# A Clinician's Guide to Nuclear Medicine

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The specialty of nuclear medicine depends on patient referrals from physicians in other disciplines. One of the missions of the nuclear medicine physician is to promote good communication with these clinicians and to educate them about the types and the value of the studies we offer. This task has been recently aided by the release of *A Clinician's Guide to Nuclear Medicine.*

Unlike conventional textbooks aimed at nuclear medicine practitioners, which are often subdivided by type of scan, this book seeks to guide clinical problem solving in a format relevant to the clinician. The first 25 chapters are divided by clinical problem, such as cardiovascular diseases, infection imaging, women's health, and a wide variety of tumors. Two chapters are devoted solely to radionuclide therapy, whereas other chapters (e.g., Thyroid Cancer) incorporate both diagnosis and therapy.

This book does not aim to be encyclopedic. Its focus is on discussing commonly encountered clinical problems rather than on detailed technical exposition. It is thus well suited to the busy clinician (intern, resident, or staff physician) who does not want to wade through a comprehensive nuclear medicine textbook when trying to answer a clinical question. The book is also suitable as an introductory text for prospective or beginning students in radiology or nuclear medicine, as well as for medical students.

Each chapter follows a standard format and, once one familiarizes oneself with this system, the information is easy to find. Each chapter includes 3 major subheadings: 1) *Scans* reviews radiopharmaceuticals, how each study is performed, patient preparation, understanding the report, and potential confounding factors or problems. 2) *Clinical Questions* discusses the advantages and limitations of the various nuclear medicine tests in a question-and-answer format of more than 200 clinically relevant questions. Examples of questions posed include "FUO: Should a nuclear imaging study be obtained to identify the cause?" and "Does my patient have a pulmonary embolus?" Some questions are more narrowly focused, such as "Should a patient with Graves' disease be made euthyroid with PTU before $^{131}$I therapy?" This section is highly readable and contains many clinical "pearls." 3) *Patient Information* includes information intended for distribution to the patient when the nuclear medicine test is scheduled. This would also be useful to nursing or nonmedical staff who are involved in setting up patient appointments.

The penultimate chapter is designed to educate the clinician about the radiation exposure from nuclear scans and alleviate concerns about risks. It has rudimentary information concerning imaging devices and radiopharmaceuticals. The book ends with a brief section on the comparative costs of diagnostic procedures. A lengthy table is based on representative 1999 Medicare reimbursement fees for various procedures and radiopharmaceuticals and includes those for competing modalities.

The book has a soft cover but is too large for a coat pocket, measuring 7 in. × 10 in. Illustrations are of high quality and have been well chosen to depict classic conditions and typical scintigraphic appearances. Arrows highlight most of the abnormalities and the figure legends are clear and easy to follow.

I have one minor quibble with the layout of this book. Whereas it is clear that the authors wished to limit the book to a manageable length (it runs 378 pages, not including the index) the format seems cramped. The patient preparation sections (which are intended to be copied and distributed) would have been more useful if each began at the top of a separate page. Likewise, the clinical information within each chapter can be overwhelming without page breaks for different major subject headings. However, this minor criticism does not diminish my overwhelming enthusiasm for the book nor my admiration for the authors, who have succeeded in producing a book of value to the entire nuclear medicine community.

As it is in the interests of the nuclear medicine physician to stimulate referrals, I recommend that this book be distributed to key clinicians. It is modestly priced, especially considering the glossy paper and high quality of the printed figures. From a cost-effectiveness point of view, just 1 additional nuclear medicine referral will have more than recouped the investment.

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## Intrahepatic $^{90}$Y-Microspheres for Hepatocellular Carcinoma

**TO THE EDITOR:** We read with great interest the article by Dancey et al. (*1*). We are pleased to learn that there was a complete response among the 19 evaluable patients treated with intrahepatic $^{90}$Y-microspheres in their study, which confirms our suggestion that this form of treatment may offer a cure to a small number of patients with nonresectable hepatocellular carcinoma (*2*). Furthermore, the median survival of 54 wk and the median time to progression of 44 wk achieved by their patients are both encouraging (*1*).

However, there are several points that need to be clarified. In an attempt to show that higher total activity in the tumors than in the nontumorous liver, as assessed from digitized images of a $^{99m}$Tc-macroaggregated albumin (MAA) scan (*1*), was associated with longer survival, the authors defined a tumor-to-liver activity ratio (TNR) as:

$$\text{TNR} = \frac{\text{total tumor counts}}{\text{total hepatic counts} - \text{total tumor counts}}.$$

They were fortunate to be able to show from multivariable analysis that a TNR $> 2$ ($P = 0.06$) is associated with longer survival, despite the fact that it is still uncertain as to whether TNR or some other measure should be used. The authors have shown very clearly that the radiation dose (Gy) to a tissue of mass M (kg) containing $A_o$ (GBq) of $^{90}$Y-microspheres is approximately given as:

$$\text{Dose (Gy)} = \frac{50\ A_o\ (\text{GBq})}{\text{M (kg)}},$$

because $^{90}$Y-microspheres do not undergo any biologic degradation and the activity decays to infinity at a mean life of 3.86 d. So the radiation dose to the tumor or the nontumorous liver depends not only on the total activity that resides in it but also on its mass. In other words, the radiation dose deposited is proportional to the radioactivity concentration (activity/mass) rather than to the total activity. We have pointed out previously (*3*) that radioactivity concentrations of the tumor and the nontumorous liver may be reflected by the counting rates per pixel (cell) taken over the respective area of interest and a tumor-to-normal uptake ratio (T/N) has been defined as T/N = count rate per pixel over the tumor/[(count rate over whole liver − count rate over all tumors)/(number of pixels over whole liver − number of pixels over all tumors)]. We assert that it is T/N rather than TNR that determines the selectivity of the treatment and, hence, its impact on patient survival. For example, a patient with tumor and nontumorous liver masses of 1.5 kg and 0.5 kg, respectively, and a T/N of 1 has a TNR of 3 but, obviously, the radiation doses to the tumor and nontumorous liver are identical. In contrast, a patient with tumor and nontumorous liver masses of 0.5 kg and 1.5 kg, respectively, and a T/N of 3 has a TNR of 1, but, clearly, the tumor cells receive 3 times as much radiation dose as the nontumorous liver parenchyma.

Dancey et al. attempted to exclude patients with flow of radioactivity to the upper gastrointestinal (GI) tract that could not be corrected by angiographic techniques through $^{99m}$Tc-MAA assessment before treatment (*1*). However, 3 of their 22 patients still developed GI ulcers. These ulcers were found within the area of distribution of the GI artery and likely reflect backflow of $^{90}$Y-microspheres during administration or shunting through aberrant small vessels within the cirrhotic liver or tumor, as Dancey et al. suggest. In our recent review (*4*), we mentioned similar observations made by Herba et al. The late GI ulcers, which had not been predicted by the $^{99m}$Tc-MAA scan, were attributed to the much higher density of the glass microspheres (3.7 g/cm$^{-3}$) than that of the MAA particle (approximately 1.3 g/cm$^{-3}$). It was postulated that the greater density increased the chance of glass microspheres falling into the GI tract under gravity. Therefore, we feel that $^{99m}$Tc-MAA provides a good simulation for the resin type of microspheres (density, 1.6 g/cm$^{-3}$) but may not do so for the glass microspheres because of the large difference in density (*4*).

The resin type and glass type of microspheres also differ very much in their specific activity (i.e., activity of $^{90}$Y carried by each microsphere). Each resin microsphere carries approximately 30–50 Bq $^{90}$Y at the calibration time (*2*), whereas 37 MBq $^{90}$Y are carried by approximately 15,000 glass microspheres with a specific activity of 2,467 Bq per glass microsphere. Thus the damaging effect of 1 glass microsphere refluxed into the GI tract is approximately 49–82 times that caused by 1 resin microsphere.

To reduce the risk of radiation-induced GI ulcer, apart from the $^{99m}$Tc-MAA assessment, we also make the suspension of $^{90}$Y-microspheres radioopaque by adding nonionic contrast Omnipaque (SIRTex Medical Limited, North Ryde, New South Wales, Australia) (*2*). The flow of the micropsheres can be monitored under fluoroscopy and the rate of infusion can be continuously adjusted to prevent reflux of the radioactivity into the GI region.

It is worthwhile to mention here the reversible gastritis or duodenitis in 4 patients observed by Andrews et al. (*5*). These patients showed no imaging or biopsy evidence of extrahepatic deposition of microspheres. The ulcers were not caused by $^{90}$Y-microspheres refluxed into GI region. We suggest that the ulcers were probably caused by $^{90}$Y-microspheres at the periphery of the liver. When the thickness of soft tissue covering the $^{90}$Y-microspheres is $<$11 mm, the β-radiation is not fully attenuated. Part of the β-rays passes out and reaches the neighouring stomach or duodenum. Thus, prophylactic antiulcer therapy is recommended for patients receiving $^{90}$Y therapy.

Dancey et al. (*1*) mentioned that one of the reasons for a patient receiving less than the planned dose was technical error. We would like to know what the technical error was so that it may be avoided in the future.

There is a typing error in the Material and Methods section (*1*). The mean diameter of TheraSphere is 25 μm, not 25 mm.

We are glad to find that the authors have applied the partition model in estimating the lung doses (but have not used it to differentiate the doses to the tumor and nontumorous liver parenchyma) and have confirmed our previous finding that a patient receiving $>$30 Gy to the lungs in a single treatment is at high risk of developing radiation pneumonitis (*4*).

In the Conclusion, Dancey et al. suggested that the procedure can be safely performed on suitable patients in an outpatient setting (*1*) because pure β-emitters do not require medical confinement of patients for radiation protection. We have some reservations about this approach; our patients are required to stay in bed for 24 h on account of the femoral puncture.

Although we have already shown that repeated doses are feasible (*2*), we agree with the authors that the efficacy of this form of internal radiation therapy using $^{90}$Y-microspheres may be improved through further studies.

## REFERENCES


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**REPLY:** We thank Drs. Ho, Lau, and Leung for their thoughtful commentary on our article (*1*). We would like to address the issues they raise with some additional comments and clarifications.

Ho et al. assert that it is the tumor-to-normal uptake ratio (T/N) rather than the tumor-to-liver activity ratio (TNR) that determines the selectivity of treatment and, hence, its impact on patient survival. However, treatment impact on survival depends on several factors, including the selectivity of the treatment, the amount of nontumor liver tissue remaining at the time of treatment, and the functional capacity of nontumor tissue at treatment. The 2 types of tissue, tumor and nontumor, can be considered as 2 compartments within the total liver volume. Okuda staging incorporates 2 of these 3 factors, which are the percentage replacement of liver by tumor and liver function. The third factor, selectivity, is measured in terms of the blood perfusion differential or ratio between the 2 compartments. The relationship between TNR and T/N is approximated by the expression TNR = (mass of tumor/mass of normal) × T/N, assuming uniform distribution of $^{99m}$Tc-microaggregated albumin (MAA) activity within the 2 compartments.

Our selection of TNR over T/N was based on TNR's increased statistical sensitivity when used in combination with radiation dose and Okuda staging. We used a stratified Cox proportional hazards regression model to evaluate the association between survival time (time from treatment to death) and each of the 3 factors, radiation dose, Okuda staging, and TNR. Three models were implemented using 1 factor as the independent regression variable and the other 2 factors as conditioning (stratification) variables. This approach allowed us to make the most efficient use of the small sample size ($n = 20$). In our 20 efficacy-evaluable cases, the median T/N was 4.5, which is similar to the median (4.1) reported by Lau et al. (*2*). Using median values for classifying high and low values (TNR and T/N of 2.0 and 4.5, respectively), 15 cases agreed as being high or low on both measures. Three cases with (mass of tumor/mass of normal) of $<0.2$ were classified as $<2.0$ for TNR, with values of 4.9, 23, and 36 for T/N. Two cases with (mass of tumor/mass of normal) = 1.9 with TNR values of 4.9 and 8.2 had T/N values of 2.6 and 4.4, respectively.

For TNR, we reported a trend toward improved survival (RR = relative risk) that we associated with dose $>$ 104 Gy versus dose $<$ 104 Gy (RR = 0.28; $P = 0.06$), TNR $>$ 2.0 versus $<$2.0 (RR = 0.26; $P = 0.06$), and Okuda stage I versus Okuda stage II (RR = 0.29; $P = 0.07$) (*1*). Using T/N instead of TNR yields dose $>$ 104 Gy versus dose $<$ 104 Gy (RR = 0.42; $P = 0.17$), T/N $>$ 4.5 versus T/N $<$ 4.5 (RR = 0.52; $P = 0.25$), and Okuda stage I versus Okuda stage II (RR = 0.51; $P = 0.28$). Using the single independent regressor TNR and T/N without stratification yielded (RR = 0.56; $P = 0.28$) and (RR = 0.47; $P = 0.15$), respectively. Consequently, when TNR was used in combination with the other 2 important risk factors (radiation dose and Okuda stage), it had a stronger association with survival than T/N. It would be of great interest to us to see the results of similar analyses performed on the 71 cases of Lau et al. (*2*), with survival computed from the time of treatment to death.

Ho et al. have suggested that the higher incidence of gastroduodenal ulcers with TheraSphere compared with $^{90}$Y resin may be caused by the presence of $^{90}$Y microspheres at the periphery of the liver. However, they indicate that they routinely recommend prophylactic antiulcer therapy for their patients receiving $^{90}$Y resin therapy. In addition, $^{99m}$Tc-MAA may not provide as good of a simulation for the distribution of glass microspheres compared with resin microspheres because of the higher density of the glass spheres.

We agree that gastrointestinal (GI) toxicity appears to be a relatively common occurrence of TheraSphere treatment; however, we did not prescribe prophylactic antiulcer medication for patients receiving TheraSphere. Combined data over the 3 reported studies (*1*,*3*,*4*) suggest that upper GI tract ulcers can be expected in 1 of 6 (10/61) patients to whom whole-liver treatment is administered. Two possible sources are suggested by Ho et al.: the first is flow of TheraSpheres into the upper GI tract, and the second is radiation exposure of the GI mucosa stemming from proximity of the treated liver and upper GI tract. Out of 61 TheraSphere-treated patients, 10 were diagnosed within 8 wk of treatment with gastric or duodenal ulcers, 8 of which were negative and 1 of which was positive for TheraSpheres on endoscopy and biopsy. One patient refused endoscopy. On the microscopic level TheraSpheres are easily seen; however, sampling may have inadvertently missed the affected areas. The TheraSphere studies were conducted using exclusion for any $^{99m}$Tc-MAA flow to the upper GI tract; in retrospect, this criterion appears to have been followed and resulted in only 1 of 9 upper-GI-tract ulcers that was associated with TheraSphere deposition.

The evidence suggests that the GI ulcerations may be more likely caused by radiation exposure stemming from proximity than actual deposition of the TheraSpheres into the upper GI tract. However, 1 patient who underwent surgery for a bleeding ulcer was not reported to have had evidence of radiation injury on the external surface of the stomach, as would be expected from radiation exposure caused by proximity of the stomach to the treated liver. This effect has not been reported by others using resin $^{90}$Y-microspheres (*2*), although the delivered activity of the resin $^{90}$Y-microspheres (median, 3.0 GBq; range, 0.8–5.0 GBq) was less than that reported for TheraSphere-treated hepatocellular carcinoma patients (median, 3.9 GBq; range, 2.0–9.2 GBq). Currently, it is unknown whether the differences in density, specific activity,

delivery technique, patient selection, antiulcer prophylaxis, activity administered, or other factors are responsible for the upper-GI toxicity differences observed between $^{90}$Y resin microspheres and TheraSpheres in the treatment of patients with unresectable liver cancer. We agree that prophylactic treatment of ulcers is a strategy worth investigating.

The technical error that led to undertreatment of 1 patient was a malfunctioning stopcock on the administration set, which prevented the tubing from being flushed properly.

Ho et al. are correct in pointing out that there is an error in the Materials and Methods section. As they state, the mean diameter of a TheraSphere is 25 μm, not 25 mm.

Lastly, Ho et al. have expressed some reservations regarding performing intrahepatic arterial injection of TheraSphere as an outpatient procedure, because their patients are required to stay in bed for 24 h on account of the femoral puncture. Although policies regarding duration of stay after femoral arterial puncture for angiography differ from center to center, there are studies that suggest that, with proper patient selection, proper technique, and adequate monitoring, the procedure can be performed safely in selected outpatients (*5*).

## REFERENCES


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