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Comparison of Macrodosimetric Efficacy of Transarterial Radioembolization (TARE) by Using 90Y Microspheres of Different Density of Activity

Traino AC[1]*, Piccinno M[1], Boni G[2], Bargellini I[3] and Bozzi E[3]

[1]Unit of Medical Physics, University Hospital Pisana, Italy
[2]Unit of Nuclear Medicine, University Hospital Pisana, Italy
[3]S.D Radiologia Vascular and Interventional, University Hospital Pisana, Italy

Abstract

Purpose: Transarterial 90Y microspheres radioembolization is emerging as a multidisciplinary promising therapeutic modality for primary and metastatic cancer in the liver. Actually two different type of microspheres are used, whose main characteristic is the different density of activity (activity per microsphere). In this paper the effect due to the possible different distribution of the microspheres in a target is presented and discussed from a macrodosimetric point of view.

Material and methods: A 100 g virtual soft-tissue target region has been builded. The administered activity was chosen to have a target average absorbed dose of 100 Gy and the number of 90Y microspheres needed was calculated for two different activity-per-microsphere values (2500) Bq/microsphere and 50 Bq/microsphere, respectively). The spheres were randomly distributed in the target and the Dose Volume Histograms were obtained for both. The cells surviving fractions (SF) for four different values of the radiobiological parameter α were calculated from the Linear - Quadratic model.

Results: The DVH obtained are very similar and the SF is almost equal for both the activity-per- microsphere values.

Conclusions: This macrodosimetric approach shows no radiobiological difference between the glass and resin microspheres. Thus the different number of microspheres seems to have no effect when the number of spheres is big enough that the distance between the spheres in the target can be considered small compared to the range of the β-particles of 90Y.

Keywords: Microspheres; β-particles; Linear-quadratic model; TheraSphere

Introduction

Radioembolization with ^{90}Y microspheres via hepatic arterial administration has been shown to be effective in the treatment of primary and metastatic liver cancer (HCC), as well as in unresectable colon carcinoma metastases [1-5] Radioembolization is a loco-regional liver directed therapy that involves transcatheter delivery of microspheres embedded with ^{90}Y. ^{90}Y microspheres are injected into the arterial supply of the liver, where they preferentially flow into hyper vascularized tumor zones, with a higher irradiation of tumour tissue compared to the normal liver parenchyma, with a consequent tumour-tissue necrosis. Actually ^{90}Y can be delivered to the hepatic tumor as either a constituent of a glass microsphere, TheraSphere®, or as a biocompatible resin-based microsphere, SIR-Spheres®. TheraSphere® was approved by the USA Food and Drug Administration for unresectable HCC in December 1999 under a Humanitarian Device Exemption. SIR-Spheres® was approved in March 2002 for colorectal cancer metastatic to the liver in conjunction with continuous infusion of intrahepatic floxuridine (FUDR) [6].

The characteristics of these two different kinds of 90Y microspheres are summarized in Table 1 [7]. From a dosimetric point of view, the main difference between SIR-Spheres® and TheraSphere® is the density of activity that in one case (SIR-Spheres® whose activity per microsphere is ~50 Bq) is much lower than in the other (TheraSphere® whose activity per microsphere is 2500 Bq).

In principle this difference could have an impact on the radiobiological effectiveness of the treatment [8], due to the much higher number of microspheres needed to have the same activity in the target tissue in one case (SIR-Spheres®) compared to the other (TheraSphere®). This because an higher number of microspheres could mean a more homogeneous distribution of activity (and consequently of target absorbed dose).

^{90}Y-Microspheres		
Material	Resin	Glass
Sphere size (mm)	20-60	20-30
Activity per sphere (Bq)	40-70	2500
Specific gravity	Low	High
Handling for dispensing	Required	Not required
Splitting one vial for more patients	Possible	Not possible

Table 1: Main characteristics of the two available kinds of 90Y microsphere: Glass spheres (TheraSphere®) and resin spheres (SIR-Spheres®).

***Corresponding author:** Traino AC, Professor, Unit of Medical Physics, University Hospital Pisana, Italy, Tel: +39 050992957; E-mail: c.traino@ao-pisa.toscana.it

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In this paper a comparison of these two different densities of activity is presented and discussed, showing that, neglecting other differences between the two types of 90Y microspheres (different material and consequent different specific gravity of SIR-Spheres® compared to TheraSphere®, for example) the therapeutic effectiveness of the two radioembolization tools is almost the same from a macrodosimetric point of view.

Materials and Methods

A cubical target was simulated to test the expected difference between the two different activities-per- sphere tools. The mass of the target was 100 g, its density was 1.04 g/cm^3, that is the density of the soft tissues [9]. The activity needed for an average target absorbed dose of 100 Gy was calculated by using the MIRD formalism:

$$D(\mathrm{r_T},\infty) = \mathrm{S}(\mathrm{r_T} \leftarrow \mathrm{r_T}) \int_0^\infty A_0 e^{-\lambda t} dt = S(\mathrm{r_T} \leftarrow \mathrm{r_T}) \frac{A_0}{\lambda}$$

where $D(r_T,\infty)$=100 Gy is the target absorbed dose; $S(r_T,r_T)$=5.08 mGy/MBq*h is the S-value for a self-irradiating 100 g spherical target treated with 90Y; A_0=administered activity and λ=0.011 h-1 is the physical decay constant of 90Y. From Equation 1 it follows A_0=213 MBq.

The target volume was divided into N=21x21x21 square voxels of 2.21 mm size.

A number n_{sph} of 90Y embedded microspheres of the same size were randomly distributed into the target, according with the equation:

$$n_{sph} = \frac{A_0}{\delta_a}$$

Where δ_a represents two different densities of activity of 2500 Bq/sphere and 50 Bq/sphere respectively. For an administered activity of 213 MBq there will be *nsph* =8.52×10^4 90Y microspheres corresponding to a density of activity δ_a =2500 Bq/sphere (glass spheres) and *nsph* =4.26×10^6 90Y microspheres corresponding to δ_a =50 Bq/sphere (resin spheres). The size was considered the same, 30μm, for both the type of microspheres.

Software was built by using the open-source environment GNU-Octave to randomly distribute a number *nsph* of microspheres in the target, to perform a 3D dosimetric calculation at the voxel level by using the MIRD 17 method [10] and to show the Dose Volume Histogram (DVH) corresponding to the different distributions of the 90Y microspheres.

The absorbed dose *di* in each voxel was calculated, according to the MIRD 17 method, by using the equation:

$$d_i = \sum_{h=0}^{n} \widetilde{A_h} S_{i \leftarrow h} = \sum_{h=0}^{n} S_{i \leftarrow h} \int_0^\infty A_0 e^{-\lambda t} dt$$

where $\tilde{A}_h$ is the cumulated activity in the ith-voxel and *Si←h* are the dose conversion factors at the voxel level. The *Si←h* values for the voxel size of 2.21 mm were taken [9] Note that *Ah* is the activity in each *h* voxel, calculated by multiplying the number of microspheres randomly placed in that voxel by the density of activity δ_a.

Results

The Dose Volume Histograms for δ_a =2500 Bq/sphere and δ_a =50 Bq/sphere are shown in Figure 1. DVHs for the two values of δa considered are very similar.

The surviving fraction SF was calculated for each of the two values of δ_a by using the Linear-Quadratic (LQ) model:

$$SF = \frac{1}{N} \sum_{i=1}^{N} e - (\alpha \mathrm{d_i} + G\beta d_i^2)$$

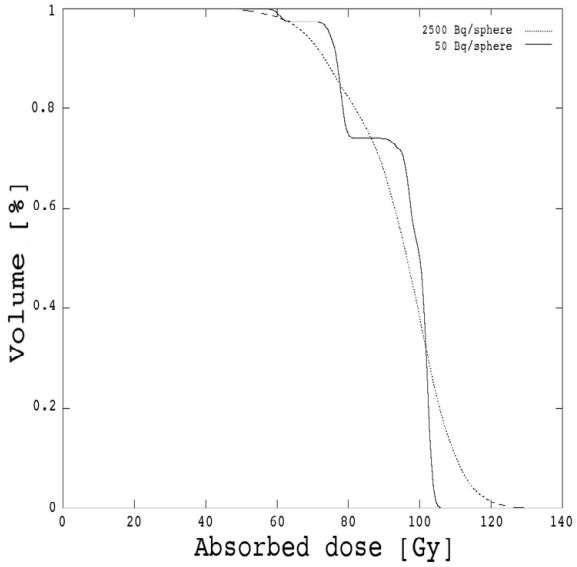

Figure 1: Integral DVH in a target region of 100 g calculated for δ_a=2500 Bq/sphere and δ_a=50Bq/sphere respectively. The administered activity A0=213 MBq, needed to have an average absorbed dose of 100 Gy from the target region.

Surviving Fraction		
a (1/Gy)	2500 Bq/sphere	50 Bq/sphere
1	5.90E-21	4.30E-27
0.1	1.02E-04	6.00E-05
0.01	0.32	0.32
0.001	0.89	0.89

Table 2: Cells surviving fractions for different values of a and different values of δ_a (2500 Bq/sphere and 50 Bq/sphere). The calculation was based on equation 4 with a /b=10 and G=0.023.

In Equation 4 β=/10 and the Lea-Catcheside factor G=0.023. This last factor for a mono-exponential decreasing dose-rate can be written as [11].

$$G = \frac{\lambda}{\mu + \lambda}$$

Where μ=ln(2)/ t_{rep} is the rate of repair of sub-lethal damages (the repair half-time constant trep=1.5 h for tumor lesions was extracted from Strigari [12] and λ=0.011h-1 is the physics decay rate of 90Y. The cells surviving fraction for four different values of α (α =1; 0.1; 0.01 and 0.001 Gy-1) is shown in Table 2.

Discussion and Conclusions

From a macrodosimetric point of view, the different number of 90Y microspheres per unit mass could have an impact on the radiobiological effect of the transarterial radioembolization therapy [8], due to the different distribution of the microspheres in the treated target region. The microspheres tend to be distributed as homogeneously as possible via the microvascularization of the target zone. The homogeneous distribution of the activity represents the better situation from a

radiobiological point of view, because it causes an uniform absorbed dose by the target. In this paper the hypothesis of a random distribution of the microspheres in the target has been done, without considering the trapping of the spheres in the blood vessels.

If the microspheres are rarefied in the target, meaning that the average distance between spheres is higher than than the double range of the β- of the radionuclide employed (90Y in this case), the dose distribution will be very unhomogeneous, leaving target zones where the absorbed dose is zero Figure 2.

In the case described in this paper, doing the hypothesis of a random distribution of the 90Y microspheres in the target, for a 100 g target treated with an activity of 213 MBq, which corresponds to a target absorbed dose of 100 Gy, the average density of 90Y microspheres is 0.852 spheres/mm^3 if δ_a =2500 Bq/sphere and 42.6 spheres/mm^3 if δ_a =50 Bq/sphere. Remembering that the range of the β- particles of 90Y is about 11 mm in the soft tissues, this means that the β- Particles of the 90Y are close also for δ_a =2500 Bq/sphere, compared to their range. Thus for the glass microspheres (δ_a =2500 Bq/sphere) there are low high-activity spheres for unit mass, compared to an higher number of low-activity resin microspheres (δ_a =50 Bq/sphere). In both cases the effect of the microspheres is almost homogeneous in the volume considered, because the average distance among the spheres is lower than the range of the β- particles of 90Y Figure 3.

In Table 3 the average density (number of spheres/mm^3) of 90Y glass and resin microspheres (δ_a=2500 Bq/sphere and δ_a =50 Bq/sphere respectively) needed for an average target absorbed dose of 100 Gy is shown for different target mass values. The average number of spheres per mm^3 of target has a very low variation depending on target mass. This means that the macrodosimetric effect of the glass and resin 90Y microspheres is almost the same in the target, because the microspheres are very close respect to the range of the β- particles of 90Y. This seems true for all the possible treated masses, if the required target average absorbed dose is 100 Gy.

The random distribution of the microspheres in the whole target is only a hypothesis. The real situation is different because the microspheres are vehiculated into the target by the arterial system: this means that the distribution of the spheres in the target is unhomogeneous in principle. In the real situation the 90Y activity

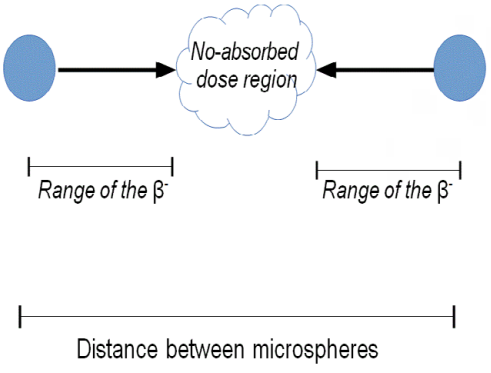

Figure 2: Representation of a rarefied distribution of microspheres in the target. If the distance between two microspheres is bigger than the double range of the β-particles there is a no-absorbed energy (and then no-absorbed dose) zone. This means a very unhomogeneous absorbed dose distribution in the target.

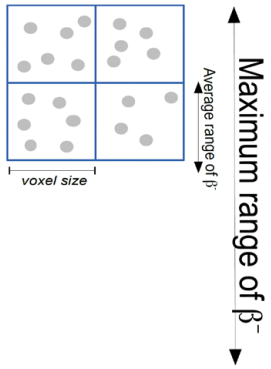

Figure 3: 2D representation of the target region, divided into cubical voxels of 2.21 mm size. The

90Y microspheres are randomly distributed in the voxels. The average number of glass microspheres per voxel is 9.2; the average number of resin microspheres per voxel is 459.8. The microspheres are closer than the β- range of the 90Y (maximum range: 11 mm; average range: 2.5 mm)

Target Mass (g)	Aministered Activity (MBq)	Average Number of Glass Spheres/mm^3	Average Number of Resin Spheres/mm^3
40	86	0.866	43.3
80	170	0.854	42.7
100	213	0.853	42.6
300	626	0.835	41.7
400	833	0.833	41.7
500	1041	0.833	41.7
100	2059	0.825	41.2
2000	4026	0.805	40.3

Table 3: Density (number of spheres/mm^3) of glass and resin microspheres (δ_a =2500 Bq/sphere and δ_a =50 Bq/sphere respectively) for different masses of soft-tissue target. The administered activity corresponds to an average target absorbed dose of 100 Gy; the density of the soft-tissue is 1.04 Kg/dm^3.

needed to have a certain absorbed dose (es.100 Gy) in a target volume (es. 100 g) is forced in a volume smaller than the target (arterial system in the target is smaller than the whole target). This means that there is the same number of microspheres (8.52×10^4 90Y microspheres corresponding to a density of activity δ_a =2500 Bq/sphere and 4.26x106 corresponding to δ_a =50 Bq/sphere) randomly distributed in a volume lower than 100 g. For this reason the ^{90}Y microspheres are much closer than the situation described in this paper, thus the macrodosimetric differences due to the different number of resin and glass microspheres in the target are probably lower.

In this paper the macrodosimetric effect due to the different number of 90Y microspheres per unit mass in a target submitted to the radioembolization procedure is treated. From this point of view, it seems that the different number of microspheres doesn't have any effect on the distribution of the target absorbed dose due to the small distance among the spheres compared to the range of the particles of 90Y. This result seems to be in agreement with those described by Gulec in their paper [13], where, starting from a microdosimetric approach, they don't find any difference in the absorbed dose due to the different number of microspheres in the target.

The microdosimetic effects due to the different density of activity (activity per sphere) between glass and resin microspheres, already treated in literature [13,14] is beyond the scope of this paper. Also the probable radiobiological effect due to the different specific gravity of the microspheres (due to the different material), which almost surely

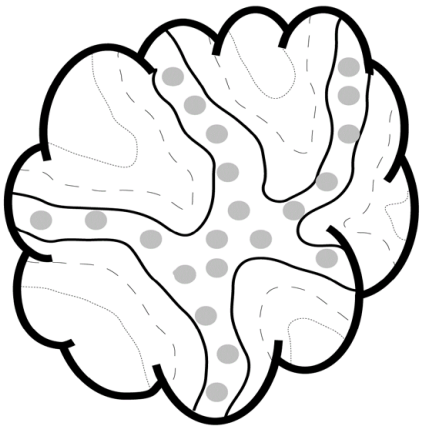

Figure 4: Representation of the real distribution of the 90Y microspheres in the target. Themicrospheres are vehiculated in the target by the arterial vascularization, thus their distributioncannot be homogeneous. The dotted lines represent the isodose curves in the target.

affects the distribution of the microspheres in the target, is not taken into consideration in this paper.

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