Oregon Health & Science University
School of Medicine

Scholarly Projects Final Report

Title *(Must match poster title; include key words in the title to improve electronic search capabilities.)*

Radiomics and the Future of Precision Oncology: The Relationship Between Solid Tumor Imaging Properties and Biopsy Data

Student Investigator's Name

Deepthi Nacharaju

Date of Submission *(mm/dd/yyyy)*

03/17/2023

Graduation Year

2023

Project Course *(Indicate whether the project was conducted in the Scholarly Projects Curriculum; Physician Scientist Experience; Combined Degree Program [MD/MPH, MD/PhD]; or other course.)*

Scholarly Projects Curriculum

Co-Investigators *(Names, departments; institution if not OHSU)*

Brett Johnson, PhD, Knight Cancer Institute

Joe Gray, PhD Knight Cancer Institute

Mentor's Name

Alexander Guimaraes, MD, PhD

Mentor's Department

Diagnostic Radiology

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Concentration Lead's Name

Lisa Silbert, MD, MCR, FAAN

Project/Research Question

In patients with solid malignancies, can radiomics in conjunction with biopsy data reveal signs of relapse or predict response to treatment better than imaging alone?

Type of Project *(Best description of your project; e.g., research study, quality improvement project, engineering project, etc.)*

Research study and workflow development

Key words *(4-10 words describing key aspects of your project)*

Radiomics, solid tumors, oncology, precision medicine, biopsy, core needle

Meeting Presentations

If your project was presented at a meeting besides the OHSU Capstone, please provide the meeting(s) name, location, date, and presentation format below (poster vs. podium presentation or other).

N/A

Publications *(Abstract, article, other)*

If your project was published, please provide reference(s) below in JAMA style.

N/A

Submission to Archive

Final reports will be archived in a central library to benefit other students and colleagues. Describe any restrictions below (e.g., hold until publication of article on a specific date).

N/A

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Next Steps

What are possible next steps that would build upon the results of this project? Could any data or tools resulting from the project have the potential to be used to answer new research questions by future medical students?

The next steps of this project include integrating the biopsy data from Knight Cancer and yield results with radiomic analysis from 3D slicer to determine if any variables can be correlated with one another.

Please follow the link below and complete the archival process for your Project in addition to submitting your final report.

https://ohsu.ca1.qualtrics.com/jfe/form/SV_3ls2z8V0goKiHZP

Student's Signature/Date *(Electronic signatures on this form are acceptable.)*
This report describes work that I conducted in the Scholarly Projects Curriculum or alternative academic program at the OHSU School of Medicine. By typing my signature below, I attest to its authenticity and originality and agree to submit it to the Archive.

Mentor's Approval *(Signature/date)*

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Report: *Information in the report should be consistent with the poster, but could include additional material. Insert text in the following sections targeting 1500-3000 words overall; include key figures and tables. Use Calibri 11-point font, single spaced and 1-inch margin; follow JAMA style conventions as detailed in the full instructions.*

Introduction *(≥250 words)*

Radiomics is an emerging field that focuses on expanding the role of human image interpretation to incorporate computer vision, artificial intelligence, and machine learning[1]. The goal is to gather statistical relationships of tumors as derived from various imaging modalities, including computed tomography (CT), and provide a deeper understanding of the properties that define a tumor in contrast with normal tissue[1]. This could explain diagnostic and prognostic attributes of disease and predict an individual's unique response to treatment[2]. By automatically segmenting tumors into three dimensional pixels, or voxels, and applying masks to different regions of interest, one can gather multidimensional information from tumors including tumor volume, surface volume ratios, entropy, gray level variance, and kurtosis[3,4].

This data becomes richer with the large 'omic analyses routinely performed on patients, most notably within the Knight Cancer Institute's Serial Measurements of Molecular and Architectural Responses to Therapy (SMMART) program. Patients in this program undergo frequent tissue biopsy surveillance to perform a "deep dive" into how their tumor may respond to novel treatment strategies based on 'omic analysis. In addition, these patients require frequent image surveillance. By applying novel radiomic tools to this imaging data, one hypothesizes whether "textural" features derived from radiomics can profile a tumor or provide early predictors of response, especially when correlated with data surrounding tissue biopsy, such as the number of passes, amount of sedation required, duration of sedation and post procedure complications.

The overall aim of this work was to develop a workflow for radiomic analysis and identify variables during biopsy procedures that could provide insight into the composition of a patient's tumor burden and predict response to treatment. The secondary phase of this study would include integration of the biopsy analysis completed by the Knight Cancer Institute in Portland, Oregon.

Methods *(≥250 words)*

Using 3D Slicer, an open-source image processing software, 4 CT scans of a single patient with metastatic breast cancer, including one at baseline and others between 2017 and 2019 during treatment, were uploaded. 3D masks were first applied using a threshold technique, in which the user chose the average density of an organ and allowed the program itself to lay the mask over all voxels with that density with some margin on either side of the indicated value. This was a starting point but required significant manual adjustment thereafter. Each frame of the CT scan was verified and manually sculpted to ensure that the masks only covered the target areas of either organ or tumor. Then, several metastatic lesions were identified and tracked over the 4 scans. Figure 1 demonstrates how the same target lesion was identified over time and was the target of a mask. Again, the thresholding and manual refinement techniques were applied. The 3D models were then exported and can be found in Figure 2. The radiomics kernel was used to analyze the masks, and the masses were tracked in their response to treatment over time.

The second phase included chart review of 71 patients to extract information regarding attributes around the biopsy event. These variables included number of samples, size of needle, complications of the procedure, and type and duration of anesthesia required. After each patient MRN included in the SMMART

trial was identified, the date of the procedure was located in the encounter tab. After opening this encounter, the event log was searched for the procedure note completed by a Diagnostic Radiologist. Within the procedure note, information regarding the anesthesia was first noted, including the duration of the procedure, and the amount and types of medication administered. Next, information about the number of core needle biopsies, the number of actual samples delivered to pathology, and complications were noted. This information was represented visually in multiple scatter plots to detect trends, with number of biopsies on the x axis and duration of the procedure on the y axis.

Results *(≥500 words)*

The 3D Slicer Radiomics Kernel yields 143 variables, ranging from center of mass to coarseness and grey level variance. First order variables are those of voxels alone, while second order variables are textural features, and describe the relationships of these voxels to one another. This kernel is publicly available and can be downloaded as a free software add-on to be used with 3D slicer.

For the purpose of this study, entropy, gray level variance, kurtosis, tumor volume, and surface volume ratio were specifically analyzed across all 4 time points for 7 chosen lesions. Variables such as volume demonstrated clear patterns as a result of treatment, as seen in Figure 3. The splenic mass was measured to be 45,337 voxels at the start of treatment, striking a nadir of 60.8 voxels 2 years later, shrinking by approximately 99.9% with a correlation coefficient of -0.898 with respect to time. Liver lesion 06 started at 4022 voxels, shrinking to 316 voxels at the last time point, reducing in size by 92% with a correlation coefficient of -0.993.

Other variables did not demonstrate as clear of a relationship with respect to treatment. Grey Level Variance, for example, was nonlinear, and is graphed in Figure 4. There is no clear relationship between starting volume, percent shrinkage, and Grey Level Variance. Kurtosis, which can be found in Figure 5, did not demonstrate a clear visual trend over time. Some lesions decreased in their Kurtosis value while most stayed stable despite a decrease in their overall size. Notably, Liver lesions 05 and 06 started with the highest kurtosis values of 9.23 and 9.15, respectively. Those values varied during treatment and at the most recent scan, measured 3.17 and 2.93, respectively.

The final workflow can be found in Appendix A Figure 6. This workflow outlines the directions for downloading the kernel and applying an image data set. This segment of the development process required great attention to detail because of 3DSlicer's practice of saving full projects repeatedly to the same folder, creating enormous stored file sizes on the user's hard drive. This pathway ensures that old data is deleted before rerunning the kernel while still being easily accessible when returning to open a project. Utilizing a standardized process for segmenting the lesions is important. While the tools for crude segmenting were easy to use and clear, the process for refined segmentation remains less so, and is subject to user error.

The data extracted from the biopsy procedure notes was visually represented in several bar and scatter plots. The average sedation time required for a core needle biopsy of the liver, bone, and lung, were 16.8 minutes, 38.4 minutes, and 36 minutes, respectively. The average number of samples taken were 4.5 for bone, 6.6 for liver, and 7 when completing biopsy of the lung. A graph of the target organ vs the amount of time required for the completion of the procedure can be found in Figure 7. The type of sedation used was always local lidocaine and centrally acting midazolam and fentanyl, with the exception of one case where the patient undergoing a bone marrow biopsy chose to forego medication altogether. The amounts of these medications frequently varied based on both length of procedure and weight of the patient.

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Discussion *(≥500 words)*

With the help of precision medicine, cancer treatment has become highly personalized. Individualized biopsy data is now providing insight into the tumor microenvironments across lesions, providing targets for future treatments and possible improvement in cancer treatment outcomes. For example, entropy has been used to describe gene expression and metabolic activity of tumors[5]. This is a descriptor of data that goes beyond the visual analysis of CT images.

Gray Level Variance is calculated by determining the difference in one voxel with its neighboring voxels, and can be used to determine the heterogeneity or homogeneity of an image, and can be used by a computer program to automatically segment images. In this case, it could be an indicator of how well 3DSlicer was able to automatically segment the organs and lesions without additional manual segmentation[6].

Kurtosis is a measure of outliers, indicating how wide the tails of a data distribution span. Literature has demonstrated use of Kurtosis in MRI and breast cancer. HER2 positive and triple negative subtypes had lower Kurtosis values than luminal subtypes, suggesting that this variable can both prognosticate and potentially diagnose subtypes of breast cancer[7]. In this study, Kurtosis alone did not seem to vary within the metastasis of the same patient, which is consistent with the idea that this variable varies between patients and diagnoses but is less heterogenous within the same patient.

Volume of the tumor was the most useful in determining response to treatment without additional biopsy information. This is consistent with how clinical practice uses imaging studies as the primary indicator of response. The workflow outlines the path to extract these variables as the first phase of larger ‘omic analysis and integration.

This study isolated several variables that may be of use when correlated with tumor biopsy data, such as Surface Volume Ratio, and Sedation Time during the procedure. Large deviations from the average could be indicative of potential positive findings on biopsy or as a marker of recurrence. Tumors that are very difficult to access or require very long sedation times with low yield may suggest that the tumor beds or surrounding tissues have been very scarred, involved with the malignancy, or locally invasive. Though there was one 1 complication detected in the 71 patients who underwent tumor biopsy, procedures that result in multiple complications or longer hospital admissions may also indicate that the surrounding tumor anatomy has become inflamed, fragile, and or heavily involved with the malignancy, again suggesting a poor prognosis.

For variables in which there is no clear relationship to treatment despite a decrease in overall volume, which traditionally is considered a response to treatment, there provides an opportunity for incorporation for biopsy data and the larger ‘omic analysis. There could be additional information hiding in the cell signaling, local protein expression, and mutation burden that could bring more meaning to the patterns of Gray Level Variance, for example.

Because the masks in this study relied heavily on manual refinement, it becomes difficult to exactly recreate the same radiomics values, though they should remain relatively close given the same lesions. Also, because this study compared radiomics values within one patient and not within a group of patients with the same diagnosis, it becomes difficult to give external validity to the results.

The next step is to integrate tumor biopsy data, identify episodes of relapse, and identify early markers of recurrence before imaging is positive. Making this algorithm large scale would be the most useful tool to investigate its validity, but again requires a larger team as the segmentation process can be very labor intensive. Earlier intervention could improve outcomes in quality of life and cancer prognosis.

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Conclusions *(2-3 summary sentences)*

There are several variables analyzed in radiomics and peri procedurally that could predict a patient's tumor makeup, response to treatment, and prognosis, including tumor volume, gray level variance, kurtosis, sedation time, and complications. However, further investigation and integration with pathology data after biopsy is necessary to determine the microenvironments of these tumors and their correlation with these variables.

Appendix A

Figure 1: Examples of targeted lesions for masking on CT scans, identified over time during active treatment for metastatic breast malignancy.

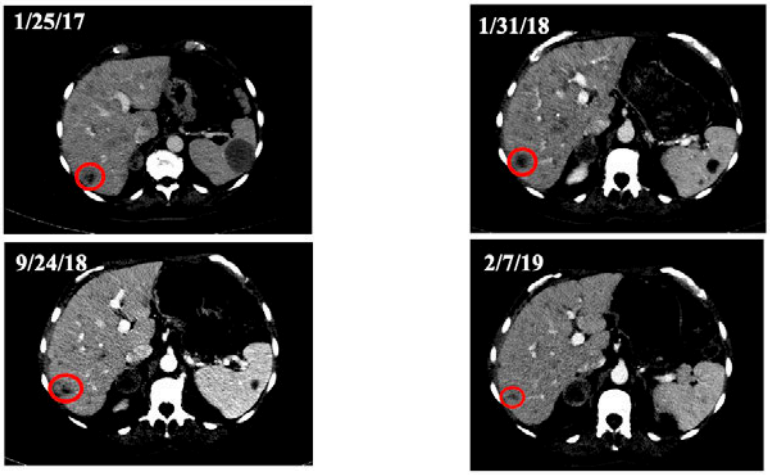


Figure 2: 3D models of targeted organs, including liver and spleen, with several tracked lesions over time.

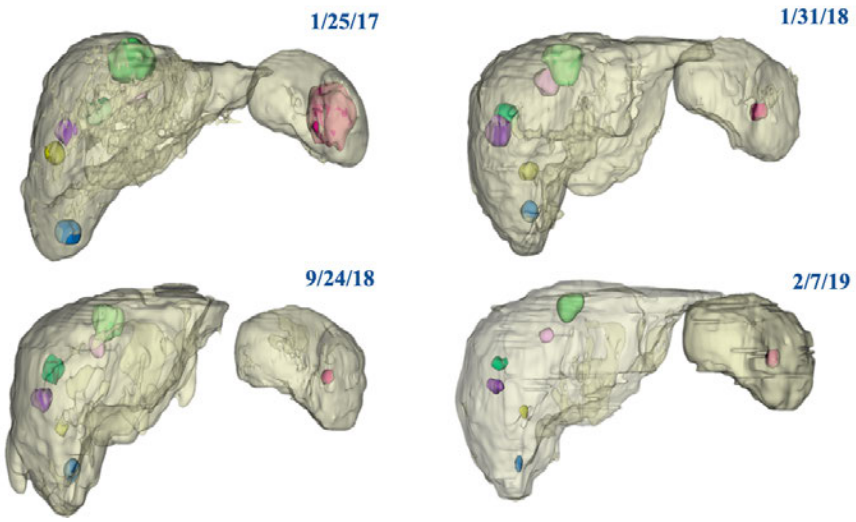


Figure 3: Scatter Plot of Tumor Volume vs Time for Each of the Chosen Metastatic Lesions

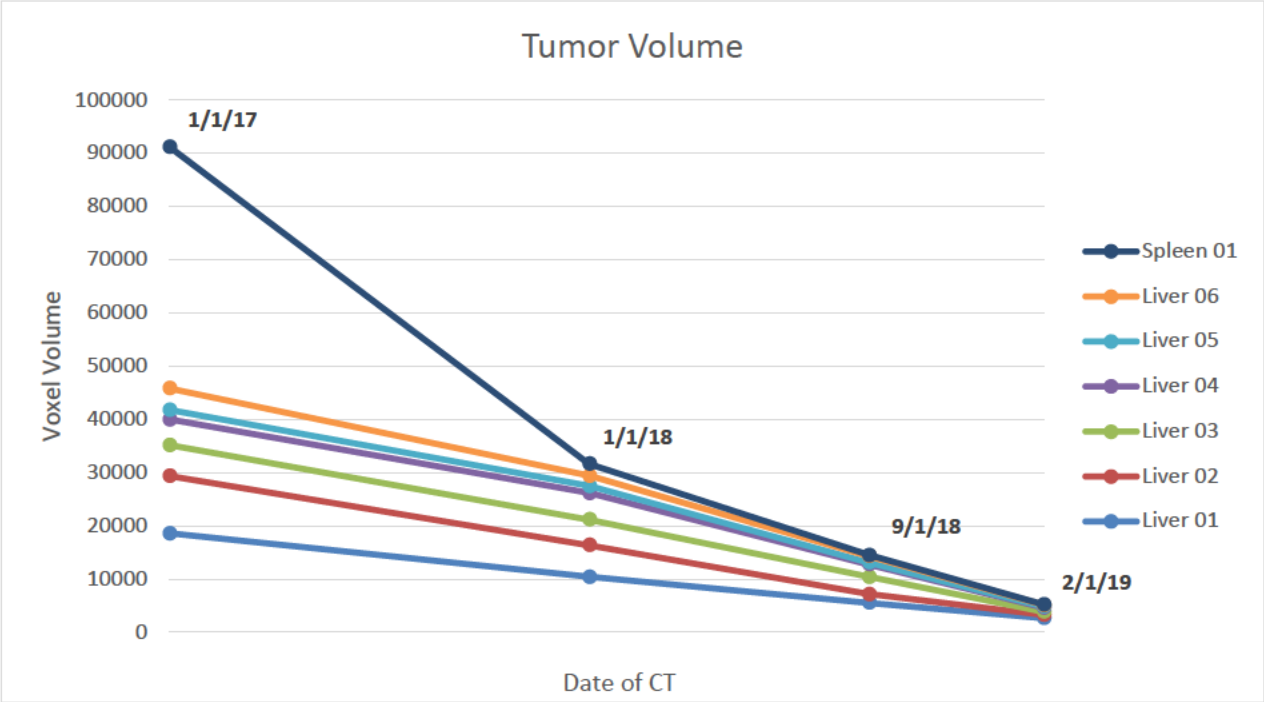


Figure 4: Scatter Plot of Grey Level Variance At Each Imaging Event

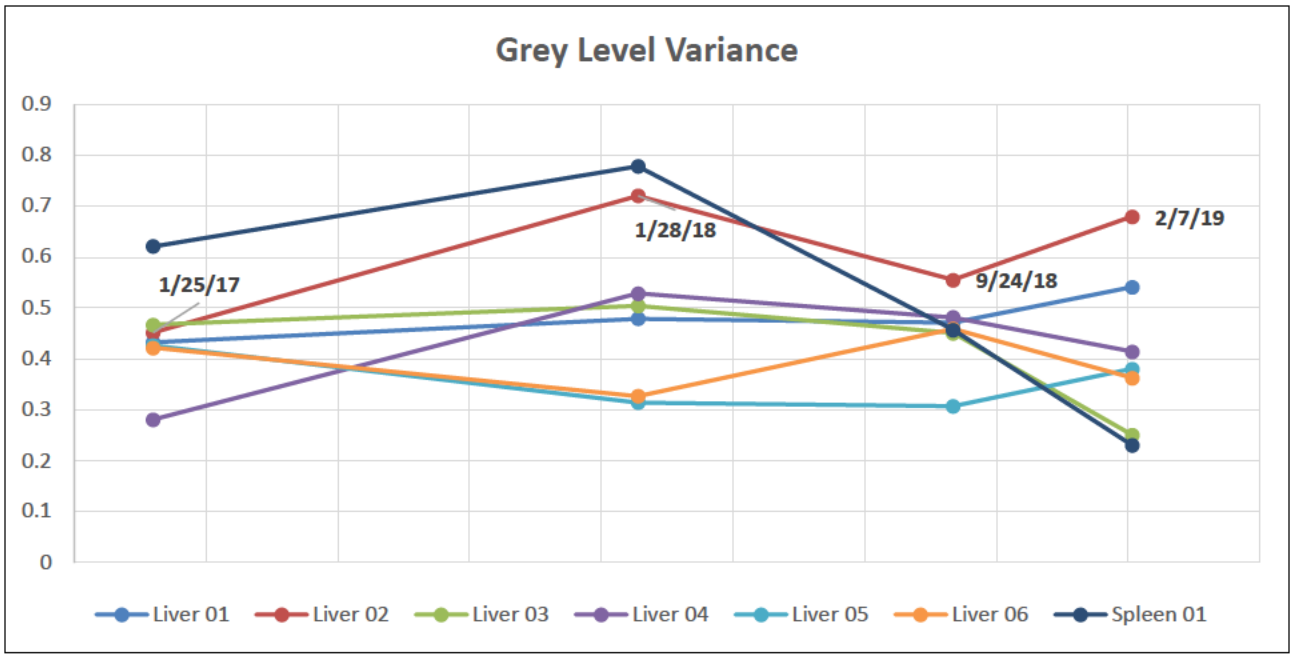


Figure 5: Scatter Plot of Kurtosis at Each Imaging Event

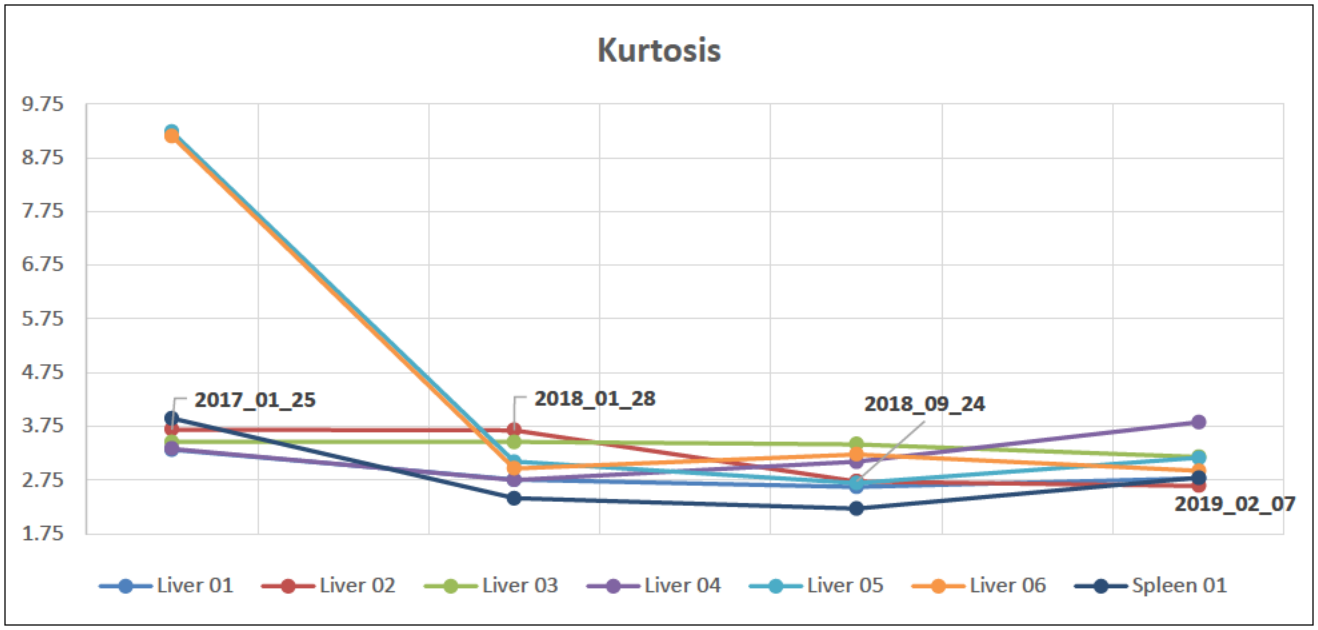


Figure 6: 3D Slicer workflow that outlines the complete process from uploading the patient CT scan to running radiomics module and extracting voxel data.

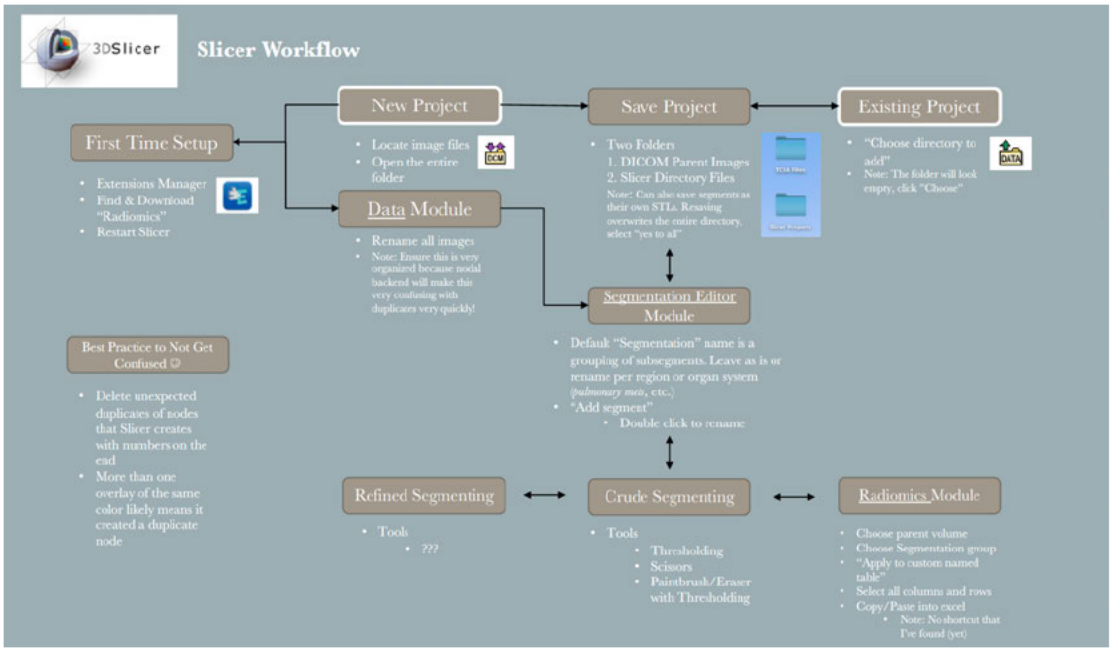
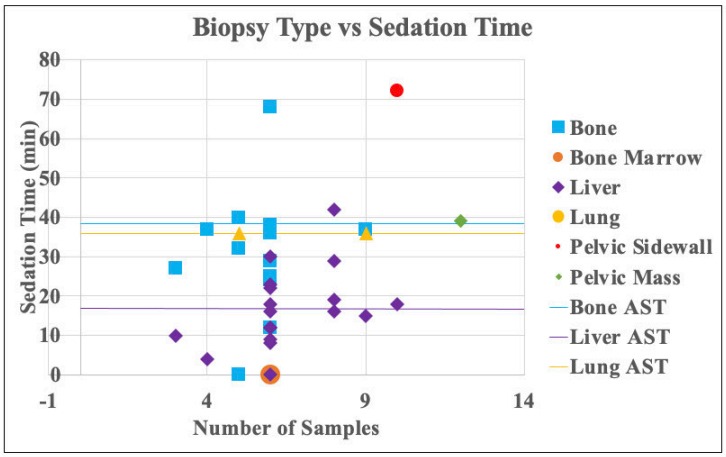


Figure 7: Scatter plot representing the amount of time under sedation required for each type of organ undergoing biopsy. AST stands for Average Sedation Time, while the Average Number of Samples is as follows: Bone – 4.5, Liver – 6.6, and Lung – 7.



References *(JAMA style format)*

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