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.

REFERENCES

1. Tian J-H, Xu B-X, Zhang J-M, Dong B-W, Liang P, Wang X-D. Ultrasound-guided internal radiotherapy using yttrium-90-glass microspheres for liver malignancies. *J Nucl Med* 1996;37:958–963.
2. Andrew JC, Walker SC, Ackermann RT, et al. Hepatic radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical follow-up. *J Nucl Med* 1994;35:1637–1644.
3. Lau WY, Leung TWT, Ho Stephen, et al. Treatment of inoperable hepatocellular carcinoma with yttrium-90 microspheres. A phase I and II study. *Br J Cancer* 1994;70:994–999.
4. Leung WT, Lau WY, Ho SKW, et al. Measuring lung shunting in hepatocellular carcinoma with intrahepatic-arterial techetium-99m macroaggregated albumin. *J Nucl Med* 1994;35:70–73.
5. Goldberg JA, Bradnam MS, Kerr DJ, et al. Arteriovenous shunting of microspheres in patients with colorectal liver metastases: errors in assessment due to free pertechnetate and the effect of angiotensin II. *Nucl Med Commun* 1987;8:1033–1046.
6. Leung WT, Lau WY, Ho SKW, et al. Radiation pneumonitis after selective internal radiation treatment with intra-arterial yttrium-90 microspheres for inoperable hepatic tumors. *Int J Radiat Biol Phys* 1995;33:919–924.
7. Fox RA, Klemp PFB, Egan G, et al. Dose distribution following selective internal radiation therapy. *Int J Radiat Oncol Biol Phys* 1991;21:463–467.
8. Yan ZP, Lin G, Zhao H-Y, Dong Y-H. An experimental study and clinical pilot trials of yttrium-90 microspheres through the hepatic artery for treatment of primary liver cancer. *Cancer* 1993;72:3210–3215.
9. Ho S, Lau WY, Leung WT, et al. Partition model for estimating radiation doses from yttrium-90 microspheres in treating hepatic tumor. *Eur J Nucl Med* 1996;23:947–952.

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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