

¹⁸⁸Rhenium-TDD-Lipiodol in Treatment of Inoperable Primary Hepatocellular Carcinoma—A Case Report

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Abstract

Introduction: The aim of this study was to investigate the potential of using ¹⁸⁸Re Lipiodol for selective internal radiation therapy of inoperable hepatocellular carcinoma (HCC). **Clinical Picture:** A 33-year-old female with poorly-differentiated multicentric HCC, elevated alpha-fetoprotein (AFP) and increased serum alkaline phosphatase. **Treatment:** Over a 2-month interval, the patient was treated twice with 4GBq of ¹⁸⁸Re-TDD-Lipiodol. **Outcomes:** There was good localisation of ¹⁸⁸Re Lipiodol in the tumours, but also in thyroid (first treatment) and gastrointestinal tract (both treatments). So far (5 months post-treatment), the patient remains well with stable disease. **Conclusions:** ¹⁸⁸Re Lipiodol can be an effective radiopharmaceutical for the treatment of HCC; however, more work must be done to minimise the uptake in bowel.

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Key words: Selective internal radiation therapy, Radiopharmaceutical, Radiation absorbed dose

Introduction

Hepatocellular carcinoma (HCC) is one of the most malignant tumours. The lack of an effective treatment modality has stimulated the use of selective internal radiation therapy for the treatment of HCC. ⁹⁰Yttrium microspheres and ¹³¹Iodine Lipiodol administered via hepatic artery have shown promising results in both inoperable and adjuvant cases.¹⁻³ Disadvantages of ⁹⁰Y include the absence of a gamma ray suitable for imaging and shunting to the lungs. ¹³¹Iodine has a long physical half-life and a high-energy gamma ray, resulting in unnecessary radiation exposure to the staff and longer hospitalisation of the patients.

¹⁸⁸Rhenium is an attractive radionuclide for therapy because of its shorter half-life (16.9 h), low-energy gamma (155 KeV) and availability through the ¹⁸⁸W/¹⁸⁸Re generator system. Although there have been reports on the preparation of ¹⁸⁸Re Lipiodol,^{4,5} no report on clinical efficacy has been published yet. We report our early experience of using ¹⁸⁸Re Lipiodol in HCC treatment.

Preparation of ¹⁸⁸Re Lipiodol

¹⁸⁸Rhenium in the form of sodium perrhenate was obtained by eluting a ¹⁸⁸W/¹⁸⁸Re generator purchased from Oak Ridge National Laboratory, Tennessee, USA. The ¹⁸⁸Re perrhenate solution was concentrated by passing through ion exchange columns as previously described.⁶

¹⁸⁸Rhenium Lipiodol was prepared according to the procedures described by Jeong et al.⁵ ¹⁸⁸Re perrhenate (7.5 GBq) was added to a vial containing lyophilised 2,2,9,9-tetramethyl-4,7-diaza-1,10-decanedithiol (TDD) which was generously provided by Dr Jeong from Seoul National University Hospital. The vial was placed in a boiling water bath for 30 to 60 min. The ¹⁸⁸Re TDD was then extracted into 3 mL of Lipiodol. Radiochemical purity of the final product was determined using thin layer chromatography as described.⁵ The Singapore General Hospital Ethics Committee approved the use of ¹⁸⁸Re-TDD-Lipiodol for advanced HCC patients on compassionate grounds

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Case Report

Treatment of HCC

A 33-year-old female HCC patient was referred to our clinic for treatment. One month prior to this, she had undergone an incomplete surgery for a suspected pancreatic tumour, which was confirmed to be a poorly-differentiated HCC on histology. Postoperative computed tomographic (CT) scan (Fig. 1) revealed large tumours in the liver and upper left abdomen. Angiography showed a vascular tumour occupying most of the right lobe of the liver and a less vascular lesion in the upper left abdomen (Fig. 2). Her alpha-fetoprotein (AFP) was 35,350 ng/mL. Serum alkaline phosphatase and γ -glutamyl transferase (GGT) were elevated, but results of other clinical chemistry tests were normal.

The tumour in the right lobe of the liver was treated with 4 GBq of ^{188}Re Lipiodol administered via a 3F microcatheter placed into the right hepatic artery (Fig. 3). The injection of ^{188}Re Lipiodol was performed under fluoroscopic guidance to ensure that there was no reflux into the gastric artery. Nuclear scintigraphy (whole body, anterior and posterior views of abdomen) was performed at 1 h, 24 h, 48 h and 72 h after injection using a high-energy general purpose (HEGP) collimator. The thicker lead septum of a HEGP collimator was necessary in order to reduce the Bremsstrahlung scattering resulting from the high-energy beta particles of ^{188}Re -188. Regions of interest were drawn over the liver and the tumours. Effective half-lives of ^{188}Re Lipiodol in the tumours and liver were calculated. The radiation dose to the non-tumour part of the liver was calculated using the MIRDose 3 and the radiation dose to the tumour was estimated using the following equation:¹

$$\text{Dose (rad)} = (73.8 \times E \times T_e \times A_o/M) + (0.0346 \times T \times T_e \times G \times A_o/M) \quad \text{eq.1}$$

where, E = average beta energy
 T_e = effective half-life (days)
 T = specific gamma ray constant (rad-cm²/mCi-h)
 A_o = injected radioactivity (uCi)
 M = tumour mass (g)
 G = geometric factor (cm)

Her AFP dropped to 11,601 ng/mL after 1 month. Results of other clinical chemistry tests were normal. A second dose of 4 GBq intra-arterial dose of ^{188}Re Lipiodol was given via the hepatic artery directed to the left lobe tumour. Nuclear scintigraphy and radiation dose estimation were repeated.

Results

The overall yield for the preparation of ^{188}Re Lipiodol was 60% and the radiochemical purity of the final product was 96%. The distribution of the injected ^{188}Re Lipiodol is shown in Figures 4 and 5. The effective half-life of ^{188}Re Lipiodol was approximately 13 h for the tumours and the rest of the liver. There was accumulation of radioactivity in the tumours, although it may appeared not significantly higher than the non-tumour part of the liver. However, the size of the tumour was much less than that of the non-tumour part of the liver; hence, the radiation dose to the tumour was much higher than to other part of the liver. In the first treatment, the estimated radiation dose to the right lobe tumour and the rest of the liver was 43 Gy and 2.4 Gy, respectively. The radiation dose to the left lobe tumour was 6.6 Gy due to its low vascularity. In the second treatment, despite the effort to deliver the ^{188}Re Lipiodol to the left lobe tumour, a majority of the dose localised in the right

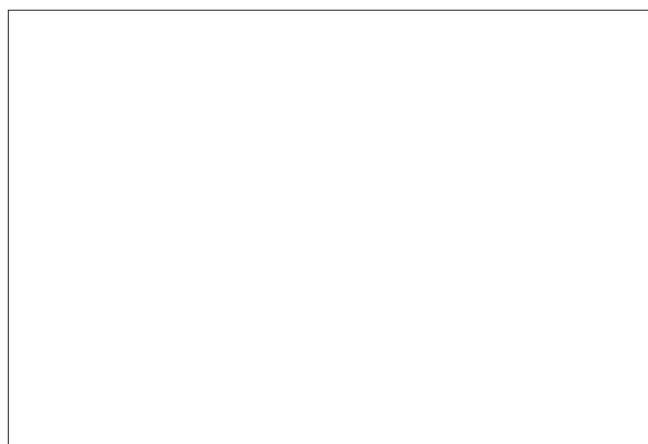


Fig. 1. Postoperative CT scan of the patient before the first radionuclide treatment showing multiple hypodense areas in the right lobe of the liver. Partial left lobe resection was noted and a large mass was seen adjacent to the lesser sac.

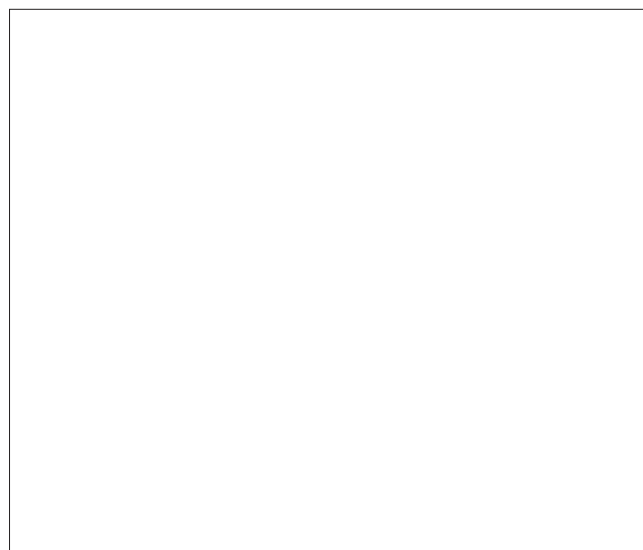


Fig. 2. Hepatic angiogram of the patient showing a large vascular tumour occupying most of the right lobe of liver (first treatment).

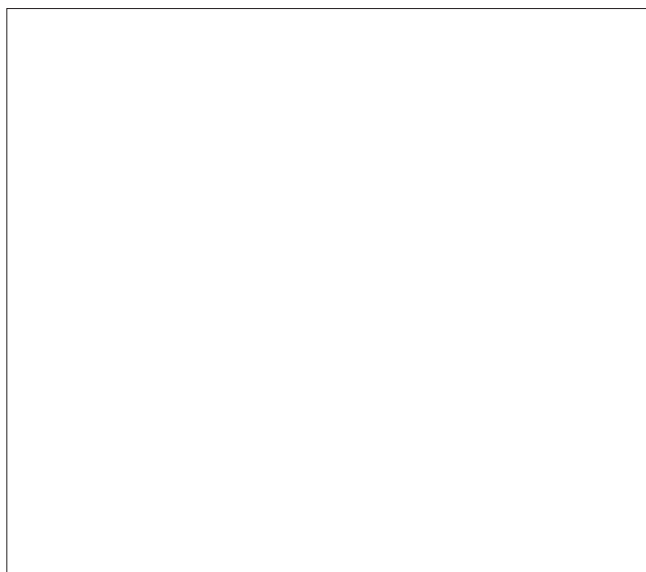


Fig. 3. Hepatic angiogram after injection of ¹⁸⁸Re-TDD-Lipiodol (first treatment) showing the distribution of the radiopharmaceutical throughout the tumour.

Fig. 4. Biodistribution of ¹⁸⁸Re-TDD-Lipiodol (first treatment) at 4 h showing uptake in thyroid, the tumour in right lobe of the liver, the bowel, and less vascular tumour in upper left abdomen. Lung uptake was absent.

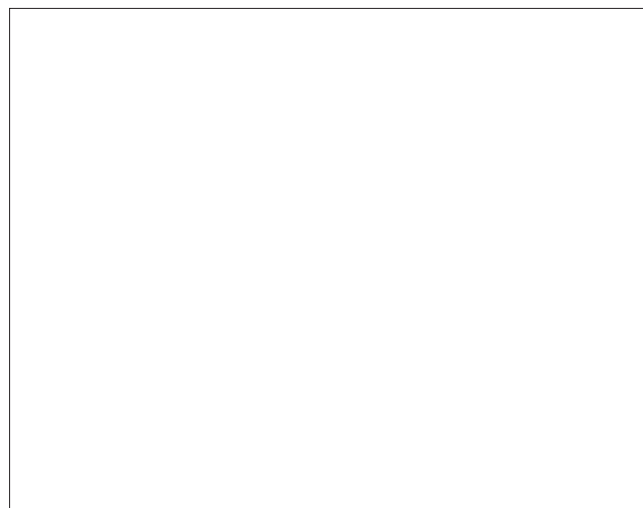


Fig. 6. Recent CT scan of the patient showing that the right lobe tumour has decreased in size while the left lobe tumour continued to grow.

Fig. 5. Biodistribution of ¹⁸⁸Re-TDD-Lipiodol after second treatment. Note the absence of thyroid uptake. The bowel radioactivity remained high. The left lobe tumour shows less uptake of the radiopharmaceutical.

lobe. The estimated radiation dose to the left lobe tumour was 7.2 Gy. The radiation dose to the right lobe tumour and the rest of liver was 40 Gy and 2.5 Gy, respectively. Up to now (5 months after the first treatment), the patient has been free of side effects and remains well, despite the very advanced disease at first presentation. A recent CT scan revealed that the right lobe tumour has decreased in size substantially, but the left lobe tumour continued to grow (Fig. 6).

There was significant localisation of ¹⁸⁸Re Lipiodol in the thyroid and gastrointestinal (GI) tract. The GI tract became the organ with most radioactivity at 24 hours after injection. At the second treatment, alpha-tocopherol (400 i.u. in

1 mL) was added to the ¹⁸⁸Re Lipiodol as an antioxidant, and thyroid uptake decreased substantially (Fig. 5), but the bowel radioactivity remained high.

Discussion

Hepatocellular carcinoma is a common malignant tumour worldwide. Surgery is the only curative treatment but it is possible only in about 10% of the patients⁷ and the recurrence rate is high. Chemoembolisation using emulsions of chemotherapeutic agents in Lipiodol is another common treatment modality, but the efficacy is disappointing.⁸

Recently, selective internal radiation therapy using ⁹⁰Y microspheres and ¹³¹I Lipiodol administered via hepatic artery has shown promising results in both inoperable and adjuvant cases.¹⁻³ Of the commonly used radionuclides for

internal radiation treatment, ^{188}Re may be the best. The high-energy beta particles emitted by ^{188}Re produce good therapeutic effects, while the short half-life and low energy gamma ray reduce the radiation exposure to staff and make external imaging feasible. An additional advantage of ^{188}Re is that it is produced by a generator system, enabling preparation of ^{188}Re radiopharmaceuticals on site. Treatment cost is reduced and more readily available. As the localisation of Lipiodol has been well documented, ^{188}Re Lipiodol may be an ideal radiopharmaceutical for HCC treatment or adjuvant therapy after resection.

This report is about our preliminary experience indicating the potential of ^{188}Re Lipiodol in HCC treatment. In our local population, patients remain asymptomatic until the tumours are discovered during other examinations, and frequently in an advanced stage. Despite the late stage of the tumour, this patient has been symptom-free and fully ambulant since the first treatment 5 months ago, with no adverse effects from the treatments. The result is encouraging since the median survival time for patients with HCC can be as short as 8 weeks.^{2,9}

There have been several reports on the preparation of ^{188}Re Lipiodol. The procedure described by Wang et al⁹ may be the ideal since it allows the ^{188}Re molecules to be labelled onto the Lipiodol molecules via a bifunctional chelating bridge. However, the procedure is complicated and not reproducible. Jeong et al described another method in which ^{188}Re is labelled to TDD to form a lipophilic complex, which is then dissolved in Lipiodol. The TDD compound can be prepared in bulk as a lyophilised powder and stored. The preparation of ^{188}Re Lipiodol using this method is relatively straightforward. The disadvantage is that ^{188}Re is not chemically bound to the Lipiodol molecules.

Unlike the biodistribution of ^{131}I Lipiodol and ^{90}Y microspheres, there was no lung uptake after ^{188}Re Lipiodol injections. This observation is in accordance with the results from a rat model.⁹ However, there was substantial uptake in the GI tract for both treatments. The thyroid uptake in the first treatment may be due to the formation of free perrhenate, which results from the radiolysis of ^{188}Re since its beta particles are of high energy. The reduction in thyroid radioactivity when alpha-tocopherol was used as an antioxidant in the second treatment supports this hypothesis.

The mechanism of the GI radioactivity uptake is not elucidated yet; it is possible that the ^{188}Re leaks out from the

Lipiodol since it is not covalently bound to the Lipiodol molecule, but dissolved in Lipiodol through the lipophilic ^{188}Re -TDD complex. It is possible also that some breakdown products from radiolysis of ^{188}Re Lipiodol is excreted via the biliary tract. The bowel uptake results in unnecessary exposure to the patient. With careful dosimetric estimation, it is possible to deliver a tumoricidal dose to the tumour while maintaining the exposure to the bowel at below the maximum tolerated limit, since the ^{188}Re Lipiodol is probably within the lumen of the bowel and is excreted by 48 h.

In conclusion, our preliminary results indicate potential use of ^{188}Re Lipiodol in selective internal radiation treatment of HCC, but more work has to be done to reduce the radioactivity in the GI tract. We are currently working on better methods to obtain chemical bonding of ^{188}Re and Lipiodol.

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