Partition model for estimating radiation doses from yttrium-90 microspheres in treating hepatic tumours

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Received 15 January and in revised form 10 April 1996

Abstract. A uniform distribution of yttrium-90 (^{90}Y) microspheres throughout the entire liver has always been assumed for dose calculation in treating hepatic tumours. A simple mathematical model was formulated which allows estimation of the activities of a therapeutic dose of ^{90}Y microspheres partitioned between the lungs, the tumour and the normal liver, and hence the radiation doses to them. The doses to the tumour and normal liver were verified by intra-operative direct beta-probing. The percentage of activity shunted to the lung and the tumour-to-normal tissue ratio (T/N) were obtained from gamma scintigraphy using technetium-99m-labelled macroaggregated albumin (MAA) which simulates the ^{90}Y microspheres used in subsequent treatment. The intrahepatic activity was partitioned between the tumour and the normal liver based on the T/N and their masses determined from computerized tomography slices. The corresponding radiation doses were computed using the MIRD formula. The estimated radiation doses were correlated with the doses directly measured using a calibrated beta-probe at laparotomy by linear regression. The radiation doses to the tumour and the normal liver, estimated using the partition model, were close to that measured directly with coefficients of correlation for linear regression: 0.862 for the tumours and 0.804 for the normal liver compartment ($P<0.001$). The partition model permits a distinction between the radiation doses received by the tumour and the normal liver to be made and the doses thus estimated are close to the actual doses received. The optimal doses to the tumour and normal liver and hence the required quantity of ^{90}Y microspheres to be administered can be easily predetermined.

Key words: Partition model – Yttrium-90 – Radiation doses – Hepatic tumours

Eur J Nucl Med (1996) 23:947–952

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Introduction

Treating inoperable liver cancer with intra-arterial infusion of yttrium-90 microspheres was pioneered in the 1960s [1, 2]. Pure beta radiation from ^{90}Y cannot penetrate soft tissue thicker than 11 mm, making direct measurement of the distribution of the microspheres within the liver impossible outside the body. The distribution of the microspheres throughout the entire liver has been assumed to be uniform in most studies [1–9], including a recent one [10]. It has been well established that ^{90}Y microspheres of both the ceramic and the resin type are non-biodegradable. Once infused into the liver, they will stay in the microvasculatures of the tumour or the liver parenchyma and decay with the physical half-life of ^{90}Y [1–9]. The radiation dose can thus be estimated using the MIRD formula [11] knowing the activity per unit mass. On the assumption of a uniform distribution the doses to tumour and normal liver are identical. Simulation using gamma-emitting ytterbium-169 microspheres to visualize the intrahepatic distribution of microspheres was attempted by Ariel and Pack [2]. Technetium-99m-labelled macroaggregated albumin (^{99m}Tc-MAA) for hepatic arterial perfusion scintigraphy [12] and assessment of arteriovenous shunting [13] became widely used in estimating the pulmonary shunting and intrahepatic distribution of ^{90}Y microspheres [6–10, 14–16]. Estimation of the radiation dose to the tumour by a partition model has been mentioned by one of the research groups [8, 9], but it has not been formally expressed, verified or adopted in dose calculation [10]. Burton et al. [17–20] pioneered intraoperative administration of ^{90}Y microspheres with direct beta-probing of the liver and tumour surface during laparotomy. The intraoperative dosimetry was further verified by liquid scintillation counting of liver biopsies containing ^{90}Y microspheres.

In the present study, a partition model for estimating radiation doses to the lungs, hepatic tumours and normal liver is formulated and applied to patients receiving ^{90}Y microspheres during laparotomy [16]. The validity of the model was verified by intraoperative dosimetry.

Materials and methods

Fourteen patients, including two recurrent cases, with inoperable hepatocellular carcinoma (HCC) and three patients with colorectal liver metastases but no extrahepatic disease were entered into the study. The whole group consisted of three females and 14 males. The median age was 50 years (range 18–74).

The patients were subjected to selective hepatic angiography (HAG) and ^{99m}Tc-MAA scan for assessment of the percentage of radioactivity shunted to the pulmonary system and the tumour-to-normal tissue ratio (T/N) of uptake of ^{99m}Tc-MAA within the liver. This technique has been reported previously [14–16].

Computerized tomography (CT) images of the abdomen were obtained with 1:1 magnification and 5 mm transaxial thickness. The tumours and normal liver were outlined on each section and the areas were digitised with reference to a phantom of a known area. The total area taken over all slices multiplied by the section thickness gave the volume. The mass of the tumour (M_T) and the mass of the normal liver (M_N) were obtained by multiplying the respective volume by the density (1.03 g/cm^3) of soft tissue.

The partition model for estimation of radiation doses assumes the distribution of ^{90}Y microspheres during the treatment is identical with the ^{99m}Tc-MAA particles during the diagnostic HAG. Although the ^{90}Y microspheres are resin based while the ^{99m}Tc-MAA particles are composed of albumin, the two types of particles have a similar average size (^{90}Y microspheres: 29–35 μm; ^{99m}Tc-MAA: 10–100 μm, average 30 μm). Between 6.6 and 23.1×10^7 ^{90}Y microspheres are injected in one treatment but the number of ^{99m}Tc-MAA particles required (3.0×10^5) for the diagnostic scan is less than 1% of the number of ^{90}Y microspheres.

It has been established that ^{90}Y microspheres will be trapped inside the microvasculature and decay at the physical half-life of ^{90}Y to infinity without biological degradation [1–10, 16–20]. From decay data of ^{90}Y [21], an activity uptake of 0.037 MBq (1 μCi) in 1 g tissue results in 183.78 cGy of radiation dose. Using the MIRD principle [11], the radiation dose to an organ of mass M (g) with an organ activity uptake of A_o GBq of ^{90}Y will be given by the formula:

$$\text{Dose(Gy)} = \frac{183.78\,A_o\,(\text{GBq})\left(\frac{1}{0.037}\right)\left(\frac{1000}{100}\right)}{M(\text{g})},$$

which on simplification becomes:

$$\text{Dose(Gy)} = \frac{49670\,A_o\,(\text{GBq})}{M(g)}. \quad (1)$$

For a total activity of A GBq of ^{90}Y administered to a patient with lung shunting=L% and T/N=r, without extrahepatic shunting of ^{99m}Tc-MAA apart from the shunting into the pulmonary system, the lung activity uptake of ^{90}Y microspheres

$$A_L = A\left(\frac{L}{100}\right)\text{GBq}.$$

By substituting 1000 g as the total mass of both lungs (including blood) for a standard man [11] (because CT volume of the lungs was not available), radiation dose to the lungs was obtained. The remaining activity of ^{90}Y was partitioned between the tumour and the normal liver. The tumour activity uptake (A_T) and the normal liver activity uptake (A_N) were obtained by solving the following simultaneous equations:

$$A_T + A_N = A\left(1 - \frac{L}{100}\right), \quad (2)$$

$$\frac{A_T / M_T}{A_N / M_N} = r. \quad (3)$$

The estimated radiation doses to the tumour and the normal liver were readily computed by substituting the respective activity uptake A_T and A_N into Eq. 1.

The average radiation dose to the liver as a whole, with no distinction between tumour and normal tissue, was also computed by substituting the total intrahepatic activity uptake (A_T+A_N) and total liver mass (M_T+M_T) into Eq. 1 for comparison.

Activity of ^{90}Y per unit mass was determined from the count rates directly measured over the tumour and normal liver surface by a calibrated beta-probe during laparotomy. Radiation absorbed dose calculations for these tissues assumed that the ^{90}Y was removed from the tissues solely by radioactive decay. Details of this technique have been described elsewhere [14, 16]. The radiation doses to the tumours and normal liver estimated by the partition model were correlated with the data from intraoperative dosimetry.

Bremsstrahlung scans of the lung and liver were performed before the patients were discharged for confirmation of the distribution of the ^{90}Y microspheres but not for dose calculation because of poor image quality [22].

Results

The patient characteristics, masses of tumour and normal liver, the percentages of lung shunting and T/N ratios determined from ^{99m}Tc-MAA images are shown in Table 1. The percentages of lung shunting varied between 2.2% and 15.0% (median 7.3%) and the T/N ratios from the ^{99m}Tc-MAA scan ranged from 3.0 to 13.6 (median 4.7).

The total activity of ^{90}Y microspheres administered ranged from 2 to 7 GBq with a median of 3 GBq. The estimated activity of ^{90}Y shunted into the pulmonary system varied between 0.044 and 0.798 GBq with a median of 0.219 GBq.

The activity of ^{90}Y microspheres retained in the tumour (A_T) and the normal liver (A_N) was estimated using the partition model. The estimated radiation doses to the lung, the tumour and normal liver obtained by substituting the corresponding activity uptake and mass into Eq. 1 are listed in Table 2. The tumour dose and normal liver dose determined by direct beta-probing of the tumour and normal liver surfaces are listed in the final two columns.

The radiation dose to the tumour, as measured by the beta-probe, varied between 107 and 305 Gy (median 162 Gy) while that to the normal liver ranged from 15 to 77 Gy (median 26 Gy). For the lungs, only radiation doses estimated by the partition model were available. The values ranged between 2 and 40 Gy (median 11 Gy).

Correlations between the radiation doses determined by the partition model and the values obtained from intraoperative dosimetry for the tumours and the normal liver compartments are illustrated in Figs. 1 and 2. Coefficients of correlation for linear regression performed on the two independent sets of data were 0.862 for the tumours and 0.804 for the normal liver compartments (P<0.001). Thus the radiation doses estimated using the partition model are close to those measured by intraoperative beta-probing, although the two sets of readings are not identical.

Table 1. Patient characteristics, activity of ^{90}Y, percentages of lung shunting and T/N ratios

Patient	Sex/age	Type of hepatic tumour	Mass (g)		% Lung shunting	T/N ratio	Activity (GBq) of ^{90}Y
			Tumour	Normal liver			
1	M/60	H	1207	759	4.2	6.6	3.0
2	M/52	H	1793	1379	11.4	7.8	7.0
3	M/18	RH	171	1228	9.8	4.5	2.0
4	M/55	H	912	1338	10.7	4.7	2.0
5	F/33	H	972	872	6.7	3.0	4.0
6	M/60	H	405	1006	4.3	7.4	3.0
7	M/56	H	487	1307	5.6	3.1	5.0
8	M/74	H	1119	987	13.7	8.5	3.5
9	M/48	RH	152	972	2.2	3.6	2.0
10	M/43	H	1627	879	11.8	7.5	4.0
11	M/49	H	820	870	15.0	4.3	3.5
12	M/50	H	639	1539	6.6	6.4	3.0
13	M/37	H	832	1347	7.5	4.2	3.0
14	M/54	H	551	1489	5.2	13.6	3.0
15	M/59	2°	1364	1503	14.8	3.5	5.0
16	F/47	2°	259	1273	3.3	5.6	4.0
17	F/36	2°	716	1137	7.3	3.9	3.0

H, HCC; RH, recurrent HCC; 2°, colorectal liver metastasis

Table 2. Radiation doses estimated by the partition model and measured by intraoperative beta-probing

Patient	Estimated activity uptake (GBq)			Estimated radiation dose (Gy)				Radiation dose (Gy) from beta probe	
	Lung	Tumour	Normal liver	Lung	Tumour	Normal liver	Whole liver[a]	Tumour	Normal liver
1	0.126	2.624	0.250	6	108	16	73	118	18
2	0.798	5.645	0.557	40	156	20	97	134	18
3	0.196	0.695	1.109	10	202	45	64	240	71
4	0.214	1.361	0.425	11	74	16	39	117	17
5	0.268	2.872	0.860	13	147	49	101	170	77
6	0.129	2.149	0.722	6	264	36	101	300	22
7	0.280	2.530	2.190	14	258	83	131	283	74
8	0.480	2.736	0.284	24	121	14	71	131	17
9	0.044	0.706	1.251	2	230	64	86	241	65
10	0.472	3.291	0.237	23	100	13	70	107	15
11	0.525	2.386	0.589	26	145	34	87	163	40
12	0.129	2.036	0.766	10	158	25	64	162	26
13	0.225	2.003	0.772	11	120	28	63	143	30
14	0.156	2.464	0.380	8	222	13	69	251	19
15	0.740	3.240	1.020	37	118	34	74	137	25
16	0.132	2.060	1.808	7	395	71	125	305	77
17	0.219	1.977	0.805	11	137	35	75	160	31

[a] Assuming uniform distribution throughout the whole liver without distinction between tumour and normal tissue

The relative distribution of ^{90}Y microspheres in the liver and tumour shown on the bremsstrahlung scans performed after treatment was again reflected as a T/N ratio. The coefficient of correlation between the T/N ratios determined from the bremsstrahlung images and those determined from the ^{99m}Tc-MAA simulation was 0.884 ($P<0.001$).

Discussion

Yttrium-90, being a pure beta-particle emitter with a physical half-life of 64 h, a mean energy of 0.937 MeV and a maximum penetration depth of about 10 mm in soft tissue, has been the radioisotope of choice for selective internal radiation (SIR) therapy for large liver tumours [23]. These physical characteristics give the advantages of longer cytotoxic range (penetrating through

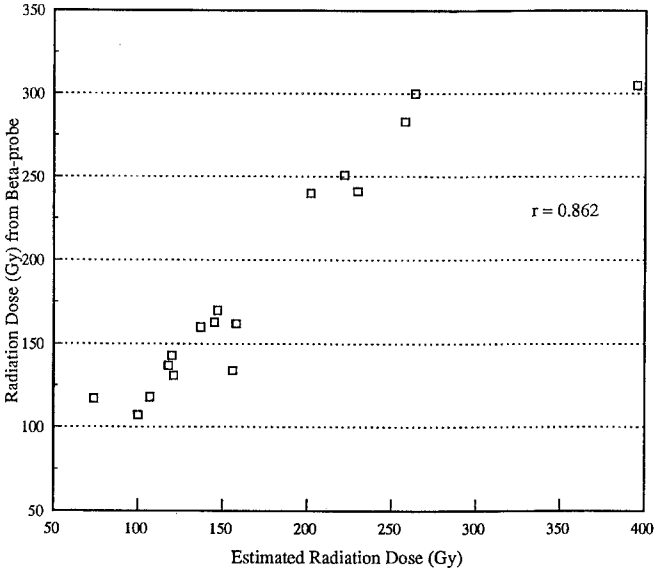

Fig. 1. Correlation between estimated and measured tumour doses

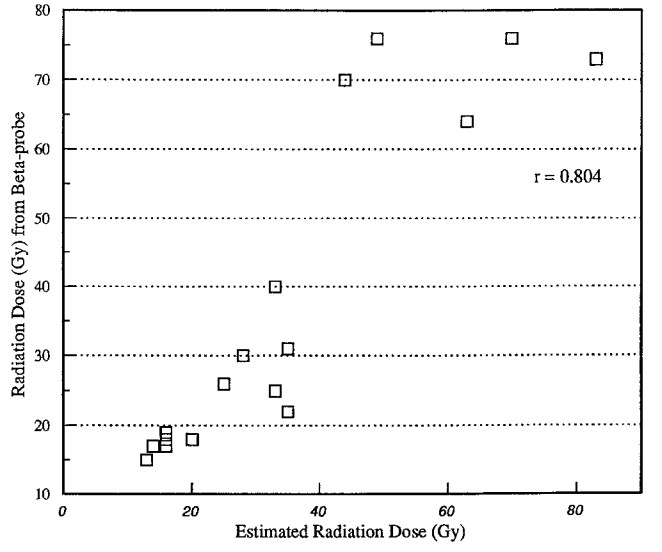

Fig. 2. Correlation between estimated and measured normal liver doses

a depth of more than 1000 cells), higher dose rate and easier radiation protection as the skin and muscles of the abdominal wall are thick enough to attenuate the beta radiation.

The ^{90}Y-labelled resin or glass microspheres do not undergo any biodegradation. The radioisotope will decay with its physical half-life and hence the radiation dose delivered to any tissue element can be easily computed using the MIRD method [11] if the radioactivity concentration is known. However, the presence of the abdominal wall makes direct measurement of the distribution of ^{90}Y microspheres impossible. In previous studies [1–10], uniform distribution of ^{90}Y microspheres throughout the entire liver was thus assumed in estimating the radiation doses to the liver.

In prescribing a therapeutic radiation dose for the tumour of a particular organ, both the threshold tumouricidal dose for eradicating the cancer cells and the maximum dose that can be tolerated by adjacent normal tissue need to be considered. Radiation doses calculated based on the assumption of a homogeneous intrahepatic distribution of ^{90}Y microspheres made no distinction between the tumour and the normal tissue and therefore did not reflect the therapeutic benefit.

Ytterbium-169 was the first gamma emitter used to simulate the distribution of ^{90}Y microspheres [2]. ^{99m}Tc-MAA with a particle size range close to that of ^{90}Y microspheres became widely used for pre-treatment assessment of arteriovenous shunting to the pulmonary system and hepatic perfusion of ^{90}Y microspheres [6–10, 14–16]. Assuming the distribution of ^{90}Y microspheres during subsequent treatment to be identical with that of ^{99m}Tc-MAA particles during the diagnostic HAG, a tumour-to-normal tissue (T/N) ratio or therapeutic gain can be calculated by dividing the average count rates of the tumour with the average count rates of the normal liver obtained from the digitised gamma scintigraphic images [14].

With this T/N ratio, the total activity (A) of ^{90}Y microspheres administered and the masses of the tumour (M_T) and normal liver (M_N) from CT, the activity of ^{90}Y microspheres partitioned between the tumour and the normal liver compartment can be computed using the proposed partition model. With these activity parameters, the radiation doses delivered to the tumour and the normal liver can be readily estimated. Alternatively, with the T/N ratio and the masses of tumour and normal liver available, the amount of ^{90}Y microspheres required to achieve a certain tumouricidal dose or to keep safely below a tolerance limit of normal hepatocytes can be predetermined.

The good correlation between the doses estimated using the partition model and the intraoperative dosimetry suggested that the model does serve the purpose. As mentioned earlier, the idea of using a partition model for estimating tumour dose has previously been mentioned very briefly by one research group [8, 9] but has not been adopted in dose estimation. It is surprising to find that with readily available T/N ratios from ^{99m}Tc-MAA scans, the assumption of a uniform distribution of ^{90}Y microspheres was still used to estimate the escalation of whole liver absorbed radiation dose from 5000 cGy to 15 000 cGy in the most up-to-date work on ^{90}Y microspheres [10]. These values can be very misleading. As has been illustrated in the present study, the real tumour doses might be much higher than these values whereas the radiation doses actually delivered to the normal liver tissues might be much lower.

Despite a new technique that has been developed for activity quantification making use of bremsstrahlung images of pure beta-emitting radioisotopes including strontium-89, phosphorus-32 and ^{90}Y [22, 24–26], bremsstrahlung scans are still not commonly used for dose calculation in treating hepatic tumours with ^{90}Y microspheres [10, 27]. Our reservations about adopting brems-

strahlung images for radiation dose estimation are mainly due to the fact that the ^{90}Y microsphere therapy dose has to be administered before the bremsstrahlung scans can be performed. As the therapeutic effect of the radioisotope is irreversible, our partition model allows planning of the radiation doses and hence the amount of radioactivity to be delivered while the refined bremsstrahlung technique might be good for retrospective checking of the relative distribution of radioactivity.

The novel strategy of opening up the abdominal wall for direct access to the surface of the tumour and the normal liver employed by the team headed by Burton and Gray [17–20] has allowed us to obtain intraoperative dosimetry data required for verification of our partition model.

Ariel and Padula [5] mentioned that the distribution of ^{90}Y microspheres throughout the normal liver is uniform whereas the radioactivity concentration in the tumour varies according to the underlying blood supply. From our experience of beta-probing the surfaces of tumour and normal liver during laparotomy, count rates over the surface of the normal liver and the tumour both varied from point to point, this being indicative of local heterogeneity of ^{90}Y distribution. Thus at least 20 readings were taken over any region to average out the heterogeneity. The inhomogeneous distribution of microspheres within normal liver was analysed in great detail by Fox etal. [28]. They found that one-third of normal liver received less than 33.7% of the dose predicted by assuming a homogeneous distribution of ^{90}Y microspheres and was therefore spared from possible radiation damage. Three-dimensional dosimetry calculated from a tumour model in the rabbit also demonstrated non-uniform distributions of microspheres within a tumour nodule and throughout the normal liver [29]. Determination of microdosimetry by incorporating stable heavy nuclides such as gold-187 into the ^{90}Y microspheres to make them radiographically detectable has been suggested [27] but the feasibility of this method remains to be confirmed.

Simulation of ^{90}Y SIR therapy using ^{99m}Tc-MAA is the most readily available technique for predicting the distribution of ^{90}Y microspheres in hepatic tumours and the normal liver. The partition of radioactivity between the tumour and the normal liver compartment based on the T/N ratio from ^{99m}Tc-MAA scan and masses of the tumour and normal liver allows a distinction to be made between the radiation doses to the tumour and to the normal liver. The different radiation doses received by the tumour and the normal liver can then be estimated with the assumption that the distribution of ^{90}Y microspheres within either the tumour or the normal liver is uniform and that there is no cross-over of doses at the boundary between the tumour and the normal liver. The heterogeneous distribution of ^{90}Y microspheres has been homogenized by averaging serial readings over the surfaces of the tumour and the normal liver during intraoperative beta-probing. This averaging process is consistent with the calculation of a T/N ratio from the mean count rate of tumour over the mean count rate of the normal liver during diagnostic ^{99m}Tc-MAA scintigraphy.

Conclusion

With the application of the verified partition model in dose estimation, ^{90}Y microspheres can now be administered percutaneously by hepatic angiography or through available arterial port-a-catheters without the need for laparotomy. The optimal doses to the tumour and the normal liver compartment and hence the required quantity of ^{90}Y microspheres for treatment of a particular patient can be easily predetermined. The treatment has become less traumatic and therefore carries less morbidity. The hospital stay is also shortened because the patient does not have a large wound to heal. Patients who receive ^{90}Y SIR therapy percutaneously can normally be discharged home in 4–5 days, when the radioactivity has decayed to a safe level.

Acknowledgements. The authors wish to thank Miss Rebecca Yau, Mr. Jimmie Wong and Mr. K.K. Man for their assistance in preparing this manuscript.

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