# Hepatic intra-arterial injection of Yttrium-loaded microspheres for Liver Metastasis secondary to colorectal cancer : Best soups are sometimes made from old recipies

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## Abstract

**Colorectal cancer is a severe disease with a significant incidence in western world.**

**In the curse of disease, about 40% of patients will eventually develop metastases to the liver. The majority of them will never be candidate for curative surgical management.**

**For those patients, systemic or intra-hepatic chemotherapy is the treatment's cornerstone. Unfortunately, despite evident improvements and apparition of several active new agents, no hope of cure emerges on the agenda for now.**

**Hepatic intra-arterial injections of radioactive devices have since a long time drawn interest from the medical community.**

**An anti-tumoural activity has been demonstrated with Yttrium-loaded microspheres injected in the hepatic artery for several liver neoplasms including metastases from colorectal cancer. We lack however the results of large randomized phase III trials to define clearly the place of those interventional therapies in the management of colorectal cancer metastatic to the liver.** (Acta gastroenterol. belg., **2006**, 69, **55-58**).

## Introduction

An estimated 376.400 persons in both Europe and USA have developed colorectal cancer (CRC) in 2004 (1).

At presentation, 15 to 17% of patients are diagnosed with a stage IV disease (2). About 40% of patients undergoing potentially curative resection for stage II and III CRC will develop subsequent appearance of metastatic disease (3). Liver involvement stands for the most common site of recurrence in CRC patients and represents a major cause of morbidity and mortality. Autopsy findings of 1,541 patients dying of colorectal carcinoma showed a prevalence of 44% for liver metastases with 20% to the liver only (4).

Without treatment, the prognosis is poor, with a median survival of 6 months (5-7). Resection of liver metastases is the only potentially curative treatment option, and can result in long-term survival for some patients. Five-year survival rates of 25-37% have been reported in a number of studies, with a median survival of 24-42 months (8). The pattern of recurrence after first liver resection shows that 41% of cases affect only the liver (9).

Unfortunately, the majority of hepatic metastatic involvements are not eligible for a curative resection. For those patients, palliative systemic or intra-arterial chemotherapy is often the treatment of choice. These treatments, usually combining diversely 5-Flourouracil (5-FU), Folinic Acid (FA), CPT-11 (Irinotécan, Camptosar®) and Oxaliplatin (Eloxatin®), can achieve good results in terms of disease and symptoms control, increasing time to tumor progression, and median survival. Tumor progression is however generally observed after a certain period of time. Monoclonal Antibodies against EGFR (Cetuximab®, ABX EGF®,…) and against VEGF (Bevacizumab, Avastin®) are promising drugs, but those treatments are not yet widely available (10,11,12), and can not be considered yet as standard treatments.

## Intra-arterial hepatic treatments

Since the early 60's, locoregional treatment for hepatic metastases from CRC has attracted many investigators (13). The strongest rationale for this approach is drawn from the particular liver vascularisation : about 90% of hepatic neoplasms blood supply comes from the hepatic artery, whereas normal parenchyma is nourished mainly by portal vein (14). The differential blood supply and the healthy liver's high extraction rate of drugs infused via the hepatic arterial route are supposed to decrease systemic, and increase intratumoral drug concentration (15-18). Additionally, given a possible stepwise spread of cancer from primary site to liver to other organs, direct treatment of hepatic metastases may prevent dissemination of tumour to other sites.

Unfortunately, intra-arterial hepatic chemotherapy and chemoembolization have failed until now to demonstrate any survival advantage over easier and less hazardous intravenous chemotherapy administration (19). Despite better control of liver metastases, indeed the rate of development of extrahepatic metastases has generally been inferior to that seen with systemic chemotherapy. Nevertheless, analysis of survival benefit should be very carefully undertaken because of methodological flaws, technical problems and severe toxicities in early studies. Moreover, the superior rates of response and survival reported with irinotecan- and

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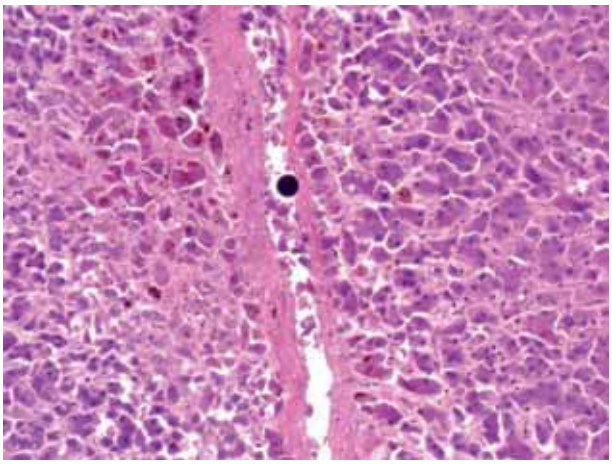

Fig. 1. — Microsphere lodged into an hepatic sinusoid

oxaliplatin-based regimens have made a new standard of care for first-line treatment of metastatic colorectal cancer and have, in retrospect, made the control arms used in previous intra-arterial hepatic chemotherapy trials today inadequate. However, due to significant liver extraction, most of the newly developed drugs are not suitable for intra-arterial hepatic administration (20).

## Selective Internal Radiation Therapy (SIRT)

Selective injection of therapeutic radio-isotopes in the hepatic artery has first been described by Grady and colleagues in the end-seventies. However, this technique never achieved wide recognition, mainly because of practical and procedural problems including microspheres material, calculation of radiation doses, and administration safety (21).

Modern devices have responded to technical flaws. SIR spheres® (Sirtex Medical Limited) are biocompatible 35 microns diameter microspheres containing the radionuclide Yttrium-90. Yttrium-90 is a high energy pure beta emitting isotope with no primary gamma emission, used to deliver Selective Internal Radiation Therapy (SIRT). The microspheres are stable, do not leach and cause minimal tissue reaction even after being in the liver for several years (22,23). After infusion into hepatic artery, they distribute evenly throughout the liver, and concentrate themselves in the tumour microvasculature, resulting in high dose of radiation selectively targeted (or delivered) into tumours (Fig. 1).

A higher proportion of hepatic arterial vessels surround a metastatic lesion compared to normal liver tissue probably due to tumour neoangiogenic effect. The vessels ratio between tumour and normal liver tissue is estimated to be about 3:1 in CRC metastasized to the liver (23-26) The size of the microspheres size between 30-40 microns are considered optimal to gain entry into tumour nodules, but too large to pass through the end capillary bed (8-10 microns) into the venous circulation.

Explanted liver review after liver transplantation for liver primary or secondary carcinoma following microspheres embolisation (27) shows that polymer microspheres dispersed in the liver heterogeneously and predominantly at the edge of the tumour nodules.

Pathologic examination of normal liver around tumor nodules showed no signs of radiation hepatitis, nor signs of veno-occlusive disease. Fibrosis was seen near the tumour nodules but not at a distance of > 1 cm.

Toxicity of the treatment is mainly related to escape of Yttrium-loaded microspheres outside the hepatic artery vasculature. Among these encountered toxicities radiation pneumonitis, secondary to microspheres passing through the hepatic vasculature and lodged into the lungs vasculature, is the most frequent one.

To determine this risk, patients receiving SIR-Spheres undergo a nuclear medicine scan performed by injecting technetium$^{99m}$ labelled macro-aggregated albumin (MAA) in the hepatic artery and measuring the radioactivity in the liver and lungs with a gamma-camera (28) The percentage of the MAA lodged in the lungs is determined as a fraction of the total amount of MAA in both lungs and liver. This so-called "lung breakthrough percentage" helps the clinicians to establish the amount of activity to administer to the patient. Previous experiment (26) have shown that a high "lung breakthrough percentage" that results in a total lung radiation dose from SIR-Spheres of more than 25Gy has a high chance of causing radiation pneumonitis.

Reflux of radioactive microspheres from hepatic artery to other regional artery (celiac artery, cystic artery, gastroduodenal artery), causing radiation damage to the pancreas, stomach and gall bladder. In order to avoid those severe complications, preventive efferent arteries embolization is sometimes mandatory.

## Results in colorectal cancer (Fig. 2)

Treatment with SIRT has been shown to result in high response rates for patients with liver tumors, especially with hepatocellular carcinoma and colorectal liver metastases.

Gray *et al.* reported the results of 29 patients suffering from non resectable CRC liver metastases treated with hepatic intra-arterial injection of SIR spheres®. Twelve of the patients also received concomitant continuous infusion of 5-FU at a dose of 600mg/m$^2$/day for 10 days. Response rates evaluated by serial CT scan showed 45% and 40% of major response rate and stable diseases, respectively. Only 18% of the patients progressed rapidly after SIR Spheres treatment (29).

The same author published toxicity and efficacy data's of a combination therapy of hepatic arterial SIR-Spheres® injection followed by hepatic arterial chemotherapy using floxuridine 0.3 mg/kg /day for 12 days repeated every 28 days until progression. Seventy-one consecutive patients were treated with that combination. Response rates of 86% (major + minor

| | Study | Patients (n) | Design | Partial response | Stable disease | Progressive disease |
|---|---|---|---|---|---|---|
| Gray *et al.* 1992 | Phase II | 29 | SIRT alone<br>12 pts 5-FU IVC | 45% | 40% | 15% |
| Gray *et al.* 2000 | Phase II | 71 | Floxuridine IA hep | 86% | – | – |
| Gray *et al.* 2001 | Phase III | 74 | Floxuridine IA hep<br>Vs<br>Id + SIRT | 18%<br><br>44% | –<br> | 23.5%<br><br>8.3% |
| Van Hazel *et al.* 2002 | Randomised Phase II | 21 | Mayo clinic<br>Vs<br>Id + SIRT | <br>79% | 31%<br><br>60% | 0%<br><br>40% |

Fig. 2. — Published data's on SIR Spheres® in liver metastases from colorectal cancer

responses) were reported. Median survival was 18.5 months after the diagnosis of the metastases. One patient died from fulminant hepatic failure probably due to radiation hepatitis (autopsy was not performed). Other toxicities were mainly mild and consisting in transient abdominal pain and nausea (30).

In a phase III randomized study (31), 74 patients with exclusive non-resectable CRC liver metastases received either hepatic artery chemotherapy (HAC) with floxuridine (FUDR 0.3 mg/kg/day 12 days every 4 weeks till progression or a maximum of 18 cycles) or the same chemotherapy plus a single injection of SIR-Spheres®. Previous chemotherapeutic treatment was allowed.

Patients receiving the combination therapy responded better than patients in the chemotherapy arm, with 44% vs. 18% of response rate, respectively. Interestingly, 8.3% of patients in the combined arm progressed after treatment, instead of 23.5% in the chemotherapy-only arm. There was no difference in median survival between groups, but the time to disease progression into the liver was statistically in favour of the combination arm. Toxicities were mild in both groups, consisting mainly of liver tests elevations and nauseas.

SIR-Spheres® have also been studied in combination with IV chemotherapy in metastatic CRC in a randomized phase II trial (32). Systemic chemotherapy consisted of bolus 5-FU and low dose Leucovorin, 5 days every 4 weeks (Mayo Clinic regimen). The size sample (21 patients) of the study is however too small to allow accurate estimation of response rates. Moreover, 2 of 10 patients in the chemotherapy-only arm died quickly due to tumour progression without even receiving the foreseen treatment. The phase II design was not adequate to agree with the conclusion of the authors that median survival was significantly longer for patients receiving the combination arm. Toxicity in the combination arm consisted of abdominal pain (40%), neutropenia (27%) and 1 toxic death due to febrile neutropenia and septic shock, 1 liver abscess necessitating drainage, 1 radiation induced cirrhosis.

SIR-Spheres® have recently been approved by the FDA and by ECC regulatory authorities for treatment of patients with colorectal metastases.

## Conclusions

SIR-Spheres injection appears to be a very promising treatment for CRC metastatic to the liver, since several studies have clearly shown antitumoral activity, especially in chemo-refractory tumors. However, the real level of activity is still to be assessed in randomized phase III trials. The association of SIRT with intravenous or intra-arterial hepatic chemotherapy will be interesting to investigate, particularly with newer drugs (i.e. antiangiogenic drugs and anti-Epidermal Growth Factor Receptor). Factors associated with response to SIRT are to date unknown and represent another matter of study. On the other hand, toxicity remained very low and easily manageable aught some precautions are taken (careful calculation of the injected dose, exclusion of important pulmonary shunts, right selection of candidates with sufficient liver reserve, etc.).

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