Y-90 DOSE DISTRIBUTIONS IN HEPATOCELLULAR CARCINOMA PATIENTS

by

Johnathan M. James

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of a senior thesis submitted by

Johnathan M. James

This thesis has been reviewed by the research advisor, research coordinator, and department chair and has been found to be satisfactory.

Date	Jon Johnson, Advisor
Date	Stephen Turcotte, Committee Member
Date	Richard Datwyler, Committee Member
Date	R. Todd Lines, Thesis Coordinator
Date	R. Todd Lines, Department Chair

ABSTRACT

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Johnathan M. James

Department of Physics

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Transarterial Radioembolization is an effective treatment to extend the lifetime of patients with Hepatocellular Carcinoma, also known as liver cancer. Radiation dose distribution calculations were made via PET/CT image guidance and microsphere segmentation. Yttrium-90 was the source of radiation in all case studies. Although this study is not conclusive, calculated dose distribution data correlates with expected values and with other studies.

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Chapter 1

Introduction

There are many underlying motives as to why this research is being conducted. Generally, software that enables healthcare professionals to conduct accurate dosage calculations has very expensive licensing fees. As a result, small clinics do not have the monetary resources or the time to invest in purchasing and learning to use such software. TriD Fusion is a software that does most of the calculations that a small clinic would be interested in. It is user-friendly, accurate, and free for anyone to download [3]. The world is progressing towards a heavier online presence, and with that, there are many forward-thinking individuals that want to reduce general expenses with more open-source tools. TriD Fusion is a direct result of this movement.

TriD Fusion was used to do image analysis on three-dimensional PET and CT scans of patients. It was also used to calculate local dosages of needle biopsies through dose point kernel convolution. A thorough discussion on dose point kernel convolution will be provided in Chapter 2.

Many researchers consider Monte Carlo simulations to be the most accurate method for calculating radiation dose distributions [4]. By comparing our findings to this best-known method, our research stands out as being comprehensive and

thorough; however, more extensive research still needs to be conducted to prove this correlation can be maintained across a larger population. The population of this study consisted of data collected from 20 patients. In all, 20 PET scans, 20 CT scans, and 28 micro-CT scans were used. Due to complications with image resolution, many of the scans could not be used.

1.1 Palliative Care

Certain diseases and illnesses that afflict people in the world get to the point where they are terminal. Palliative care is a type of treatment available to people with terminal illnesses which treats the patient's complicated symptoms [5]. It is important to realize that palliative care will not save a patient. Palliative care can at best prolong the life expectancy of the patient and relieve some of the patient's suffering. Palliative care, in this sense, is generally a last resort for most people.

In general, the 5-year survival rate (post-diagnosis) of liver cancer patients in the United States is 20 % [6]. Liver cancer is one such illness where many people will resort to some form of palliative care such as Transarterial Radioembolization.

1.2 Transarterial Radioembolization

Transarterial Radioembolization (TARE) is a form of palliative care for people with liver cancer. When a liver tumor begins to grow, it hijacks a significant portion of the liver's circulatory system and uses the blood flow to supply itself with the nutrients it needs to grow. TARE involves injecting small beads that are about 30 micrometers in diameter into an artery. This artery supplies the liver with blood and other nutrients needed for basic function. The beads are either made of glass or resin

and carry a radioactive isotope, usually Yttrium-90 (Y-90), and are commonly called microspheres. There are two types of Y-90 microspheres used in TARE. The first is SIR-Spheres and the second is Theraspheres. SIR-Spheres are resin microspheres with a diameter between 20-60 micrometers and Theraspheres are glass microspheres, usually with a diameter between 15-35 micrometers. The Y-90 inside of both these microspheres is activated via neutron bombardment of Y-89. Theraspheres are usually more active than SIR-Spheres. This is due to the higher levels of Y-89 incorporated into the microspheres during manufacturing.

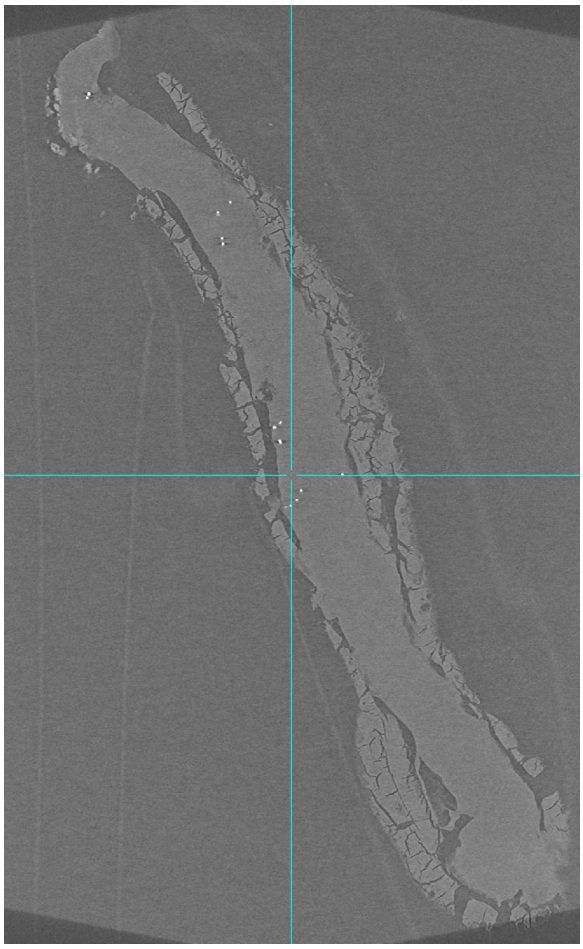

Figure 1.1 The micro-CT of a 2mm by 14mm needle biopsy. Individual microspheres are visible.

Due to the amount of blood flowing to a tumor in the liver, the majority of the radioactive microspheres will end up localizing in and around the tumor. The radiation emitted by the microspheres is able to cause damage to both the tumor and the blood vessels supplying the tumor with nutrients. This combination usually leads to tumor necrosis. The benefit of TARE is that it is able to maximize dosage to tumor tissue while minimizing the dosage to healthier tissue. Generally, TARE will not kill a tumor but will stunt tumor growth. After diagnosis and without further treatment a patient with stage 4 liver cancer will live for about 4 months [7]. The overall survival of patients in the same situation after TARE treatment can be between 11.2 and 25.7 months [8, 9]. This might not seem like much of an extension, but it is a relatively simple way to extend a patient's life and give them more time with family and loved ones.

1.3 Needle Biopsies

A significant part of a medical physicist's job is ensuring that healthy tissue receives a minimal dose while maximizing the dose received by a tumor. To assess the distribution of microspheres in the liver's soft tissue, needle biopsies are taken from the patient's healthy and cancerous tissue. Needle biopsies are taken by sticking specialized needles through epidermal tissue into the abdominal cavity and removing small samples of the liver. These samples are about 2-3mm in diameter and 15-25mm in length. By subjecting these samples to a micro-CT machine, individual microspheres can be seen and counted (See Figure 1.1). A CT scan is what results from a Computed Tomography machine which uses a heavy dose of X-ray radiation to scan a region of the body in about 10 minutes. A micro-CT scan is essentially a mini CT machine. By analyzing a biopsy specimen, one can have an idea of what kind of radiation dose

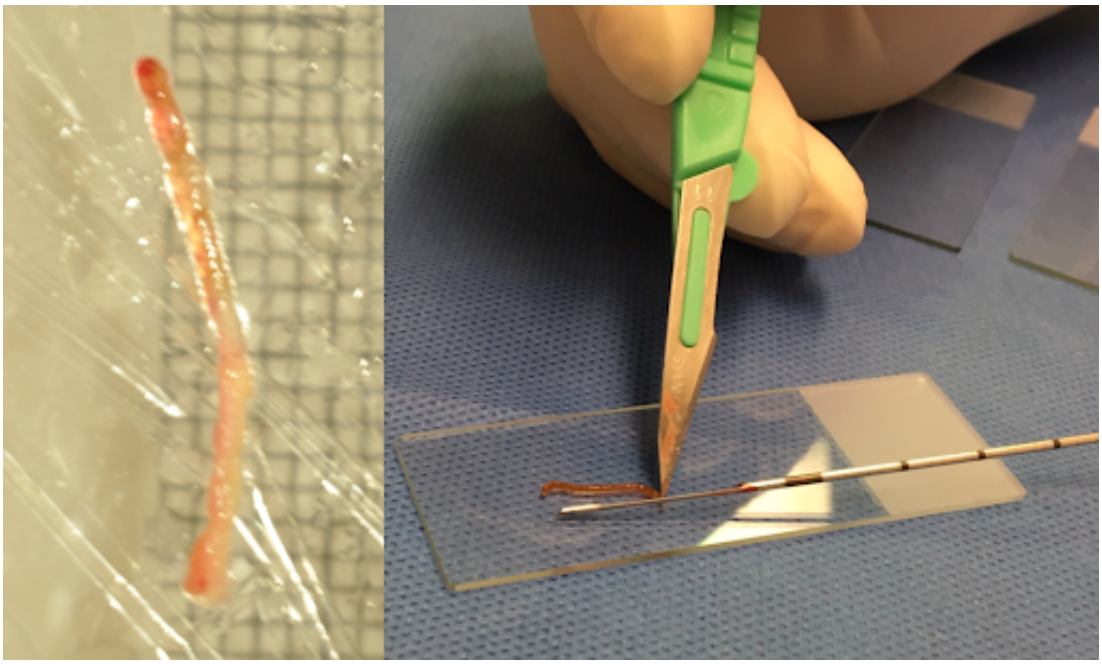

Figure 1.2 Once removed from the needle, biopsies are placed on microscope slides or on plastic wrap. From there, they are prepped for the micro-CT machine with a variety of dyes and contrasting agents.

the healthy tissue in the body is being exposed to.

1.4 Positron Emission Tomography

Positron Emission Tomography (PET) is a specialized type of imaging that uses radioactive tracers. Tracers tend to be radioactive isotopes that are attached to a sugar, protein, carbohydrate, or other molecules. Where a tracer goes usually depends on where it is injected or ingested, and what type of molecule it is attached to. Tracers tend to be β^+ emitters. These β^+ emissions are positrons. Positrons will only travel a short distance before being annihilated by an electron. The annihilation event usually releases energy in the form of photons in exactly opposite directions which allows a γ-ray detector to determine the line that goes through each annihilation event. Each

event picked up by the γ-ray detector allows for a clearer final image resolution. PET scans can also be taken using the radiation emitted from Yttrium 90 (Y-90) microspheres. Y-90 is a pure β^- emitter. This means that it only emits electrons. Not all of these electrons can trigger annihilation events. Only the ones that are very high energy can trigger an annihilation event through pair production. Annihilation following pair production will cause photon emissions in the opposite directions and ultimately a relatively clear image. One very important concept to understand is that the location of the annihilation event is not the same location as the radioactive atomic decay. A β particle can travel up to a few centimeters in the air before annihilation, and up to a few millimeters in soft tissue before annihilation [10]. This means that images from PET scans are usually a little fuzzy. Because the electron in a β^- emission travels a certain distance before triggering pair production, PET scans from β^- emitters are usually a little fuzzier than PET scans from β^+ emitters. This is especially important when trying to calculate the dosage for a patient by looking at the data collected from a PET scan.

Chapter 2

Method

2.1 Dose Point Kernel Convolution

In computer science, a kernel is the core of a program or an operating system and serves to provide basic services to the rest of the operating system. In radiation therapy, a kernel is a mathematical function used to model the behavior of ionizing radiation as it interacts with matter. In this research specifically, a kernel represents the probability distribution from a single radiation interaction event within a small volume of the patient's tissue. The shape of the kernel depends on several factors, including the type and energy of the radiation, and the type of tissue. The kernel that we used was developed using Monte Carlo simulations, as most kernels used in radiation therapy are.

A dose point kernel (DPK) is a specific type of kernel that characterizes the radiation dose deposited at a point in the patient's tissue due to a single radiation interaction event at a different point. In other words, it describes how radiation deposited at one point in the patient's tissue contributes to the radiation dose at a different point. The dose point kernel is an essential component of dose calculation

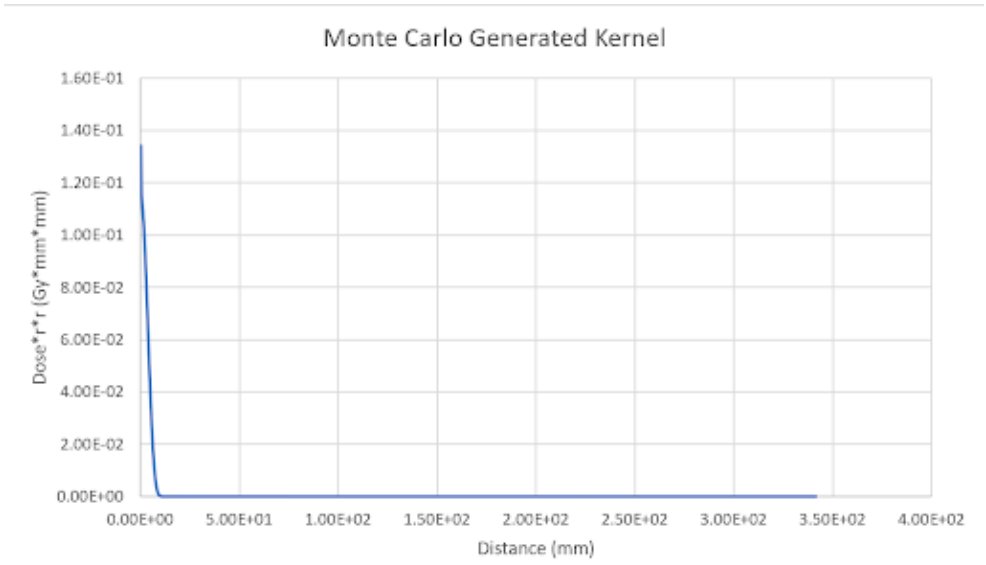

Figure 2.1 The kernel used for dose distributions in patients. The dose has units of Grays, and the distance has units of millimeters. This kernel was developed using GATE [1], an advanced open-source software based on the Geant4 toolkit from CERN [2]. Geant4 is a toolkit for the simulation of particles through matter. To see more detail of the kernel see Figure A.2

algorithms used in radiation therapy treatment planning.

Convolution is a mathematical operation used in signal processing and mathematics. Convolution combines two functions to produce a third which expresses how one function modifies the other. Specifically, convolution is a mathematical operation that involves the integration of the product of two functions. In the context of dose point kernel convolution, the two functions being convolved are the kernel and the patient's anatomy. The result of the DPK convolution is a 3D dose distribution that takes into account the effects of both the radiation source and the patient's anatomy. The convolution process involves sliding one of the functions (usually the kernel) over the other and calculating the integral of the product at each point. This is repeated for every point in the patient's volume to obtain the final dose distribution.

Figure 2.1 is an example of a dose point kernel that was developed in GATE. GATE

is an advanced open-source software based on the Geant4 toolkit from CERN. Geant4 is used for the simulation of particles traveling through and interacting with matter. To create the kernel, Monte Carlo simulations are used to simulate how the radiation interacts with tissue. These simulations employ stochastic calculations to determine where and how the energy from the radiation is deposited in the tissue. Once the kernel is created no more Monte Carlo simulations are needed. To calculate dose profiles, TriD Fusion will take as inputs, the kernel that is to be used, the type of tissue or material the radioisotope is in, the radioisotope, and the interpolation method (see Figure A.1). The interpolation changes how the integration of the convolution is executed. Dose profiles are created by drawing a contour over the region of interest. This automatically creates a plot of the dose as a function of distance (see Figure 3.1).

2.2 PET and CT Convolution

As described in the previous section, the convolution of a dose point kernel requires two functions or inputs in order to calculate a dose distribution. The software that executes the convolution takes as an input a CT scan and a PET scan. The PET scan is the source of radiation and is the focus of the kernel, while the CT scan provides anatomical and spatial data for the dose distribution. Both the PET and CT scans contain spatial information about the patient's anatomy, but because of the poor resolution of the PET scan, only the CT scan is used. Before the convolution calculation is executed, it is encouraged to resize both files so that the PET and CT files overlap and have the same spatial resolution.

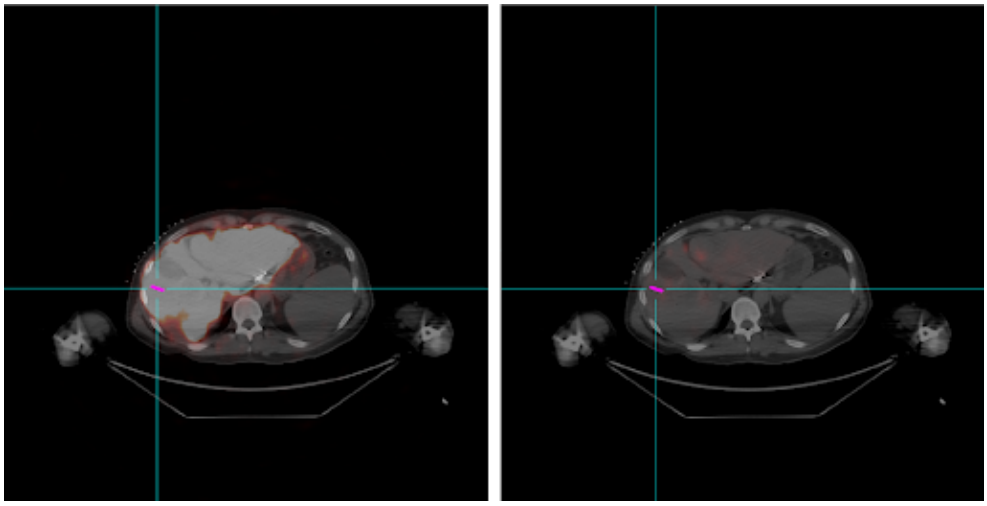

Figure 2.2 An overlapped CT and PET scan of a patient's abdominal cavity. Raw PET scan data can be seen on the left. Once the DPK convolution is applied, the locations of the tumors can be seen as radiation hot spots (right). The purple silhouette seen in both images is the location of a needle biopsy. A micro-CT of the needle biopsy can be seen in Figure 1.1, and a microsphere-segmented version of the needle biopsy can be seen in Figure 2.3.

2.3 Micro-CT Convolution

Unlike PET and CT convolution, micro-CT convolution is only dependent on the information contained within the micro-CT. When viewing a micro-CT of a needle biopsy specimen, individual microspheres can be seen. When a patient is administered a radioactive treatment such as TARE, initial activity calibration data is also tracked with the patient's dose. This data is used to figure out what the average activity of each microsphere is within a biopsy specimen. A segmentation algorithm that uses ISO (sensitivity of the sensors) light and dark contrast is able to outline the location of each microsphere and calculate the volume in voxels. A voxel is similar to a pixel but is three-dimensional. After the location and volume of each microsphere are known, each voxel pertaining to a microsphere is assigned an average level of activity based on its size and the average microsphere activity at the time of injection.

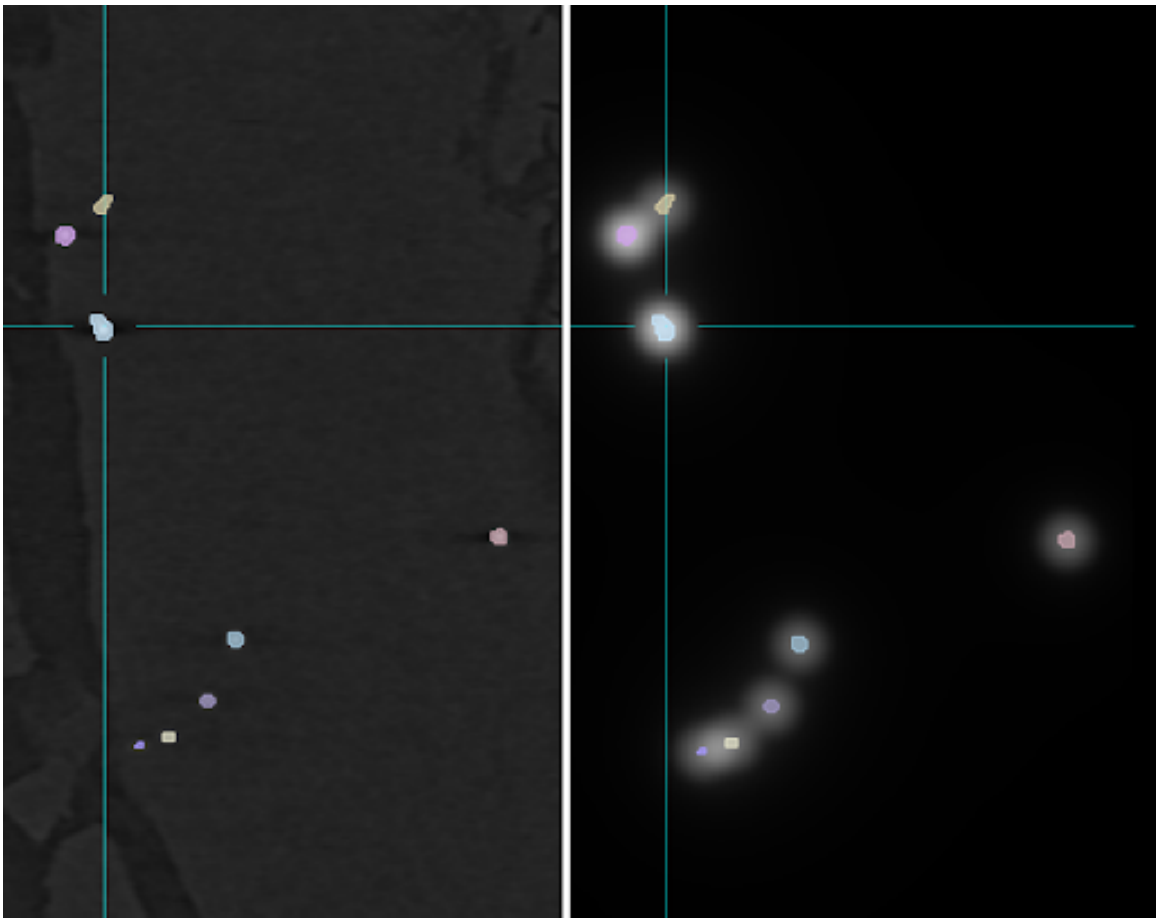

Figure 2.3 A zoomed-in view of a few of the individually segmented microspheres before (left) and after (right) the kernel is applied. The smaller flecks towards the bottom are either the tops or bottoms of microspheres centered in a different slice.

Chapter 3

Results

Each calculation that was done served two purposes. One was to find the radiation dosage to a region of interest (ROI), and the other was to compare the software against itself. As is mentioned in the procedures (See appendix), there were several different options for computing the dose convolution. Each interpolation method (linear, nearest, spline, and cubic) applied a different computational technique and changed the calculated amount of dosage received. The radiation dosage profiles for all of the convolutions with the two selected microspheres are all between 4.5-5.5 Gy. Dosage profiles of patients' ROIs varied depending on whether the ROI was marginal (healthy tissue) or tumor based. Unfortunately, a conclusive set of data could not be collected. Most of the Micro-CT scans that I had to work with could not be segmented resulting in no calculated dose. Data could only be collected from 3 out of the 28 specimens.

3.1 Dose Profiles

Here you will see a figure that correlates with the data that was collected.

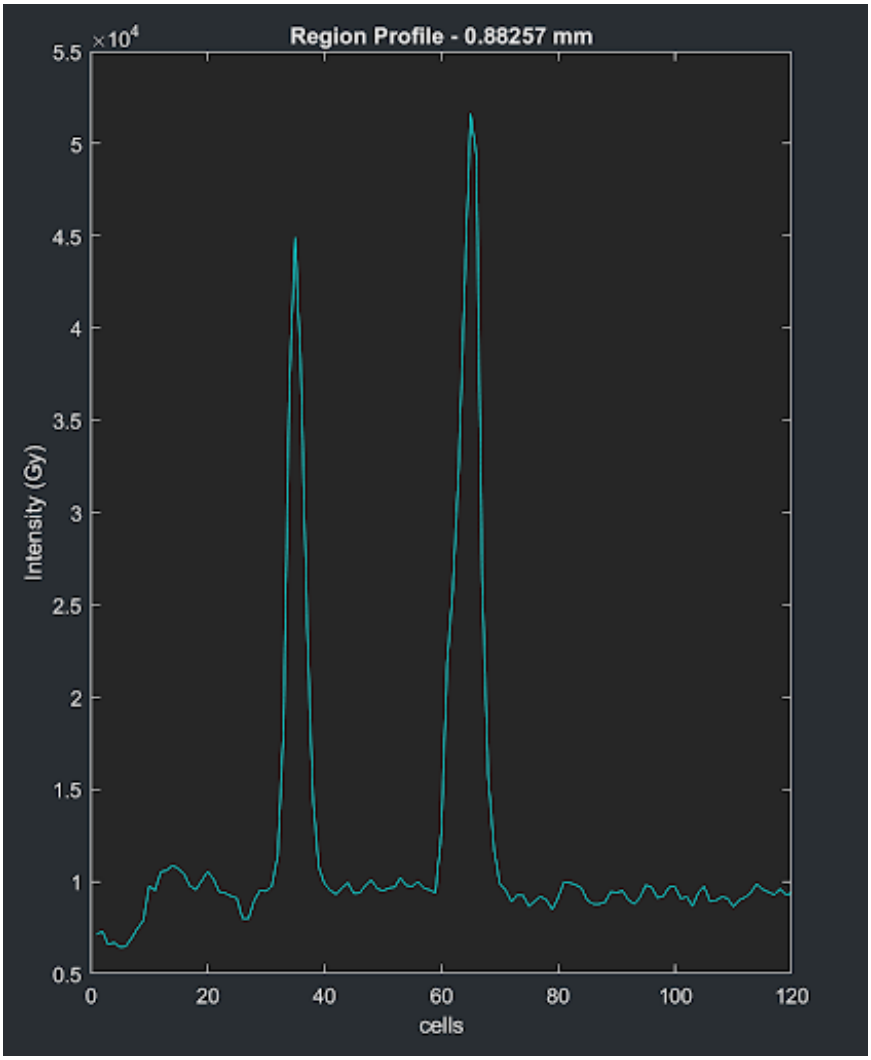

Figure 3.1 A dose profile from two of the larger microspheres from Figure 2.3. A line was drawn through Figure 2.3 that connected two microspheres. The peaks at about 37 and 65 cells are where the microspheres are located. Each microsphere is about 35 micrometers in diameter. The units *cells* on the X-axis means digital cells or voxels and the value will change based on the resolution of the micro-CT. Spatial information entered into Figure A.4 comes out to be the unit of each *cell*. The Y-axis is given in units of *Gray* or *Gy* which has units of Joules/kilogram.

Chapter 4

Analysis

Due to the nature and the outcomes of this research, a full analysis will not be possible until more data is collected. A new set of patient scans will be needed for this to be conclusive. The goal of this research was to further the capabilities of the TriD-Fusion software and accurately measure the dosage received by patients. The data that was collected shows that a reasonable dosage calculation can be made. Data resembles data collected from MiM software and Monte-Carlo simulations and are within an acceptable range of accuracy of both. Data from Monte-Carlo simulations and MiM software hasn't been released. For more information please contact the Medical Physics department at Memorial Sloan Kettering Cancer Center. It is likely that more debugging of the code needs to take place and more tests run on different patients' data before more conclusive results can be shown.

Chapter 5

Conclusion

This research is on track to show that the convolution is consistent with other measured results, but more work needs to be done on the kernel in order to sort out certain issues in the interpolation of the dose. Based on the data collected, Microsphere Segmentation of needle biopsies proves to be a very accurate method for calculating doses to small ROIs. However, because we were only able to collect data from 3 out of the 28 specimens, more work will need to be done with more specimens in order to have more conclusive research.

5.1 Future Research

There are many areas in this topic that need to be more thoroughly explored. The data that our research was based on analyzing consisted of CT scans, PET scans, and needle biopsies from 20 patients. This isn't a very large pool of data, to begin with. In addition to this, some of the patient's data had been collected poorly, such as the lack of contrast in the micro-CTs of needle biopsies, and was unable to be used. This was likely due to the rushed preparation of samples. Procedures could be followed to

collect better patient data and allow for a more thorough analysis of a population.

Much of the time that I spent working on this research was spent going through and testing the different modalities of TriD fusion and debugging the code. These items were important to the project as a whole but were time-consuming. This ultimately limited the amount of time that could be spent on conducting experiments and collecting data for analysis.

More research should be conducted to find out what the long-term impact on soft tissue (such as liver tissue) from TARE is. More extensive research could show better methods for delivering dosage to patients, i.e. many low-activity microspheres, or fewer high-activity microspheres.

Our research found that the developed dose point kernel that was used to calculate the radiation dose distributions from our data is an accurate model. More thorough research can be conducted to see if there are any shortcomings in our model and should also include efforts to refine TriD Fusion.

Appendix A

Procedure

A.1 Calculation of dosage via CT and PET guidance

This method for dose calculation gives the best idea of the amount of radiation that is being given to a patient's cancerous tissue and to a patient's marginal tissue. Marginal tissue is healthy noncancerous tissue.

CT and PET scans are usually output into a 3D file format called DICOM [11]. DICOM files are similar to stack files in that each image has a length, width, and thickness to it; the unit dimension of each of the previous measurements ultimately constitutes the voxel size that is used in each dose calculation.

The first step to be done is to upload the PET and CT files to TriD-Fusion (3DF) with any supporting RT-structures. An RT-structure is a data format that has the locations of specific ROIs.

CT and PET scans cannot be taken at the same time since they both require different and very expensive pieces of equipment. As a result, the scaling of each scan and the position of the patient are likely to be slightly different in each scan.

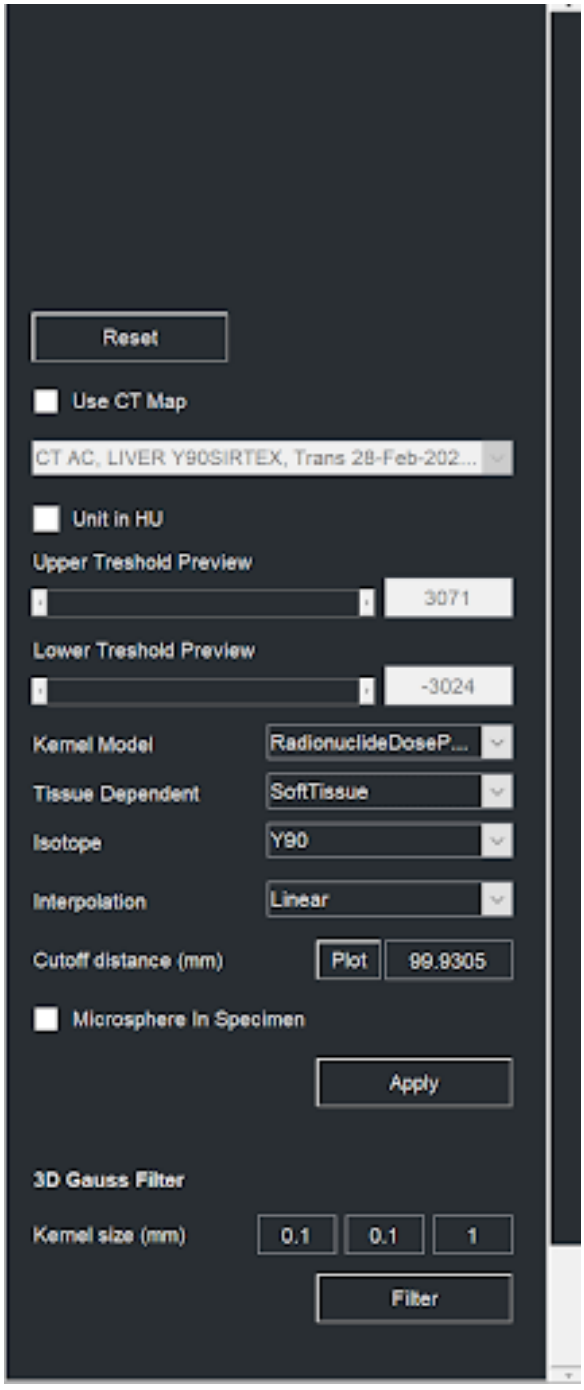

Figure A.1 General settings for the kernel.

To account for this change, one must resample the two images so that they overlap one another and so the resolution of the two images is compatible enough to do the

calculations. This is done by clicking on "Tools" in the upper left corner of the screen and then on "Registration". A new screen will pop up which will have an options menu on the left and a list of the files that have been uploaded on the right. On the right, select the menu with the higher resolution (this will usually be the CT scan) first, then select the one that remains (usually the PET scan). On the left click on the drop-down menu that says "interpolation" and select the interpolation method that you desire. Finally, click "Resample". Both the PET and CT files will now have the same resolution and the final calculation will be much more accurate.

In order to run the convolution first click on "View" on the top left of the screen. You will see a drop-down menu. Select "Kernel Panel". Once the kernel panel pops up you will have to select the correct settings. Enter the following settings: "Kernel Model" $\longrightarrow$ "RadionuclideDosePointKernel.mat", "Tissue Dependent" $\longrightarrow$ "SoftTissue", "Isotope" $\longrightarrow$ "Y90", "Interpolation" $\longrightarrow$ "select interpolation that you desire to use". These settings might be different if a different type of therapy is being done, but for the research that is covered here, these settings will not change. See Figure A.1.

The "cutoff distance" (see Figure A.2) option is an option that allows you to speed up the execution of the code by giving a shorter and shorter approximated value of the possible distance traveled by each β emission. Finally, select "Apply".

Depending on the size of the resampled image, the cutoff distance that was applied, and the type of interpolation that was used, the time that it will take for the dosage calculation could be anywhere from a couple of seconds to half an hour. To see the effect of the dosage calculation, there are two drop-down menus just below the ROI toolbar, one on the left and one on the right. Select the CT scan on the left-hand side of the screen and then the PET scan on the right. Click on "Fusion" to see the two images laid on top of one another. This gives a visual representation of the data

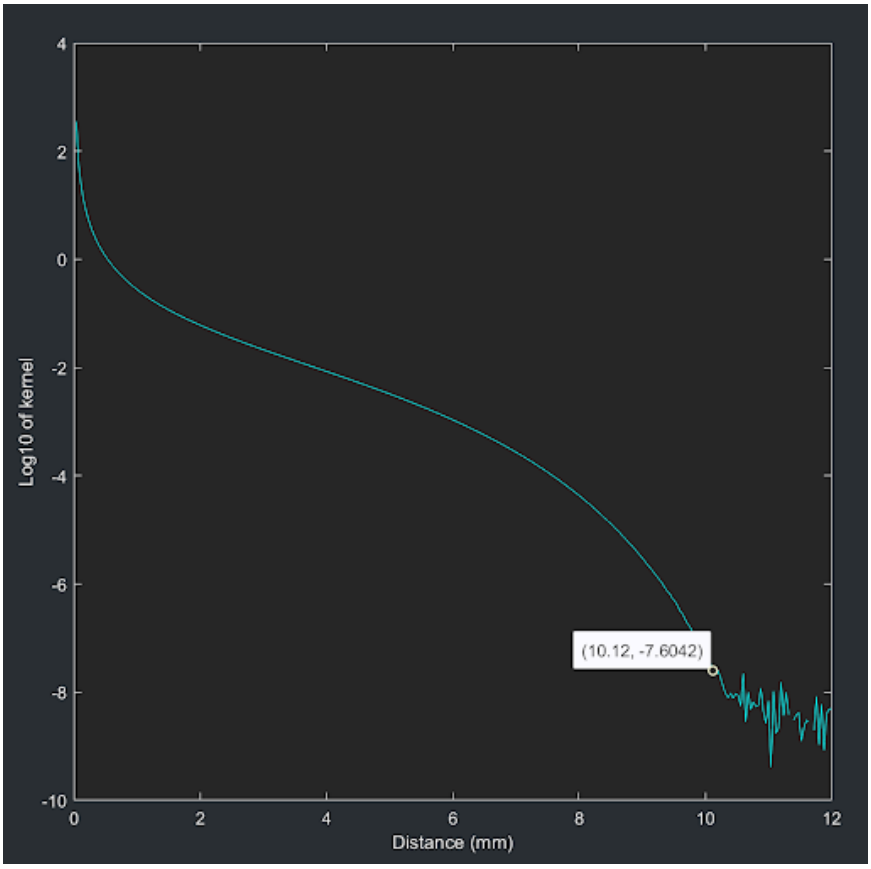

Figure A.2 The "cutoff distance" for the kernel. Since the scale is logarithmic, small decreases in the distance will greatly reduce the runtime

similar to a contour plot. To see the actual data for the dosage calculation, click on the "results" icon at the top left-hand side of the screen. The icon looks like a little piece of paper.

A.2 Calculation of Dosage Using Micro-CT Scans

In Figure 2.2 you can see a little purple silhouette. This silhouette is an RT-structure and is the location of a needle biopsy. An RT-structure is a radio-therapy structure and is used as an object on which different functions within the program can operate. As was described earlier, micro-CT machines are able to scan small specimens that

are only a few millimeters in diameter with astounding resolution. The micro-CT is also capable of capturing the individual microspheres in each of the images that were scanned. If one knows the location of each sphere and the average radioactivity of each sphere at the time of infusion, then one can calculate what the dosage to the tissue in and around the sample would be by applying a similar method and process as the one described in the previous section.

First, you will want to upload the DICOM file of the micro-CT to 3DF. Next, click on "View" in the upper left-hand corner and scroll down to "Contour Panel". The contour panel allows you to segment through the three-dimensional file and find the location and volume of each microsphere based on the color contrast between the soft tissue of the liver and the glass material in each microsphere. The settings on the contour panel will vary for each sample but in most cases, a value around 21 for the "Upper Threshold" will work just fine. You will also want to make sure that you check the box that says "Multiple Objects". Each case file is different so you will have to do some trial and error before knowing the ideal settings for each specimen. Click on "Segment" (see Figure A.3).

A lot of times after the segmentation algorithm has been executed, there will be small objects that come up as VOIs (volume of interest) even though they are obviously not microspheres. This is not a problem at all. At the top of the contour panel is a small section called "Contour Review". In this section, there is a drop-down menu that contains a list of all the VOIs, and buttons that say "Next", "Previous", "Add", and "Delete". Here you can go through and manually delete any VOIs that do not look like microspheres or that have fallen outside of the sample. The file containing all of the locations and positions of microspheres can then be saved as an RT-structure and used for later calculations.

Once the microspheres have been segmented and reviewed, click on "View" and

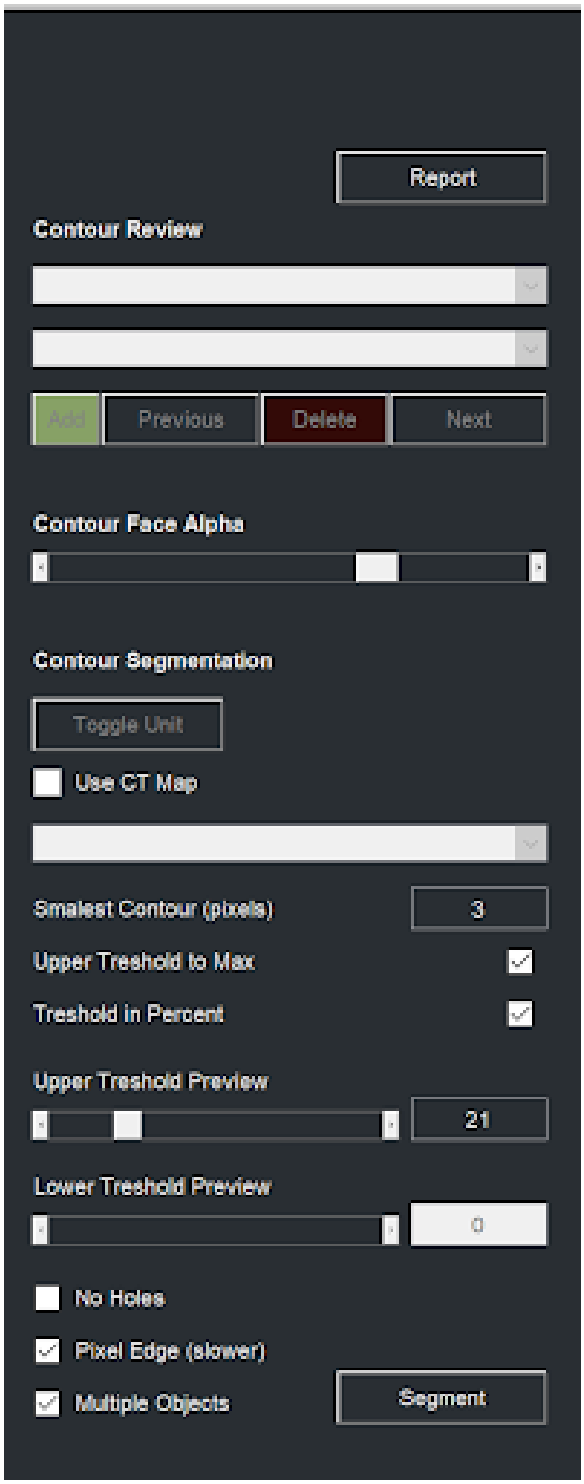

Figure A.3 General settings for segmenting a biopsy specimen.

then click on "Kernel Panel". The Kernel panel here does a similar calculation to get the radiation dosage as the kernel panel in the PET/CT guidance. The main difference between the two is how the activity is calculated. For the microspheres, an average activity level is assigned to each voxel based on the size of the microsphere and the date of microsphere infusion. Enter the following settings on the kernel panel: "Kernel Model" $\longrightarrow$ "kernelRadionuclideDosePointKernelsMicoSphere.mat", "Tissue Dependent" $\longrightarrow$ "SoftTissue", "Isotope" $\longrightarrow$ "Y9010E8", "Interpolation" $\longrightarrow$ "select interpolation that you desire to use", "Cutoff distance" $\longrightarrow$ "choose the distance that you would like to truncate the calculation". You will also want to be sure that you check the little box that says "Microsphere In Specimen".

Unlike the last calculation, once you click "Apply" a new small window will pop up (see Figure A.4). This window is called "Microsphere In Specimen" and is for you to enter biopsy-specific data that includes voxel size (X, Y, and Z spacing), the calibration date and time for the Y-90 microspheres, the date and time that the microspheres were infused into the patients, the half-life of the radionuclide that is being used, and whether the microspheres were TheraSpheres or SIRspheres.

This convolution will generally take a little longer than the PET/CT convolution described in the previous section. The results of the calculation can also be seen by clicking on the "results" icon.

A.3 Calculation of Dosage Using Local Deposition Method

As was mentioned in Section 1.3, when a radioactive event occurs, the emitted β particle will travel a certain distance before being annihilated and ultimately detected. The disparity between locations of emission to annihilation poses a risk of error when

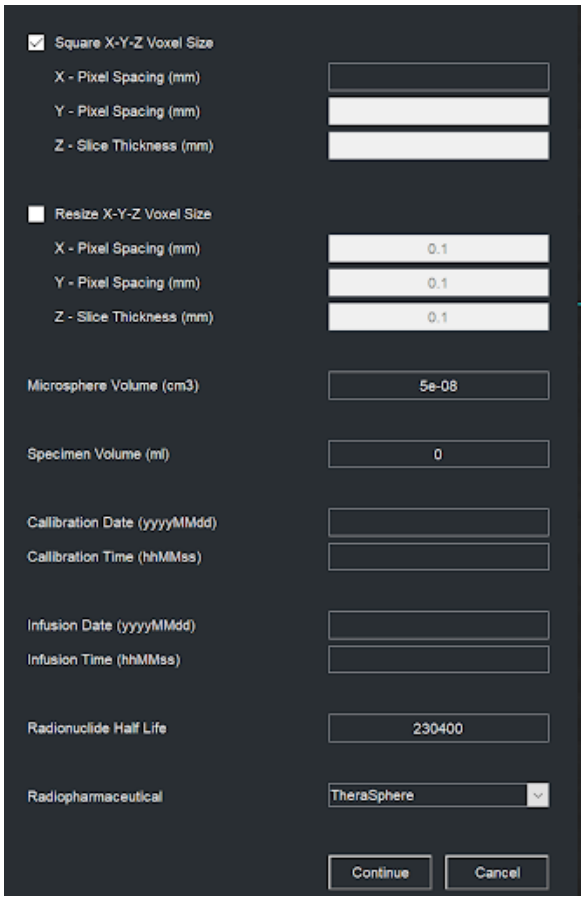

Figure A.4 Microsphere In Specimen window.

trying to calculate the dosage to a specific region of tissue. The most simple way around this conundrum is to assume that the region where the annihilation photons come from, is also the area where the dose is received. This method is known as the Local Deposition Model. During the course of this research, this method was used periodically to test results and see if the values that we were getting were within reason of expected calculations. This was done by taking the initial activity in an ROI on a PET SCAN and not applying a convolution calculation to it but instead just measuring the activity within the ROI and comparing it to the radiation that was calculated from the needle biopsy.

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