DEVELOPMENT OF A MONTE CARLO-BASED TREATMENT PLANNING SYSTEM FOR PERSONALIZED DOSIMETRY IN YTTRIUM-90 HEPATIC RADIOEMBOLIZATION

MUHAMMAD FAHMI RIZAL BIN ABDUL HADI

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by

MUHAMMAD FAHMI RIZAL BIN ABDUL HADI

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TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF SYMBOLS

A	Radioactivity
Bq	Becquerel
cm	Centimeter
g/cm3	Gram Per Centimeter Cubic
GBq	Giga-becquerel
Gy	Gray
J	Joule
kg	kilogram
MeV	Megaelectronvolt
3D	3-Dimensional
^{90}Y	Yttrium-90
^{99m}Tc	Technetium-99m

LIST OF ABBREVIATIONS

APE	Absolute Percentage Error
AEIT	Analog Event-Driven Interaction Techniques
A_L	Activity Uptake in Lung
A_{NL}	Activity Uptake in Normal Liver
ARF	Angular Response Function
A_T	Activity Uptake in Tumour
CERN	European Organization for Nuclear Research
CPU	Central Processing Unit
CT	Computed Tomography
D	Absorbed Dose
DICOM	Digital Imaging and Communications in Medicine
D^{PM}	Absorbed Dose volume from Partition Model calculation
D^{MC}	Absorbed Dose volume from Monte Carlo Simulation
D_L	Absorbed Dose in Lung
D_{NL}	Absorbed Dose in Normal Liver
DREL	Dosimetry For Radioembolization of Liver
D_T	Absorbed Dose in Tumour
EXM	Organ Level Internal Dose Assessment/Exponential Modeling
FBP	Filtered Back projection
FLUKA	Fluktuierende Kaskade
GATE	Geant4 Application for Emission Tomography
GB	Gigabytes
GPS	General Particle Source
GUI	Graphical User Interface
HCC	Hepatocellular Carcinoma
HU	Hounsfield Unit
ICRP	International Commission on Radiological Protection
IDE	Integrated Development Environment
LS	Lung Shunting

LTS	Long Term Supports
M	Mass
MAA	Macroaggregated Albumin
MAE	Mean Absolute Error
MC	Monte Carlo
MCNP	Monte Carlo N-Particle
MHD	Metaimage
MIM	Medical Image Merge
MIRD	Medical Internal Radiation Dose
MLEM	Maximum Likelihood Expectation Maximization
NURBS	Non-Uniform Rational B-Splines Modeling
PET	Positron Emission Tomography
PM	Partition Model
PRRT	Peptide Receptor Radionuclide Therapy
PSF	Point Spread Function
RFA	Radiofrequency Ablation
RILD	Radiation-Induced Liver Disease
RMSE	Root Mean Square Error
SIRT	Selective Internal Radiation Therapy
SPECT	Single-Photon Emission Computed Tomography
T/N	Tumour To Normal Tissue Ratio
TACE	Trans arterial Chemoembolization
TARE	Trans arterial Radioembolization
TI	Tumour Intake
TPS	Treatment Planning System
UI	User Interface
UMMC	University Of Malaya Medical Centre
VOI	Volumes Of Interest
VRT	Variance Reduction Techniques
WSL	Windows Subsystem for Linux
XML	Extensible Markup Language

PEMBANGUNAN SISTEM PERANCANGAN RAWATAN BERASASKAN MONTE CARLO UNTUK DOSIMETRI PERIBADI DALAM RADIOEMBOLISASI HEPATIK YTTRIUM-90

ABSTRAK

Radioembolisasi hepatik Yttrium-90 (^{90}Y) ialah terapi yang disasarkan untuk kanser hati dan bergantung pada pengiraan dos yang tepat bagi memastikan keberkesanan rawatan dan keselamatan. Anggaran dos konvensional menggunakan Partition Model (PM) sering mengabaikan anatomi khusus pesakit dan kesan sinaran crossfire, yang boleh menyebabkan ketidaktepatan. Kajian ini membentangkan satu sistem perancangan rawatan merentas platform yang menggabungkan simulasi Monte Carlo (MC) untuk mempertingkat penilaian dosimetri secara khusus bagi setiap pesakit. Imej CT pra-rawatan dan SPECT ^{99m}Tc-MAA daripada pesakit di Pusat Perubatan Universiti Malaya telah diolah menggunakan 3D Slicer bagi menentukan kawasan tumpuan (VOI), termasuk paru-paru, hati dan tumor. Imej voxel yang telah dipisahkan ini diimport ke dalam GATE 9.1/Geant4 10.6 untuk menjalankan simulasi taburan ^{90}Y dan dos terserap di setiap VOI. Perbandingan dosimetri dilakukan antara kaedah PM dan MC menggunakan kedua-dua fantom MIRD dan imej pesakit. Simulasi pengimejan Bremsstrahlung ^{90}Y dilakukan menggunakan GATE 9.1 dengan Angular Respond Function (ARF) bagi mempercepat masa simulasi. Projeksi SPECT dibina semula menggunakan algoritma MLEM dan FBP serta ditambah baik dengan penapis Gaussian, Butterworth, Metz, dan Wiener. Keputusan menunjukkan bahawa PM menganggar lebih rendah pada dos paru-paru berbanding simulasi MC dan nisbah tumor-ke-hati normal (T/N) memberi kesan ketara terhadap anggaran dos hati. Dosimetri berasaskan MC memberikan gambaran pengagihan dos yang lebih tepat

dengan mengambil kira kepelbagaian anatomi dan kesan sinaran crossfire. Gabungan MLEM dengan penapis Metz menghasilkan kejelasan imej yang lebih baik untuk visualisasi tumor, seperti yang ditunjukkan oleh peningkatan Nisbah Isyarat-kepada-Hingar (SNR). Sistem perancangan rawatan ini, yang dibangunkan dalam C# dengan Avalonia, menyediakan antara muka untuk pengiraan dos, dan perancangan rawatan. Penambahbaikan masa depan akan merangkumi modul segmentation dan registration imej bagi menyokong penggunaan klinikal yang lebih meluas..

DEVELOPMENT OF A MONTE CARLO-BASED TREATMENT PLANNING SYSTEM FOR PERSONALIZED DOSIMETRY IN YTTRIUM-90 HEPATIC RADIOEMBOLIZATION

ABSTRACT

Yttrium-90 (^{90}Y) hepatic radioembolization is a targeted therapy for liver cancer that depends on accurate dosimetry for both treatment efficacy and safety. Conventional dose estimation using the Partition Model (PM) often overlooks patient-specific anatomy and radiation crossfire effects, leading to potential inaccuracies. This study presents a cross-platform treatment planning system (TPS) integrating Monte Carlo (MC) simulations to improve personalised dosimetric evaluation. Pre-treatment CT and ^{99m}Tc-MAA SPECT images from patients at University of Malaya Medical Centre were segmented using 3D Slicer to define volumes of interest (VOIs), including lungs, normal liver, and tumour. These segmented voxel images were imported into GATE 9.1/Geant4 10.6 to simulate ^{90}Y distributions and absorbed doses. Dosimetric comparisons were performed between PM and MC methods using both MIRD phantoms and patient image. ^{90}Y Bremsstrahlung imaging simulation were simulated using GATE 9.1 with Angular Respond Function (ARF) to speed up simulation time. SPECT projections were reconstructed with MLEM and FBP algorithms and enhanced using Gaussian, Butterworth, Metz, and Wiener filters. Results showed that PM underestimated lung dose compared to MC simulation and tumour-to-normal liver (T/N) ratios significantly influenced liver dose estimates. MC-based dosimetry more accurately reflected dose distribution by incorporating anatomical heterogeneity and cross-irradiation. MLEM combined with the Metz filter yielded higher image clarity for tumour visualisation, as reflected by improved Signal-to-Noise Ratio (SNR). The

TPS, developed in C# with Avalonia, offers interface for dose calculation, visualisation, and planning. Future enhancements will integrate segmentation and registration modules, supporting broader clinical adoption.

CHAPTER 1

INTRODUCTION

1.1 Background

Liver cancer is among the most prevalent and lethal cancers worldwide, with hepatocellular carcinoma (HCC) being the most common primary type. Conventional treatment options for HCC include surgical resection, liver transplantation, and various locoregional therapies. However, these treatments are often not feasible for patients with advanced disease or poor liver function [1]. Radioembolization using Yttrium-90 (^{90}Y) microspheres has emerged as a promising therapeutic option for HCC, particularly for patients who are not candidates for surgery [2].

^{90}Y radioembolization involves the delivery of radioactive microspheres directly into the hepatic artery, allowing for targeted radiation therapy to liver tumours while minimizing exposure to healthy liver tissue. The effectiveness and safety of this treatment are highly dependent on accurate dosimetry, which ensures that the tumour receives a sufficient radiation dose while sparing normal tissues [3]. Traditional dosimetry methods, such as the Partition Model (PM), often fail to account for patient-specific factors, leading to potential inaccuracies in dose estimation and suboptimal treatment outcomes [4, 5].

Recent advancements in medical imaging and Monte Carlo (MC) simulation techniques have significantly improved the accuracy of dosimetric calculations in radioembolization therapies. Incorporating 3D Slicer software with GEANT4 Application for Tomographic Emission (GATE) MC simulation allows for a more precise analysis of absorbed dose distribution within the liver and other organs [3]. Studies have shown that personalized dosimetry, which accounts for individual patient

anatomy and tumour characteristics, leads to better treatment outcomes and reduces the risk of radiation-induced complications [1, 2, 6].

Personalized dosimetry is critical for optimizing the therapeutic efficacy and minimizing the adverse effects of ^{90}Y radioembolization. By considering individual patient anatomy and the specific characteristics of their tumours, personalized dosimetry ensures that the prescribed radiation dose is accurately delivered to the target tissues [7-10]. This approach contrasts with traditional models that often assume uniform distribution of radiation and neglect patient-specific variations, leading to potential underdosing or overdosing [3-5].

MC simulation techniques, such as those implemented in the Geant4 and GATE software packages, provide a robust framework for personalized dosimetry. These simulations can model the complex interactions of radiation with human tissues, accounting for variations in tissue density, composition, and geometry [11-14]. By integrating patient-specific imaging data, such as CT and SPECT scans, MC simulations can accurately predict the distribution of absorbed dose within the liver and other organs [3].

The integration of advanced imaging techniques with MC simulations has revolutionized the field of dosimetry in ^{90}Y radioembolization. Technologies such as PET/CT and SPECT/CT provide high-resolution images that can be used to create detailed anatomical models of the liver and surrounding tissues [1, 2]. These images serve as the basis for segmentation and registration processes, which delineate the volumes of interest (VOIs) for dosimetric analysis [3].

3D Slicer, an open-source software platform for medical image informatics, has been instrumental in facilitating these processes. It allows for the importation,

segmentation, and registration of tomographic images, which can then be used as input data for MC simulations in GATE [3]. This integration enables the precise calculation of absorbed dose distributions, enhancing the accuracy of treatment planning and potentially improving patient outcomes [1].

Despite the advancements in personalized dosimetry, several challenges and limitations remain. One of the primary challenges is the computational complexity and time required for MC simulations. High-fidelity simulations can be computationally intensive, necessitating significant processing power and time, which may not be feasible in all clinical settings [11, 13, 14].

Another challenge is the accurate representation of tissue heterogeneity and the distribution of radioactive microspheres within the liver. Variations in tissue density, composition, and the non-uniform distribution of microspheres can affect the accuracy of dosimetric calculations [4].

1.2 Problem Statement

Hepatocellular carcinoma (HCC) is a prevalent and lethal form of liver cancer that poses significant treatment challenges due to its typically late diagnosis and the limited availability of effective treatment options. Traditional interventions such as surgical resection and liver transplantation are often not feasible for many patients due to the advanced stage of the disease at diagnosis and the scarcity of donor organs [15, 16] ^{90}Y radioembolization has emerged as a promising locoregional therapy for patients with unresectable HCC, offering a targeted approach to delivering radiation directly to liver tumours [17].

The efficacy of ^{90}Y radioembolization largely depends on the precise delivery and distribution of the therapeutic dose to the tumour while minimizing exposure to

healthy tissues. Accurate dosimetry is crucial to achieving optimal therapeutic outcomes and minimizing side effects. Current treatment planning systems (TPS) for ^{90}Y radioembolization employ various imaging modalities and computational models to estimate radiation dose distribution within the liver [16, 18]. However, there is a need for further refinement in these methods to enhance their accuracy, practicality, and ability to provide personalized treatment plans.

Advanced MC simulations, particularly using the Geant4-GATE platform, offer significant potential for improving the accuracy of dosimetric calculations by modelling the complex interactions of radiation with tissues in a detailed and patient-specific manner. By integrating pre-treatment imaging data such as CT and ^{99m}Tc-MAA SPECT-CT into Geant4-GATE MC simulations, it is possible to achieve more precise estimations of absorbed doses in different compartments of the liver.

However, a thorough comparison between dosimetric results from Geant4-GATE MC simulations and the traditional Partition Model (PM) is still required to validate and standardize these methods. Furthermore, there is a need to develop user interfaces for these advanced TPS to facilitate their clinical implementation and ensure they are accessible for routine clinical use.

Optimizing the dosimetry of ^{90}Y radioembolization through the use of advanced MC simulations can potentially enhance treatment outcomes for HCC patients. This research seeks to address the current limitations in dosimetric precision and clinical usability, ultimately aiming to improve the efficacy and safety of ^{90}Y radioembolization therapy.

1.3 Aim & Objective of Research

The aim of this study was to develop a treatment planning system (TPS) for clinical dosimetric application of ^{90}Y hepatic radioembolization.

OBJECTIVES

i. To estimate the absorbed dose to lung, normal liver and tumour compartment by incorporating the pre-treatment CT images and SPECT-CT images into Geant4-GATE MC simulation.
ii. To compare between the absorbed dose obtained via Geant4-GATE MC simulation and PM calculation.
iii. To compare between simulated ^{90}Y Bremsstrahlung images obtained using Geant4-GATE MC simulation and the actual post-treatment ^{90}Y bremsstrahlung images.
iv. To develop a GUI base on Geant4-GATE as a treatment planning system (TPS) for clinical dosimetric usage.

1.4 Scope Of Study

This study encompasses several key stages to achieve the objectives related to optimizing dosimetric calculations for Yttrium-90 (^{90}Y) radioembolization in hepatocellular carcinoma (HCC) patients. The scope of the study is outlined as follows:

i. Acquisition of Patient Images: Patient images were obtained from Universiti Malaya Medical Centre following the necessary ethical approval to ensure compliance with medical and research standards.

ii. Image Preparation: The acquired images will be prepared using 3D Slicer software. This involves segmenting the relevant anatomical structures, registering the images to align them accurately, and exporting them into file formats compatible with further processing.

iii. Importing Patient Images into GATE: The prepared patient images will be imported into the GATE (Geant4 Application for Tomographic Emission) simulation toolkit. The CT images will be used to create voxel phantoms representing the patient's anatomy, while the SPECT images will be utilized as voxel sources for simulating the distribution of radiopharmaceuticals.

iv. Absorbed Dose Calculation: The absorbed dose will be calculated using two approaches: the traditional partition model (PM) and the advanced Monte Carlo simulations with GATE. Comparisons will be made between the dosimetric results obtained using patient-specific images in GATE and those derived from the MIRD phantom in Geant4.

v. Imaging Acquisition Simulation: Simulations of imaging acquisition will be conducted to generate bremsstrahlung images of ^{90}Y. These simulated images will be compared to actual post-treatment bremsstrahlung images to validate the accuracy and reliability of the simulations.

vi. Development of Treatment Planning System (TPS): A new TPS will be developed using C#, Visual Studio 2020, and Avalonia UI. This system will integrate the findings and methodologies from the study to provide a user interface for clinical dosimetric usage, facilitating accurate and personalized treatment planning for HCC patients undergoing ^{90}Y radioembolization.

By addressing these steps, the study aims to enhance the precision and effectiveness of ^{90}Y radioembolization therapy, ultimately improving patient outcomes.

1.5 Significance Of Study

The partition model (PM) [19] is widely used in clinical practice for dosimetric purpose in ^{90}Y radioembolization. However, since this model neglects the presence of crossfire irradiations between the compartments, the accuracy of dose estimated using this method is thus, hardly reliable [20]. The crossfire effect has been successfully investigated by simulating various ^{90}Y distributions within the compartments of the MIRD human phantom, using Geant4 MC package [20]. However, this study has a limitation as it did not consider the heterogeneity of both tissues and ^{90}Y distribution within the patients. In addition, since every patient's tumour is different in terms of shape, size and distribution, the use of reference mathematical phantom may not be accurately representative of the actual patient. Personalised dosimetry using patient's tomographic images has been performed by various researchers to estimate the radiation dose received by the compartments [21]. However, the solution to tissue and source heterogeneity have yet to be fully established.

1.6 Thesis Outline

This thesis is structured into five main chapters. Chapter 1 introduces the background, problem statement, research objectives, scope, and significance of the study. Chapter 2 presents a critical review of the literature, with emphasis on the rationale for adopting Geant4/GATE over other Monte Carlo codes and outlines current limitations in treatment planning systems for internal dosimetry. Chapter 3 details the methodology, including patient image acquisition, image preparation, absorbed dose calculations using both the Partition Model and Monte Carlo

simulations, and the development of a treatment planning system (TPS). Chapter 4 reports and discusses the findings, comparing dosimetric results from different approaches and evaluating simulation accuracy. Chapter 5 concludes the study by summarizing the outcomes relative to the objectives, addressing limitations, and proposing future work. This structure ensures a logical flow from problem identification to methodological implementation and results interpretation, reinforcing the study's focus on personalized dosimetry and TPS development for Y-90 hepatic radioembolization.

CHAPTER 2

REVIEW OF LITERATURE

2.1 Anatomy of the Liver

The liver is one of the largest and most complex organs in the human body. It is located in the upper right-hand portion of the abdominal cavity, beneath the diaphragm, and above the stomach, right kidney, and intestines. The liver is a large, reddish-brown organ located in the upper right-hand portion of the abdominal cavity, beneath the diaphragm and above the stomach, right kidney, and intestines [22, 23]. It is the body's largest solid organ, weighing about 3 pounds and is shaped approximately like a cone [22, 24]. The liver is divided into two primary lobes as shown at Figure 2.1 and Figure 2.2 [24]: the larger right lobe and the smaller left lobe. These lobes are further subdivided into smaller segments, each supplied by its own branch of the hepatic artery and portal vein and drained by its own branch of the bile duct [22].

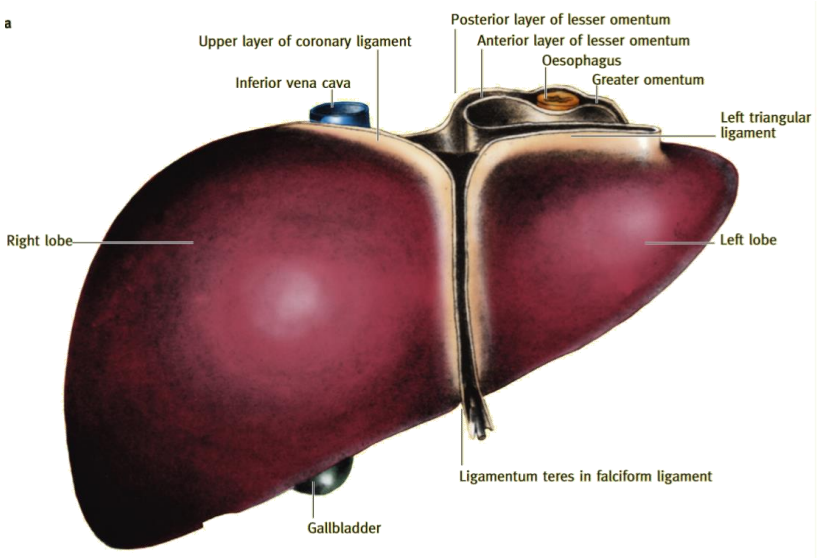

Figure 2.1 Posterior of Liver Organ.[22]

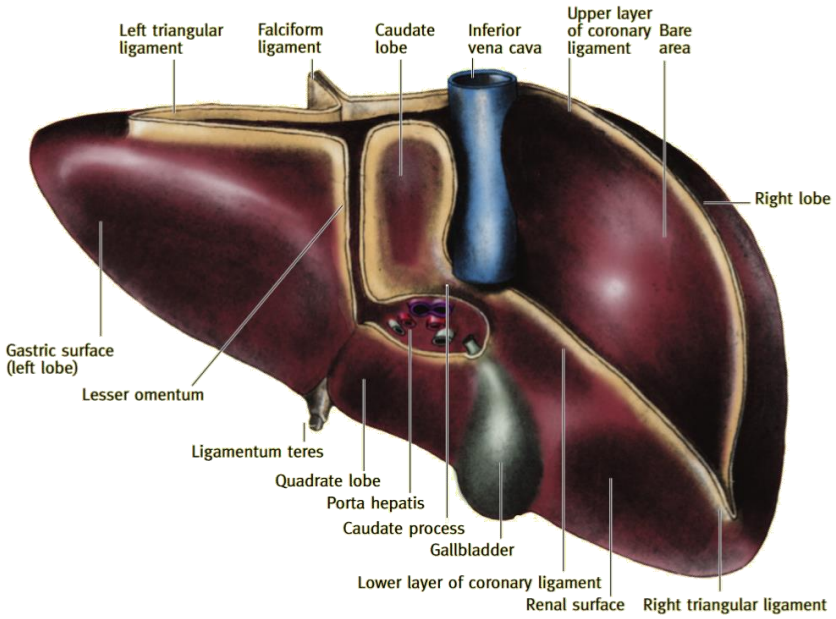

Figure 2.2 Anterior of Liver Organ.[22]

The surface of the liver is covered by a thin, fibrous layer known as Glisson's capsule, which provides protection and maintains the organ’s shape. Internally, the liver is organized into microscopic functional units called lobules. Each lobule is composed of hepatocytes (liver cells) arranged in plates radiating from a central vein. These lobules are surrounded by a network of blood vessels and bile ducts[23, 25]. The liver receives blood from two primary sources: the hepatic artery, [22, 24]which supplies oxygenated blood from the aorta, and the portal vein, which supplies nutrient-rich blood from the gastrointestinal tract. This dual blood supply is essential for the liver's metabolic, detoxification, and synthetic functions. One of the liver's key roles is the production of bile, which is vital for the digestion and absorption of fats. Bile produced by hepatocytes is collected in bile canaliculi, which merge to form larger bile ducts. These ducts eventually transport bile to the gallbladder for storage or directly to the small intestine for use in digestion.

Additionally, the liver plays a critical role in regulating blood glucose levels, synthesizing plasma proteins, storing vitamins and minerals, and metabolizing drugs and toxins[25, 26]. It is also involved in the synthesis of cholesterol and lipoproteins, which are essential components of cell membranes and hormone production. Overall, the liver's intricate anatomy and diverse functions are crucial for maintaining homeostasis and overall health.

2.2 Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, accounting for approximately 75-85% of all liver cancer cases worldwide [27]. It typically arises in the context of chronic liver disease, particularly cirrhosis caused by hepatitis B and C infections, alcohol abuse, and non-alcoholic fatty liver disease [28]. HCC is a significant global health problem due to its high incidence and mortality rates.

2.2.1 Treatment Options for Hepatocellular Carcinoma (HCC)

The treatment of HCC depends on various factors, including the stage of the disease, the underlying liver function, and the patient’s overall health. The main treatment options include surgical resection, liver transplantation, locoregional therapies, and systemic treatments [29, 30].

Surgical Resection [27, 28] is removal of the tumour is considered the treatment of choice for patients with early-stage HCC and well-preserved liver function. Resection offers the possibility of a cure, especially when the tumour is small and confined to one part of the liver. However, the risk of postoperative liver failure must be carefully assessed, particularly in patients with underlying cirrhosis. Liver transplantation [29, 30] is another curative option for patients with early-stage HCC,

particularly those who are not candidates for resection due to impaired liver function. This approach not only removes the tumour but also addresses the underlying liver disease, reducing the risk of tumour recurrence. The Milan criteria (single tumour ≤5 cm or up to three nodules ≤3 cm) are commonly used to select patients for transplantation.

Locoregional Therapies are used for patients with intermediate-stage HCC or as a bridge to transplantation. They include trans arterial chemoembolization (TACE), radiofrequency ablation (RFA), and selective internal radiation therapy (SIRT) [29, 31]. TACE involves the injection of chemotherapeutic agents directly into the hepatic artery supplying the tumour, followed by embolization to block blood flow and trap the drugs in the tumour. Systemic Treatments for advanced-stage HCC, systemic therapies are the mainstay of treatment. Sorafenib, an oral multichines inhibitor, was the first systemic therapy approved for HCC and has been shown to improve survival in patients with advanced disease. Other systemic therapies include Lenvatinib, regorafenib, and immunotherapy agents such as nivolumab and pembrolizumab [30, 31]. These treatments work by targeting specific pathways involved in tumour growth and immune evasion.

2.2.2 Trans arterial Radioembolization (TARE) with ^{90}Y -microspheres

Trans arterial radioembolization (TARE) with ^{90}Y-microspheres is an advanced locoregional therapy used primarily for the treatment of unresectable hepatocellular carcinoma (HCC) [27-30]. This therapy involves the trans arterial delivery of radioactive microspheres directly to the liver tumours via the hepatic artery. The microspheres emit beta radiation, which causes localized tumour cell death while sparing the surrounding healthy liver tissue.

The procedure begins with an angiographic evaluation to map the hepatic arterial anatomy and identify any potential extrahepatic shunts that could lead to non-target radiation. After this, a small dose of Technetium-99m macroaggregated albumin (^{99m}Tc-MAA) is injected to simulate the distribution of ^{90}Y-microspheres and calculate the lung shunt fraction, ensuring that the amount of radiation reaching the lungs is within safe limits [27]. There are two main types of ^{90}Y -microspheres used in TARE: resin-based and glass-based. Each type has different physical properties and dosimetric characteristics, but both have been shown to be effective in treating liver tumours [28, 30]. The choice between resin and glass microspheres depends on various factors, including the tumour's vascularity and the patient's liver function.

The microspheres are lodged in the tumour's microvasculature, where they deliver high-dose radiation directly to the tumour cells. The beta radiation from ^{90}Y has a limited penetration depth, which confines its effects to the tumour and minimizes damage to surrounding healthy tissue[28, 29]. Clinical studies have demonstrated that TARE can significantly improve survival rates and quality of life in patients with unresectable HCC. It is particularly beneficial for patients who are not candidates for surgical resection or liver transplantation. Additionally, TARE can be used as a bridge to transplantation by downstaging tumours to within transplant criteria [28, 31].

The most common side effects of TARE include fatigue, abdominal pain, nausea, and transient liver function abnormalities. Serious complications are rare but can include radiation-induced liver disease (RILD) and gastrointestinal ulceration due to non-target embolization [27, 29]. In conclusion, TARE with ^{90}Y-microspheres is a highly effective treatment option for patients with unresectable HCC, offering the potential for improved survival and quality of life with a favourable safety profile [27, 30].

2.3 Internal Dosimetry of Trans arterial Radioembolization

Internal dosimetry is a critical component of trans arterial radioembolization (TARE) that involves the calculation and assessment of the radiation dose delivered to the targeted tissues. Accurate dosimetry is essential to ensure effective tumour treatment while minimizing radiation damage to healthy tissues. Various dosimetric models and methodologies are employed in TARE to predict the distribution and absorbed dose of ^{90}Y microspheres within the liver.

2.3.1 Medical Internal Radiation Dose (MIRD)

The Medical Internal Radiation Dose (MIRD) [32, 33] schema is a comprehensive framework developed by the MIRD Committee of the Society of Nuclear Medicine for calculating radiation doses received by organs and tissues from radiopharmaceuticals used in nuclear medicine. This schema has become the standard approach for internal dosimetry, providing a systematic and standardized method to ensure accurate dose assessments.

The MIRD schema is based on a series of mathematical models and equations designed to estimate the absorbed dose in target tissues. The fundamental components of the MIRD schema include source organs, which contain the radiopharmaceutical and emit radiation, and target organs, which receive radiation. A critical element of the schema is the S factor, a dose conversion factor that relates the amount of radioactivity in the source organ to the absorbed dose in the target organ, accounting for the type and energy of the emitted radiation as well as the geometry of the organs [34].

The MIRD schema is widely utilized in various applications within nuclear medicine, including diagnostic imaging to estimate radiation doses from diagnostic procedures, ensuring they are within safe limits, and therapeutic applications to plan and optimize treatments involving radiopharmaceuticals, such as radioiodine therapy

for thyroid cancer and radioembolization for liver cancer [35, 36]. The primary advantages of the MIRD schema are its standardization, flexibility, and accuracy. It provides a consistent and standardized approach to internal dosimetry, can be applied to a wide range of radiopharmaceuticals and clinical scenarios, and incorporates patient-specific anatomical and physiological data to improve dose estimates. Despite its success, there are ongoing efforts to enhance the MIRD schema's accuracy and applicability. These efforts include developing more sophisticated models that account for individual patient variability, advanced imaging techniques to better delineate source and target regions and integrating personalized dosimetry approaches.

2.3.2 Partition Model Calculation

The Partition Model (PM) [19, 37-39] is a widely used method for calculating internal dosimetry in the context of radiopharmaceutical therapy. This model provides a means to estimate the absorbed dose in different compartments of the liver, such as the tumour, normal liver tissue, and lungs, by partitioning the administered radioactivity among these compartments based on their respective volumes and uptake fractions. The Partition Model operates by dividing the liver into multiple compartments, each receiving a fraction of the total administered activity of the radiopharmaceutical. The model considers the differential uptake of the radiopharmaceutical by the tumour and normal liver tissue.

The key components of the Partition Model include the tumour compartment, which represents the portion of the liver occupied by the tumour and typically exhibits higher uptake of the radiopharmaceutical, the normal liver compartment, representing the non-tumourous liver tissue, and the lung compartment, accounting for any potential shunting of the radiopharmaceutical to the lungs, which is particularly relevant in radioembolization therapies.

The absorbed dose to each compartment is calculated using the Formula 2.1:

$$D = \frac{AS}{m} \qquad 2.1$$

where D is the absorbed dose, A is the activity of the radiopharmaceutical, S is the S factor specific to the compartment, and mm is the mass of the compartment [19]. The S factor is a dose conversion factor that accounts for the type and energy of the emitted radiation as well as the geometry and radiological properties of the compartments. This method is particularly useful in radioembolization therapies, such as those involving ^{90}Y microspheres, where it helps in optimizing the distribution of the radiopharmaceutical to maximize tumour dose while minimizing exposure to normal liver tissue and other organ [37, 38]. It is also employed in other therapeutic contexts, such as radioiodine therapy for thyroid cancer and peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumours [37, 40].

The primary advantages of the Partition Model are its simplification of complex dosimetric calculations through the use of predefined compartments and standardized S factors, its utility in planning and optimizing radiopharmaceutical therapies by predicting the dose distribution and potential toxicity, and its flexibility to be adapted to different radiopharmaceuticals and therapeutic scenarios, making it a versatile tool in nuclear medicine[19, 37, 39, 40]. However, while the Partition Model provides a robust framework for internal dosimetry, it has limitations in terms of its accuracy and applicability to highly heterogeneous tumours and complex anatomical situations. [4, 19, 37] Ongoing research aims to enhance the model's precision through the incorporation of advanced imaging techniques, patient-specific anatomical data, and more sophisticated dosimetric algorithms.

While the PM has served as a foundational approach in clinical dosimetry due to its simplicity and speed, it inherently lacks the capacity to account for patient-

specific anatomical heterogeneity and radiation crossfire effects. This results in potential underestimation of dose, especially in cases with high tumour-to-normal liver (T/N) ratios or complex vascular distributions. In contrast, MC simulations, such as those implemented using Geant4 and GATE, provide a voxel-level resolution of dose distribution by incorporating individual patient imaging data. These simulations can model stochastic radiation transport through heterogeneous media, improving the precision of dosimetric assessment. However, their computational intensity and complexity have limited widespread clinical adoption. This study aims to bridge this gap by leveraging the accuracy of MC methods while integrating them into a TPS for practical clinical use.

2.4 Monte Carlo Simulation

Monte Carlo simulations are a powerful and versatile tool used in internal dosimetry to model the transport and interaction of radiation within the human body. These simulations are essential for accurately calculating the dose distribution of radiopharmaceuticals, allowing for precise treatment planning and optimization in nuclear medicine therapies. [41, 42] By using stochastic methods to solve complex physical problems, Monte Carlo simulations can account for the heterogeneous nature of human tissues and the intricate geometries involved in radiopharmaceutical distribution.

2.4.1 Monte Carlo Simulation Software

Several software packages have been developed to facilitate Monte Carlo simulations for radiation dosimetry. These tools are designed to provide dose calculations by simulating the interactions of particles with matter based on established physical principles. Key software used in this domain includes Geant4, GATE (Geant4 Application for Tomographic Emission), MCNP (Monte Carlo N-Particle), EGSnrc

and FLUKA and several others. Geant4 is an open-source toolkit developed by CERN for the simulation of the passage of particles through matter. It is widely used in medical physics for both external beam radiotherapy and internal dosimetry. Geant4 [12] provides comprehensive libraries for particle interactions and a flexible framework for modelling complex geometries and materials. GATE [13, 14], an extension of Geant4, is specifically designed for applications in medical imaging and radiotherapy. It offers advanced features for simulating emission and transmission tomography, as well as dosimetry for targeted radionuclide therapy. GATE supports voxelized geometries, allowing for detailed patient-specific simulations based on medical imaging data.

MCNP [43] is a general-purpose Monte Carlo radiation transport code developed by Los Alamos National Laboratory. It is used in a variety of applications, including nuclear medicine, radiation protection, and reactor design. MCNP's capabilities in handling complex geometries and diverse particle types make it suitable for internal dosimetry simulations. EGSnrc [44]is a Monte Carlo code system for simulating the coupled transport of electrons and photons. It is particularly well-suited for medical physics applications, including internal dosimetry. EGSnrc provides detailed modelling of radiation interactions and has been validated against experimental data, ensuring high accuracy in dose calculations.

FLUKA [45] is a comprehensive MC code used for calculating particle transport and interactions with matter. It is widely used in radiotherapy, radiation protection, and high-energy physics experiments. FLUKA's ability to handle different radiation types and energies with high precision makes it an invaluable tool for detailed dosimetric studies. These software tools enable researchers and clinicians to perform highly detailed and accurate simulations of radiopharmaceutical distribution and dose

deposition, facilitating the development of personalized treatment plans and improving patient outcomes in nuclear medicine therapies.

Although MC simulations (Geant4, MCNP, EGSnrc, FLUKA) provide accurate modeling by accounting for tissue heterogeneity and crossfire effects, their integration into clinical TPS remains limited by steep computational demands and lack of user interfaces. Traditional models such as the PM simplify dosimetry at the cost of underestimating organ doses and ignoring patient-specific anatomy. Moreover, most commercial TPS rely on fixed compartmental approaches that cannot adapt physics models for different radionuclides or imaging challenges (e.g., bremsstrahlung SPECT). By pinpointing these shortcomings—PM's dose underestimation and standard TPS's rigid physics configurations—we highlight the need for a more flexible, voxel-based platform that couples efficient Monte Carlo workflows with customizable physics lists and streamlined image handling. This gap underpins the development of our GATE-based TPS, which uniquely combines clinical usability with MC accuracy.

Table 2.1 Comparison of Selected Studies on Dosimetric Approaches for Y-90 Radioembolization.

Study	Dosimetry Method	MC Tool Used	Key Findings	Limitations
Kokabi et al. (2023)	Voxel-based dosimetry	Not specified	Identified tumor dose thresholds predicting objective and complete responses; established non-tumoral liver dose thresholds predicting adverse events.	Single-arm study; limited to resin microspheres.
Chen et al. (2023)	Voxel-S-Value (VSV) methods	Monte Carlo (MC)	Proposed a new VSV method (LiCKLuKD) showing improved agreement with MC simulations for 3D dosimetry.	Requires validation in diverse clinical settings.

d'Andrea et al. (2024)	Lung dosimetry comparison	Monte Carlo (MC)	Demonstrated that traditional methods significantly underestimate lung doses compared to MC simulations; introduced optimized VSV kernel for lung tissue.	Simulation-based; clinical applicability needs further study.
Costa et al. (2023)	Personalized dosimetry	GATE (MC)	Showed good agreement between prescribed and calculated doses; CFD simulations predicted microsphere deposition aligning with high-dose regions.	Single-patient study; requires broader validation.
Bozkurt et al. (2023)	Personalized MC dosimetry	MCNP6.2	Developed a voxel-based MC approach for determining absorbed doses in tumors and critical organs; emphasized the importance of patient-specific models.	Simulation-based; clinical implementation pending.

Table 2.1 presents a summary of recent studies (2023–2024) that highlight contemporary approaches to dosimetry in Y-90 hepatic radioembolization. Kokabi et al. (2023) emphasized the clinical utility of voxel-based dosimetry in predicting therapeutic response and toxicity, underscoring the importance of accurate tumor and non-tumoral liver dose estimation. Chen et al. (2023) and d'Andrea et al. (2024) contributed to methodological advancements by demonstrating improved agreement between Voxel-S-Value (VSV) models and full Monte Carlo (MC) simulations, particularly in accounting for lung shunting and non-uniform dose distribution. Costa et al. (2023) illustrated how integrating multimodal imaging with computational fluid dynamics (CFD) and MC simulations can refine absorbed dose prediction, while Bozkurt et al. (2023) proposed a personalized voxel-level dosimetry framework using MCNP, validating the importance of patient-specific anatomical modeling.

These recent works collectively affirm the growing shift towards individualized, image-based dosimetry using voxel-level and Monte Carlo techniques. However, many of these studies are either simulation-based or case-specific, with limited integration into a fully functioning clinical software environment. In contrast, the current research builds upon these advancements by not only employing Geant4/GATE for high-fidelity MC dose simulations using patient-specific CT and SPECT data but also developing a cross-platform treatment planning system (TPS) with an intuitive graphical user interface (GUI). This approach addresses the clinical usability gap by translating complex dosimetric computations into an accessible format suitable for routine practice.

2.4.2 Geant4 Simulation Toolkit

The Geant4 Simulation Toolkit is a comprehensive software package extensively used in radiation physics research and medical applications. Developed by CERN, Geant4 is designed to simulate the passage of particles through matter using Monte Carlo methods. This toolkit provides a wide range of functionalities, including tracking, geometry, physics models, and visualization, making it a versatile tool for simulating complex physical interactions in various environments. [11, 12] Geant4 has been instrumental in advancing research in particle physics, medical physics, and space science by enabling precise modelling of particle interactions with materials. Studies [4, 51] using Geant4 have demonstrated its capability of using to run internal dosimetry simulation study.

Geant4 was selected for its extensive validation in internal dosimetry applications, detailed geometry handling, and integration with GATE for voxel-based simulation. Compared to MCNP and EGSnrc, Geant4 offers more flexibility and is open source with a large community, making it more practical for development and

integration into clinical workflows. Additionally, the research team had prior experience with Geant4, which accelerated the implementation process. The toolkit also provides an excellent collection of physics lists, allowing researchers to easily select appropriate configurations for specific simulation needs. Furthermore, the flexibility of Geant4 supports the customization of simulations for each individual patient, enabling personalized dosimetric analysis tailored to unique anatomical and clinical conditions.

2.4.3 Geant4 Application for Tomographic Emission (GATE)

GATE (Geant4 Application for Tomographic Emission) is a specialized extension of the Geant4 toolkit, developed to meet the specific needs of nuclear medicine and medical imaging. GATE provides advanced capabilities for simulating positron emission tomography (PET), single-photon emission computed tomography (SPECT), and other tomographic imaging modalities. [13, 14] By integrating detailed patient-specific models and sophisticated physical processes, GATE enables accurate simulation of the imaging systems and radiopharmaceutical distributions used in clinical practice[52]. This application supports various features, such as modelling the movement of patients and organs, time-dependent phenomena, and the inclusion of realistic detector responses, making it a powerful tool for optimizing imaging protocols and improving diagnostic accuracy. Recent studies have utilized GATE for ^{90}Y radioembolization, showing its effectiveness in simulating the dose distribution and assessing the treatment's impact, thus contributing significantly to personalized treatment planning and enhancing patient outcomes [53].

In this study, both Geant4 and GATE were used, as they share the same Monte Carlo foundation. GATE was chosen for patient image simulations due to its built-in features for handling medical imaging data, which simplify the import and processing

of CT and SPECT images. This user functionality made GATE more practical and time-efficient for patient-specific dosimetry compared to the more technical setup required in Geant4.

2.4.4 Mathematical Phantoms Used in Monte Carlo Simulation

In Monte Carlo simulations for internal dosimetry, mathematical phantoms are essential for accurately modelling human anatomy and predicting radiation interactions within the body. Two prominent types of phantoms frequently used in these simulations are the MIRD (Medical Internal Radiation Dose) phantom and the ICRP (International Commission on Radiological Protection) 110 phantom.

The MIRD phantom, [54, 55] developed by the Society of Nuclear Medicine's MIRD Committee, is one of the foundational models in internal dosimetry. It employs a series of mathematical equations to describe the phantom geometry as shown at Figure 2.3 and composition of human organs, simplifying the complex human anatomy into a set of standard shapes and sizes. This approach facilitates routine dose calculations in nuclear medicine by providing a straightforward and standardized framework. The MIRD phantom is particularly useful in radiopharmaceutical therapy simulations, where it helps estimate the distribution and absorption of radiation within the body, thereby aiding in the development of personalized treatment plans.

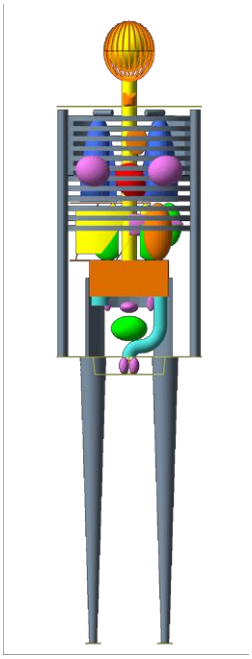

Figure 2.3 MIRD phantom used in Geant4.

The ICRP 110 phantom [56, 57] represents a more advanced and detailed approach to anatomical modelling. Published in ICRP Publication 110, these phantoms are voxel-based models derived from high-resolution medical imaging data, offering a realistic representation of human anatomy, including the spatial relationships and heterogeneous composition of different tissues and organs as shown at Figure 2.4. These phantoms are used in conjunction with Monte Carlo simulations to achieve highly accurate dosimetric calculations, which are crucial for complex dose assessments in various radiation therapy and protection scenarios.