Radioembolisation – A New Treatment for Primary and Secondary Liver Tumours

a report by
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Primary liver tumours, in particular hepatocellular carcinoma, usually cause death without having spread outside the liver. The liver is also sometimes the only or predominant site of metastatic disease for several other cancers, mainly colorectal and neuroendocrine tumours, but also breast and pancreatic cancer. For that reason, regional liver chemotherapy has been explored as an anti-tumoural treatment for decades. A low threshold for relevant toxicity has denied a role for external radiation in the treatment of patients with multiple liver tumours, even though with conformal radiation it has been shown that primary and common secondary liver tumours might well be sensitive to radiation. Any medical device that could deliver significant doses of radiation to liver tumours irrespective of their size, number or location, while at the same time preserving the surrounding liver tissue from harmful irradiation, would certainly be appealing. The term 'radioembolisation' has been recently used and defines those therapeutic strategies in which radiation is delivered by means of implantable devices delivered intravascularly. In this sense, radioembolisation microspheres sit astride the border separating conventional brachytherapy from radiopharmaceuticals. Although the first reports on the medical use of radioembolisation came during the 1980s, only recently has it emerged as a promising regional therapy for patients with primary and secondary liver tumours.

Devices

Radioembolisation microspheres are minute beads that a carry a radionuclide. Two devices are so far available for liver radioembolisation, and they have distinctive properties that should warn against indiscriminate extrapolation of the clinical experience from one to the other (see *Table 1*). Both devices use yttrium-90 as a source of beta radiation, its main characteristic being a reduced penetration that averages 2.5mm in tissues.

Procedures

Evaluation of candidates for radioembolisation start with a thorough angiographic evaluation to identify the vessels that give arterial blood supply to every liver tumour nodule, to detect any possible vessel that may result in the undesirable embolisation of microspheres into extra-hepatic organs (particularly, the gastrointestinal tract); and to evaluate portal vein blood flow. Prophylactic embolisation of problematic vessels (most commonly the gastroduodenal artery) is performed whenever necessary. If treatment is deemed feasible, then Tc99-labeled macroaggregates of albumin are injected as a surrogate for the trail of the radioisotope-containing microspheres measuring the degree of intra-hepatic/intra-tumoural shunt to the lung after nuclear medicine imaging. This may also be used to detect misplacement of microspheres in the gastro-intestinal tract, and to evaluate the relative amount of activity going to the liver tumours and the non-tumoural liver (see *Figure 1*).

Treatment is performed a few days later by injecting microspheres into the artery or arteries feeding the tumours. Patients with tumours restricted to one hepatic lobe or segment can be treated in a lobar or segmental fashion, avoiding unnecessary radiation to the contralateral lobe. For those with whole-liver involvement, both lobes can be treated either at the same time or in a sequential approach. The amount of activity to be injected is previously calculated on the basis of an estimation of tumour and non-tumoural liver volume.

Patients can be discharged early after the procedure or can even be treated as out-patients. Proton pump inhibitors are usually prescribed for 1–2 months. When considering follow-up, it should be kept in mind that maximal tumour response takes not less than three months to fully develop, although positron emission tomography (PET) scan responses can be observed earlier.

Contraindications

Liver radioembolisation should not be considered for patients with a poor functional reserve. A serum

bilirubin level of 2mg/dl is usually the cut-off point for indication, although segmental treatment of primary liver tumours can still be considered in patients with higher values. Treatment should not be carried out in the presence of ascites and other symptoms of advanced portal hypertension. External beam irradiation to the liver or lung should be considered absolute or relative contraindications, respectively.

Complications

An overt post-embolisation syndrome is hardly ever observed, but mild to moderate pain may appear during injection, particularly with resin microspheres. Non-target radiation is the main source of complications and may involve the liver, the gastrointestinal tract or the lung.

The most onerous complication is radiation-induced liver damage, which may appear 1–2 months after treatment in the form of jaundice and ascites. At present, the true mechanism of this liver injury is not fully understood. This complication is particularly threatening for cirrhotic patients with hepatocellular carcinoma, a population in which patient selection and dose calculation should be very conservative. Portal hypertension may also rarely develop in the absence of recognised liver injury. Gastrointestinal tract ulcerations are uncommon but very distressing, and their incidence can be minimised with aggressive embolisation of collateral vessels and the use of fluoroscopic guidance to detect flow decline during treatment. The risk of radiation pneumonitis is brought down to anecdotal if the corresponding dose reduction is accomplished for patients with a significant lung shunt. A frequent finding apparently lacking clinical significance is lymphopenia.

Results

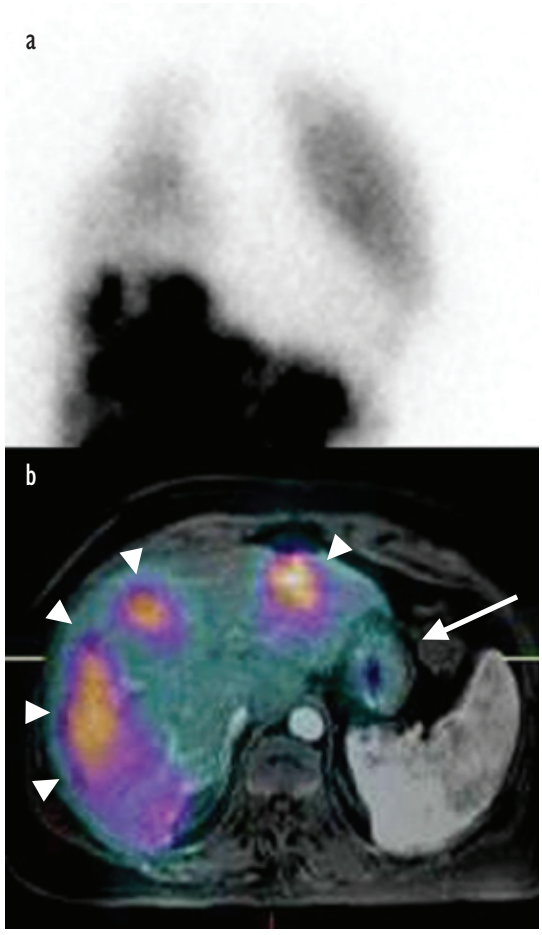
Radioembolisation of hepatocellular carcinoma results in objective tumour response (using volumetric criteria, World Health Organization (WHO) or Response evaluation criteria in solid tumors (RECIST)) in 25–50% of patients (see *Figure 2*). Prolonged stable disease is observed in a larger proportion of patients and downstaging to surgical criteria can sometimes be achieved. Comparisons with historical controls suggest that radioembolisation may have a favourable effect in the survival of patients with advanced hepatocellular carcinoma, but definitive evidence is lacking. Randomised studies are currently under way to elucidate how radioembolisation compares to transarterial chemoembolisation in the treatment of non-resectable disease and whether it may improve survival compared with best supportive care among patients with fairly advanced tumours.

The picture is clearer for the treatment of patients with liver metastases from colorectal cancer. In early clinical trials, a fall in carcinoembryonic antigen (CEA) was consistently observed after radioembolisation and patients usually progressed with extra-hepatic disease. In a randomised phase II trial of 21 patients, the addition of radio-

Table 1: Features of Microspheres Available for Radio-embolisation

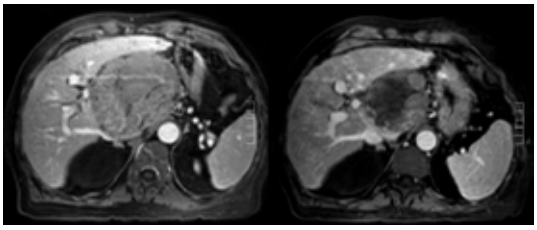
Trade Name	*TheraSphere*	*SIR-Spheres*
Material	*Glass*	*Resin*
Isotope	*Yttrium-90*	*Yttrium-90*
Average Diameter	*35µm*	*25µm*
Activity per particle	*2500Bq*	*50Bq*
Microspheres per dose	*One to five million*	*40-80 million*
Average activity per treatment	*5GBq*	*1.5GBq*

Figure 1: Nuclear Medicine Imaging After Injection of Radio-labelled Macroaggregates of Albumin into the Hepatic Artery Feeding the Tumors



a) planar images are used to calculate lung shunt; and b) SPECT-TAC fusion images can be used to detect misplacement of microspheres in the GI tract (arrow), and to evaluate the relative amount of activity going to the liver tumours (head arrows) and the non-tumoural liver

Figure 2: Partial Tumour Response After Radio-embolisation in a Patient with Hepatocellular Carcinoma and Compensated Viral Cirrhosis



embolisation to five-fluorouracil/leucovorin chemo-therapy resulted in a statistically significant increase in response rate, time to progression (18.6 months versus 3.6 months), and overall survival (29.4 months versus 12.8 months). In a larger randomised trial, radioembolisation improved the effect of continuous intra-arterial infusion of floxuridine in terms of response rate (50% versus 24%), time to progression of disease in the liver (19.2 months versus 10.1 months) and overall survival. A large multi-institutional series with more than 300 patients treated with microspheres alone mostly as salvage therapy, a median actuarial survival of 11 months compared favourably with the five months of a similar cohort of patients not receiving radioembolisation. Clinical trials combining state-of-the-art chemotherapy with radioembolisation are in progress. They include phase I trials searching for the optimal dose of oxaliplatin and irinotecan to be used in combination with radioembolisation, and phase II studies on the combination with 'Folfox Six' plus bevacizumab as first-line treatment of liver-predominant disease, and on the combination with 'Folfiri' plus cetuximab as second-line therapy for patients who have failed oxaliplatin therapy. From current available data, it is likely that radioembolisation adds very little toxicity to chemotherapy for patients with colorectal cancer metastatic to the liver.

In regards to liver metastases from other primary tumours, very little has been published, but clinically meaningful tumour responses have been observed by virtually all experienced groups in neuroendocrine tumours and other epithelial cancers, including breast cancer, pancreatic cancer, renal cell carcinoma or peripheral cholangiocarcinoma.

Expectations

Liver radioembolisation is emerging as a very promising therapy for primary and secondary liver tumours. It requires the close co-operation of different teams, including medical and radiation oncology, hepatology, interventional radiology and nuclear medicine. It has shown a noticeable anti-tumour effect against hepatocellular carcinoma and liver metastasis from colorectal cancer and its role in the treatment of these malignancies will be established by on-going clinical trials. In the near future, the role of radio-embolisation in the treatment of other conditions should also be explored. The door is open for new materials to improve the efficacy and safety of the currently available microspheres. ■

The term 'radioembolisation' has been recently used and defines those therapeutic strategies in which radiation is delivered by means of implantable devices delivered intravascularly.

Further Reading

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SIR-Spheres microspheres (Yttrium-90 resin microspheres) and associated delivery apparatus are indicated in the EU for the treatment of unresectable liver tumours. Selective Internal Radiation Therapy (SIRT) using SIR-Spheres is an effective and well-tolerated treatment for liver-only or liver-predominant disease from primary and secondary metastases.[1–7] SIR-Spheres may be used at any point throughout the patient journey, from first-line setting through to salvage therapy.[3,4] Safety and maximum tolerated doses have been established in combination with FOLFOX, irinotecan, 5-FU/LV, FUDR HAC and as monotherapy, with an on-going clinical studies programme covering other regimens.[1–5]

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