Personalized dosimetry in ^{90}Y microspheres therapy of liver cancer using the OEDIPE software and SPECT-CT images

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ABSTRACT

The Selective Internal Radiation Therapy (SIRT) is used to treat unresectable hepatic tumors by injecting microspheres labelled with ^{90}Y into the hepatic artery. In clinical practice, two conventional methods, the Body Surface Area (BSA) method and the Partition Model, are used to determine the activity to administer to the patient. Whether based on an empirical approach or on the MIRD formalism, both techniques suppose a uniform repartition of the microspheres. However, the ^{90}Y-microspheres distribution is heterogeneous. **Methods:** In collaboration with the HEGP, a predictive and personalized 3D-dosimetry, which takes into account the distribution heterogeneity, has been developed and applied to a 70 years-old woman with hepatic metastases. Patient's anatomy and tumor were segmented using CT images to create a patient-specific voxel phantom. Activity distribution was defined using SPECT images acquired after the injection of ^{99m}Tc albumin aggregated (^{99m}Tc-MAA). Dose calculations were performed at the voxel scale with the MCNPX transport code associated to OEDIPE, French acronym for "tool for personalised internal dose assessment", developed at IRSN. For a given injected activity, tumor and healthy liver mean absorbed doses were compared to those predicted by conventional methods, lungs' mean absorbed doses were estimated and isodose curves superimposed on anatomical images were obtained. Finally, dose volume histograms (DVHs) were analysed to determine the activity which is optimum for treatment efficiency and patient's radiation protection. **Results:** The Partition Model overestimates tumor and healthy liver absorbed doses by 36% and 45% respectively, and underestimates lungs absorbed dose by 34%. Whereas the BSA method and the Partition Model recommend respectively the injection of 1.42 GBq and 0.74 GBq, the analysis of healthy liver's DVH leads to an optimum activity of 1.33 GBq. **Conclusion:** In the context of SIRT, a predictive dosimetry has been performed and used for treatment optimization.

KEY WORDS

Liver cancer, SIRT, patient-specific 3D-dosimetry, activity heterogeneity, OEDIPE

INTRODUCTION

The primary cancer being treated or not, hepatic metastases will strongly impair patient's health condition. Their treatment is thus an indispensable condition for patient's survival or a better life expectancy. Only 20% of those patients will be eligible for surgical resection. The Selective Internal Radiation Therapy (SIRT) has been introduced in clinical practice in the 1990s in Australia as an alternative in the treatment of unresectable hepatic tumors, either primary or secondary. This therapy consists in the injection of microspheres, labelled with Yttrium 90 (^{90}Y), into the lesions via the hepatic artery. Due to the vascular specificity of the liver, those microspheres are then trapped preferentially in the tumoral tissue's capillaries irradiating the surrounding tissue.

In order to ensure both patient's radiation protection and treatment optimization, accurate treatment planning is crucial in SIRT. Prior to the injection of microspheres, ^{99m}Tc albumin aggregated (^{99m}Tc-MAA) are injected in the same conditions as those planned for the ^{90}Y-treatment. SPECT images are then acquired to visualize the ^{99m}Tc-MAA biodistribution which provides an evaluation of the ^{90}Y-microspheres biodistribution that should be obtained with the treatment. The maximum activity to be injected to the patient is then determined using one of the following conventional dosimetric methods, the Body Surface Area (BSA) method or the Partition Model. The former is an empirical approach where injected activity is adjust depending on tumor burden and patient's physical characteristics, the latter is based on the MIRD approach which considers limit values for mean absorbed doses to healthy liver and lungs. Those dosimetric methods both rely on the hypothesis of a uniform distribution of the radionuclide in the different tissues.

In this context, in collaboration with the Hôpital Européen Georges Pompidou (HEGP, Paris, France), a patient-specific 3D dosimetry, which makes allowance for the activity distribution's heterogeneity, has been developed. Patient anatomy and tumoral lesions were segmented from CT images and activity distribution was defined using SPECT images. Absorbed dose calculations were performed at the voxel scale using the MCNPX transport code associated with OEDIPE, french acronym for "Tool for personalized internal dose assessment", a software developed at IRSN. Absorbed doses, isodoses curves superimposed on anatomical images and dose volume histograms (DVHs) were obtained from the biodistribution of ^{99m}Tc-MAA which leads to a predictive dosimetry. Those results were compared to conventional dosimetric methods results and DVHs were analyzed to determine the optimum activity to be injected to the patient.

1. The Selective Internal Radiation Therapy (SIRT)

Used in the treatment of certain hepatic tumors, either HepatoCellular Carcinoma (HCC) or hepatic metastases, the SIRT consists in the diffusion of ^{90}Y-microspheres in the liver through the vascular bed [1]. Thanks to transfemoral catheterization under fluoroscopic guidance, ^{90}Y-microspheres are injected into the hepatic artery, are then conveyed through the hepatic vascular system and finally get trapped into hepatic capillaries. Because tumoral tissue's blood supply comes from the hepatic artery whereas normal tissue's blood supply is mainly provided through the portal vein, a selective delivery of ^{90}Y-microspheres to tumoral tissue can be performed.

Three different stages are required for a SIRT treatment. The first stage is a diagnostic stage with a high-resolution CT scan and an ^{18}F-FDG injected PET/CT scan. The second stage, called SPHERE 1, is an evaluation stage which consists in the administration of ^{99m}Tc-MAA in the exact same conditions as those planned for the ^{90}Y-microspheres injection. Straight after the ^{99m}Tc-MAA injection, a SPECT/CT scan and a whole-body scintigraphy are performed. The former is used to describe the specific biodistribution of ^{99m}Tc-MAA, the latter is used to evaluate the Lung Shunt Fraction (LSF) which is the fraction of activity shunting to the lungs through the capillary bed. The third stage, called SPHERE 2, is the treatment itself, i.e. the injection of ^{90}Y-microspheres, also followed by a SPECT/CT scan and a whole body scintigraphy.

2. Conventional dosimetric methods

2.1. The BSA method

The activity to be delivered, calculated with the BSA method, depends on the patient's height and weight and on tumor burden, i.e. the fraction of the liver taken up by tumoral tissue. The recommended activity can be calculated from equations (E1) [2].

$$Activity\ (GBq) = (BSA(m^2) - 0.2) + (V_{tumor} / V_{whole\ liver}) \qquad (E1)$$

where BSA is the Body Surface Area, defined by equation (E2), $V_{whole\ liver}$ is the volume of whole liver and V_{tumor} is the tumor's volume, both estimated from CT images.

$$BSA\ (m^2) = 0.20247\ x\ H^{\,0.725}\ x\ W^{\,0.425} \qquad (E2)$$

where H is the patient's height in meters (m) and W is the patient's weight in kilograms (kg). The activity obtained from equations (E1) and (E2) is then adjusted depending on the LSF [2].

Apart from the microspheres shunting to the lungs, all microspheres are considered to go exclusively to the tumor. Healthy liver is thus supposed to receive zero absorbed dose whereas absorbed dose to the tumor can be calculated using equation (E3) [2].

$$D_{tumor}(Gy) = \frac{49670 \times A_{injected}(GBq) \times (1 - LSF)}{W_{tumor}(g)}$$ (E3)

where D_{tumor} is the mean absorbed dose to the tumor, $A_{injected}$ is the injected activity and W_{tumor} is the tumor's weight.

2.2. *The Partition Model*

The Partition Model takes into account the difference in microspheres' fixation between healthy liver and tumor. It aims to determine the maximum of activity that can be injected to the patient while meeting tolerance criteria on absorbed doses to the lungs and healthy liver [2,3].

The amount of activity shunting to the lungs is estimated as previously from whole body scintigraphy images by calculation of the LSF. The definition of several ROIs (Regions Of Interest) in healthy liver and in tumor on SPECT images acquired at stage SPHERE 1 enables to evaluate the amounts of activity going respectively to healthy liver and tumor. The tumor-to-normal-tissue ratio (T/N) is then defined by equation (E4).

$$\frac{T}{N} = \frac{A_{tumor}/W_{tumor}}{A_{healthyliver}/W_{healthyliver}}$$ (E4)

where A_{ROI} is the activity in the ROI and W_{ROI} is the weight of that ROI. As for the BSA method, healthy liver and tumor volumes are estimated from CT images and both tissue densities are taken equal to 1.05 g/cm³.

Absorbed dose to the lungs and to healthy liver, depending on the injected activity ($A_{injected}$), are then calculated using equations (E5) and (E6); lungs' weight being taken equal to 1 kg.

$$D_{lungs}(Gy) = \frac{49670 \times LSF}{W_{lungs}(g)} \times A_{injected}(GBq)$$ (E5)

$$D_{healthliver}(Gy) = \frac{49670 \times (1 - LSF)}{W_{healthyliver}(g) + \frac{T}{N} W_{tumor}(g)} \times A_{injected}(GBq)$$ (E6)

where D_{ROI} is the mean absorbed dose to the ROI and W_{ROI} is the weight of that ROI.

The activity to be injected to the patient is then the maximum value of $A_{injected}$ that guarantee an absorbed dose to healthy liver that does not exceed 30 Gy and an absorbed dose to the lungs that does not exceed 15 Gy.

Deleted: is possible to inject

Once the activity to be delivered determined, the absorbed dose received by the tumor can be calculated using equation (E7).

$$D_{tumor}(Gy) = \frac{49670 \times (1 - LSF)}{W_{tumor}(g) + \frac{N}{T}W_{healthyliver}(g)} \times A_{injected}(GBq) \qquad (E7)$$

3. OEDIPE software

3.1. Patient-specific voxel phantom

SPECT/CT scans and PET/CT scans being realized in similar breathing conditions, a patient-specific voxel phantom is created from the anatomical images of the ^{18}F-FDG injected PET/CT scan. Organ delineation is performed using the imaging module IMAgo of Isogray software from Dosisoft (Cachan, France). Outlines are then exported from Isogray and imported into OEDIPE, which creates a voxel phantom [4,5].

The created voxel phantom only models the patient's trunk and is constituted of five regions. Those regions are the healthy liver, the tumor, the right lung, the left lung and the soft-tissues which correspond to all the remaining tissues in the trunk.

3.2. A patient-specific map of cumulated activity

To describe the activity distribution, a patient-specific map of cumulated activity is generated from the SPECT images acquired after the injection of ^{99m}Tc-MAA. However, the SPECT/CT scan and the ^{18}F-FDG injected PET/CT scan are performed on different days and are not acquired with the exact same patient position. Moreover, SPECT/CT images and PET/CT images do not have the same spatial resolution. Image registration between SPECT/CT and PET/CT images is thus essential to generate a patient-specific map of cumulated activity which could be superimposed to the voxel phantom.

Image registration is performed with the registration module of Isogray software which creates registered SPECT images with the same resolution as the PET/CT images used to create the patient specific voxel phantom.

3.3. Absorbed dose calculations at the voxel scale using Monte Carlo code

Absorbed dose is assessed with MCNPX [6]. The MCNPX input file contains information about the geometry, coded in repeated structure, the source definition, the physical characteristics of the radionuclide and the type of results that are searched for. The OEDIPE software is used to generate the MCNPX input file from the patient-specific voxel phantom and the patient-specific map of cumulated activity.

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An input file is generated for the stage SPHERE 1 with an injected activity equal to the activity recommended by the Partition Model. Monte Carlo calculations are performed using the 2.6c version of MCNPX on a cluster composed of 1 master and 1 node of two Intel (R) Xeon (TM) processors of 3.20 GHz CPU with 8Go RAM. One hundred millions of particles are launched and the tally F6 is used. Around 70 hours are required per simulation.

3.4. *Results display*

The MCNPX output files are analyzed thanks to OEDIPE software which provides three types of results. First, minimum, maximum and mean absorbed doses are obtained for each region of the voxel phantom. Second, isodoses curves are calculated and superimposed on the voxel phantom. Third, a Dose-Volume Histogram (DVH) is generated for each region of the voxel phantom.

3.5. *Treatment optimization*

In accordance with previous studies on SIRT [7,8] and to ensure patient's radiation protection, the chosen tolerance criterion is a fraction of healthy liver volume receiving more than 30 Gy inferior to 50%. Healthy liver's DVH obtained from the simulation can thus be used to determine the optimum injected activity, defined as the maximum activity that can be injected to the patient while meeting this tolerance criterion. That optimum activity can be deduced by proportionality from the absorbed dose received by 50% of healthy liver volume which can be read from the DVH.

4. Application to a patient study

This methodology has been applied to Patient P1, a 70-years-old woman with hepatic metastases who underwent whole liver perfusion of ^{90}Y-microspheres (SIR-Spheres, SIRTEX) at HEGP. Patient P1 was 1,61m tall and weighed 55kg. High resolution CT images, ^{18}F-FDG injected PET/CT images and SPECT/CT images for both SPHERE 1 and SPHERE 2 stages were also available.

RESULTS

1. Conventional dosimetric methods

The volume and weight of healthy liver, tumor and both lungs obtained from the organ segmentation performed on Isogray for patient P1 are presented in Table 1. Patient P1's lung shunt fraction (LSF), evaluated from whole body scintigraphy images, was 0.03%. Patient P1's tumor-to-normal-tissue ratio (T/N), evaluated from ROI definition on SPECT images, was equal to 2.0.

For these values, the BSA method recommends an activity of 1.42 GBq whereas the Partition Model recommends an activity of 0.74 GBq.

	Volume (cm³)	Density (g/cm³)	Weight (g)
Left lung	1367	0.26	356
Right lung	1694	0.26	440
Healthy liver	1048	1.05	1100
Tumor	57	1.05	60

Table 1 : Segmented organs' volume and weight obtained with patient P1's voxel phantom

2. Mean absorbed doses

Monte Carlo calculations on the patient-specific phantom have been performed for the ^{99m}Tc-MAA biodistribution and an injected activity equal to 0.74 GBq. Mean absorbed doses obtained from this simulation are reported in Table 2 and compared to those predicted by the BSA method and the Partition Model for that injected activity.

	BSA method	Partition model	Personalized method
Remaining tissue	-	-	0.52
Left lung	-	0.01	0.02
Right lung	-		0.59
Healthy liver	0.00	30.01	20.69
Tumor	644.62	60.42	44.23

Table 2 : Mean absorbed doses, expressed in Gy, for an injected activity equal to 0.74 GBq, predicted by the BSA method, the Partition Model and the personalized method

3. Absorbed doses at the voxel scale - Personalized method

Absorbed dose calculations being performed at the voxel scale, different types of results were obtained for patient P1 with the personalized method. First, the OEDIPE software enables the superimposition of isodose curves on the patient-specific voxel phantom. Isodose curves obtained for one particular location and for three different angles are presented on Figure 1.
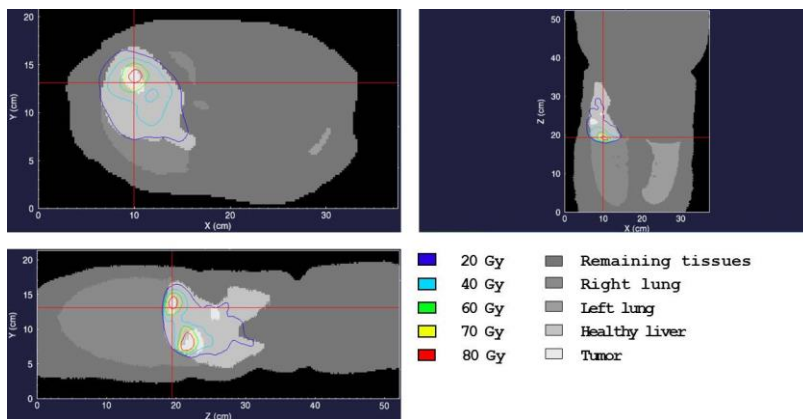
Figure 1 : Isodose curves for one particular location and three different angles, superimposed to the voxel phantom, obtained for patient P1 from the ^{99m}Tc-MAA biodistribution using the OEDIPE software and the MCNPX code

Extremum absorbed doses were extracted for each region of the voxel phantom and a Dose-Volume Histogram was generated for each organ of interest, i.e. the healthy liver, the tumor and the right lung. Minimum and maximum doses are presented in Table 3 and DVHs are presented on Figure 2.

	Minimum absorbed dose (Gy)	Maximum absorbed dose (Gy)
Remaining tissue	0.00	55.59
Left lung	0.00	4.37
Right lung	0.00	**43.13**
Healthy liver	0.05	114.66
Tumor	**5.87**	116.99

Table 3 : Minimum and maximum absorbed doses obtained for patient P1 with the personalized method
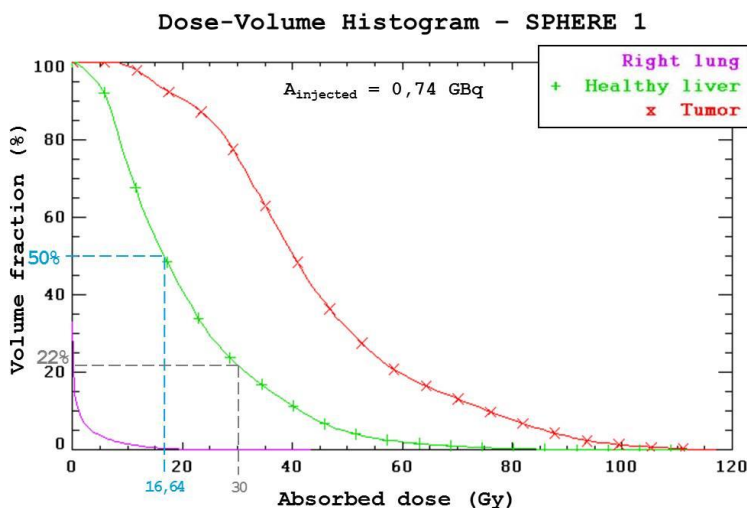
Figure 2 : Dose-Volume Histograms for the right lung, the healthy liver and the tumor for patient P1 using the personalized method with an injected activity equal to 0.74 GBq

DISCUSSION

1. Mean absorbed doses

Mean absorbed doses for an injected activity equal to 0.74 GBq estimated using the BSA method (Table 2) are strongly misleading. In fact, the BSA method relies on the premise that all the microspheres are trapped in the tumor thus leading to a significant overestimation of the absorbed dose to the tumor and the non-consideration of the absorbed dose received by the healthy liver.

Mean absorbed doses for an injected activity equal to 0.74 GBq obtained with the Partition Model and the personalized method (Table 2) are in the same order of magnitude. However, the Partition Model overestimates the absorbed dose to healthy liver by 45% and the absorbed dose to tumor by 36% while it underestimates the absorbed dose to the lungs by 34%.

The personalized method gives a more accurate estimation of absorbed doses to healthy liver and tumor for different reasons. In fact, the personalized method considers the activity distribution's heterogeneity and thus better evaluates the tumor-to-normal-tissue ratio than the Partition Model. Moreover, inter-region contributions, due to the fact that both tumor and healthy liver are source regions, are taken into account by the personalized method whereas there are ignored in the Partition Model.

Regarding the absorbed dose to the lungs, the personalized method has several advantages compared to the Partition Model. First, the personalized method uses a patient-specific weight for the lungs whereas the Partition Model considers a standard weight of one kilogram, thus leading to an underestimation of the absorbed dose. Second, thanks to the OEDIPE software and the MCNPX code, the absorbed dose to the lungs can actually be calculated at the voxel scale and the contribution of healthy liver as a source region can be taken into account.

2. Minimum and maximum absorbed doses

Both on a therapeutic and a radiation protection point of view, it is important to quote that all tumor voxels receive an absorbed dose at least equal to 5.87 Gy (Table 3) whereas some voxels of other regions do not receive any absorbed dose.

Table 3 shows that, for patient P1, the maximum dose to the right lung was 43.13 Gy and the maximum dose to the left lung was 4.37 Gy even with a negligible LSF. Thereby, the presence of ^{90}Y-microspheres in hepatic lesions located in the proximity of the lungs can lead locally to non-negligible absorbed doses.

3. Activity recommendations and treatment optimization

Given the appearance of tumor's and healthy liver's DVHs, a clear selectivity has been reached for that patient using the SIRT therapy. Moreover, from Figure 2, we can see that the fraction of healthy liver volume receiving more than 30 Gy is only equal to 22%. The performed simulation thus confirmed that an injected activity of 0.74 GBq leads to a verified tolerance criterion on healthy liver. However, this simulation also demonstrated that the treatment was not optimum.

In fact, the dose received by 50% of healthy liver volume, deduced from healthy liver's DVH on Figure 2, is equal to 16.64 Gy. An activity of 1.33 GBq could thus be prescribed to maximize the absorbed dose to the tumor while ensuring the patient's radiation protection. Mean absorbed dose to the tumor would then be around 79.49 Gy while mean absorbed dose to healthy liver would be 37.19 Gy.

Finally, even if the calculation time was significant for the patient application presented in that proceeding, that methodology can be used in clinical practice. In fact, the number of particles to be launched in the Monte Carlo calculations could be reduced for clinical applications.

CONCLUSION

In the context of the SIRT therapy for liver metastases, a personalized predictive dosimetry taking into account the heterogeneity of the microspheres distribution has been performed. Calculations at the voxel scale using the OEDIPE software and the MCNPX Monte Carlo code have permitted to generate isodose curves and Dose-Volume Histograms, useful for treatment optimization. Moreover, besides the calculation of absorbed doses at the voxel scale in different soft tissues, the association of the MCNPX code and the OEDIPE software allows a precise calculation of absorbed doses to the lungs. The developed methodology should now be applied to other patient studies. ^{90}Y-microspheres biodistribution should be used to obtain the post-treatment dosimetry in addition to the predictive dosimetry obtained from SPHERE 1 biodistribution. The optimum number of particles to be launched for Monte Carlo calculations should be investigated.

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