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How PET ameliorates 90-Yttrium therapy in inoperable liver cancer patients?

Increased synthesis of blood vessels and blood supply are essential characteristics of a tumor to secure nutrient delivery and growth. One of the treatment options for inoperable liver cancer (hepatocellular carcinoma, HCC) is to apply a form of internal radiation therapy by infusion of radioactive particles via the arteries supplying the tumors. The particles are glass spheres in micron size (microspheres), encasing a radioactive metallic element ^{90}Yittrium, which emits beta radiation for killing of cancer cells at a close distance. The radioactive ^{90}Y-microspheres are infused into the tumor's vascular bed by selective placement of a catheter through the arteries supplying the liver (Fig. 1). They are trapped inside the small arterioles (intentional embolic effect) but some might escape due to shunting via collateral vessels to other organs (random/unintentional embolization, Fig. 2). Therefore, the strategic design of ^{90}Y glass-microsphere-radioembolization (^{90}Y-GMRE) protocol for treatment of inoperable HCC should aim at optimizing the treatment dose to the tumors while minimizing the bystander damage to normal liver and shunting to other organs.

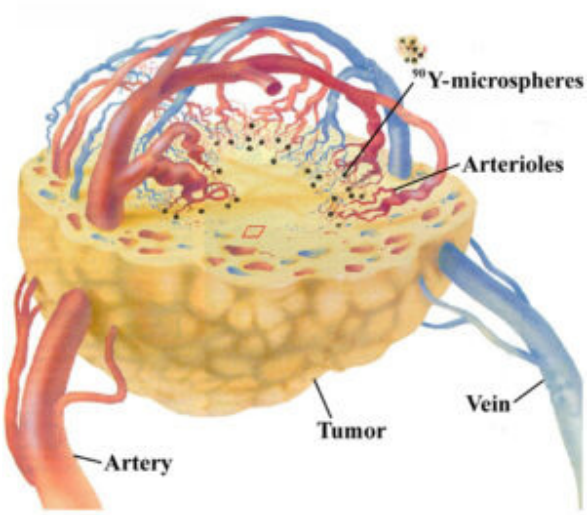

Fig. 1. Infusion of 90Y-microspheres through the arteries supplying the liver are mostly trapped in the arterioles of the tumor's vascular bed. Radioactive 90Y emits beta (β-) radiation for killing of cancer cells at a close distance.

The conventional GMRE treatment protocol is to prescribe an intended dosage of ^{90}Y-microspheres based on a recommended fixed dose (120 Gy) with empirical adjustment according to the patient's liver volume containing the tumor and a simplified compartmental calculation. Before the actual treatment protocol, a simulation test by injecting a form of bio-degradable particles, ^{99m}Tc-labeled albumin aggregate (MAA), comparable to the ^{90}Y-microsphere in size, was routinely performed to evaluate the vascular distribution of the ^{90}Y-microspheres to the tumors and severity of shunting to the normal liver and other organs, particularly the lungs and viscera.

The tumor burden for the adjustment of dosage was traditionally based on physical parameters obtained from CT or MR imaging. Our study, however, proposed that dosage calculation should be individually adjusted based on an algorithm that takes into consideration the cytokinetic information of the tumors obtained from pretreatment dual-tracer (^{11}C-acetate and ^{18}F-FDG) PET/CT. The algorithm specifies 2 prerequisite technical validations and 2 dose limit boundary conditions.

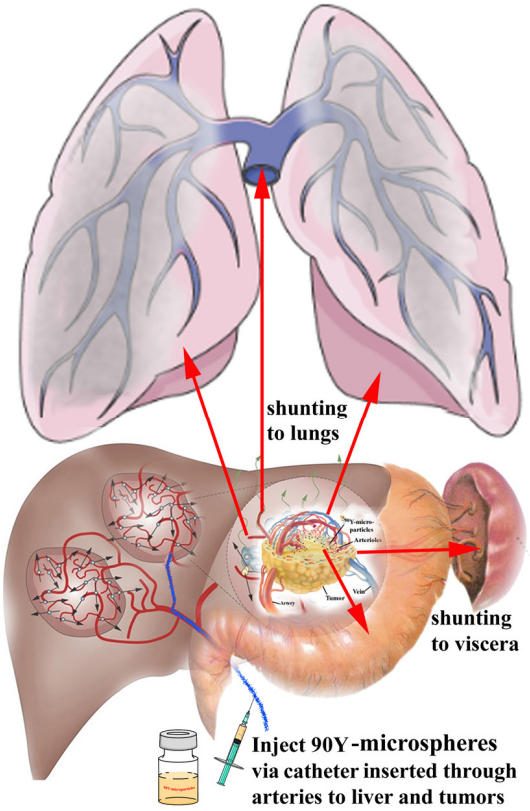

Fig. 2. The amount of 90Y-glass-microspheres lodged in HCC is dependent on (i) location of the catheterized blood vessels supplying the tumor, (ii) blood vessel density ratios between tumor and normal liver, and (iii) collateral circulations leading to shunting and escape of microspheres to the lungs and viscera.

The first technical validation is to investigate the reliability of PET/CT to provide accurate measurement for the minute amount of positron (β+) radiation from the ^{90}Y-particle which primarily exerts its GMRE therapeutic effect by beta-minus (β-) emission. The second technical validation is to evaluate the performance of the MAA-particles measured by pretreatment SPECT/CT in predicting the distribution ratio of tumor-to-nontumor ^{90}Y-microspheres on posttreatment ^{90}Y PET/CT.

The 2 dose boundary conditions to avoid bystander damages in ^{90}Y-GMRE are designated as 30 Gy in lung and 70 Gy in normal liver parenchyma, which are the upper safety limits of recommended radiation exposure to these organs, respectively. HCC is well known to be a highly heterogeneous tumor but much of the reported data in the literature on ^{90}Y-GMRE treatment did not include the heterogeneity factor or cytokinetic properties

of HCC. We have previously showed that *de novo* conversion of acetyl-coA from acetate is the preferred biochemical substrate for early, well-differentiated HCC (WDHCC), but as tumors grow in a bizarre microenvironment with increasing nutrient and oxygen stress, they would dedifferentiate into poorly-differentiated HCC (PDHCC), with concomitant change in biochemistry and a switch to a more convenient form of energy production, Warburg glycolysis, for tumor growth. Therefore, ^{11}C-acetate and ^{18}F-FDG are 2 PET tracers serving as biomarkers, respectively, for these 2 cancer types of different cellular differentiation and with different radiosensitivities. Our data showed that by resolving the metabolic heterogeneity and including the cytokinetic information obtained from dual-tracer PET/CT into the dosage calculation of individual patients (WDHCC >152 Gy, PDHCC >262 Gy), we may significantly improve both treatment response and overall survival with least damage to bystander organs.

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Publication

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