

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

⁹⁰YTTRIUM 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.

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Question at issue:

Does treatment with ^{90}Y trium 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}Y trium-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}Y trium-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}Y trium-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}Y trium-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. Lymphopenia 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.

Liver metastases from colorectal cancer

The systematic literature search identified eight studies that have reported the therapeutic outcome of radioembolisation with ⁹⁰Yttrium-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 ⁹⁰Yttrium 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 ⁹⁰Yttrium-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 ⁹⁰Yttrium 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 ⁹⁰Yttrium-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

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