Ultrasound Guided Internal Radiotherapy Using Yttrium-90 Glass Microspheres for Liver Malignancies

TO THE EDITOR: We enjoyed reading the article by Tian et al. (*1*) and were fascinated by their novel method of intra-tumoral injection of ^{90}Y microspheres.

We are concerned, however, about the radiation hazard associated with the procedure. The authors mention that perilesional injection of alcohol before the treatment session has been used to prevent extratumoral leakage of ^{90}Y microspheres from the puncture site in 11 patients treated at the early stage. The incident rate of leakage, the amount of radioactivity involved and the contingency procedures required were not mentioned in the article. The leakage of a radioactive source with beta energy up to 2200 keV from the puncture site into the peritoneal cavity can result in a major disaster to the patient as 1 mCi of ^{90}Y on decay to infinity will deliver 1837 Gy of radiation to 1 g of tissue. The activity observed in the intestines of four patients in the present study is indeed alarming.

If surgical intervention is needed for hemoperitonium, which results from puncture site bleeding, surgeons will receive a long exposure to radiation. The article also did not mention the level of radiation the medical personnels who carried out the injection were exposed to and what precautions were taken to protect them.

If all the injected microspheres really stayed within the tumor, this could be a better route of administration of the microspheres than the commonly used intra-arterial route (*2,3*) in delivering a high radiation dose specifically to the tumor while sparing the adjacent non-tumorous liver parenchyma and neighboring organs such as the lungs. However, the actual delivery of the radioisotope to the tumor by this method is not ideal. Flow of the microspheres beyond the boundaries of the space-occupying lesions has been observed by the authors. The count ratios of hot spot (lesion) to adjacent liver (8.6:1 ~ 32.2:1) in this study indicate that 3.0% to 10.4% of the injected activity actually ended up outside of the tumor.

We have demonstrated previously that as high as 67.2% of radioactivity infused into the hepatic artery in patients with hepatocellular carcinoma could be shunted into the lungs (*4*). The observation of the lack of action of angiotension II, a vasoconstrictor, which is known to constrict normal but not neoplastic blood vessels, on the degree of lung shunting by Goldberg et al. (*5*) and by us (*4*) suggests a neoplastic nature of the arteriovenous vascular shunt between the liver and the lungs. This was further supported by the disappearance of shunts in a patient after resection of his tumor (*4*). The possibility of the ^{90}Y microspheres injected into the tumor being shunted to the lungs exists. An excessive amount of radioactivity getting into the lungs can cause radiation pneumonitis (*6*). In this study (*1*), shunting of mild amounts of the glass ^{90}Y microspheres into the left lungs of six patients was observed. Furthermore, the lesion-to-lung ratios which varied from 4.8 to 11.3 mean that 8.1% to 17.2% of the activity was shunted to the lungs if the lesion and the lung were taken as the only organs which contained the radioactivity. It is fortunate that these patients did not develop lung complications. This is probably because the total activity used was relatively low.

The method used for estimating the radiation doses in this study may apply in treatments which use ^{125}I or ^{198}Au seeds, as these isotopes really stay in fix points after being implanted interstitially. The distribution of ^{90}Y microspheres is known to be heterogeneous (*7*). The microspheres were shown in Figure 2 of the article (*1*) to spread throughout the tumor, rather than concentrated at a certain point. Thus, we consider it inappropriate to regard all the injected ^{90}Y microspheres to be a point-source of irradiation inside the tumor. In fact, our experience shows that the radioactive agent usually concentrates more on the periphery of the tumor because larger vascular space is available there.

There are some minor criticisms which we would also like to point out. First, the sizes of space-occupying lesions stated under the Patients Section in the article (*1*) were 2.0 to 8.8 cm, whereas tumor size of Patient 7 shown in Table 1 was 10.7 × 7.6 cm. Second, Yan et al. (*8*) actually published their complete data in 1993 (*8*). An international journal should be quoted as far as applicable. Third, the energy window set at 80 keV for Bremsstrahlung radiations from ^{90}Y is reasonable. However, with this energy value, a low-energy, general-purpose collimator should be used instead of a medium-energy collimator. Finally, although the use of alcohol and chemotherapy was stopped in the middle of the study, the study has been contaminated and doubts have been introduced into the evaluation of response.

With the simulation using ^{99m}Tc-labeled macroaggregated albumin, the distribution of ^{90}Y microspheres given through the hepatic artery can be predicted (*9*). The flow of ^{90}Y microspheres, which becomes radio-opaque in mixing with suitable contrast, can be monitored closely under fluoroscopy. Thus, the fate of ^{90}Y microspheres infused by the arterial route is more certain than as the authors have suggested in their article (*1*). With the partition model for estimating radiation doses to the various compartments (*9*), intra-arterial infusion has become a safe and repeatable method for administering ^{90}Y microspheres.

We agree with the authors that there are some aspects of the intratumoral injection, including radiation safety, which needs to be explored further before this procedure can be accepted as one of the standard methods for delivering ^{90}Y microspheres to malignant hepatic tumors.

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REPLY: We thank Ho and his colleagues for their interest in our article (*1*), and we are grateful as well for the opportunity to reply to their comments.

First, we did not think radiation hazard was a serious problem in our study. In our group of patients, there was very little leakage of ^{90}Y-GMS out of the injection site, as monitored by Bremsstrahlung imaging. There were indeed four patients with activity in intestine, but the radioactivity moved with the intestinal contents and was out of the body within 1–2

days. Since the radiation effect is time-dependent, none of the four showed any evidence of damage. (There was not the slightest hint in any patient of leakage into abdominal cavity.) Control of radiation exposure to the staff was not difficult. For beta-particle, and a layer of glass or plastics with certain thickness was enough to serve as effective shields. We would appreciate it if Ho et al. (*2*) could kindly inform us about the methods they use to protect their surgeons during intraoperative probing.

On most of the Bremsstrahlung images of our patients, the liver could be dimly seen behind the hot spot of the injected dose. We did not think that this implies leaching of the tracer because the liver was visualized so early (30 min after injection of highly insoluble 20–45-μm particles), and the liver activity was too uniform. However, the mechanism of liver's "showing out" was not clear, but scatter of the higher energy Bremsstrahlung radiation might account for that.

We are concerned about the radioactivity shunted to lungs as Ho et al. (*2*) mentioned. Moreover, Ho et al. (*2*) kindly calculated the shunt index in six of our patients. However, we would like to point out that the most significant difference between their studies and ours lies in the incidence of the shunt [six patients in our study versus almost all patients in the Ho et al. (*2*) study (*3,4*)]. Just as Ho et al. (*2*) kindly indicated, the dose of ^{90}Y-GMS was much smaller in our study (less than 0.7–1.1 GBq for any patient), therefore, no patient received a lung dose higher than 0.07GBq (*2*). That is, in fact, one of our reasons for choosing interstitial instead of intra-arterial treatment for liver cancer.

We sincerely agree with Ho et al. (*2*) that the dose-calculation in our study is far from proper. However, it was our belief that the distribution of interstitial injected ^{90}Y-GMS in the liver was not as unpredictable as given intra-arterially. As Fox et al. (*5*) indicated, the heterogeneous distribution of ^{90}Y microsphere introduced intra-arterially was so unpredictable that it varied even at different parts of the liver in the same patient. The uncertainty resulted in an "inferred dose." By careful surgery with real-time guidance of ultrasound, GMS could be administered to almost any part one wanted inside the tumor. Besides, we did take into account the volume of source in our calculation, and it showed the size of source had little effect on the periphery dose as calculated in our study. As in our article, we think the radiation to that part of the tumor is the most important, since many investigators indicated that the most active, recurrence-potential part of a tumor is around the periphery (*5,6*). The Valley's method served the purpose well.

We thank Dr. Ho for mentioning some of our mistakes such as lesion sizes. We apologize that the biggest lesion (Patient 7, 10.7 × 7.6 cm) was not included in our statistics when we prepared the first manuscript because the patient died early after his treatment. We did not see any relation between the second point given by Ho et al. As for collimators, we used a medium-energy collimator merely for fear of higher energy penetration degrading the already not-so-good image since Bremsstrahlung from ^{90}Y has a wide energy range (*7*). Finally, we realized the combination of alcohol and chemotherapy at the beginning of our study might cause doubt on the effectiveness of ^{90}Y-GMS treatment. Though it was not our intention to compare the different modalities, we had the impression, although not verified, that the alcohol and chemical agents used in our institute for interventional treatment of liver cancer was not as good as radionuclide therapy, since fewer patients could survive such a long time.

As we mentioned in our article and Dr. Ho agreed, the interstitial use of ^{90}Y-GMS is not ideal, but it provided certain possibilities that enable us to reach our common goal. Many factors need further exploration, and we like to have more options and interests in this field.

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Technetium-99m-Sestamibi Cellular Uptake: Passive or Secondary Active Transport?

TO THE EDITOR: Since it has been demonstrated that the cellular accumulation of ^{99m}Tc-sestamibi is driven by the plasma and mitochondrial membrane potentials (*1*), this agent is commonly considered as being taken up by the cells through a mechanism of passive diffusion. However, in biochemistry, the difference between passive and active transport is based on the fact that in passive transport the solute moves down its concentration gradient, while in active transport the solute moves against this gradient. Active transport resembles passive transport in its overall mechanism and kinetics properties, the only difference being that it requires energy to move the solute up its concentration gradient. Depending on the nature of this energy, two kinds of active transport are defined (*2*). Primary active transport uses energy directly from ATP hydrolysis, light or electron transport. Examples of active transport proteins utilizing ATP and involving common radiopharmaceuticals are the Na^+-K^+ ATPase, which can transport ^{201}Tl (*3*), and the P-glycoprotein involved in the multidrug resistance, which accepts ^{99m}Tc-sestamibi as a substrate (*4*). Secondary active transport uses a formerly established gradient across the cell membrane to transport a molecule of interest up its concentration gradient. The gradient used as a source of energy can be either an ion concentration gradient or a transmembrane potential, both being a form of potential energy. Finally, since only transmembrane electrical potentials drive the ^{99m}Tc-sestamibi cellular accumulation, this agent should be recognized as undergoing a secondary active transport, not a passive distribution. This would not only be a more accurate classification but it would be in better accordance with the fact that this agent can be used clinically for the study of myocardial viability and of tumor malignancy, two situations characterized by the presence of active metabolic phenomena.

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