QUANTIFICATION OF ABSORBED DOSE IN ^{90}Y SELECTIVE INTERNAL RADIATION THERAPY FOR HEPATOCELLULAR CARCINOMA TREATMENT: A REVIEW

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Abstract

Selective internal radiation therapy (SIRT) has emerged as a viable strategy for the treatment of incurable hepatic cancers. Although SIRT is a well-known therapy, continuous improvement in personalised dosimetry is required to improve the treatment planning and delivery of therapy. The ability to precisely foresee, plan, and administer the ideal dose to the tumour and non-tumoral tissues, including a final validation of the dose distribution, is the primary principle of radiation. The main way for safely personalised therapy for a maximum response while respecting normal tissue tolerances is to know the true absorbed dose to tissue compartments. Recent clinical studies highlighted the significance of personalised dosimetry to make it safer and more effective. Quantification of the absorbed dose distribution is of utmost importance in SIRT ^{90}Y to optimise the hepatocellular carcinoma (HCC) treatment. The aim of this article was to review various dosimetric approaches in quantifying the absorbed dose of tumours and healthy liver tissue in ^{90}Y SIRT. This article also compares the capabilities of organ-level dosimetry, voxel-level dosimetry and Monte Carlo simulation in assessing the absorbed dose in organs especially liver. The quantification of absorbed dose influences ^{90}Y SIRT tumour dosimetry, while healthy liver absorbed dose values were comparable for all investigated imaging data. Personalised dosimetry for the tumour and healthy liver parenchyma after ^{90}Y SIRT is recommended for patient-tailored therapy with enhanced therapeutic outcomes and for the safe administration of additional treatment cycles.

Keywords**:** Absorbed dose, HCC, Quantification, SIRT, Yttrium-90 (^{90}Y)

Introduction

The liver which makes up approximately 2% of an adult's body weight, is the largest internal organ in the human body. It is responsible for a multitude of crucial functions such as metabolism, immunity, digestion, detoxification, and vitamin storage. If liver cancer develops, it causes severe and potentially fatal harm to the body. (1, 2). Following these problems, many cancer treatments including selective internal radiation therapy (SIRT) has become widely used as liver cancer treatment, specifically for the unresectable hepatocellular carcinoma (HCC) (3). SIRT is known to deliver a radioactive substance, Yttrium-90 (^{90}Y) to the tumours through its blood supply with the help of angiographic procedure (4, 5). It is a catheter-based therapy that can minimise the effects on healthy liver parenchyma while directly treating liver tumours with high-energy β^-radiation (5–7). Tiny radioactive beads are also

known as microspheres are placed into a blood vessel (artery) that transports blood to the liver. The beads become lodged in the small blood vessels in and around the tumour, and the radiation kills the cancer cells.

The International Agency for Research on Cancer (IARC) has predicted around 905 677 (4.7%) of new cases and 830 180 (8.3%) of death caused by liver cancer in 2020 from all around the globe. This shows that HCC is the fourth common cancer that leads to death globally for both men and women (8). In men, the areas of high incidence are Eastern Asia and Micronesia (8). In women, the rates are generally much lower, the highest being in Northern Africa and Melanesia. Unfortunately, almost 608 898 (73.3%) of these mortality cases originated from Asia. Therefore, making Asia on top of the pyramid for number of mortalities caused by liver cancer. In Malaysia, liver cancer ranks as the sixth most frequently occurring cancer in males and the ninth most frequently occurring cancer in females (9). The occurrence is almost three times higher than women. Liver cancer has become a significant cause of mortality in Malaysia, and the incidence has been steadily increasing from 1990 to 2010. This trend is projected to continue in the future (10).

Survival rates indicate the percentage of individuals with a particular type and stage of cancer who are still alive for a specified duration, usually five years, following their diagnosis. Surgery is the only confirmed curative therapy in the majority of cases, either by resection part of the liver or transplant (1). Unfortunately, majority of patients (70%) do not pass the surgical candidates evaluation. Candidates with resectable hepatocellular cancer are in the early stages. SIRT can help those who are unable to undergo surgeries in cancer treatment. According to a study, the estimated median survival time following SIRT was approximately 23.9 months. The survival rates at 6 months, 12 months, 24 months, 36 months, and 48 months were 77.9%, 56.7%, 39.2%, 31%, and 18.5%, respectively (11).

The measurement and calculation of radiation exposure or absorbed dose is referred to as dosimetry. It is the amount of radiation energy deposited in tissue divided by the tissue's mass (12). The amount of radiation absorbed determines the extent to which tumours and normal tissues are damaged. As this therapy employs small radioactive beads, it is crucial to evaluate the amount of radiation absorbed by the liver to ensure that the tumor receives an optimal amount of radiation necessary for treatment. Even though SIRT is capable to treat only the liver, yet some irradiation of normal organs is totally unavoidable. This can occur when a small number of radioactive beads travel to other areas. It also causes some inflammation to other organs after therapy specifically the lungs and the digestive systems (13, 14). As a result, the role of radiation dosimetry is important to ensure the safety of patients during this procedure.

In radioembolization planning, several dosimetry models such as the body surface area approach (used for activity calculation), the Medical Internal Radiation Dose (MIRD) model, and the partition model, have been employed to anticipate the absorbed dose to both the tumor and the healthy liver (14). The partition dosimetry model incorporates the use of single photon emission computed tomography-computed tomography (SPECT-CT) with Technetium-99m (^{99m}Tc) macroaggregated albumin (^{99m}Tc-MAA) instead of ^{90}Y imaging, and it considers the deposition of radioactivity outside the liver (15). Furthermore, it also offers the most personalized model for each patient, which can predict the uptake of radiation in both healthy and cancerous tissues. Relying solely on pre-treatment radiation dose estimations may cause clinicians to overlook the biological factors that can impact treatment outcomes. (16). in order to accurately evaluate the distribution of activity and dosage delivery, dose-response and toxicity studies need to be conducted, and it is crucial to verify imaging studies following SIRT to provide therapeutic treatment for extrahepatic deposits.

Quantification of absorbed dose in ^{90}Y SIRT for HCC treatment.

Organ level dosimetry

Organ level dosimetry used imaging to quantify activity using two dimensional (2D) or three dimensional (3D) images. The 2D images display spot views or whole-body scans of the relevant regions. The 3D SPECT scan focuses on the essential structures of interest, providing a narrow field of view. On the other hand, the positron emission tomography (PET) is gaining popularity due to the trouble-free and accuracy of radiotracer measurement with this modality. Loevinger and Berman developed the Medical Internal Radiation Dose (MIRD) methodology to quantify the absorbed doses from internal radionuclides to organs for treatment planning and radioprotection purposes. The dose to be given to a target organ (r_k) from a source organ (r_h) is calculated as the sum of the cumulative activity in the source organ under consideration and the *S* value (15, 16).The D$(r_k \leftarrow r_h)$ shows the absorbed doses to organs from internal radionuclides as shown in Equation 1.

$$D(r_k \leftarrow r_h) = A_h S(r_k \leftarrow r_h) \qquad \text{(Equation 1)}$$

The cumulative activity A_h is a total number of disintegrations in the source organ. $S(r_k \leftarrow r_h)$ is the average energy deposited in the target organ per disintegration in the source organ. The MIRD protocol is influenced by the isotope and the geometry of the source and target. The MIRD has been used to calculate the *S*-values and anthropomorphic phantoms portraying the average man, woman, and children of various ages.

Although *S*-values are highly beneficial for estimating the absorbed dose, there are certain assumptions made in MIRD that limits its applicability (15).

These limits are summarised as follows:

1. The source to target geometries are standardised. There are no options for taking the patient's unique anatomy into account.
2. It is assumed that activity is distributed uniformly within the source organs, which is not necessarily true.
3. The average dose is used to estimate the absorbed dose in target organs.
4. The prediction of biological effects may contain significant errors due to the ignorance of the intracellular distribution of radionuclides that emit short-range particles.

Organ Level Internal Dose Assessment (OLINDA) software was used worldwide to assess absorbed dose to various organs in the body. A biokinetic analysis module in OLINDA enables users to fit an exponential equation to data entered on an organ's activity at various time intervals (17). It has ten type of phantoms and five different types of organ models. Tumours are not displayed on the phantoms. However, determination of self-absorbed dose to the tumour can be done by using the unit density of spheres. Conversely, the limitation of the OLINDA software is that it cannot consider the cross-absorbed dose from normal organ activity to the tumor or the contribution of tumor activity to normal organs in the calculations. These values can be adjusted by inserting the patient's mass as the software has been programmed to scale by mass. However, this only valid if the patients are not obese or slim. Based on international recommendations for personalised SIRT of primary and metastatic liver diseases with ^{90}Y, a personalised approach is advised for activity prescription when either whole liver or selective, non-ablative or ablative SIRT is planned. This approach uses either partition model and/or voxel-based dosimetry.

Voxel-Level Dose Kernel Convolution

The voxel models are created using real image data from cryosections, magnetic resonance imaging, and computed tomography imaging. As a result, the voxel models' shapes are more realistic than those of stylised models like the MIRD mathematical model (19). Organ volumes are formed by combining the tissue voxels into relevant groups. Each voxel in an organ or tissue is allocated a specific identification number, and the necessary attenuation properties are assumed to be constant across all voxels in the organ or tissue and are also assigned to each voxel. For patients receiving treatment for HCC, earlier studies suggested creating 3D dosimetry based on voxel dosage kernel convolution. (17, 20, 21).

In addition, voxel level can also quantify the activity from an image. This type of dosimetry is shown to be more accurate and personalised compared to organ level dosimetry (22). This approach produces good results in a short amount of time (17). Images that show the activity distribution at various interval after injection can be co-registered and exponentially fit on a voxel-by-voxel basis. It is possible to perform calculations to generate a parametric image that shows the time-integrated activity, which is the cumulative number of decays, at the voxel level. This type of dosimetry will produce a parametric image that gives the biological half-life for each voxel. To estimate the time-integrated activity, first the images need to be recorded. Then, the total number of counts per voxel of the images are acquired. Next step is performing attenuation correction and finally compute calibration factor which refers to number of counts to activity.

Image interpretation is made simpler in dynamic imaging techniques like hybrid SPECT/CT and PET/CT because the CT offers anatomical structure to assist the functional images, that can vary from one acquisition to another acquisition. The deposited energy is described by the dose point kernel (DPK) as a function of radiation source distance. The absorbed dose rate can be obtained by combining the activity distribution from an image captured at a specific time after injection and a dosage point kernel. It provides a tool for quickly calculating the absorbed dosage at the voxel level (20, 23–25). The disadvantage of DPK is it is only valid in a homogeneous medium, which is typically believed to be uniformly unit density soft tissue in the body. It is advised to employ the Monte Carlo approach when the clinical region of interest has non-spherical geometry and irregular forms, even if voxel level dosimetry is superior to organ level dosimetry.

Voxel-based dosimetry software has only been used in a small number of studies so far. Using the Medical Imaging Interaction Toolkit (MITK) Workbench programme, Hermann et al., recently demonstrated the positive effects of higher tumour radiation absorbed dose based on ^{99m}Tc-MAA SPECT/CT (26). Levillain *et al* utilised Dosisoft software version Planet Onco 3.0 to evaluate the tumour's response by predicting the absorbed dose received by the tumour through SIRT in patients suffering from metastatic colorectal cancer, which was assessed by ^{18}F-FDG-PET/CT. (23). Despite the promising findings, further verification is necessary since the study was based on a small sample size and over half of the lesions were excluded due to their small size (less than 2 cm in diameter) (27).

In addition, Brosch *et al.* discovered that the estimates of tumour absorbed dose from ^{90}Y bremsstrahlung SPECT/CT showed significant underestimation of dose when compared to ^{90}Y PET/CT (21). All three imaging techniques

including ^{99m}Tc MAA SPECT/CT, ^{90}Y bremsstrahlung SPECT/CT, and ^{90}Y PET/CT provides equivalent estimates of the absorbed dosage for healthy liver tissue. The preliminary evaluation of absorbed dose estimates after therapy based on imaging methods in ten SIRT patients with HCC, using phantom measurements, suggests the need for further studies with larger patient groups and multiple centers.

Three Dimensional (3D) Personalised Monte Carlo Simulation

Monte Carlo simulation is utilized in radiation therapy for cancer patients to simulate radiation transport, predict absorbed dose distributions, and calculate relevant quantities (28). A general-purpose transport code called MCNPX was created by the Los Alamos National Laboratory. The geometry in MCNPX is described using repeated structures by input file and it is provided automatically by OEDIPE. In clinical case, the activity prescription is limited by the irradiation of organs at risk such as the lungs and non-tumoural liver. Therefore, dosimetry plays a key role in clinical implementation.

The usefulness of patient-specific voxel phantoms was validated by the observation that the liver masses of individual patients are mostly higher than the reference masses for both males and females, with a wide range of variability. (29). Previous studies demonstrated the use of 3D personalised dosimetry technique by using personalised Monte Carlo dosimetry based on patient-specific data and Monte Carlo calculations to evaluate clinical data retrospectively (28–30). According to a study by Alice Petitguillaume et al., the comparison between the maximum-injectable activities obtained using the partition model and the personalised Monte Carlo simulation dosimetry using mean absorbed doses (D_{mean}) tolerance criteria highlights the influence of the dosimetric method on activity prescription. (29). It also shows that the maximum-injectable activities estimated with personalised Monte Carlo simulation dosimetry was superior compared to partition model (20, 25, 29, 30). Furthermore, the personalised Monte Carlo dosimetry also considers both fixation heterogeneities and crossfire that contribute toward treatment optimisation in HCC (29).

In addition, the individualised Monte Carlo simulation dosimetry allows an increase of at least 40% of the injected activity when combined with tolerance criteria, making it of high interest for strongly individualised therapy optimisation. From an optimisation perspective, this result also emphasises the interest of methods, such as the partition model and 3D personalised methods that integrate the fixation difference into the determination of the activity to be injected. Absorbed doses to tumour were maximised for each patient depending on its evaluation. There, it leads to potentially better treatment efficiency.

A thorough analysis of the absorbed dose in the liver using Couinaud's liver segments enables a better knowledge of the distribution of the microspheres and evaluation of the therapy (30). Costa et al., demonstrated that computed whole liver absorbed doses from two distinct PET scans were highly concordant, demonstrating that both conventional and entire body PET offer accurate ^{90}Y dosimetry. This agreement increases confidence in the use of ^{90}Y PET over bremsstrahlung SPECT with the potential for post-treatment evaluation of microsphere implantation and dosimetry. Segmental liver dosimetry can assist patients to receive better care by demonstrating the dose-response of the medication. Understanding the activity may either support the rise in the injected activity when low toxicity is confirmed, or it may clarify an unexpected distribution.

A study shows that Monte Carlo is a better approach for dosimetry as it has the average absorbed dose compared to other voxel-based dosimetry methods. This study managed to assess the absorbed dose for tumour, liver and lung following ^{90}Y microsphere SIRT based on ^{90}Y bremsstrahlung SPECT/CT. For tumour and non-tumoural liver mean absorbed doses, soft tissue kernel with density, soft tissue kernel, and local deposition are equivalent to Monte Carlo. While local deposition and soft-tissue kernel with density overestimate, soft kernel underestimates mean absorbed doses to the right lung in comparison to Monte Carlo (31). The nominal distance from the liver-lung interface was estimated using simulations of the interface for various effective spatial resolutions and lung shunt fractions, and good accuracy was obtained both deep inside the liver and deep inside the lung. The liver-lung interface has a significant impact on the mean absorbed dosages for the right lung. Table 1 shows the absorbed dose obtained with OLINDA1.1, VoxelMed and RAYDOSE in each of phantom. OLINDA 1.1 software was used to represent organ level dosimetry, while VoxelMed was used to represent voxel level dosimetry and RayDose was used to represent Monte Carlo simulation (17).

Table 1: The mean absorbed dose (Gy) calculated with organ level dosimetry, voxel level dosimetry and Monte Carlo simulation.

Organ	Mean absorbed dose (Gy)		
	Organ level dosimetry	Voxel level dosimetry	Monte Carlo Simulation
Lesions	102.3	91.3	97.9
Pancreas	13.6	11.9	12.2
Kidney	12.9	11.4	11.8
Spleen	22.0	19.6	20.3
Liver	10.4	9.3	9.8

In Table 1, the deviations were minimised by the bigger insert capacity and the application of a more suitable model in OLINDA. These findings demonstrated the RADAR organ dosimetry (OLINDA) method's propensity to produce greater values of absorbed doses computed relative to voxel-level dosimetry techniques. OLINDA makes the assumption that all electron sources are locally deposited, whereas voxel-based techniques do not take this assumption into account. This causes the overdose in organ-level dosimetry as seen in the Table 1. The VoxelMed and RayDose values of absorbed dose were similar as they are both using 3D image-based dosimetry.

A voxel-level approach should be adopted if individualised dosimetry is desired. A voxel-based technique can be used to calculate the mean absorbed dose value by averaging the voxel values within an interest volume. However, the Monte Carlo method should give the most accurate dosimetry compared to the voxel-level dosimetry. Although, it may consume more time and effort compared to the conventional voxel-level dosimetry.

Future Direction

Quantification of absorbed dose in SIRT ^{90}Y can also incorporate calculations of absorbed dose through other organ at risks. In addition, quantification of the dose-response relationship is also necessary to optimise and comprehend the effects of delivered activity and the potential need for re-treatment or therapy of undesirable effects. In addition, in order to accurately establish tolerance parameters for organs at risk during SIRT, it would be beneficial to have more information on the distribution of activity in the lungs, as well as on the hepatic and pulmonary tolerances to internal irradiation when assessing maximum injectable activities. Therefore, personalised SIRT with ^{90}Y-resin microspheres on personalised SIRT from blinded or prospective randomised controlled trials must be included in future study. Moreover, verifying the dosimetry after SIRT is crucial in establishing a consensus on the required tumor dose threshold to achieve an optimal response and the normal liver dose threshold associated with treatment-induced toxicity.

Conclusion

In conclusion, this review provides an insight into understanding and the knowledge gap about the quantification of absorbed dose in ^{90}Y SIRT. Numerous researches have studied the dosimetry of SIRT using either simulation-based (MAA-based) dosimetry or post-therapeutic-based dosimetry (^{90}Y-based). Absorbed dose received by the targeted organ is the most appropriate when using Monte Carlo personalised dosimetry method. Practitioners should keep this information in mind when performing personalised SIRT with ^{90}Y-resin microspheres. Personalised activity prescription based on dosimetry and multidisciplinary care, particularly utilising the Monte Carlo approach, are recommended to maximise safety and effectiveness. To confirm that the intended and delivered radiation doses agree, post-treatment dosimetry is necessary to study dose-response connections. Currently, there is a limited number of publications that have investigated the dose-response relationship using actual post-treatment dosimetry. Moreover, further research is required to validate post-treatment dosimetry after selective internal radiation therapy (SIRT) in order to establish a consensus on the tumor dose threshold necessary to achieve an ideal response and the normal liver dose threshold linked to treatment-related toxicity.

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Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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