ADIPOSE TISSUE

CLASSIFICATION & QUANTIFICATION

Using Analyze

AnalyzeDirect

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Introduction

The study of adipose tissue is motivated by the negative consequences of obesity, both medical and economic in nature. The medical consequences of obesity can be divided into two groups: those resulting from increased mass of adipose tissue, and those resulting from metabolic changes in enlarged adipocytes[1].

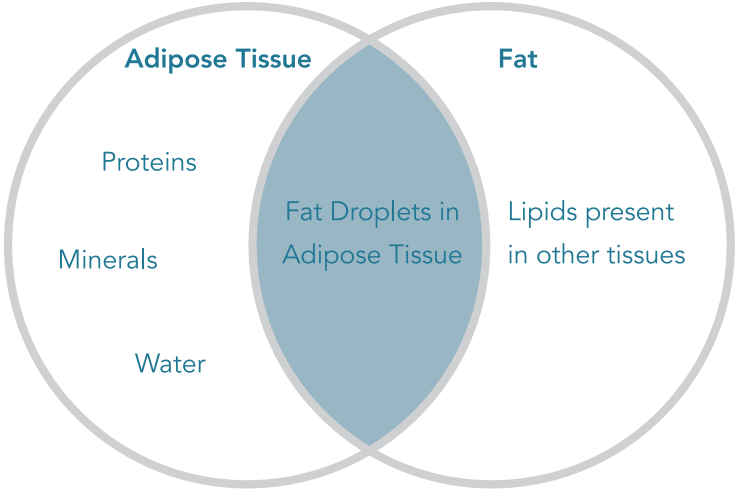
Medical Consequences of Obesity

Increased Fat Mass	Metabolic Changes in Fat Cells
Social Stigma	Type 2 Diabetes
Discrimination	Inflammation
Sleep Apnea	Cardiovascular Disease
Osteoarthritis	Hypertension

Economic consequences of obesity can be classified as direct or indirect. Direct consequences include increased medical costs: obese patients incur 46% higher inpatient costs, 27% more physician visits and outpatient costs and spend 80% more on prescription drugs compared to patients of healthy weight. Indirect economic consequences include lost productivity due to absenteeism and presenteeism (lower productivity while at work), decreased number of disability-free years of life, increased mortality before retirement, early retirement, and disability pensions[2]. These indirect costs may be much greater to society than the direct costs[3]. Individuals experience decreased personal opportunity due to a number of causes, employers experience lost productivity, absences and higher insurance premia for obese employees. In addition, government programs such as unemployment insurance, the VA, Medicare, and Medicaid experience increased costs which are then passed to the taxpayers[3].

Adipose Tissue vs. Fat

Although often used synonymously, the terms “adipose tissue” and “fat” are not the same. Adipose tissue is comprised mostly of fat molecules in adipocytes (fat storage cells), but also contains protein, minerals and water. Fat molecules, predominantly triglycerides, are present in other tissues outside of adipose tissue, but not always in quantities measurable by MRI or CT[4]. The quantification method shown here quantifies adipose tissue, not fat or triglycerides.



Adipose Tissue Compartments and Metabolic Disease

In the abdominal region, subcutaneous adipose tissue can be separated into superficial (SSAT) and deep (DSAT) compartments divided by Scarpa's fascia, which is visible in MRI and CT images. There have been shown to be metabolic differences between superficial and deep subcutaneous adipose tissue. In particular, SSAT exhibits higher levels of expression of metabolic regulatory genes, while DSAT exhibits higher levels of expression of inflammatory genes[5]. It has also been found that a higher volume of DSAT is correlated with insulin resistance[6] and that adipocytes in DSAT exhibit more lipolytic activity than those in SSAT, so that a higher volume of DSAT correlates to a higher concentration of free fatty acids[7].

Visceral adipose tissue (VAT) also contains different types of adipose tissue that vary in their metabolic properties. VAT can be classified by which main body cavity it occurs in: intrathoracic adipose tissue (ITAT) in the thoracic cavity, intraabdominal adipose tissue (IAAT) in the abdominal cavity and intrapelvic adipose tissue (IPAT) in the pelvic cavity[4].

Little is known about the physiological role of ITAT, which mostly surrounds the heart. It is thought that adipose tissue around the heart has a relatively high capacity for fatty acid release, supplying energy to the myocardium. There are also differences between the metabolic properties of IAAT and IPAT. The adipose tissue contained in IAAT is intra- and extraperitoneal, whereas IPAT contains mostly extraperitoneal adipose tissue[4].

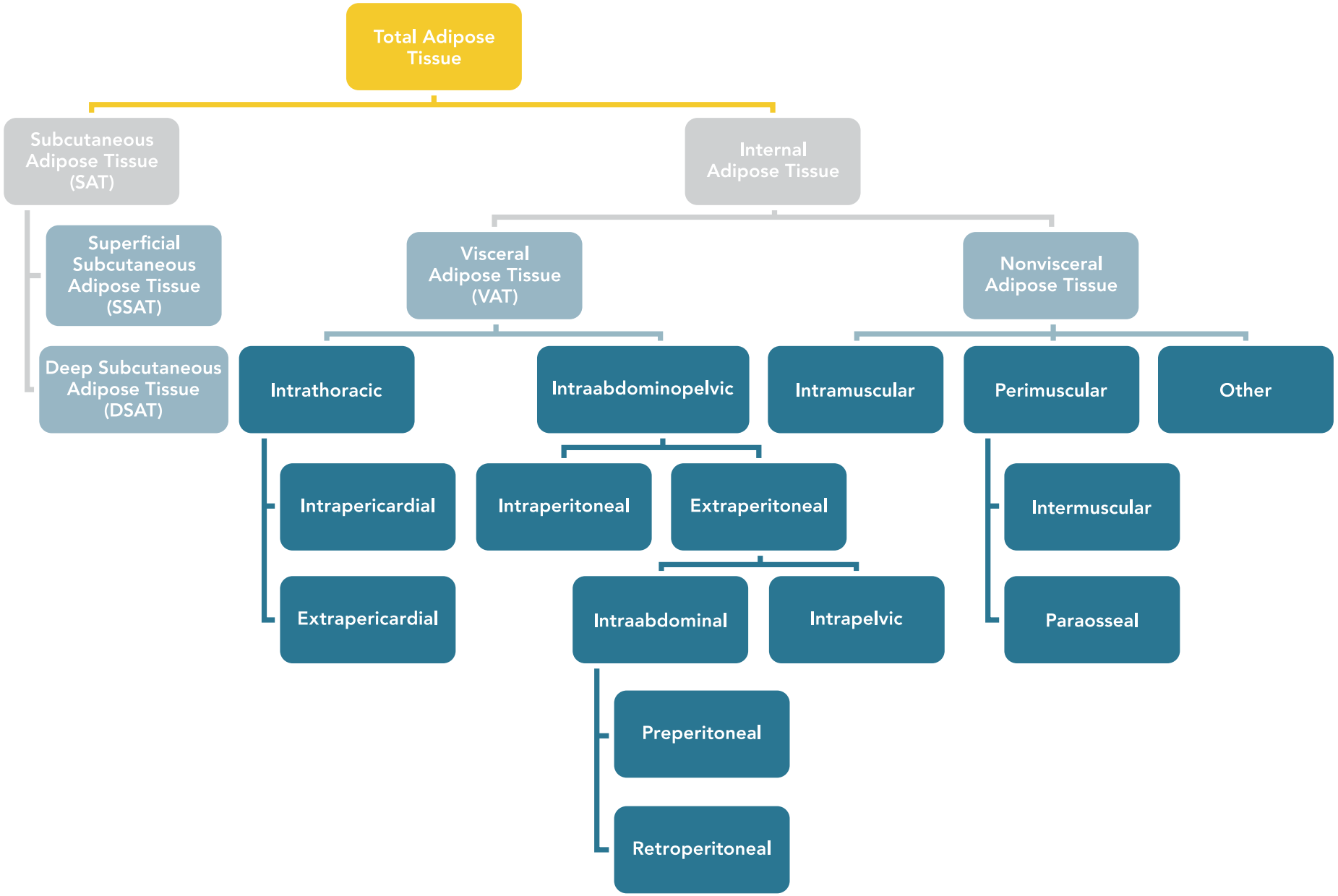
The significance of differentiating between intra- and extraperitoneal adipose tissue has been proposed to be due to a few different factors. An early theory was based upon the observation that intraperitoneal adipose tissue drains into the hepatic portal vein, whereas extraperitoneal adipose tissue drains into the inferior vena cava. This view posits that the exposure of liver cells to free fatty acids or metabolites from the intraperitoneal adipose tissue causes metabolic complications[4,8]. However, removal of extraperitoneal adipose tissue improved insulin sensitivity in rats, suggesting that extraperitoneal adipose tissue may also play a role in metabolic disease[8].

Another view is based on the role of adipose tissue as an endocrine organ. Anti-inflammatory and anti-atherogenic adipocytokines released by adipose tissue, such as adiponectin, may mediate insulin resistance, but the action of these molecules is reduced in obese and diabetic subjects due to lower concentrations of these adipokines and reduced expression of their receptors. Conversely, inflammatory molecules are increasingly secreted in hypertrophic (enlarged) intraperitoneal adipocytes of obese subjects[8].

Classification of Adipose Tissue

Historically, adipose tissue has been classified as subcutaneous, organ-surrounding, interstitial, or bone marrow adipose tissue. This approach worked well until the pathology attributable to adipose tissue began to be studied. Another system classified adipose tissue according to biological function, identifying adipose tissue as white, mammary gland, brown, or bone marrow. These categories each have different functions, such as energy storage and insulation for white adipose tissue and thermogenesis for brown adipose tissue. However, this system does not account for the metabolic properties of adipose tissue compartments such as visceral adipose tissue and also names categories as anatomic regions and functional properties with the potential for overlap.

The complete classification of total body adipose tissue based on anatomic landmarks proposed by Shen *et al.*[4] and outlined below is not necessarily achievable using images produced by current technology. As higher resolution imaging becomes available, this classification may be more completely achieved.



Shen et al. Adipose Tissue Classification

- **Total adipose tissue** includes all adipose tissue except bone marrow adipose tissue and the adipose tissue in the head, hands and feet.
- **Subcutaneous adipose tissue (SAT)** is the adipose tissue located between the dermis and the muscle fasciae, including mammary adipose tissue.
  - » **Superficial subcutaneous adipose tissue (SSAT)** is the layer of adipose tissue located between the dermis and the fascial plane in the lower trunk and gluteal-thigh area.
  - » **Deep subcutaneous adipose tissue (DSAT)** is the layer of adipose tissue located between the muscle fascia and the fascial plane in the lower trunk and gluteal-thigh area.
- **Internal adipose tissue** is equal to total adipose tissue minus subcutaneous adipose tissue.
  - » **Visceral adipose tissue (VAT)** includes the internal adipose tissue within the chest, abdomen, and pelvis.
    - – **Intrathoracic adipose tissue** is the VAT located in the thoracic cavity.
      - · **Intrapericardial** refers to VAT within the pericardium.
      - · **Extrapericardial** refers to VAT in the thoracic cavity outside the pericardium.
  - » **Intraabdominopelvic adipose tissue** is the VAT located in the abdominopelvic cavity.
    - – **Intraperitoneal** refers to abdominopelvic VAT within with the peritoneum, including omental and mesenteric adipose tissue.
    - – **Extraperitoneal** refers to abdominopelvic VAT outside the peritoneum.
      - · **Intraabdominal** refers to extraperitoneal VAT in the abdominal cavity.
        - ~ **Preperitoneal** refers to adipose tissue between the parietal peritoneum and the abdominal wall.
        - ~ **Retroperitoneal** refers to adipose tissue around retroperitoneal organs, including perirenal, pararenal, periaortic, and peripancreatic adipose tissue.
      - · **Intrapelvic** refers to extraperitoneal VAT in the pelvic cavity, including parametrial, retropubic, paravesical, retrouterine, pararectal, and retrorectal adipose tissue.
  - » **Nonvisceral internal adipose tissue** is equal to internal adipose tissue minus visceral adipose tissue.
    - – **Intramuscular adipose tissue** is located within a muscle, i.e. between fascicles.
    - – **Perimuscular adipose tissue** is located around the muscle fascia.
      - · **Intermuscular adipose tissue** is located between muscles.
      - · **Paraosseal adipose tissue** is located in the interface between muscle and bone, such as paravertebral adipose tissue.
  - » **Other nonvisceral adipose tissue** includes orbital adipose tissue and pathologic adipose tissue, such as lipoma.

Quantification of Adipose Tissue from MRI and CT

The two imaging modalities capable of quantifying adipose tissue from different compartments are MRI and CT. Each has its advantages and disadvantages.

Comparison of MRI and CT for Adipose Tissue Quantification

MRI	CT
Higher resolution possible	Lower resolution
No Radiation Exposure	Radiation Exposure
Safer for Multi-Slice Longitudinal Studies	Limited by Safety Constraints
Expensive	Less Expensive
Signal Intensity Varies with Magnetic Field	Attenuation Values Consistent Between Images
Longer Acquisition Times Cause Peristaltic Artifacts	Shorter Acquisition Times

MRI can be acquired at a higher resolution than CT, allowing for the identification of smaller pockets of adipose tissue that would not be visible otherwise. The lack of radiation exposure from MRI allows for full body scans and thus more accurate quantification of adipose tissue. Whole body MRI is expensive, so this type of study is usually limited by availability of funds. MRI signal intensity can vary with heterogeneities in the magnetic field, and slower scanning can produce artifacts from peristaltic movement in the gastrointestinal tract.

CT has a shorter acquisition time and thus produces clearer images without artifacts from peristaltic movement as in MRI. The attenuation values (in Hounsfield units) generated by CT are consistent between images, facilitating the accurate and straightforward identification of adipose tissue. However, CT carries the risk of increased radiation exposure. This can be managed by acquiring only a few sections instead of a whole body scan.

Single-slice studies are performed to reduce cost and radiation exposure in the case of CT. Most single-slice studies have traditionally focused on the L4-L5 level which contains omental, mesenteric, retroperitoneal, and smaller visceral adipose tissue compartments, along with deep and superficial subcutaneous compartments. Later studies have found that the optimal level for single-slice studies is about 5-10 cm above the L4-L5 level, or around the L3 level[9,10]. Ng *et al.*[11] most recently found that VAT volume is best correlated to VAT area at the L2-L3 level in Chinese and Indian men.

Single-slice studies may be used to estimate the volume of VAT, but may not be able to accurately differentiate between intra- and extraperitoneal adipose tissue within the VAT compartment[8].

If high accuracy is needed, a larger volume of the body should be scanned. Thomas *et al.* found that uncertainty increases as the number of slices used to quantify adipose tissue decreases[12]. Single-slice studies provide a rough estimate but may not be accurate enough for some studies. It is recommended in particular for studies that determine the relationship between adipose tissue and biological markers to use a more comprehensive volume to quantify adipose tissue.

Note that when using MRI for adipose tissue quantification, a water suppression pulse sequence may increase the accuracy of the volume measurement[13,14].

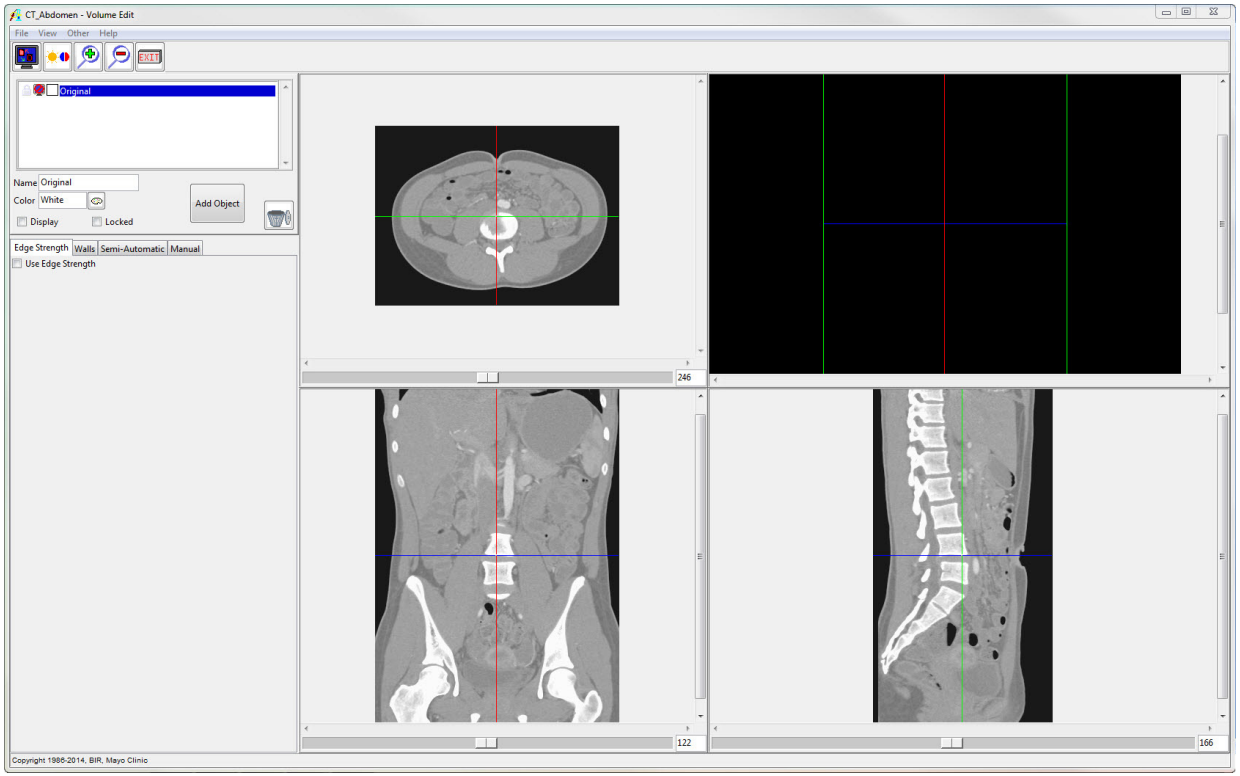
Segmenting VAT/DSAT/SSAT

This section will demonstrate how to define all regions of adipose tissue by using threshold based segmentation tools.

Single-Slice Segmentation

First, load a CT data set into the Analyze workspace and select the data set.

Open **Segment > Volume Edit**.

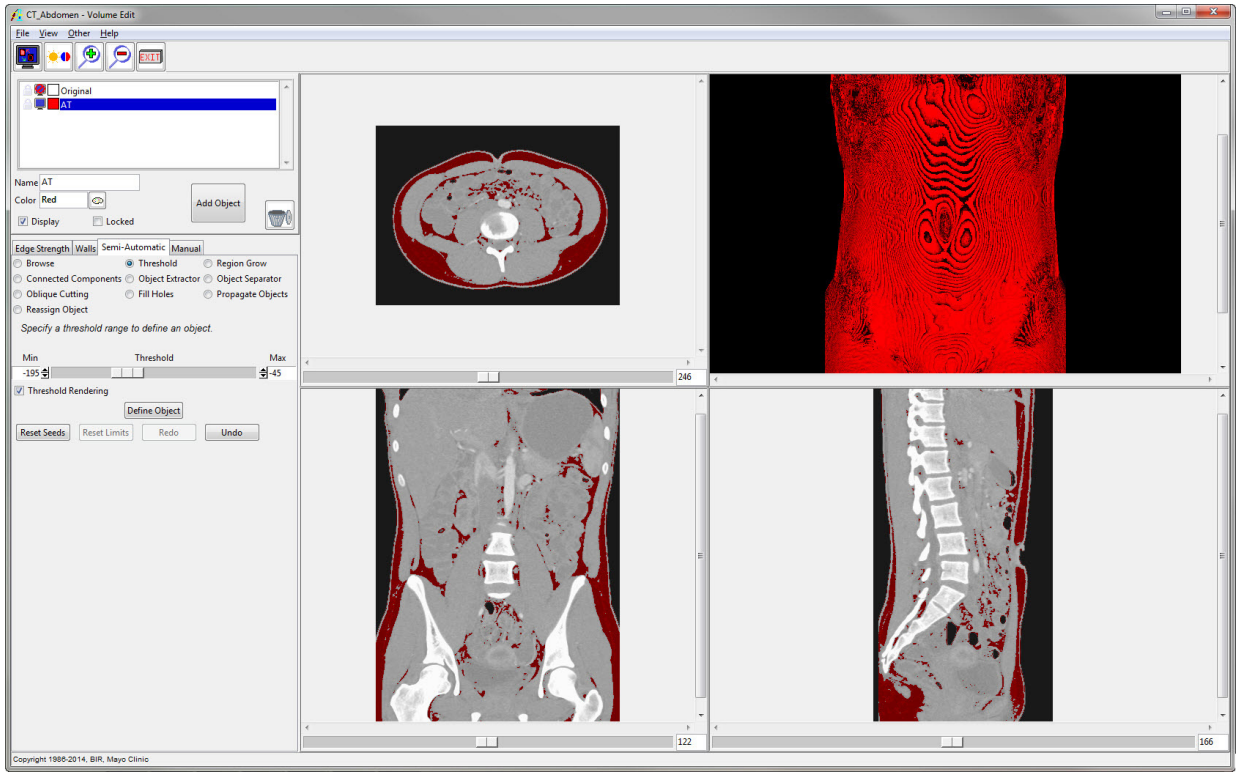


The first step in classifying adipose tissue is to identify the voxels in a data set that correspond to adipose tissue.

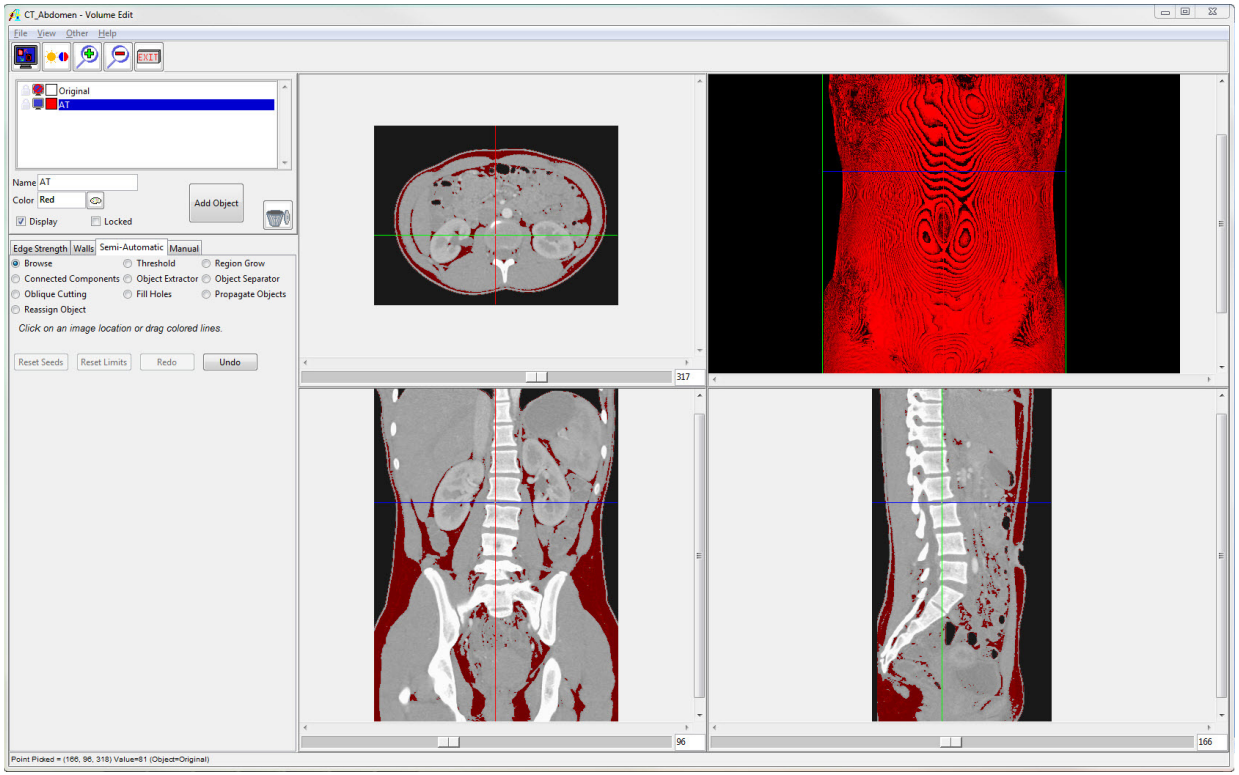
In CT data, adipose tissue occurs in a certain range of densities which corresponds to the range -195 to -45 Hounsfield units[11] or, more recently reported, -190 to -30 Hounsfield units[6,15].

Select the **Semi-Automatic tab**, and then choose the Threshold option. This abdominal CT data set is calibrated to Hounsfield units, so the threshold range was set to -195 to -45.

Click **Define Object** and change the name of the object to AT.



Since many studies use a single slice to quantify adipose tissue, we will choose a slice on the level of L2-L3 to demonstrate this method. The vertebrae can easily be seen in the sagittal view. Choose the Browse option and click between the L2 and L3 vertebrae.



Ng *et al.*[11] used an approximate technique based on anatomical features to separate intraperitoneal from retroperitoneal adipose tissue in the abdomen.

However, this type of technique for estimating the boundary between intra- and extraperitoneal adipose tissue has been shown to have an error of 3.8 – 49.4% when compared to high-resolution MRI[8].

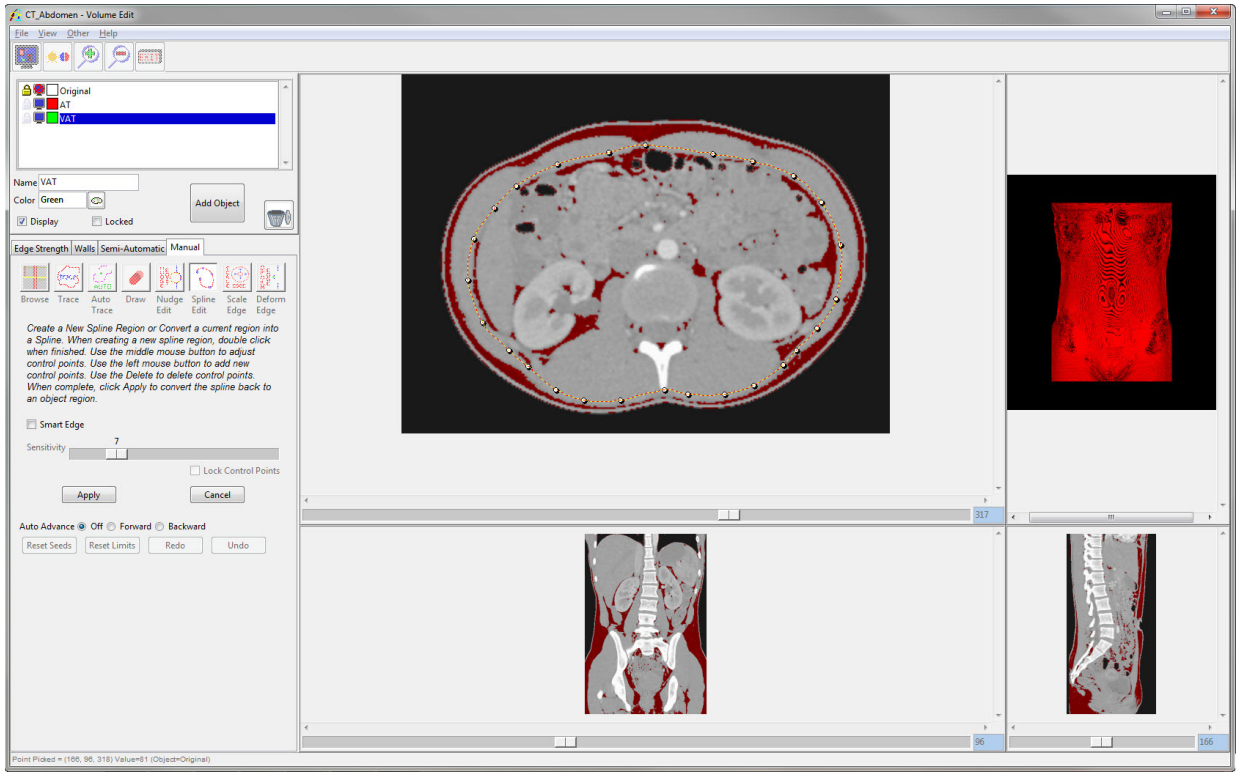
In adults, intraperitoneal and extraperitoneal adipose tissue are often adjacent to each other, and most MRI scanners are not capable of producing high enough resolution images to view the fascia between the two compartments[8].

The resolution of this scan is only sufficient to identify VAT, SSAT, and DSAT. First we will use a spline to identify the VAT on this transverse slice. Select the **Manual tab** and choose the **Spline Edit** option.

When defining the visceral adipose tissue on a transverse slice, the outer edge of the VAT should be defined by the inner boundary of the abdominal muscle wall[4].

In order to better view the transverse slice, right-click in the transverse view and set size to Double. Then Click the **Halve Current Size** button to reduce the size of the other views.

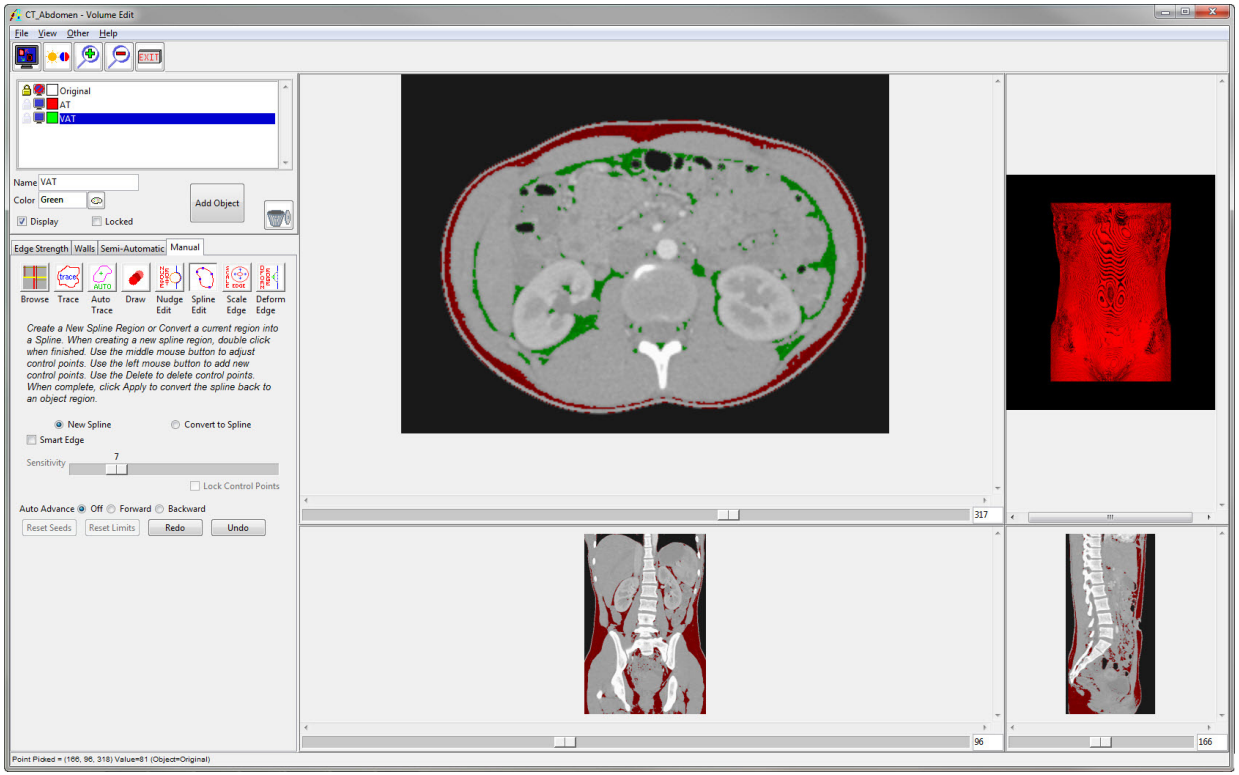
Lock the Original object, then click **Add Object** and name the new object VAT.



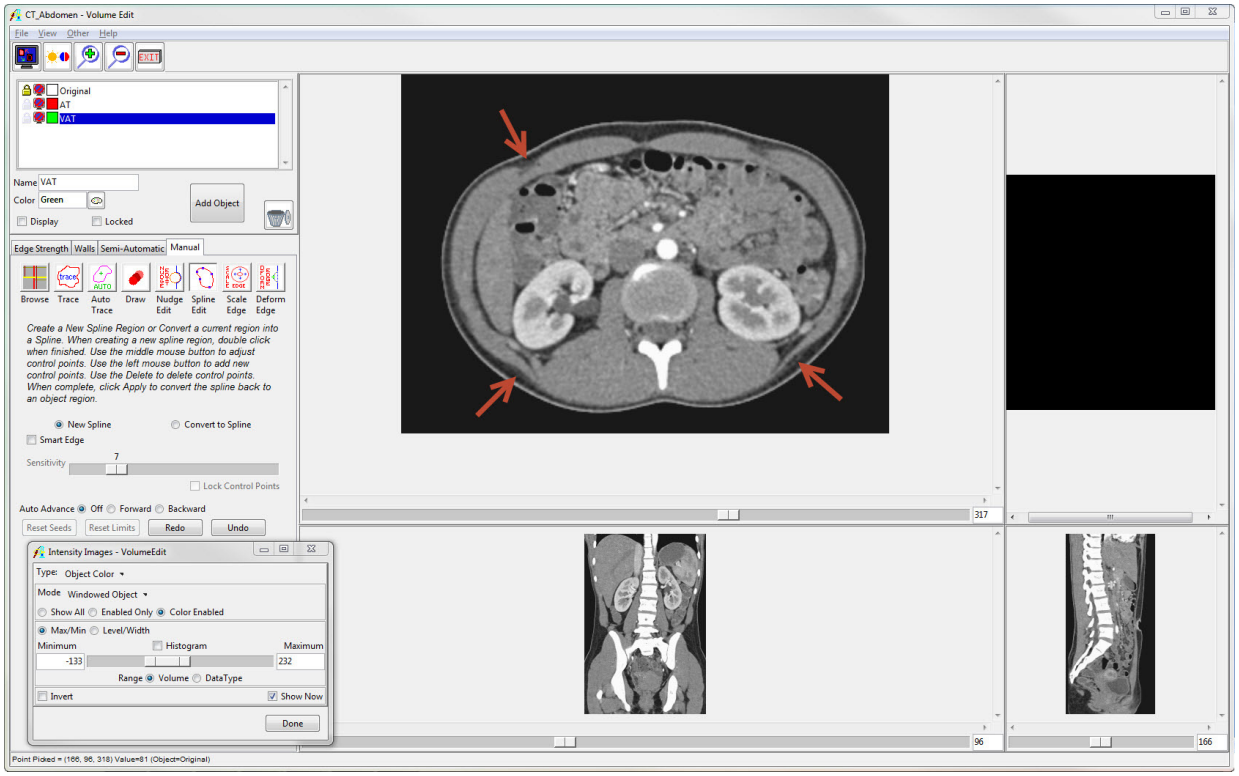
Click around the inner boundary of the abdominal muscle wall to set a spline around the VAT. Double click to close the spline, and adjust any control points as necessary by clicking and dragging with the middle mouse button. If necessary, right-click on a control point and select Delete Control Point to remove a control point from the spline.

Click **Apply** or press the A key to apply the spline to this slice.

If there is fecal matter or bowel gas present in the VAT object, manually remove them by selecting the Original object, unlocking it, and using the Draw tool to reassign those regions back to the original.



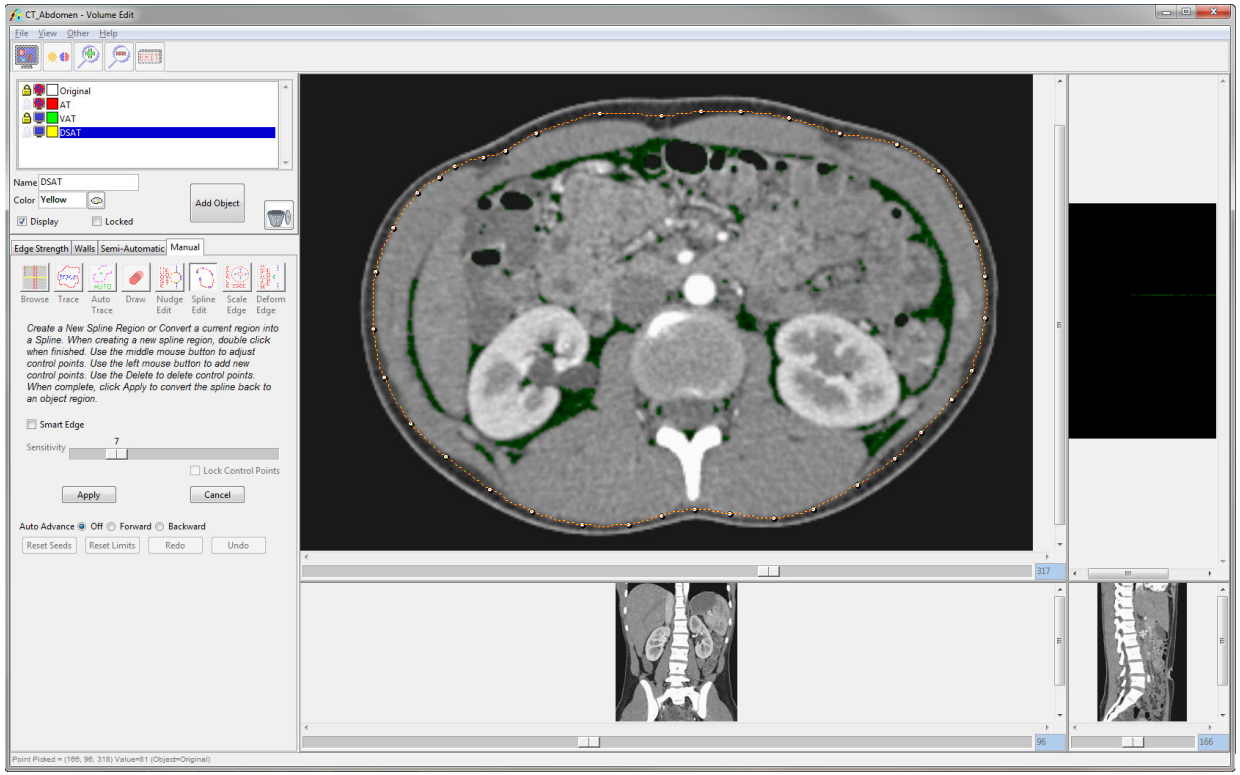
The next compartment to be quantified is DSAT. In order to make the fascia that divides DSAT from SSAT visible, the intensity display options will have to be changed. To do this, click **View > Intensities** to open the Intensity Images window. Adjust the intensity minimum and maximum values until the fascia becomes visible.



For this data set, the minimum was increased to -133 and the maximum was decreased to 232. There is not much DSAT present on this particular slice, so the fascia is still a bit difficult to see. Turn off the display of the AT and VAT objects to better visualize the fascia, and if necessary navigate to a lower slice containing more DSAT when choosing these intensity values.

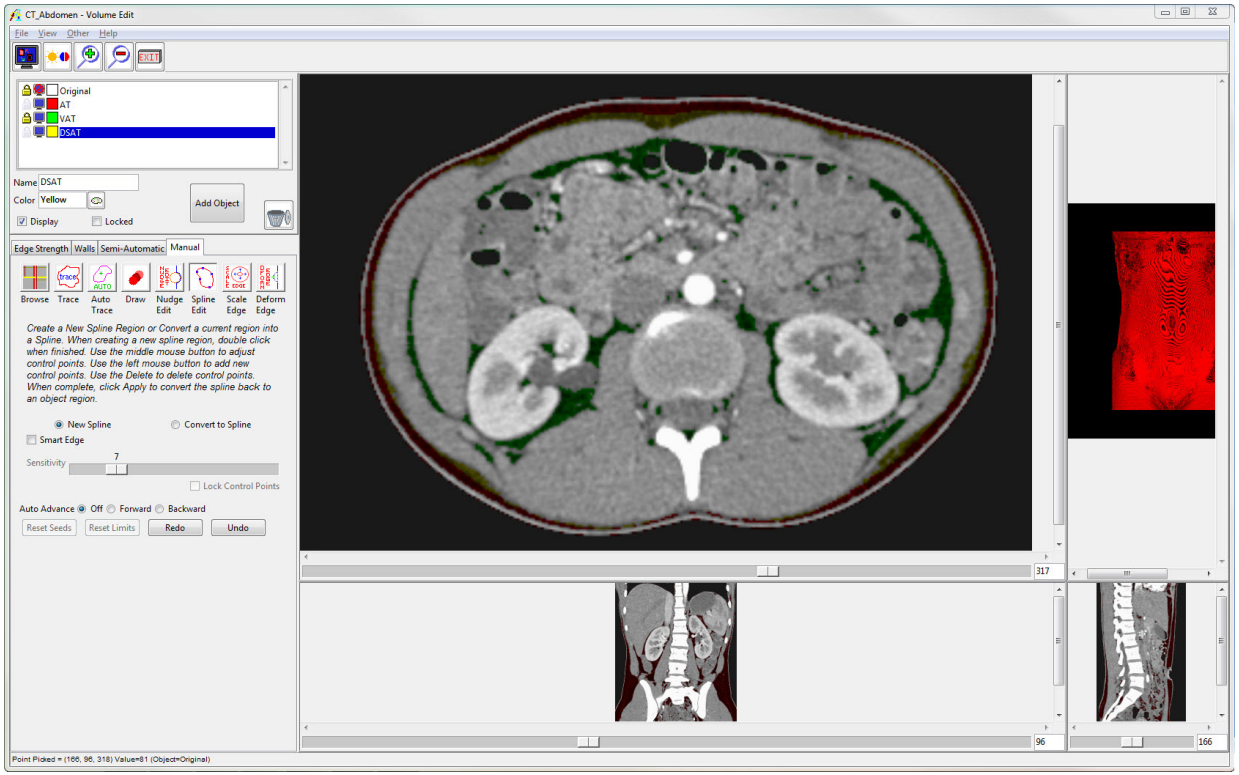
Lock the VAT object, then click **Add Object** and name the new object DSAT.

Using the Spline Edit tool, draw a spline following Scarpa's fascia. It may be easier to see if the transverse object size is set to Triple and the display of the AT object is turned off.



Click **Apply** or press the A key on your keyboard to apply the spline.

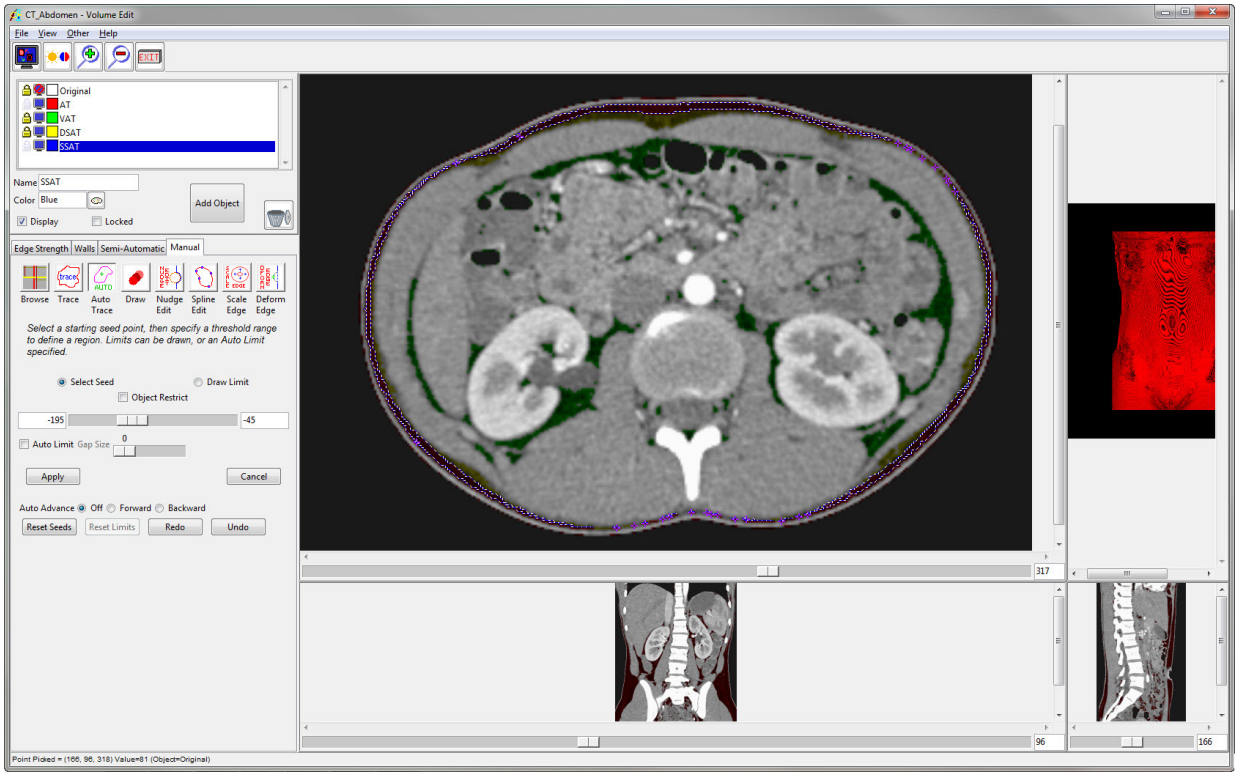
Some of the voxels remaining in the AT object belong to the skin.



To define the SSAT, we will use the Auto Trace tool.

Choose the **Auto Trace tool** and lock the DSAT object. Click **Add Object** and name the new object SSAT, then select a seed point in the SSAT.

The threshold range should already be set to that chosen for adipose tissue. It may be necessary to select multiple seed points if the SSAT object is discontinuous.

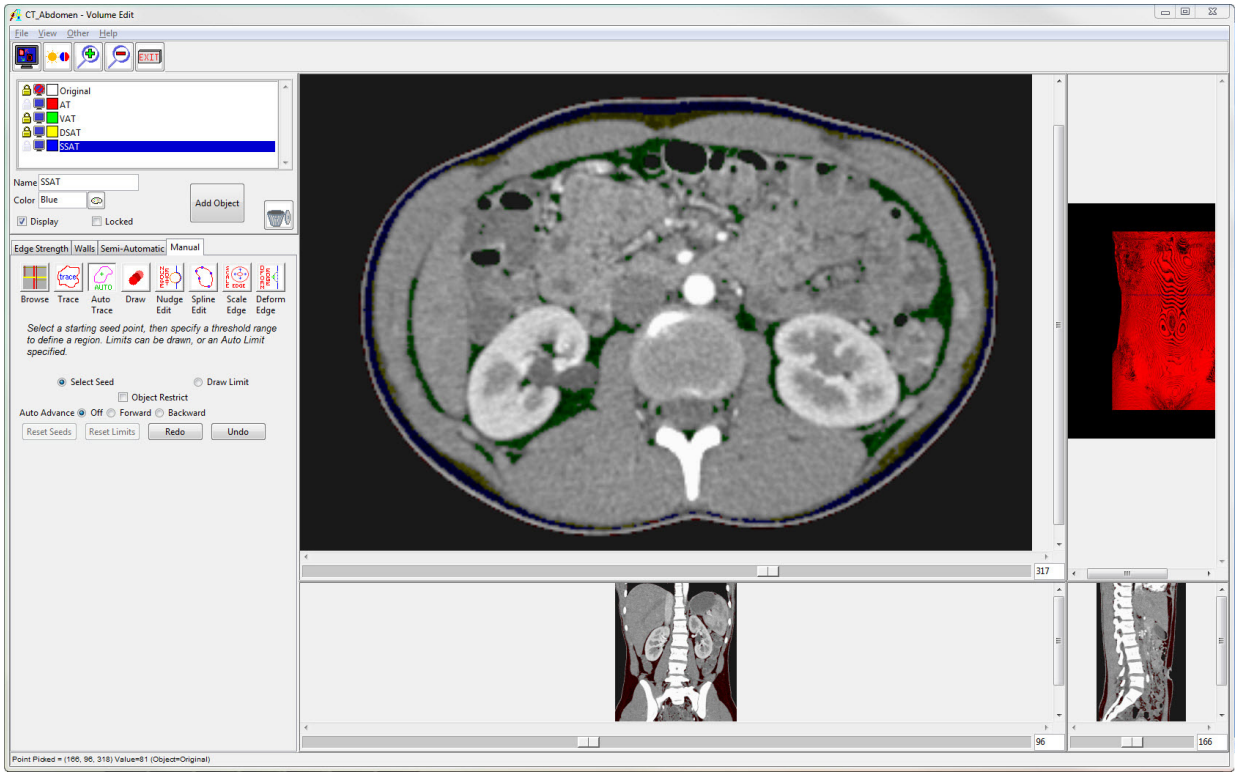


Click **Apply** to apply the auto trace and define the SSAT object.

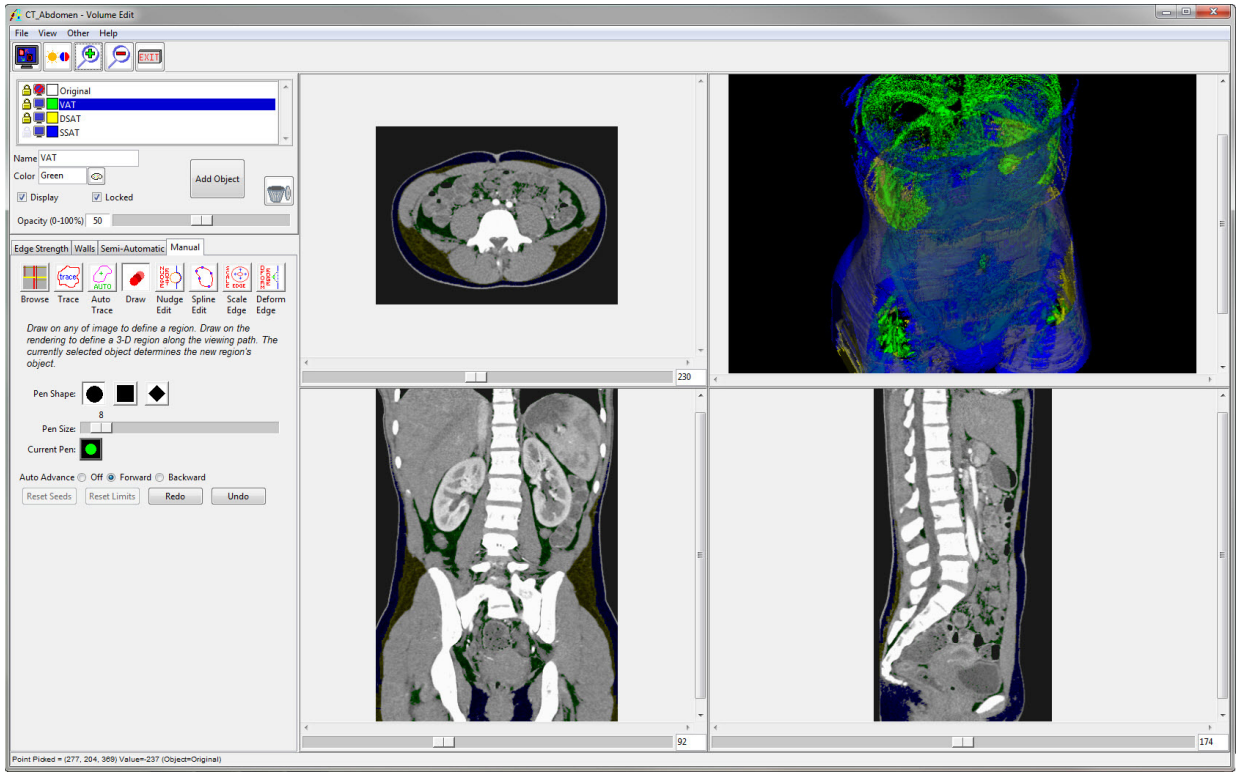
Now that all three adipose tissue objects have been defined, the first object (AT) can be deleted. Select the AT object and click the trash can button to delete it.

When the dialog box pops up, choose Yes. Now we are ready to measure the area of each adipose tissue object on the L2-L3 slice.

Save the object map by navigating to **File > Save Object Map**. Exit the Volume Edit module.



Multi-Slice Segmentation



In order to obtain more accurate volume measurements of the various adipose tissue compartments, adipose tissue in the whole body or a chosen region of the body can be classified and measured. Options include the range from the top of the liver to the pubic symphysis[16] or the top of the liver to the bottom of the pelvis[17]. This data set spans from the top of the liver to the bottom of the pelvis, so the adipose tissue in this region will be quantified.

Follow the instructions at the beginning of the single-slice classification and quantification section to threshold the adipose tissue for the entire volume, then follow the instructions for using a spline to define the VAT on one slice, starting at the lower end of the pelvis. In the Spline Edit tool, set Auto Advance to Forward to speed up the segmentation process for the VAT. Next, adjust the intensity range, and segment the DSAT as described in the previous section. Last, segment the SSAT using the Auto Trace tool. A completed segmentation of the data set from the top of the liver to the bottom of the pelvis is shown below.

Measuring VAT/DSAT/SSAT

Analyze assigns the corresponding voxels to each object during segmentation. These objects are used for quantification to return the desired measurements using the Region of Interest module.

Single-Slice Measurement

From the Analyze workspace, select the data set and then open **Measure > Region of Interest**.

Select **File > Load Object Map** and select the object map saved from the last section.

Navigate to the transverse slice of interest using the slice slider.

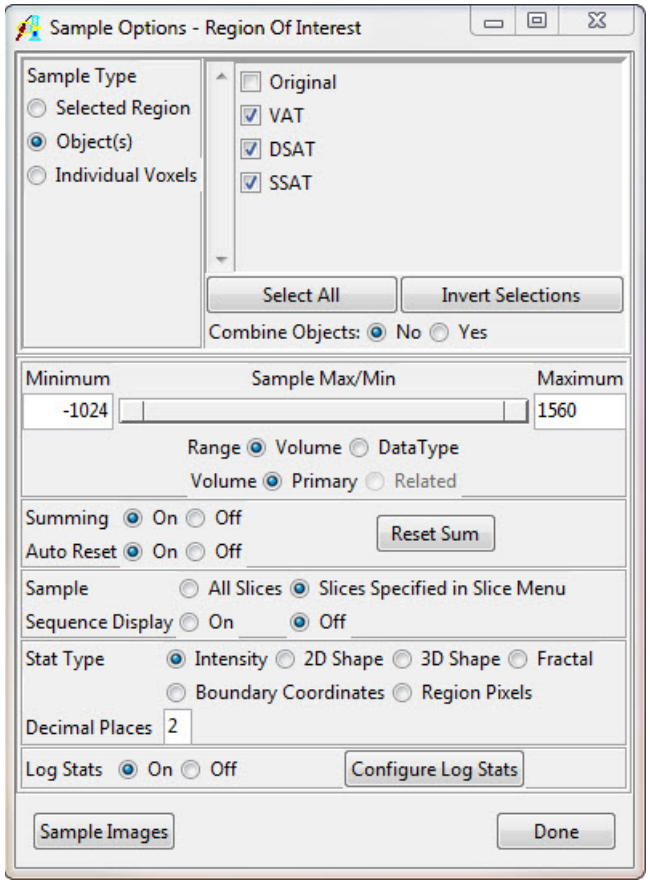
Open the **Generate > Sample Options** window.

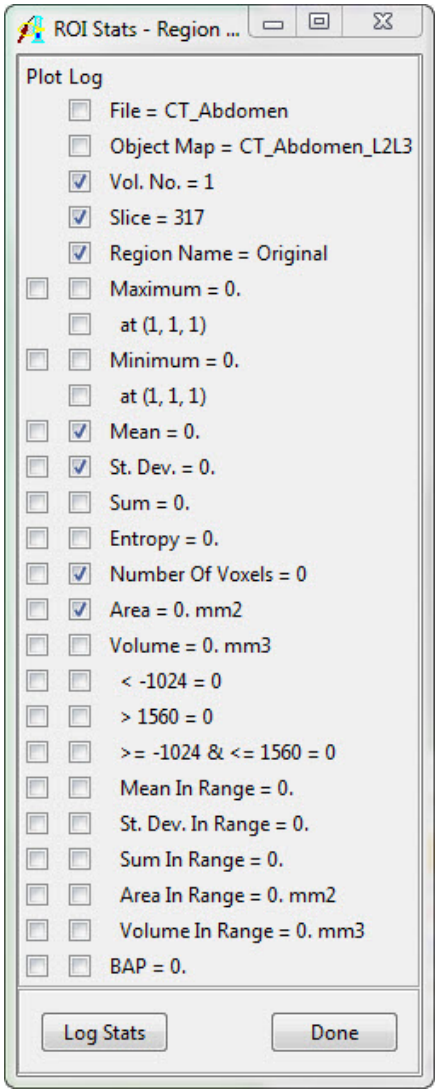
In the Sample Options window, set the following parameters:

- **Sample Type** to Object(s)
- Check the Objects **VAT, DSAT and SSAT**
- **Summing** to **Off**
- **Sample** to **Slices Specified in Slice Menu**
- **Sequence Display** to **Off**
- Choose the desired number of decimal places
- Set Log Stats to On

Click on the **Configure Log Stats button**.

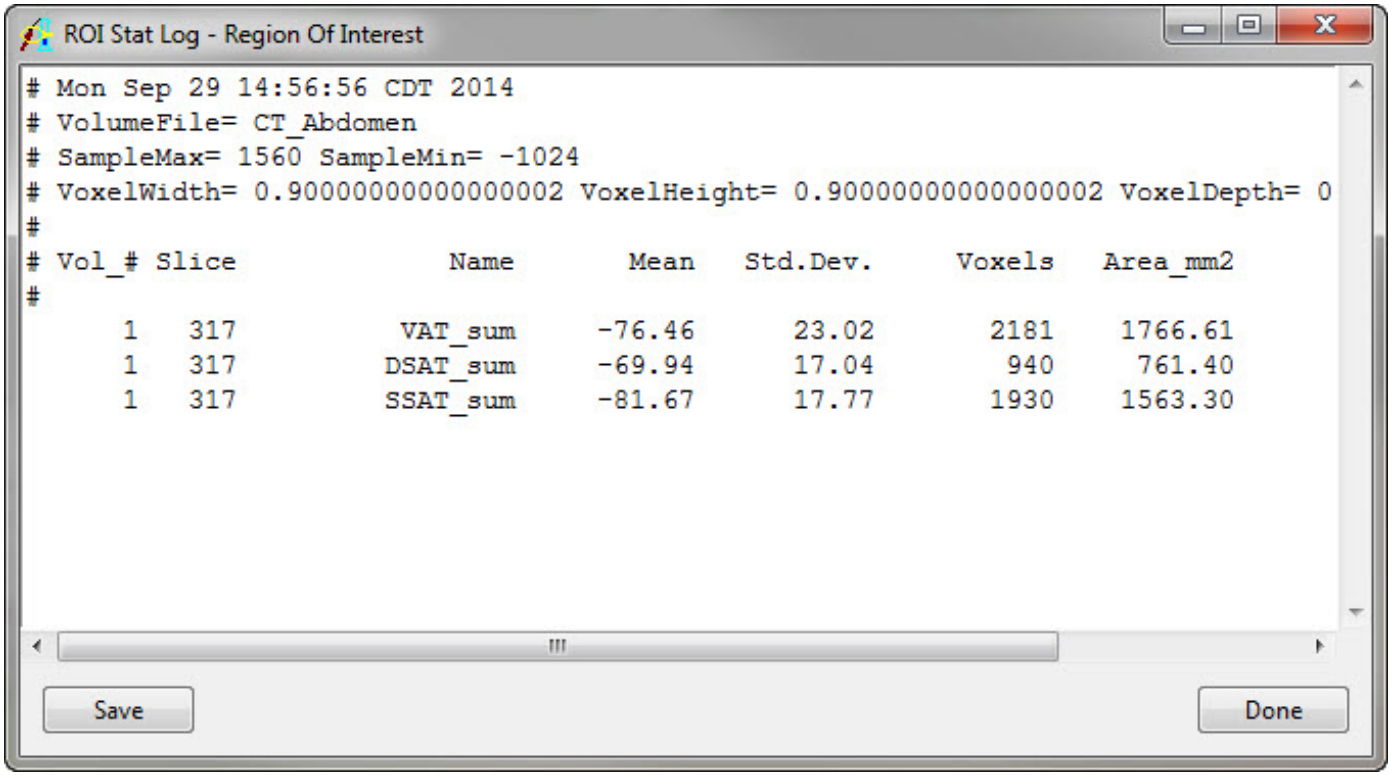
The ROI Stats window will open, showing the measurements that can be generated. Uncheck Volume, as we are only interested in the area of each object on a single slice.





Click the **Sample Images** button at the bottom of the Sample Options window. This will initiate the measurement routine. The ROI Stat Log window will open and show the area of each adipose tissue compartment on this slice.

Click Save to save the measurements as a .stats file. This can be imported into Excel or another program for further use. The single-slice area measurements can then be input into a previously determined correlation to estimate volume.



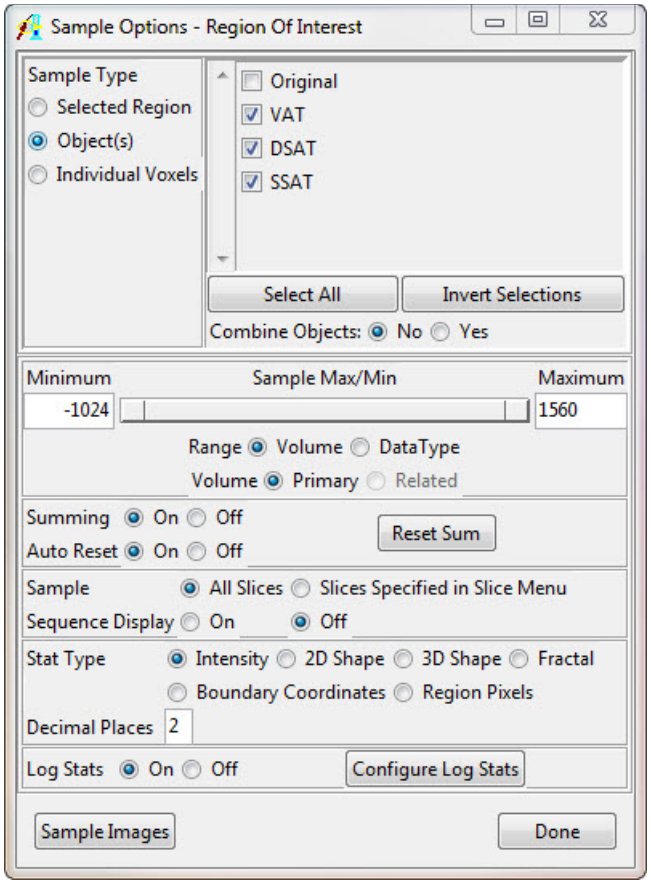
Multi-Slice Measurement

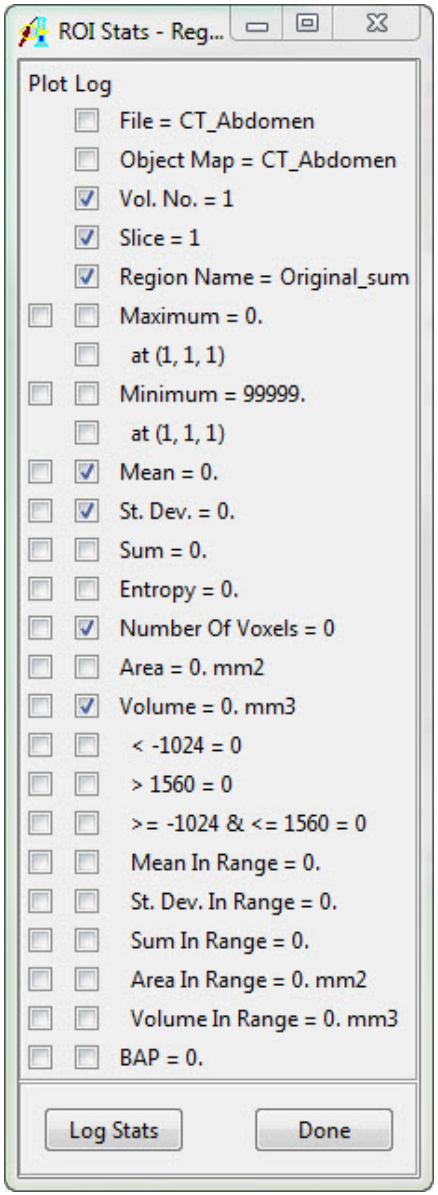
To quantify the adipose tissue from a multi-slice segmentation, open the data set in the Region of Interest module as before and load the object map.

Open the **Generate > Sample Options** window.

In the Sample Options window, set the following parameters:

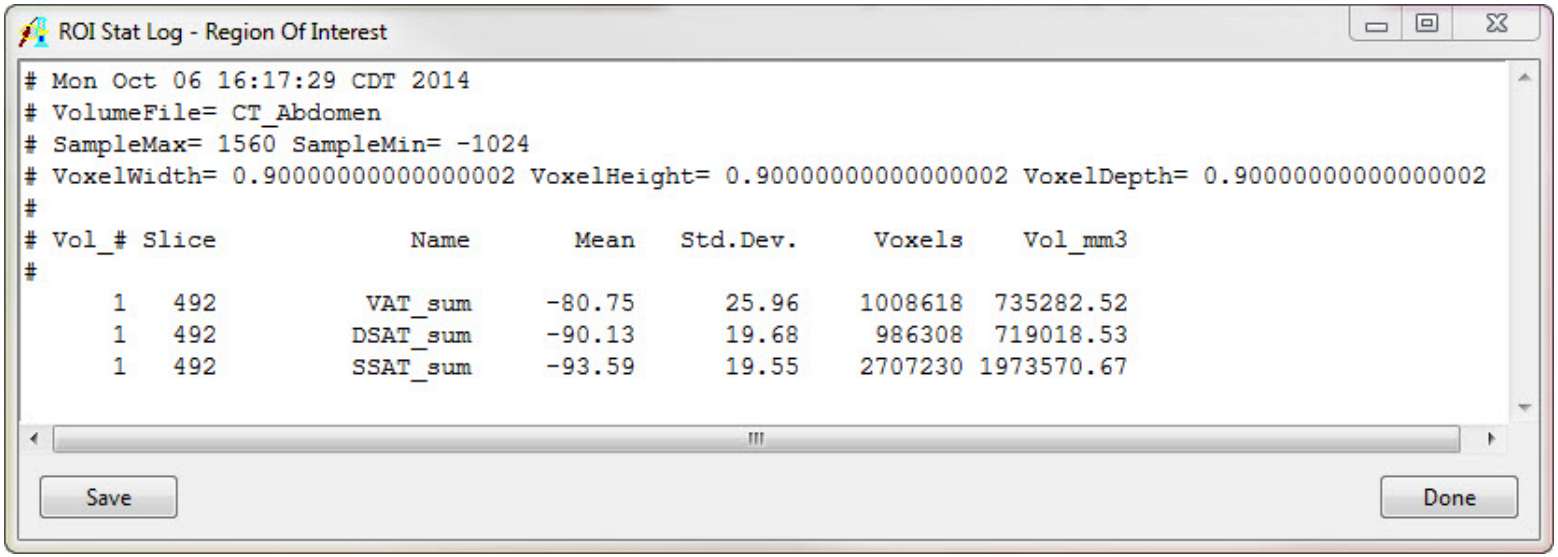
- **Sample Type** to Object(s)
- Check the Objects **VAT, DSAT and SSAT**
- **Summing** to **On**
- **Sample** to **All Slices**
- **Sequence Display** to **Off**
- Choose the desired number of decimal places
- Set Log Stats to On





Click on the Configure Log Stats button. The ROI Stats window will open, showing the measurements that can be generated. For a multi-slice segmentation, the measurement of interest is volume rather than area, so uncheck the Area measurement.

Click the **Sample Images** button at the bottom of the Sample Options window. The .stats file can be saved to disk and opened in Excel or another software package for further analysis.



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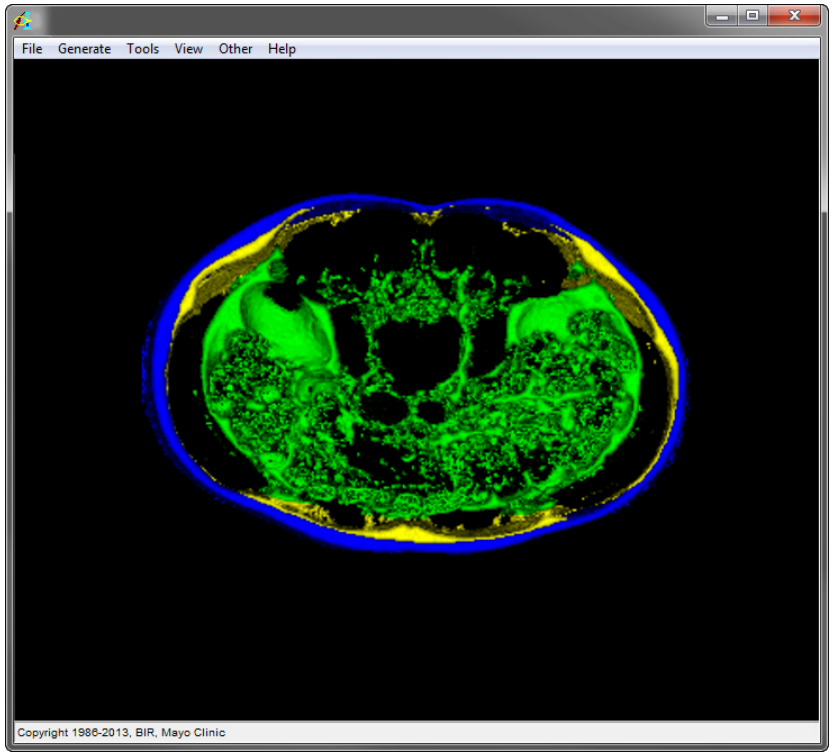

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