

## Treatment of Inoperable Liver Cancers with Radioactive Microspheres

a report by

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### Universal Challenge in Oncology

All oncologists must deal with the frequent and frustrating occurrence of patients dying of liver-dominant disease. Exciting new advances in biologic, genetic and cytotoxic agents have produced important and significant prolongation of time to progression and survival for many solid tumours, particularly colorectal adenocarcinoma. However, nearly all patients with metastatic liver disease will die of that condition. In the US that is over 80,000 patients per year, and a similar number in Europe. Radiation therapy is a cornerstone of curative and palliative therapy in nearly all malignancies, but has not been applied with much success to hepatic disease due to the low tolerance of the organ to radiation compared with tumour. Although technology advances in radiation delivery have improved to some degree, use of hepatic radiation, the best opportunity to irradiate the tens of thousands of potential patients with hepatic tumours, may be via implantation internally with radioactive particles, i.e.  $^{90}\text{Y}$ -microspheres.

### New Approach to an Established Idea

Brachytherapy – physically implanting tumours with radiation – has a long and established history of successful anti-tumour activity in many organs, with the most common use in prostate, uterine cervix and head and neck malignancies. The key principles of brachytherapy involve delivery of tumouricidal doses of radiation to the malignant tumour, but, due to rapid radiation dose fall-off, minimal adjacent normal tissues are damaged. Currently, a few specialised centres can place radiation sources manually into the liver percutaneously or via open laparotomy. A more easily and broadly applied technique is  $^{90}\text{Y}$ -microspheres, which use the unique vascular anatomy of the liver to preferentially implant hepatic tumours. It is established that the hepatic arterial system supplies 80% to 100% of the blood to liver tumours (primary and metastatic); however, the normal liver derives nearly all of its blood flow from the parallel portal system. In

addition, metastatic tumours in particular form up to 200 times more vessels in plexus around tumours compared with the normal liver immediately nearby. This combination has led to the discovery that  $^{90}\text{Y}$ -microsphere release in the hepatic artery produces preferential accumulation of spheres in the tumours of at least 3:1 and up to 20:1 ratio compared with normal liver. Thus, the therapeutic index is favourable just like in other brachytherapy approaches, i.e. prostate. The diameter of the microspheres enables them to become implanted in the tumour, but they cannot pass through the end arterioles in the capillary bed, which have a restrictive diameter of only 8–10 $\mu$ . Only if arterial-venous fistulas in the tumour are present with diameters of >30 $\mu$  would microspheres pass into the next capillary bed, which is the lung. The active radiation source – yttrium – is a pure beta emitter, with energy deposition and dose rate close to that of external beam therapy, yet the effective range is only 3mm from the sphere.

### $^{90}\text{Y}$ -Microsphere Treatment Evaluation and Procedure

The treatment of liver tumours should be carried out in appropriately staffed, multidisciplinary oncology teams that have proven expertise in treating patients with liver-related illnesses, complications and special therapeutic interventions. The liver brachytherapy programmes do not require capital expenditures as they utilise the personnel, skills, equipment and physical infrastructure already in place. The radioactive source ( $^{90}\text{Y}$ -microspheres) is contained in a small acrylic holder that provides radiation protection, and is typically handled in the hot laboratory of the nuclear medicine or radiation oncology sections. Therefore, new containment facilities are not needed for acceptance, storage or disposal of the radiation therapy system. Most patients will be referred from a medical oncologist for evaluation by the team. Diagnostic imaging, typically computed tomography (CT) and (as appropriate by tumour type) fluorodeoxyglucose positron emitted tomography (FDG-PET) scanning, are standard, but magnetic resonance



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imaging (MRI) or OctreoScan may also be used as complementary information. The liver vasculature is meticulously mapped with angiogram by interventional radiology, with special attention to any vessels that could carry microspheres away from the liver and into the stomach, duodenum or gall bladder. At the conclusion of the hepatic angiogram, a simulation of the actual treatment is performed, with albumin particles that approximate the size of microspheres, tagged with technetium-99m, a gamma source that is easily imaged. The test is called macro aggregated albumin (MAA). It will also reveal the amount of abnormal shunting of particles that allows microspheres to bypass the hepatic capillary bed to collect in the pulmonary vasculature. The nuclear medicine team will calculate the percentage of shunt from acquired axial single photon emission computed tomography (SPECT) and planar AP-PA gamma scans obtained from the MAA injection. The amount of activity injected into the liver is known, and the ratio of uptake in the lungs compared with the total (lungs and liver) represents the shunt fraction of particles. If this exceeds 15%, then a significant dose reduction is used or the  $^{90}\text{Y}$ -microsphere treatment aborted to avoid pulmonary fibrosis from radiation. The treatment delivery itself occurs on a separate day and uses all the data acquired from the angiogram, MAA and radiation treatment planning to safely deliver  $^{90}\text{Y}$ -microspheres to the affected lobes of the liver, or whole liver as needed.

Immediately after treatment, an additional gamma scan is obtained in planar and SPECT to confirm the location of the majority of microspheres. Characteristic X-rays are emitted during beta decay of  $^{90}\text{Y}$ , which can be captured and imaged. Patients are seen in follow-up every few weeks and liver function tests obtained to monitor for radiation or tumour-related complications and/or dysfunction.

#### Historical Results of $^{90}\text{Y}$ -Microsphere Treatment

Prior to 2002, the majority of patients had received microspheres as a stand-alone therapy, usually as salvage after the hepatic tumours had become refractory to best chemotherapy options, and recurred after cryotherapy, radiofrequency ablation and/or transarterial chemoembolisation. In Australia (1990 to 2002), a resin-based microsphere was developed and used predominately in colorectal liver metastases, but also

in hepatocellular – primary – liver cancer. In North America a glass microsphere, also using  $^{90}\text{Y}$  as the therapeutic moiety, was used in Canada for hepatocellular cancer until 2000, when it was reintroduced into the US medical system and used to treat all types of solid tumours in the liver.<sup>1</sup> However, it was not US Food and Drug Administration (FDA)-approved, and could only be used under protocol and Institutional Review Board oversight due to its FDA humanitarian device exemption, which is still in place. Encouraging results as salvage therapy were reported for both microspheres in a variety of metastatic and primary liver tumours, and resin microspheres were granted full FDA approval in 2002 for treatment of colorectal cancer metastases given concurrently with hepatic artery chemotherapy.

In 2002, Sirtex Medical obtained CE mark, and initial treatments began in late 2003 in several EU countries. The glass microsphere is not available outside of North America. The key early clinical results in the largest patient cohort colorectal cancer metastases have come from Australia and the US. Clinical trials of selective internal radiation therapy (SIRT) for colorectal cancer have been conducted in Australia in chemotherapy-naïve patients, and in the US in salvage patients. The pivotal SIRT trial accepted by the FDA was interesting but not applicable to most patients today. Gray<sup>2</sup> randomised 74 patients with liver-only colon cancer metastases to hepatic artery infusion of floxuridine (FUDR) versus FUDR plus one treatment of resin microspheres, termed SIRT. The partial and complete response rate by CT and carcinoembryonic antigen (CEA) was improved for patients receiving SIRT. The median time to disease progression in the liver was significantly longer for patients receiving SIRT in comparison with patients receiving hepatic artery chemoembolisation (HAC) alone. The one-, two, three- and five-year survival for patients receiving SIRT was 72%, 39%, 17% and 3.5%, compared with 68%, 29%, 6.5% and 0% for HAC alone, respectively. Cox regression analysis suggested an improvement in survival for patients treated with SIR-Spheres<sup>®</sup> who survive more than 15 months ( $p=0.06$ ). There was no increase in grade 3 to 4 treatment-related toxicity for patients receiving SIRT in comparison with patients receiving HAC alone.

Resin microspheres in the US are used in patients with chemorefractory liver metastases but minimal extrahepatic disease, treated with one, two and

1. Kennedy A S, et al., "Outpatient Hepatic Artery Brachytherapy for Primary and Secondary Hepatic Malignancies", *Radiology* (2001);221P (Suppl): p. 468.
2. Gray B, et al., "Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer", *Ann. Oncol.* (2001);12 (12): pp. 1,711–1,720.

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sometimes three courses of SIRT without concurrent chemotherapy. The largest experience with either glass microspheres or resin was presented recently with 329 patients in the US treated with microspheres alone.<sup>3</sup> The abstract was updated from 243 patients to 329 patients at presentation (201 resin, 128 glass), with the median survival of both resin and glass microsphere patients (actuarial) of 11 months versus a similar cohort of patients without microsphere treatment of 5.0 months ( $p=0.001$ ).

All patients were followed until alternate therapy was given at which point they were censored in the analysis or, if no other therapy, until death. Acute and late toxicities were reported based on CTC 2.0,

effectiveness and safety have been established in microsphere-alone-treated patients. Two important phase I studies have been reported this year in patients with liver metastases from colon cancer. Van Hazel<sup>4</sup> treated newly diagnosed patients with FOLFOX4 and one application of microspheres during the first week of chemotherapy. The dose escalation involved oxaliplatin, which was found to be well tolerated at full dose ( $85\text{mg}/\text{m}^2$ ) for that regimen with microspheres. Response (RECEIST) by CT scan was significant in 10 of 11 evaluable patients. Van Hazel<sup>5</sup> also tested chemotherapy and microspheres in 23 patients that had failed fluorouracil (5-FU), but were irinotecan-naïve. Dose escalation of irinotecan was not yet complete at the time of the report, but the

### *Nearly all solid tumours that are treated with radiation also benefit from concurrent chemotherapy or a biologic agent.*

with all gastrointestinal (GI)-related side effects added together for a total of 30% grade 3 (nausea, emesis, anorexia and abdominal pain, gastric or duodenal ulceration). No cases of veno-occlusive disease or procedure-related mortality occurred. Three cases of radiation-induced liver dysfunction were found, with chronic ascites and low albumin and CT scan evidence of hepatic fibrosis. Objective response rates were encouraging with CT scan (35%), PET (90%) and CEA (70%) achieving a maximal response at three months post-treatment.<sup>3</sup>

#### **<sup>90</sup>Y-Microsphere Treatment Comes of Age**

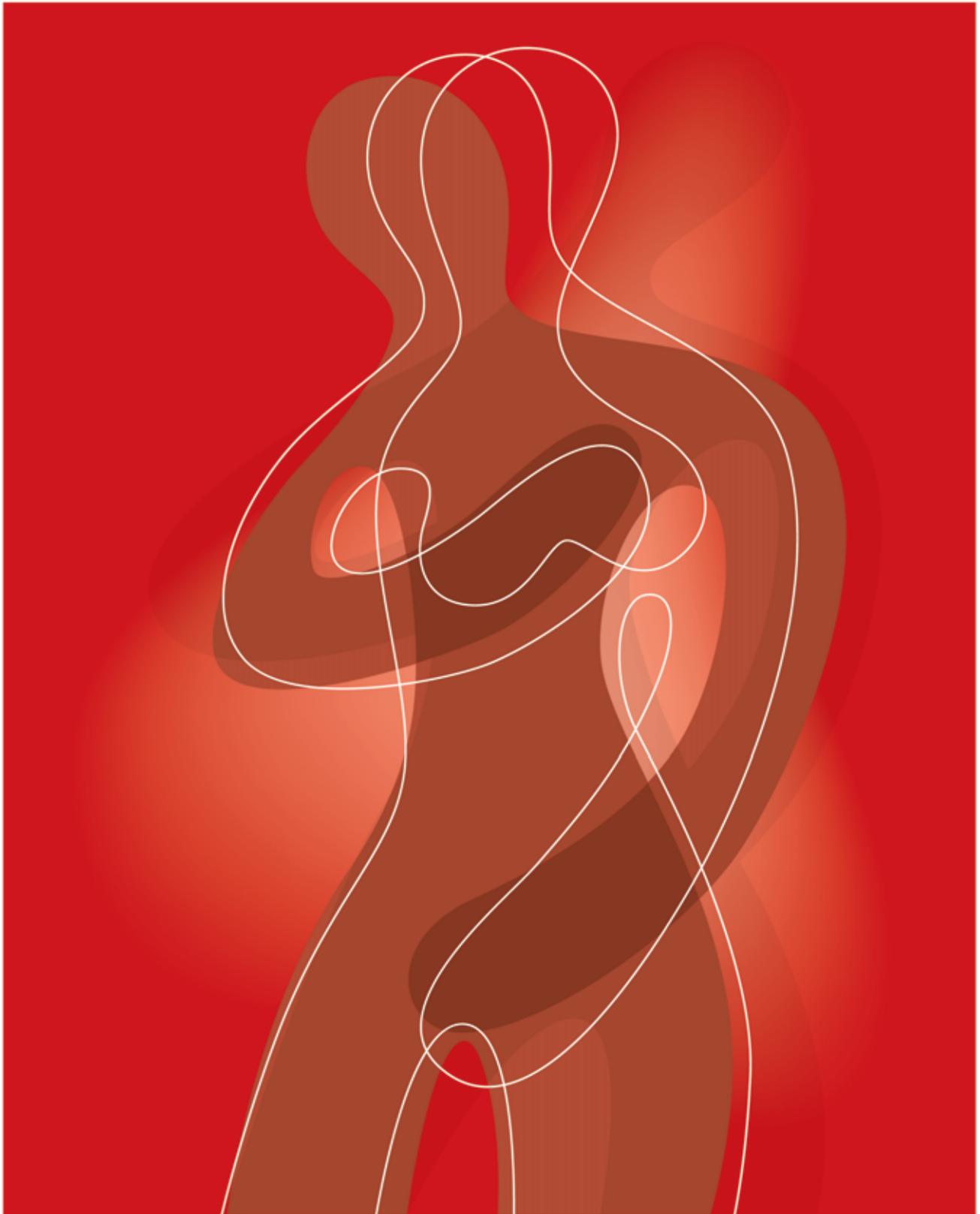
Nearly all solid tumours that are treated with radiation also benefit from concurrent chemotherapy or a biologic agent to sensitise and produce at least additive, but usually synergistic, cell killing. Cancers of the colon and rectum are the prototypical chemoradiotherapy tumour type and the most common metastatic lesion in the liver in Europe and North America. Combining the newest and most effective chemotherapy agents for colorectal cancer with microspheres is the logical next step now that the

desired dose of  $100\text{mg}/\text{m}^2$  concurrent with microspheres was well tolerated in all patients treated thus far. Interestingly, the median time to liver progression was 6.3 months, and median survival 12.0 months (2–25+ months).

Additional phase I/II clinical trials combining chemotherapy, biologics and resin microspheres are on-going in Europe and the US for colorectal cancer liver disease. Additional experience with resin spheres is also being gained for metastatic breast, neuroendocrine and hepatocellular cancers in Europe, the US and Asia.

By the end of this year, additional advances will be published regarding radiation dosimetry and fractionation. These will include more than one application of microspheres, imaging and follow-up guidelines, and long-term results in colon, breast, neuroendocrine, hepatocellular and many other solid tumours. It is a therapeutic approach that has shown promise, safety and flexibility in the application to many tumour types, in patients with both early and advanced hepatic disease, even with heavy pre-treatment profiles. ■

3. Kennedy A S, et al., "Liver brachytherapy for unresectable colorectal metastases: US results 2000-2004", *Proceedings of the 2005 Gastrointestinal Cancers Symposium*, 2005: p. 155.
4. Van Hazel G, et al., "Selective internal radiation therapy (SIRT) plus systemic chemotherapy with FOLFOX A phase I dose escalation study", *Proceedings of the 2005 Gastrointestinal Cancers Symposium*, 2005: p. 216.
5. Van Hazel G, et al., "Selective internal radiation therapy (SIRT) plus systemic chemotherapy with irinotecan. A phase I dose escalation study", *Proceedings of the 2005 Gastrointestinal Cancers Symposium*, 2005: p. 137.



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