrahim S, Mulcahy MF, Ryu RK, Atassi B, Sato KT, Newman S, Omary RA, Benson A 3rd, Salem R. Yttrium-90 Radioembolization for Liver Malignancies: Prognostic Factors Associated with Survival.
J Vasc Interv Radiol. 2010 Jan:21(1):90-95.

Ho S, Lau WY, Leung TW, Chan M, Chan KW, Lee WY, Johnson PJ, Li AK. Tumour-to-normal uptake ratio of 90Y microspheres in hepatic cancer assessed with 99Tcm macroaggregated albumin. *Br J Radiol.* 1997 Aug;70(836):823-8.

Jakobs TF, Hoffmann RT, Dehm K, Trumm C, Stemmler HJ, Tatsch K, La Fougere C, Murthy R, Helmberger TK, Reiser MF. Hepatic yttrium-90 radioembolization of chemotherapy-refractory colorectal cancer liver metastases.
J Vasc Interv Radiol. 2008 Aug;19(8):1187-95.

Kennedy AS, McNeillie P, Dezarn WA, Nutting C, Sangro B, Wertman D, Garafalo M, Liu D, Coldwell D, Savin M, Jakobs T, Rose S, Warner R, Carter D, Sapareto S, Nag S, Gulec S, Calkins A, Gates VL, Salem R. Treatment parameters and outcome in 680 treatments of internal radiation with resin 90Y-microspheres for unresectable hepatic tumors.
Int J Radiat Oncol Biol Phys. 2009 Aug 1;74(5):1494-500.

Konda A, Savin MA, Cappell MS, Duffy MC. Radiation microsphere-induced GI ulcers after selective internal radiation therapy for hepatic tumors: an underrecognized clinical entity.
Gastrointest Endosc. 2009 Sep;70(3):561-7.

Lau WY, Ho S, Leung WT, Chan M, Lee WY, Johnson PJ. What determines survival duration in hepatocellular carcinoma treated with intraarterial Yttrium-90 microspheres?
Hepatogastroenterology. 2001 Mar-Apr;48(38):338-40.

Leung TW, Lau WY, Ho SK, Ward SC, Chow JH, Chan MS, Metreweli C, Johnson PJ, Li AK. Radiation pneumonitis after selective internal radiation treatment with intraarterial 90yttrium-microspheres for inoperable hepatic tumors.
Int J Radiat Oncol Biol Phys. 1995 Nov 1;33(4):919-24.

Lewandowski RJ, Riaz A, Ryu RK, Mulcahy MF, Sato KT, Kulik LM, Gates VL, Baker T, Omary R, Salem R. Optimization of radioembolic effect with extended-shelf-life yttrium-90 microspheres: results from a pilot study.
J Vasc Interv Radiol. 2009 Dec;20(12):1557-63.

Miller FH, Keppke AL, Reddy D, Huang J, Jin J, Mulcahy MF, Salem R. Response of liver metastases after treatment with yttrium-90 microspheres: role of size, necrosis, and PET.
AJR Am J Roentgenol. 2007 Mar;188(3):776-83.

Moroz P, Anderson JE, Van Hazel G, Gray BN. Effect of selective internal radiation therapy and hepatic arterial chemotherapy on normal liver volume and spleen volume.
J Surg Oncol. 2001 Dec;78(4):248-52.

Riaz A, Ryu RK, Kulik LM, Mulcahy MF, Lewandowski RJ, Minocha J, Ibrahim SM, Sato KT, Baker T, Miller FH, Newman S, Omary R, Abecassis M, Benson AB 3rd, Salem R. Alpha-fetoprotein response after locoregional therapy for hepatocellular carcinoma: oncologic marker of radiologic response, progression, and survival.
J Clin Oncol. 2009 Dec 1;27(34):5734-42.

Salem R, Parikh P, Atassi B, Lewandowski RJ, Ryu RK, Sato KT, Gates VL, Ibrahim S, Mulcahy MF, Kulik L, Liu DM, Riaz A, Omary RA, Kennedy AS. Incidence of radiation pneumonitis after hepatic intra-arterial radiotherapy with yttrium-90 microspheres assuming uniform lung distribution.
Am J Clin Oncol. 2008 Oct;31(5):431-8.

Sangro B, Gil-Alzugaray B, Rodriguez J, Sola I, Martinez-Cuesta A, Viudez A, Chopitea A, Iñarrairaegui M, Arbizu J, Bilbao JI. Liver disease induced by radioembolization of liver tumors: description and possible risk factors.
Cancer. 2008 Apr 1;112(7):1538-46.

Sato KT, Lewandowski RJ, Mulcahy MF, Atassi B, Ryu RK, Gates VL, Nemcek AA Jr, Barakat O, Benson A 3rd, Mandal R, Talamonti M, Wong CY, Miller FH, NewmanSB, Shaw JM, Thurston KG, Omary RA, Salem R. Unresectable chemorefractory liver metastases: radioembolization with 90Y microspheres--safety, efficacy, and survival.
Radiology. 2008 May;247(2):507-15.

Schultz CC, Campbell J, Bakalyar D, Beauvais M, Feng W, Savin M. Y-90 microsphere therapy: prevention of adverse events.
Cancer Biother Radiopharm. 2009 Aug;24(4):427-33.

Stubbs RS, Cannan RJ, Mitchell AW. Selective internal radiation therapy with 90yttrium microspheres for extensive colorectal liver metastases.
J Gastrointest Surg. 2001 May-Jun;5(3):294-302.

Townsend A, Price T, Karapetis C. Selective internal radiation therapy for liver metastases from colorectal cancer
Cochrane Database Syst Rev. 2009 Oct 7(4):CD007045

Vente MA, Wondergem M, van der Tweel I, van den Bosch MA, Zonnenberg BA, Lam MG, van Het Schip AD, Nijsen JF. Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis.
Eur Radiol. 2009 Apr;19(4):951-9.

Other references:

Cancer incidence in Sweden 2007/Socialstyrelsen, Epidemiologiskt centrum ; The National Board of Health and Welfare, Centre for Epidemiology. Stockholm, 2007.

Forner A, Ayuso C, Real MI, Sastre J, Robles R, Sangro B, Varela M, de la Mata M, Buti M, Martí-Bonmatí L, Bru C, Tabarnero J, Llovet JM, Bruix J. Diagnosis and treatment of hepatocellular cardionoma.
Med Clin (Barc), 2009;132(7):272-86.

Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects.
Semin Liver Dis. 2010 Feb;30(1):61-74.

GRADE Working Group. Grading quality of evidence and strength of recommendations.
BMJ. 2004 Jun 19;328(7454):1490-4.

GRADE Working Group. List of GRADE working group publications and grants [Internet]. [Place unknown]: GRADE Working Group, c2005-2009 [cited 2010 Mar 9]. Available from: www.gradeworkinggroup.org/publications/index.htm

Llovet JM, Bruix J. Molecular targeted therapies in hepatocellular carcinoma. *Hepatology*. 2008 Oct;48(4):1312-27.

Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008 Jul 24;359(4):378-90.

Primär cancer i lever, gallblåsa och gallvägar. Regionalt vårdprogram. Göteborg : Onkologiskt centrum, Västra sjukvårdsregionen, 2008. www.oc.gu.se

Sjövall A, Järv V, Blomqvist L, Singnomklao T, Cedermark B, Glimelius B, Holm T. The potential for improved outcome in patients with hepatic metastases from colon cancer: a population-based study. *Eur J Surg Oncol.* 2004 Oct;30(8):834-41.

Wagner AD, Arnold D, Grothey AA, Haerting J, Unverzagt S. Anti-angiogenic therapies for metastatic colorectal cancer. *Cochrane Database Syst Rev*. 2009 Jul 8:(3):CD005392.

Table 1a. Hepatocellular carcinoma
Outcome: Survival

Study	Publication Year	Design	Number of patients	Survival Median (months)	Survival 1-year	Survival 2-year	Survival 3-year	Quality of study
Carr	2010	Non-randomized, controlled	n= 691 TACE n= 99 ^{90}Y-RE	8.5 11.5	≈ 42 %* ≈ 50 %*	≈ 18 %* ≈ 28 %*	≈ 9 %* ≈ 15 %*	Moderate-low
Lewan-dowski	2010	Non-randomized, controlled	n= 43 TACE n= 43 ^{90}Y-RE	18.7 35.7	73% 77%	28% 59%	19% 45%	Moderate
Steel	2003	Non-randomized, controlled	n= 13 TACE n= 15 ^{90}Y-RE	- -	≈ 85 %*,** ≈ 87 %*,**	- -	- -	Low
Carr	2004	Cohort	65	17.5***	-	-	-	-
Geschwind	2004	Case series	80	18.3***	-	-	-	-
Goin	2005	Case series	121	12.3***	-	-	-	-
Goin	2005	Case series	(88) overlap	(16) overlap	-	-	-	-
Inarrairaegui	2010	Case series	72	13	-	-	-	-

Table 1a continued. Hepatocellular carcinoma
Outcome: Survival

Study	Publication Year	Design	Number of patients	Survival Median (months)	Survival 1-year	Survival 2-year	Survival 3-year	Quality of study
Keppke	2007	Case series	42	14.4***	-	-	-	-
Kooby	2009	Retrospective controlled? cohort	n= 44 TACE n= 27 ^{90}Y-RE	6 6	20% (9) 16% (4)	- -	- -	-
Kulik	2008	Case series	108	14.6***	-	-	-	-
Lau	1998	Case series	71	9.4	-	-	-	-
Salem	2009	Prospective cohort	291	10.9***	-	-	-	-
Salem	2005	Prospective cohort	43	18.9***	-	-	-	-
Young	2007	Retrospective cohort	41	18.1***	-	-	-	-

Abbreviations:
TACE = transarterial chemoembolization
^{90}Y-RE = Yttrium-90 radioembolization

Fotnot: * data extracted from Kaplan-Meier-curves,
** survival 6 months
*** recalculated

Table 1b. Hepatocellular carcinoma
Outcome: Tumour response

Study	Publication year	Design	Number of patients	Tumor evaluation	TTP (months)	CR (%)	PR (%)	SD (%)	PD (%)	Quality of study
Carr	2010	Non-randomized, controlled	n= 691 TACE n= 99 ^{90}Y-RE	WHO	- -	5 3	55 33/38	29 35	11 23	Moderate-low
Lewan-dowski	2010	Non-randomized, controlled	n= 43 TACE n= 43 ^{90}Y-RE n= 43 TACE n= 43 ^{90}Y-RE	WHO EASL 	19.6 48.6 - -	0 0 17 47	37 61 54 39	49 37 - -	14 2 - -	Moderate
Steel	2003	Non-randomized, controlled	n= 13 TACE n= 15 ^{90}Y-RE	- -	- -	- -	- -	- -	- -	Low
Carr	2004	Cohort	65	Own criteria	-	-	38.4	-	-	-
Geschwind	2004	Case series	80	-	-	-	-	-	-	-
Goin	2005	Case series	121	-	-	-	-	-	-	-
Goin	2005	Case series	88	-	-	-	-	-	-	-

Table 1b. Continued. Hepatocellular carcinoma
Outcome: Tumour response

Study	Publication year	Design	Number of patients	Tumor evaluation	TTP (months)	CR (%)	PR (%)	SD (%)	PD (%)	Quality of study
Inarrairaegui	2010	Case series	50	RECIST	-	-	8	70	22	-
Keppke	2007	Case series	42	RECIST WHO Necrosis Combined	3.9 4 1 1	- - - -	23* 26* 57* 59*	54 52 - -	- - - -	-
Kooby	2009	Retrospective controlled? cohort	n= 44 TACE n= 27 ^{90}Y-RE	RECIST	- -	2 0	4 11	36 41	36 33	-
Kulik	2008	Case series	108	WHO EASL	- -	- -	42* 70*	- -	- -	
Lau	1998	Case series	71	”WHO”	-	-	26.7	-	-	-
Salem	2009	Prospective cohort	273	WHO EASL	7.9 -	- 23	42* 34	- -	- -	-
Salem	2005	Prospective cohort	43	WHO EASL	- -	- -	47* 79*	- -	- -	-
Young	2007	Retrospective cohort	41	18,1***	-	-	-			-

TTP = time to progression, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease,
AFP = alfa-fetoprotein, WHO = WHO tumor response criteria
*CR+PR

Table 1c. Hepatocellular carcinoma
Complications

Study	Publication Year	Design	Number of patients	Bilirubin grade ¾ /hepatic total	Gastro-intestinaI	Pain/Other	Circulatory/ Pulmonary	Grade V (death)
Atassi	2008	Case series	n=190	7 % (13)	-	-/ 4 % (7) biliary	-/-	-
Carr	2010	Non-randomized, controlled	n= 691 TACE n= 99 ^{90}Y-RE	-/- -/-	- -	-/- -/-	-/- -/-	- -
Carr	2004	Cohort	65	38,5%??/-	2% (1)	-/-	-/-	-
Geschwind	2004	Case series	80	16% (13)/ 28% (22)	5% (4)	13% (10)/ 6% (5)	4% (3)/ 3% (2)	1% 1) Inconclusive
Goin	2005	Case series	121	-/-	-	-/-	-/-	9% (11) related
Goin	2005	Case series	88	27% (24)/ 42% (37)	-	-/-	-/-	3% (2) unrelated
Goin	2005	Case series	121	-/-	-	-/-	-/-	9% (11) related
Inarrairaegui	2010	Case series	72	-/-	-	-/-	-/-	-
Keppke	2007	Case series	42	-/-	0	Groin hematoma	-/-	-

Table 1c. Continued. Hepatocellular carcinoma
Complications

Study	Year	Design	No of pat.	Bilirubin grade ¾ /hepatic total	GI	Pain/Other	Circulatory/Pulmonary	Grade V (death)
Kooby	2009	Retrospective controlled ? cohort	n= 44 TACE n= 27 ^{90}Y-RE	-/14 -/22% (incl gr 1+2)	20 15	-/36% (all) -/30% (all)	-/-	4% (2) 7% (2)
Lau	1998	Case series	71	-/-	-	-/-	-/-	-
Lewandowski	2010	Non-randomized, controlled	n= 43 TACE n= 43 ^{90}Y-RE	26% (11)/- 7% (3)/-	- -	-/- -/-	-/- -/-	- -
Salem	2009	Prospective cohort	291	19% (54)/-	-	-/-	-/0	3% (9)
Salem	2005	Prospective cohort	43	14% (6)/ 2% (1)	-	-/-	-/-	0%
Steel	2003	Non-randomized, controlled	n= 13 TACE n= 15 ^{90}Y-RE	-/- -/-	- -	-/- -/-	-/- -/-	- -

Abbreviations:
TACE = transarterial chemoembolizat
^{90}Y-RE = Yttrium-90 radioembolizatio

Footnote: * data extracted from Kaplan-Meier-curves,
** survival 6 months
*** recalculated

Table 2a. Hepatic metastases from colorectal cancer
Outcome: Survival

Study	Publication Year	Design	Number of patients	Survival Median (months)	Survival 1 year	Survival 2 year	Survival 5 year	Quality of study
Cianni	2009	Case series	41	12	-	-	-	
Gray	2000	Case series	71	9.9	-	-	-	
Gray	2001	Randomised, controlled	n= 34 HAC n= 36 HAC + ^{90}Y-RE	15.9 17	68 % 72 %	29 % 39 %	0 % 3,5 %	Moderate
Hong	2009	Non-randomised, controlled	n=21 TACE n= 15 ^{90}Y-RE	7,7 6,9	43 % 34 %	10 % 18 %	0 % 0 %	Low
Kennedy	2006	Case series	208	-	-	-	-	
Mulcahy	2009	Case series	72	14.5	-	-	-	
Stubbs	2006	Case series	100	11	48%	18%	-	
Van Hazel	2004	Randomised, controlled	n= 10 Chemo n= 11 Chemo+ ^{90}Y-RE	12,8 29,4	≈ 52 %* ≈ 75 %*	≈ 10 %* ≈ 55 %*	- -	Low

Abbreviations:
HAC= Hepatic artery chemotherapy
TACE = Transcatheter arterial chemoembolisation
^{90}Y-RE = Yttrium-90 Radioembolization

Footnote: * data extracted from Kaplan-Meier-curves

Table 2b. Hepatic metastases from colorectal cancer
Outcome: Tumour response

Study	Publication year	Design	Number of patients	Tumour evaluation	TTP (months)	CR (%)	PR ((%)	SD (%)	PD (%)	Quality of study
Cianni	2009	Case series	41	RECIST	9.3	5	41	34	20	
Gray	2000	Case series	51	Ettinger (volym)	-	-	75	12	14	
Gray	2001	Randomised, controlled	n= 34 HAC n= 36 HAC+ ^{90}Y-RE	volym	7,6 12,0	3 6	21 44	35 28	26 14	Moderate
Hong	2009	Non-randomised, controlled	n= 21 TACE n= 15 ^{90}Y-RE	-	- -	- -	- -	- -	- -	Low
Kennedy	2006	Case series	175	Tumour area	-	0	36	55	10	
Mulcahy	2009	Case series	72	WHO		0	40	45	15	
Stubbs	2006	Case series	80	Tumour area		1	72	20	6	
Van Hazel	2004	Randomised, controlled	n= 10 Chemo n= 11 Chemo + ^{90}Y-RE	RECIST	3,6 18,6	0 0	0 73	60 27	40 0	Low

Abbreviations:
TTP = time to progression
CR = complete response
PR = partial response
HAC = hepatic artery chemotherapy
SD = stable disease
PD = progressive disease
RECIST = Response Evaluation Criteria in Solid Tumors

Appendix 3

Ref nr	Study	Reason for exclusion
	Ariel IM (J Surg Oncol,1978)	Another treatment modality
	Ariel IM (Cancer,1967)	Another treatment modality
	Carretero C (Am J gastroent,2007)	Does not fulfil PICO-criteria
	Cianni R (Radiol Med,2010)	Heterogeneous study groups with different diagnoses
	Ho S (Br J Radiology,1997)	Does not fulfil PICO-criteria
	Jakobs TF (J Vasc Inerv Rad,2008)	Does not fulfil PICO-criteria
	Kennedy AS (Int J Rad O B P,2009)	Too few patients
	Konda A (Gastrointest Endos,2009)	Too few patients
	Lau WY (Hepatogastroent, 2001)	Does not fulfil PICO-criteria
	Leung TW (Int J Rad O B P,1995)	Heterogeneous study groups with different diagnoses
	Lewandowski RJ (J Vasc Int R,2009)	Heterogeneous study groups with different diagnoses
	Miller FH (Am J Roentgen,2007)	Does not fulfil PICO-criteria
	Moroz P (J Sorg Oncol,2001)	Does not fulfil PICO-criteria
	Salem R (Am J Clin Oncol,2008)	Does not fulfil PICO-criteria
	Sangro B (Cancer,2008)	Does not fulfil PICO-criteria

Appendix 3

Ref nr	Study	Reason for exclusion
	Sato KT (Radiology,2008)	Heterogeneous study groups with different diagnoses
	Schultz CC (Cancer Bio Radio,2009)	Does not fulfil PICO-criteria
	Stubbs RS (J Gastroint Surg,2001)	Data presented in included article (Stubbs RS et al. ANZ J Surg,2006
	Townsend A (Cochrane Database Syst Rev,2009)	Reviewed

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset, HTA-centrum
Röda Stråket 8, 413 45 Göteborg
www.sahlgrenska.se/hta-centrum