AUTOMATIC DETECTION AND SEGMENTATION IN L YMPHOMA WITH PET/CT

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Abstract

In this thesis a system for automatic detection and segmentation of malignant lymph nodes in PET/CT is developed and tested. PET/CT is an important tool when determining treatment and the response to treatment for lymphoma patients. The location of the malignant lymph nodes is important, as well as their size and shape. Manual segmentation is time consuming and an automatic method would increase productivity among clinicians.

The PET images are searched for possible malignant areas and these are transferred to the CT image. The areas shape and position in the PET image together with the fact that tumors are even in color in the CT image is the base for the segmentation. It is done with graph cuts in the CT image. Due to computational intensity, the segmentation is done for one transaxial image at a time.

The PET image is blurry and without detail. That makes it very difficult to know what tissue is malignant and not, based on the PET image alone. Only a physician with the knowledge of how a healthy person looks in CT images can tell what is malignant and not. However, the PET image together with the structural details in the CT image can give a good estimate on how the structure of the tumor is in detail.

The segmentations of tumors from the system are compared visually to a clinicians detailed statements on five patients. In 40% of the tumors the segmentation is correct, i.e. all malignant tissue is included and no healthy tissue is part of the segmented area.
**Nomenclature**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CAD or CADe</td>
<td>Computer-Aided Detection</td>
</tr>
<tr>
<td>CADx</td>
<td>Computer-Aided Diagnosis</td>
</tr>
<tr>
<td>coronal plane</td>
<td>The anatomical plane orthogonal to the line of sight when looking straight ahead.</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>FDG</td>
<td>2-fluoro-2-deoxy-D-glucose</td>
</tr>
<tr>
<td>HL</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>HU</td>
<td>Hounsfield Units</td>
</tr>
<tr>
<td>malignant</td>
<td>Tissue that can invade and destroy nearby tissue and that may spread to other parts of the body.</td>
</tr>
<tr>
<td>NHL</td>
<td>non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>pathological</td>
<td>Relating to or caused by disease.</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>sagittal plane</td>
<td>The anatomical plane that divides the body in its left and right side.</td>
</tr>
<tr>
<td>SUV</td>
<td>Standard Uptake Value</td>
</tr>
<tr>
<td>TBR</td>
<td>Tumor to Background Ratio</td>
</tr>
<tr>
<td>transaxial plane</td>
<td>The anatomical plane orthogonal to the spine.</td>
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1 Introduction

In this master’s thesis a computer-aided detection system is developed for detection and measurement of malignant lymph nodes in PET/CT images. The aim is to create an automatic system to help clinicians in their daily work by presenting thresholds to distinguish pathological tissue, pointing out possible pathological lymph nodes and other pathological tissue and giving the clinician relevant data to easily follow their patients progress. The aim of the CAD1 system is to find all malignant areas and measure them in size and present relevant data to the clinician, such as SUV values for the found tumors.

The PET images are used to find suspected malignant areas and the CT images are used to segment these areas and determining which tissue is part of the tumor and which is not. This segmentation is the difficult part of the work in this thesis due to the blurry and coarse PET image which gives only a general idea of the tumors structure. Clinicians rely on their experience on how a healthy body generally looks like in CT images to determine this.

The system should ideally find all malignant areas, but a reasonable goal is 90% in this stage of the work. It is of course also desirable if all sites pointed out by the system actually are malignant, i.e. the positive predict value is high2. This is always on the cost of a lower sensitivity3 since by discarding false positives there is always a risk of discarding true positives by mistake. In this work it is much more important with a high sensitivity. This is due to the nature of CAD systems and their purpose of being a helpful tool to make sure that the user does not miss any malignant tumors.

The CAD system is developed on 12 patients and tested on a set of 5 patients with lymphoma. Parts of the system, not specific for lymphoma, are tested on a group of 17 healthy patients.

To our knowledge, there is no previously published material on an automatic CAD system for lymphoma. There are some previous work on segmentation of lymph nodes given a starting position inside the lymph node. A study on such a system involved 47 patients and was found to be sufficiently accurate in 80% of the lymph nodes but the segmentation method however was never mentioned [2]. Two other methods used previously for segmenting lymph nodes is Stable Mass-Spring Models [3] and Fast Marching Methods [4]. Stable Mass-Spring Models resemble the classic method snakes, but in 3D with a system of springs to keep the shape of the model and a vector field to achieve the correct shape. Fast Marching Methods is an iteratively expanding area which is stopped by a criteria set by the user. None of these two methods presented an overall sensitivity of the method, but their results seem relatively good. In this thesis the chosen method is graph cuts [5, 6] which is a stable and fast method for segmentation in 2D and 3D.

For those readers who are not familiar with lymphoma, PET/CT or computer-aided detection systems, further information is found in Section 2. In Section 3 the segmentation method graph cuts is explained as well as a general overview of the CAD system of the thesis, followed by details on the system. The results are presented in Section 4. A discussion of the results and where to

1Computer Aided-Detection
2Number of true positives divided by the number of positives from the system. Ideally 100%
3Number of true positives divided by the number of actual positives. Ideally 100%
go from here is found in Section 5. The author of this thesis is reached on karin.m.nystrom[at]gmail.com for further information and questions.
2 Background

For those readers not familiar with the medical aspects of this master's thesis, theory about lymphoma is presented in Section 2.1. PET/CT is presented is Section 2.2 and details given in Sections 2.3 and 2.4. Computer-aided detection systems in general are presented in Section 2.5.

2.1 Lymphoma

In this section background information on lymphoma is given. See [7] for more details. Lymphoma is a type of cancer that involves the lymphatic system, which is a part of the immune system. The lymphatic system consists mainly of lymph nodes which are about 8 mm across and the fluid lymph which is transported in a network through the entire body. The lymph nodes are seen in clusters or alone. Other lymphatic tissues are the spleen, bone marrow, the tonsils and the thymus gland. The fluid lymph is filtered through the lymph nodes where lymphocytes, a type of white blood cells, search for pathological material such as bacteria or viruses and destroy it. The lymphocytes come in two types: B-lymphocytes which produce antibodies and T-lymphocytes which kill the pathological material.

Cancer is a disease where cells grow and reproduce uncontrollably and thereby become malignant. Lymphoma is a type of cancer where lymphocytes transform to malignant cells. They travel from one lymph node to another, or to other lymphatic tissues, via the lymph. Non-lymphatic organs can also be involved and in that case the disease is named extranodal disease.

There are 35 different subtypes of lymphoma which are categorized into two groups, Hodgkin lymphoma HL with 5 subtypes and non-Hodgkin lymphoma NHL with 30 subtypes. NHL is the more common type. There are two major age groups among HL-patients, 16-34 years and 55 years and older which is different from NHL where most of the patients are elderly. Differences between HL and NHL are only seen in a microscope, making biopsy⁴ necessary to distinguish the types. One difference is that HL only involves B-lymphocytes and NHL can involve B- or T-lymphocytes. It is important to determine a patient's specific type because all types react different to various treatments.

The causes for developing lymphoma are not known but risk factors include:

- age, where the risk increases with age,
- infections and diseases to the immune system, such as HIV and hepatitis B and C,
- exposure to toxic material, for instance pesticides, herbicides and solvents and
- relatives with lymphoma.

2.1.1 Symptoms and Diagnosis

Symptoms of lymphoma are mainly enlarged lymph nodes, due to the tumor, which results in painless swelling in one or more cites where lymph nodes are

⁴Removal and analysis of sample tissue.
common, such as the neck, armpit and the groin. The swollen lymph nodes can cause numbness or a swollen arm or leg. Often a swelling of the spleen is present, causing abdominal pain. Some patients have symptoms similar to the flu or a viral infection. Suspicion arises when these infectious symptoms are persistent over a long time period. If a suspected tumor is found a biopsy is made and from that tissue a pathologist can tell whether the patient is suffering from lymphoma or not, and in that case the subtype will be determined. Often a additional biopsy of the bone marrow is made to study possible involvement.

How far the cancer has spread and how serious the illness is, is quantified in four stages [8].

**Stage I** The disease is only present in one group of nodes.

**Stage II** More than one group of lymph nodes on the same side of the diaphragm are involved. A non-lymphatic organ nearby the nodes may be involved.

**Stage III** The disease involves groups of lymph nodes on both sides of the diaphragm, alternatively the spleen is involved.

**Stage IV** Non-lymphatic organs are involved, which are far away from the lymphatic sites of the disease. Stage IV is also reached when the liver, bone marrow or lung is involved.

To further describe the lymphoma additional letters may be added [8].

**A or B** If the patient has symptoms such as fever, weight loss or night sweats a B is added. If the patient does not suffer from such symptoms an A is added. Patients with B symptoms generally have poorer prognosis.

**E** Patients with involvement of organs and tissue which are not part of the lymphatic system are given an E as in extranodal.

**S** Involvement of the spleen is marked with an S.

All together, the stage and the descriptive letters, is the patients staging which is used to give the patient a prognosis.

The imaging systems CT and PET are often used in medicine and they are also used in combination (PET/CT) which is briefly described in Section 2.2. The staging of lymphoma was earlier done with CT combined with biopsy but after the commercial release of PET/CT the use of this system has increased extremely among many fields and specially in oncology. Studies on the efficiency of PET/CT have been made and they show a high accuracy for identifying lymphoma lesions using PET/CT compared to other imaging techniques. A study involving 43 patients showed an accuracy of 88% for PET/CT, 65% for PET alone and 62% for only CT [9]. The study showed a high sensitivity for both PET/CT and CT, but a low specificity for CT lowered its accuracy. While PET/CT is very popular among clinicians others claim that the evidence of the benefits are not studied enough to support the extensive use of the method [10].
2.1.2 Prognosis

The staging together with other information is collected to make a prognosis for the patient. The International Prognostic Index describes risk factors that should be taken into account when a prognosis is made.


- Age over 60 years
- Lactate dehydrogenase levels higher than normal in the patient's blood
- Stage III or IV
- Performance status. Patient is bedridden and not ambulatory
- Extramedal involvement on more than one site

Hodgkin Lymphoma (HL). See [12].

- Albumin levels less than 4 g/dl
- Hemoglobin levels less than 10.5 g/dl
- Male
- Age over 45 years
- White cell count, more than 15 000/mm$^3$
- Lymphocyte count, less than 600/mm$^3$ or less than 8% of white cell count

Depending on the number of present risk factors the survival rates differ. For NHL the percentage of surviving patients after 5 years from diagnosis varies from 83% with one riskfactor to 32% for patients with four or five factors. That is for patients younger than 60 [11]. If the patient is older than 60 the figures turn to 56% and 21% [11]. Patients with HL have a generally better chance of survival and the overall survival ranges from 56% to 90% when five or more factors are present [12].

2.1.3 Treatment

Treatment for lymphoma is primarily radiotherapy and chemotherapy [13-16], which are often used to treat many other cancer types as well.

Chemotherapy with high doses and stem cell transplant is sometimes used in cases involving children [14, 16]. Stem cells from the patients or a donors bone marrow are taken out and stored to be inserted into the patient after treatment with chemotherapy [14, 16].

For some types of NHL-patients, monoclonal antibody therapy can be used. Antibodies created in a laboratory specifically made for the patient's type of NHL are given to the patient [13, 14]. This method has minimal side-effects since antibodies are a part of the human immune system. For HL-patients, surgery is sometimes possible [15, 16].

The National Cancer Institute in the U.S. provide statistics on different types of cancer [1]. The institute has estimated the rate of incidence presented in Table 1. The data is collected under the years 2001-2005 and are presented per 100,000 U.S. citizens. The survival rate can be seen in Table 2. The rate is
based on a 5-year survival and is the likelihood that a patient will survive the five first years after diagnosis, compared with survival of healthy people. The rates are collected under the years 1996-2004.

<table>
<thead>
<tr>
<th>Incidence per 100,000</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin Lymphoma</td>
<td>2.5</td>
<td>2.7</td>
<td>2.3</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>13.0</td>
<td>15.5</td>
<td>10.9</td>
</tr>
</tbody>
</table>

Table 1: Incidence of lymphoma per 100,000 U.S. citizens over the years 2001-2005. [1]

<table>
<thead>
<tr>
<th>5-year survival rate in percent</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>younger than 65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>88.7</td>
<td>86.3</td>
<td>91.6</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>71.3</td>
<td>67.3</td>
<td>77.2</td>
</tr>
<tr>
<td>older than 65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>51.5</td>
<td>52.2</td>
<td>50.6</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>55.7</td>
<td>53.4</td>
<td>57.8</td>
</tr>
</tbody>
</table>

Table 2: 5-year survival rate relative normal death rate, years 1996-2004. [1]

It can be seen in Table 1 that non-Hodgkin lymphoma is far more common than Hodgkin lymphoma. Also, males have a slightly higher risk of falling ill in NHL compared to females. The chance of surviving if the patient is younger than 65 years old is almost 9 out of 10 for HL and 6 or 7 out of 10 for NHL, see Table 2. If the patient is older than 65 the chances drop to 1 out of 2.

2.2 PET/CT

PET/CT is a relatively new imaging technique which combines the earlier used PET and CT in one imaging device. CT stands for Computed Tomography and is, in general, x-ray in 3 dimensions, compared to classical flat x-ray which is in 2 dimensions. This gives a detailed anatomical map of the interior of a human body. The other technique, PET, is short for Positron Emission Tomography. This images the function of the organs, rather than the physical appearance. The function imaged is most often metabolism. Combining these images gives a detailed map of the body’s metabolism. Malignant tumors have high metabolism due to their rapid growth and therefore show up on the PET image. The CT image shows where in the body the tumor is located.

Both the CT and the PET machines are constructed as a very short cylinder with detectors on the cylindrical walls, pointing inwards, see Figure 1. To obtain images, the patient is slowly slid through the cylinder. In the combined construction, the PET and CT are placed next to each other, forming a longer cylinder. The patient is first slid through to take the CT images followed directly by another slide through for the PET images. The total scan time is about 45 minutes, where PET is the most time consuming part. The following sections describe CT and PET in more detail.

Continuously throughout the report a slice or image refers to the transaxial plane in PET or CT which is an images from the plane orthogonal to the
Figure 1: A PET/CT system from philips. One of the detector rings, probably the CT ring, is seen inside the tube as a dark band.

spine. Examples of transaxial (Figures 2 and 4) and coronal\(^6\) (Figures 3 and 5) PET/CT images are shown below. The CT images are to the left and the PET images from the same location in the body are to the right. In the CT image air is black, soft tissue and similar density is gray and bone is white, in a linear scale according to density. The PET slices represent the radioactive radiation where the scale goes from white to black, from low to high radiation. Note that the coronal CT images are slices, but for the PET the whole volume is stacked and the maximum value from each stack of pixels is taken.

![PET/CT images](image)

Figure 2: An example of a slice from a PET/CT scan. Between the lungs the trachea is found as the small, black, round opening. To the right of the trachea is a gray rounded object which is the aortic valve.

\(^6\)Orthogonal to the line of sight when looking straight ahead.
Figure 3: The location of the cut in Figure 2 is marked with a line. The brain, heart, kidneys and the bladder are clearly visible. The ureters are partly visible as a thin line between the kidneys and the bladder.

Figure 4: An example of a slice from a PET/CT scan. The spine is seen in the middle and the rib cage as small white bones along the outer side of the body. Parts of the liver are seen to the left and on each side of the spine the kidneys appear as rounded objects.
2.3 CT

In short CT is x-ray in 3 dimensions. The principle is a ring of detectors around the patient with an x-ray tube moving along the detector ring, making several circles around the patient. As the tube rotates, projections of the body from different angles are obtained. Since the source is a point source the projection is a fan-beam projection. A reconstruction algorithm is used to retrieve an image of the slice that resulted in the given projections. Further information on the algorithms is found in [17, ch. 3]. As the tube rotates the patient is moved through the scanner and several slices are collected and stacked to create a complete 3D volume of the patient.

Nowadays several detector rings are placed after one another to make several slices at once, shortening scan time. In 2005 the most advanced CT and PET/CT scanners had 64 rings [18]. To shorten scan time the x-ray tube’s lap time has decreased over the years down to 330 ms for a full lap [18], which is about 3 revolutions per second. The resolution is down to 25 lines per cm [18], which is equal to a resolution of 0.4 mm in an image. The slice thickness is lower than 1 mm [18].

Just as conventional flat x-ray, CT gives a image of the body’s density where fat, muscles and bone are distinguishable although different organs and muscles are hard to tell from one another. This gives a good map of the body's anatomy. The intensities in a CT-image are given in Hounsfield units, abbreviated HU where air is -1 000 HU and water is 0 HU. This leads to approximately -50 HU for fat, 40 HU for muscle and organs and bone from 200 HU to 1 000 HU. In the image colors are black for air, dark grey for fat, gray for organs and muscles and white for bones. This gives a good map of the body's anatomy. Examples of CT images can be viewed in Figures 2 to 5.
2.4 PET

Compared to CT which is an anatomical imaging technique, PET is a functional imaging. The general idea is to give the patient a radioactive material that spreads in the body and the nuclear radiation can be detected. Several detectors form a ring through which the patient is slid giving volumetric information of the spread of the radioactive molecule. In oncology the most common substance used is 2-fluoro-2-deoxy-D-glucose [19], known as FDG, which is a modified glucose molecule together with an additional flour-18 atom. It is well known that cells convert glucose to carbon dioxide and water to obtain energy. Since malignant cells grow rapidly, their consumption of glucose is high. Therefore the tracer substance, which is FDG in the case of lymphoma, will accumulate in cells with high metabolism. The modification prevents the molecule from forming into carbon dioxide and water [19] which otherwise would leave the cell and enter the bloodstream together with flour-18 rather quick. This results in the FDG’s concentration being proportional to the metabolism in every cell of the body. Later on the substance is extracted through the urine.

To get a good signal-to-noise ratio the glucose uptake for normal cells should be kept low. Food raises the insulin levels, making the cells consume more glucose instead of free fatty acids. Malignant cells on the other hand consume a lot of glucose even if the insulin level is low [19]. Therefore the patient should fast for several hours prior to the scan. It is also important for the patient to lay still and not freeze after given FDG since that will cause normal cells to use glucose. After 30 minutes to 1 hour the FDG concentration in the blood is low [19] and most of the FDG is in the cells. Since the half life of the radioactive nuclide F-18 is 110 minutes [19], time between administration of FDG and the scan is generally 45-60 minutes [19].

Many sites in the human body have a natural high metabolism, such as the brain and the heart, and give high PET values even if not malignant. All other moving muscles also show on the PET, such as the digestive tract\(^7\), shivering or talking. As mentioned earlier, FDG is extracted through the urine, making the kidneys, ureters and the bladder visible. Brown fat in the body may sometimes also gather glucose, especially when the patient is freezing. Even severed joints may show and then often in symmetry, both shoulder joints for instance. All this must be taken into account for when analyzing PET images.

2.4.1 Physics

The fluorine-18 atom is radioactive and decays to the stable isotope oxygen-18 through emission of a positron. The positron rapidly annihilates together with an electron, forming two gamma photons of 0.511 MeV which each set of in opposite directions at the speed of light. These gamma photons are used to detect the FDG concentration in a patient. A couple of factors must go right for the annihilation to be detected.

- None of the photons may be scattered.
- The photons can not be absorbed in the body.
- They must both be emitted in the direction of the detectors.

\(^7\)The digestive tract is the collection of organs involved in digesting food.
They must both be detected.

Since the efficiency of the detectors is not 100% the possibility of both the photons being detected is limited. The annihilation that gave rise to the detected photons lies somewhere along the line connecting the two detectors. A large set of lines are used to calculate the FDG concentration in a single slice. As the patient is slowly slid through the detector ring, slices of the patient’s FDG spread are calculated.

2.4.2 Attenuation

Photons traveling through matter undergo scattering and absorption which leads to a stream of photons becoming weaker and weaker while passing through material. This effect is known as attenuation. A PET scan of a uniformly distributed radioactive source will appear as being less radioactive in the center than close to the surface due to attenuation of photons emerging from the center of the object. In ordinary PET two scans are made, a transmission scan with an external photon source, and the normal emission scan. The external source in the transmission scan shows how the photons attenuate through the body. This information is used to make the emission scan attenuation corrected, visualizing the true FDG concentration [20]. The attenuation depends on the density and geometry of the scanned object, which the CT images show very well. Therefore the CT images from a PET/CT scan can be used as transmission images [20], making the PET image attenuation corrected. The PET transmission scan is therefore unnecessary in a PET/CT system and the total scan time is shortened.

2.4.3 Resolution

The resolution limit is of course dependent on the number of detectors but there is also a physical resolution limit. This is since the distance between the F-18 atom and the place of the annihilation is not zero, meaning that the positron travels a short distance before annihilating with an electron. That means that the FDG molecule not necessarily lies along the line of detection. The distance the positron travels is at average 0.64 mm and has a maximum of 2.3 mm [19]. This gives a blurring of the image of around 1.2 mm and up to a few millimeters. This limitation is completely independent of the system and sets the ultimate resolution limit. The resolution of scanners from 2006 is between 3.5 and 6 mm in the axial direction and the transaxial resolution is 4 to 6 mm [21].

2.4.4 Standard Uptake Value

The resulting PET image shows the radioactivity in Bq i.e. decays per second. This value will of course increase if the initial dose of FDG would be higher, and decrease if the patients would be bigger, making it impossible to compare images from different scans or patients. Therefore the PET data is transformed to standardized uptake values, SUV. The activity \(\nu(x)\) from the PET scan is divided by the mean activity which is the total dose \(d\) in kBq divided by the patients weight \(m\) in kg. It is expressed as

\[
\nu(x) = \frac{\text{Total Activity}}{\text{Mean Activity}} = \frac{d}{\text{Total Weight}}
\]

\(^{8}\)The direction along the body.
\[ u(\pi) = \frac{v(\pi) \cdot m}{d}. \]

A SUV value \( u(\pi) \) of 1 in the entire body is obtained for a completely uniform distribution of the drug. A high value represents a high concentration of FDG. The SUV values are more comparable between patients that Bq. Still other factors such as metabolism affect the values and comparison should be done carefully.

There must be some means of telling unnaturally high metabolism from natural and the classic is a SUV of 2.5 [20] where a higher value suggests malignancy and a lower is probably due to natural reasons. Recently, ways of obtaining a threshold for malignancy other than calculating SUV have been tested. The International Harmonization Project has recently presented guidelines for evaluation of PET/CT images of lymphoma. For tumors equal to or larger than 2 cm the activity of the mediastinal blood pool, the aortic arch\(^9\) for instance, should be used as the reference [22]. If the tumor is smaller the surrounding tissue’s activity is the reference [22]. All tumor sizes should be measured in the CT images. Values higher than the reference indicate malignancy.

### 2.5 Computer-Aided Detection Systems

Computers have influenced medicine in many different ways for a long time. In the 1970’s and 1980’s systems for helping clinicians in drug administration were being used with good results [23]. Other computer systems in health care are data banks and automation of laboratory work [23].

The many new imaging systems together with a rise in use of them gives a lot of additional information to process for every patient, especially for the 3D techniques including MRT\(^10\), CT and PET. These new imaging techniques result in a more accurate diagnosis and earlier findings of illnesses, for instance in cancer where early treatment is critical. This is revealed in NCI’s statistics [1] where the mortality in cancer has decreased since 1950 by 80% for 0-4 year olds and by 50% up to 44 years old. Older than 44 years, the mortality has not decreased as much and it has even risen if you are older that 65 years. Although this may be due to that we live longer nowadays.

In recent years, the rapid research in the field of image analysis together with the many new imaging systems available in clinics have led to a completely new use for computer systems in medical care. Commercial computer programs are available that analyze medical images in search for abnormalities, such as lesions. These programs are called computer-aided detection systems, CAD or CADe. Some systems even give a diagnosis and are therefore named computer-aided diagnosis, CADx. There is little evidence of these systems being more accurate than a trained human being i.e. a doctor, but the idea is the program assisting the human and here several studies have been made. Heang-Ping Chan et.al. [24] reviewed a total of 16 articles on studies of the improved performance of radiologists with CAD or CADx systems for lung cancer. An improvement was considered being a statistically significant increase of the radiologists AUC

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\(^9\)The early part of the aorta where it emerges from the heart and makes a bend.

\(^10\)Magnetic Resonance Imaging
with a CAD or CADx system compared to without it. The AUC is the area under the curve, the curve being the ROC curve, short for Receiver Operating Characteristic, which is a curve where the false positive rate is plotted against the sensitivity. A high AUC is equivalent to a high accuracy. In all the studies the radiologists improved with a statistical significance, although in three of the studies all groups of radiologists improved, but not all improved with statistical significance [24]. But the author points out that there still is no studies made on improvement in the daily clinical work.

The information a clinician has to analyze has increased dramatically over the past few years with the extensive use of 3D imaging systems. This is a very time consuming matter and CAD and CADx systems probably decreases the time it takes to analyze the scan and thereby increasing the efficiency. However, it is hard to find evidence on this in studies.

\[^{11}\text{specificity}\]
3 Methods

This section consists of two main parts, description of the algorithms used in this work and an overview of the implemented CAD system. Three well known methods, graph cuts and Hough transform filters are used in this work and are presented in Sections 3.1 and 3.2. The CAD system that from PET/CT images finds malignant lymph nodes is described in Section 3.3 and details are given in Sections 3.4 and 3.5.

3.1 Graph Cuts

A recent segmentation method, introduced by Boykov and Jolly in 2001 [5] is graph cuts. It has in many aspects replaced snakes [25] which is a method where a boundary in the form of a curve, i.e. a snake, is iteratively moved to minimize a energy function which forces the curve towards edges in the image while keeping the snake sufficiently smooth. Simply put, graph cuts is a way to solve the snakes problem and finding the global minimum, where snakes only finds the local minimum.

The graph cut method segments an image (2D, 3D or higher dimensions) by labeling all pixels as object or background. A graph $\mathcal{G}(\mathcal{E}, \mathcal{V})$ is built up by vertices $\mathcal{V}$ and edges $\mathcal{E}$. Every vertex represents a pixel in the image. Two additional vertices are added to the set $\mathcal{V}$, the source $S$ representing the object and the sink $T$ representing the background. An edge connects two vertices and come in three types: n-links that connects two neighboring pixels, s- or t-links connecting each vertex with both the source and the sink. A graph for a 1D image is shown in Figure 6. Non-negative weights

$$w_e \geq 0, e \in \mathcal{E}$$

are placed on all edges according to the connected vertices properties, such as intensity of the corresponding pixels. An algorithm finds a cut $\mathcal{C} \subset \mathcal{E}$ which separates the two terminals $S$ and $T$ and segments the image. The most optimal cut is the cut where the sum of the weights is smallest, where the cost of the cut is

$$|\mathcal{C}| = \sum_{e \in \mathcal{C}} w_e.$$

As seen in Figure 6 the cut divides the vertices in object and background, depending on which terminal edge is cut for that vertex.

The optimal cut is found by minimizing the energy function in (1) [6]. To set up the energy function, all pixels $p$ are part of the set $\mathcal{P}$. Define the set $\mathcal{N}$ consisting of all neighboring pixels $p, q$ in $\mathcal{P}$. The vector $A = (A_1, ..., A_{|\mathcal{P}|})$ defines a segmentation where $A_n$ can be either 1 (object) or 0 (background). In the energy function (1) $E(A)$ is a linear combination of a regional term $R(A)$ and a boundary term $B(A)$. The constant $\lambda \geq 0$ determines the relative proportion of the boundary and regional term,

$$E(A) = \lambda \cdot R(A) + B(A).$$

(1)
Figure 6: The graph of a 1D image. The cut divides the vertices as being object (light gray) and background (dark gray).

The regional term summarizes the probability that the current segmentation $A$ is correct according to the weights of the s- and t-links,

$$R(A) = \sum_{p \in P} R_p(A_p)$$

where

$$R_p(1) = -\ln P(I_p|1) \text{ (object)}$$
$$R_p(0) = -\ln P(I_p|0) \text{ (background)}.$$  \hspace{1cm} (2)

$P(I_p|1)$ is the s-link’s weight for vertex $p$ and $P(I_p|0)$ is the t-link’s weight for the same vertex.

The boundary term is the summarized penalties for cutting the n-links in this current segmentation,

$$B(A) = \sum_{p,q \in N} B_{p,q} \delta_{A_p \neq A_q}$$

where

$$\delta_{A_p \neq A_q} = \begin{cases} 1 & \text{if } A_p \neq A_q \\ 0 & \text{if } A_p = A_q. \end{cases}$$

$B_{p,q}$ is the weights of the n-links, earlier denoted $w_c$. There are many ways to construct this term and it is very dependent on the current segmentation problem. A usual weight function is

$$B_{p,q} \propto \exp \left( -\frac{(I_p - I_q)^2}{2\sigma^2} \right)$$  \hspace{1cm} (4)

where $\sigma$ is the sensitivity of the weight function and $I_{p,q}$ are the intensities at vertices $p$ and $q$. This gives a high penalty for separating similar vertices, thereby segmenting objects with homogeneous intensity.
The behavior of the algorithm varies if the t- and s-links are given high values or if the n-links have high values. Increasing the values of the n-links makes the classification of a pixel more dependent on what its neighbors are classified as. This will give objects with rounder, smoother edges.

The segmentation $A$ that gives the lowest energy in (1) is the optimal cut in the graph. In this thesis the algorithm implemented by Boykov and Kolmogorov (2004) [26] is used. The matlab implementation is written by Michael Rubinstein in 2008\textsuperscript{12}.

### 3.2 Circle Detection

Circular objects can be found in images using Hough transform filters. A filter that detects a range of circles sizes is described below [27]. For a 2D image two filters are used,

$$H_x(m, n) = \begin{cases} \frac{\cos \theta_{m,n}}{\sqrt{m^2 + n^2}} & \text{iff } r_{\text{max}}^2 \leq m^2 + n^2 \leq r_{\text{min}}^2 \\ 0 & \text{otherwise} \end{cases}$$

$$H_y(m, n) = \begin{cases} \frac{\sin \theta_{m,n}}{\sqrt{m^2 + n^2}} & \text{iff } r_{\text{max}}^2 \leq m^2 + n^2 \leq r_{\text{min}}^2 \\ 0 & \text{otherwise} \end{cases}$$

where

$$\theta_{m,n} = \arctan \frac{n}{m}.$$

These filters are applied to the gradient of the image $\nabla I = (I_x, I_y)$ to produce a peak map,

$$M = I_x \ast H_x + I_y \ast H_y.$$  \hspace{1cm} (5)

The values in the resulting image $M$ in equation (5) is proportional to the likelihood of that pixel being in the center of a circle with the size from $r_{\text{max}}$ to $r_{\text{min}}$. Circles meaning a light, filled circle against a dark background. Dark circles on a light background give low values. All peaks in $M$ are considered to emerge from round or partially round objects within or close the size limits.

The filter can be generalized to 3 dimensions, but that is not done in this thesis, since the use of 3D-filters takes much computational power to use, compared to 2D filters. Convolution with second order Gaussian derivatives of varying sizes can also be used for circle detection [28]. This will require more computational power, since the kernels are bigger but the result is similar. To detect circles with varying size, several filters must be applied, which is not necessary with the Hough transform filter described above.

### 3.3 CAD System

The goal of the CAD system is to find malignant lymph nodes and other possible malignant tissue. The found lymph nodes should be measured in size as well as mean and maximum SUV. Both the PET and the CT images are used but for different purposes. CT is an anatomical map and is used to segment lymph

\textsuperscript{12}Matlab file exchange (http://www.mathworks.com/matlabcentral/fileexchange/)
nodes and orient through the body by finding organs. PET is a functional image where the metabolism has been imaged. As said earlier in Section 2.4, malignant tumors have a high metabolism. The PET images are therefore used to find suspected pathological areas and the CT image is used to segment these areas. In the case of lymphoma the whole torso is scanned, from the base of the skull and halfway down the thigh.

The CAD system consists of two major steps; preparation of the data and analysis. In the preparation a SUV threshold is calculated to distinguish between normal and pathological tissue. Also, organs with a naturally high FDG uptake are segmented. In the analysis step, the SUV threshold is used to find areas suspected of malignancy. These areas are segmented in the CT images and measured in size and SUV value. In Figure 7 the general steps of the CAD system are presented in a flowchart.

![Flowchart of the CAD system](image)

Figure 7: A flowchart of the CAD system in this thesis.

### 3.3.1 Preparation

As mentioned in Section 2.4.4 the SUV value of the aortic arch is used as a reference when determining if a lymph node is malignant or not. If the aortic arch is found in the CT images the points can be transformed to the equivalent location in the PET images where the SUV values can be retrieved. To be able to find the aortic arch in the CT images a general orientation is necessary to know where to look for it. The aortic arch is placed between the lungs and more precisely above the splitting of trachea into two main bronchi. The steps of finding the SUV threshold are listed below.

1. Find the lungs
2. Find the trachea's splitting into two bronchi
3. Find the aortic arch

4. Transfer the aortic arch to the PET images

5. Determine the SUV mean and standard deviation in the aortic arch

The threshold for SUV values is, according to [22], SUV values greater than the SUV of the aortic arch. Since the aortic arch is not homogeneous in SUV values, the threshold is in this thesis said to be the mean plus one standard deviation. If the values were from a normal distribution, 84.2% of the voxels in the arch would have a SUV lower than the threshold.

To keep the specificity in the CAD system high the most prominent areas with naturally high SUV values are found. These are the brain, the bladder and the heart. The kidneys also show on PET but are not segmented in this thesis. The organs are detected in the PET images and also segmented to know which voxels are included in the organs.

1. Find and segment the brain in the PET image

2. Find and segment the bladder in the PET image

3. Find and segment the heart in the PET image

3.3.2 Analysis

At this stage the PET and CT images are ready to be analyzed to find tumors. Lymph nodes are small and elliptical and result in a rounded shape in the PET images. That makes a circle detector ideal for finding malignant lymph nodes in PET images.

The response peaks from the circle detector are the full set of possible tumors. Peaks within the brain, bladder or heart are dismissed. According to the guidelines mentioned in Section 2.4.4 a majority of the peaks can be sorted out. The guidelines are summarized below.

**Smaller than 2 cm.** The SUV value of the surrounding tissue should be lower that the SUV value of the tumor.

**Larger than 2 cm.** The tumor must exceed the SUV value of the mediastinal blood pool.

A problem arises because the size and shape of the lymph node must be measured in the CT image, making it impossible to know what condition it should follow, or if it follows it or not. That means all possible tumor locations must be segmented and after that said to have a good tumor to background ratio TBR or an SUV over the threshold.

To reduce the computational time, an approximation is necessary. All tumors are said to be formed as a box with the side 2 cm centered at the SUV peak. The surrounding tissue is a box with the side 5 cm and all possible tumors in this box are removed so they won’t affect the ratio. The sites where the SUV peak exceeds the surrounding box’s SUV are said to be possible small tumors. Together with all sites with an SUV above the threshold, this is the set of possible tumors.
The reduced set of possible tumor locations are now ready to be segmented. The segmentation algorithm used is graph cuts, described in Section 3.1. Depending on what is being segmented there is a number of parameters to be set. In the Section 3.5 implementation details such as parameter settings are given.

When the segmentation is done, all sites are checked if they satisfy the conditions stated in the list above. The areas left are said to be possible tumors. Below is a summary of the steps in this stage of the CAD system.

1. Find circular patterns in the PET images 
2. Remove sites inside the brain, bladder or heart 
3. Approximate a tumor to background ratio for all sites 
4. All sites with an SUV over the threshold or with a good TBR are selected 
5. Segment the selected sites with graph cuts 
6. Discard tumors not satisfying guidelines in the list above 

### 3.4 Finding Organs

In the PET image the brain and bladder are to be identified and in the CT image the lungs and the trachea\(^\text{13}\) should be found. All these objects are fairly easy to find and the descriptions of the algorithms are therefore quite brief. The trickier organs such as the heart and the aorta are described in the two following sections.

Both the brain and the bladder have very high SUV values and a threshold where both organs are included is not hard to find. The brain is simply the thresholded area highest up in the body. The bladder is aligned with the brain in the sagittal plane\(^\text{14}\) and is found as a fairly round, fairly big object far down in the body.

The problem of segmenting the brain, bladder and the heart may not be so trivial as it seems since nearby tumors can not be included in the organ. Therefore, several SUV thresholds for the organs are tested. The threshold which results in an organ with the most fitting size and shape is the threshold for that organ.

The trachea has a nice property of being constantly open due to horseshoe shaped cartilage\(^\text{15}\) in a stack which keeps the trachea from collapsing. It is seen in the CT images as a black, hollow tube. Figure 2 displays the trachea in a CT slice. Analyzing each CT slice from head and down, the first slice with one single dark area, except from the surrounding air, is probably the trachea. To follow the trachea further down is easy and it ends naturally in the lungs where the area of the trachea in the slice suddenly grows.

The lungs are simply the two biggest hollow areas after the trachea has temporarily been filled with voxels with the HU of tissue to avoid that the lungs are in contact with the outside air.

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\(^{13}\) Connects the throat to the lungs. 
\(^{14}\) The plane that divides the body in its left and right side. 
\(^{15}\) Is generally known to be found in joints, intervertebral discs and the outer ear.
3.4.1 Heart

The heart is easily identified by a human in the PET image by its peculiar bowl shape with the opening pointing upwards and forward. The shape is because the left ventricle is the one that consumes by far the most energy and is therefore the only part of the heart showing on PET scans. To find the heart in the PET image automatically it is advantageous to use the heart’s unique shape. This is done by constructing a 3D filter $f_{\text{heart}}$ which resembles the heart. The filter is constructed by averaging a couple of representative hearts and the result is viewed in Figure 8. This filter can now be convoluted with the PET image to find the most probable place of the heart. This is done with the equation

$$M(\alpha, \beta, \gamma) = \left\{ \frac{\sum_{x \in S_x} \sum_{y \in S_y} \sum_{z \in S_z} f_{\text{heart}}(x, y, z) * I_{\text{PET}}(\alpha + x, \beta + y, \gamma + z)}{\sum_{x \in S_x} \sum_{y \in S_y} \sum_{z \in S_z} I_{\text{PET}}(\alpha + x, \beta + y, \gamma + z)} \right\}$$

where $M(\alpha, \beta, \gamma)$ is the normalized filter response at the point $\alpha, \beta, \gamma$ in the PET image and $S_x, S_y, S_z$ is the set of possible coordinate values in the filter $f_{\text{heart}}$. The normalization has the advantage of making the filter response independent of the absolute SUV values and only measuring the actual match with the filter.

The problem is that this convolution is very time consuming if all possible points $\alpha, \beta, \gamma$ in $M$ where to be computed. To reduce the number of calculations, but still have high probability of finding the right spot, the algorithm is divided into two steps. First, 300 random points $M_{\alpha, \beta, \gamma}$ are calculated. From these a probability map is built up, which has high values in the vicinity of high filter responses. In the next step 700 draws are taken from the distribution of the probability map. More draws will now be made in regions with high filter response. The maximum filter response from the two sets of draws is said to be the place of the heart.

3.4.2 Aortic Valve

The aortic valve must be found in the CT image to be able to get its SUV value from the PET image. Figure 9 shows how tricky it can be to find the aortic valve, especially in the case of lymphoma where the area around the splitting of the trachea, which is just below the aortic valve, is a site for lymph nodes, which can grow as in the case of Figure 9.

The first to be noted is the rounded shape of the aorta, which is ideal to find with a circle detector, such as the one in Section 3.2. The diameter of the
aorta is at the valve approximately 25 mm, which is used in the circle detector. The area to search for the aortic valve is below the top of the lungs and above the splitting of the trachea. To avoid circular findings in the spine and rib cage, only hits between the lungs are accepted. Furthermore circles with clearly have the wrong HU value are discarded together with circles with too uneven color. But still many circles not being part of the aortic valve are still in the set. When studying several scans in detail it is found that the aortic valve appears as straight in transverse images and that it has a certain angle, which is 26 degrees counter clockwise from a vertical position, displayed in Figure 10. Of course the angle varies, but in general the angle is 26 degrees. This is used to select circles in the aortic valve with a RANSAC algorithm [29] optimized to find circles belonging to the straight line of approximately 26 degrees, or at least between 0 and 90 degrees. All steps in the algorithm to find the aortic valve are listed below.

Figure 10: The aortic valve has a certain angle which is approximately 26 degrees.

1. Cut out the area between the lungs, below the top of the lungs and above the trachea’s splitting.
2. Smooth of the CT images with a small 3x3 kernel.
3. Find circles with the diameter of approximately 25 mm.
4. Remove circles not being completely in between the lungs.
5. Remove circles with wrong HU.
6. Remove circles with uneven color.
7. Find circles on a straight line at about 26 degrees counter clockwise from the vertical position.

The set of pixels within the selected circles are transformed to the PET image and the mean and standard deviation is calculated. SUV values above the value of the aorta is said to be higher than the mean plus one standard deviation.

3.5 Parameters in Graph Cuts

For graph cuts the segmentation depends only on the weights of the links which are s-links, t-links or n-links. They represent links to the source (object), the terminal (background) and links between pixels, respectively. The optimal segment is defined as a set of links which are cut off, where the sum of the links in the set is the smallest possible that separates the source from the sink (terminal). The nodes (pixels) attached to the source after the cut are the object and the rest, attached to the sink are the background. A high weight on a link makes it harder to cut, and therefore the involved nodes get a higher probability to become objects (s-links), background (t-links) or stay together in the same segment (n-links). More information on the method is found in Section 3.1.

The smooth step function

\[ f_s(x, y_1, y_2, k, x_p) = \frac{y_2 - y_1}{1 + \exp(-k(x - x_p))} + y_1 \]  

is used throughout this section, where \( y_1 \) and \( y_2 \) are the minimum resp. maximum value of \( f_s \), \( k \) is the incline and \( x_p \) is the midpoint for the step. If \( k < 0 \) the step is reversed and \( f_s \) is inverse proportional \( x \).

The input image \( I_{ct} \) is transformed with

\[ \hat{I}_{ct} = f_s(x = -|I_{ct} - m|, y_1 = -100, y_2 = 0, k = 1/5, x_p = -25) \]

to give pixels with a HU of \( m \) high values (0) and pixels with other HU low values (-100), resulting in the transformed image \( \hat{I}_{ct} \). The HU of the tumor \( m \) is approximated by taking the mean of a small area around the center of the tumor \( x_0, y_0 \) where \( x_0 \) and \( y_0 \) are determined by (7). The image is also smoothed with a small kernel of 3x3. The center of the tumor is approximated by the position of the SUV peak,

\[ \max_{x_0 \in S_x, y_0 \in S_y} I_{pet}(x_0, y_0) \]  

where \( S_x \) and \( S_y \) are sets of all possible values of \( x \) and \( y \) for the current segmentation and \( I_{pet} \) is the intensities (SUV-values) of the PET image. In this section and the following subsections, the PET and CT images are assumed to have the same coordinate system. It is actually a linear transformation between the coordinate systems, which is ignored here.

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3.5.1 S-links

The s-links consist of two parts \( f_{\text{hu}} \) and \( f_{\text{suv}} \). In the first, the pixels with good HU values, i.e. \( I_{ct} = 0 \) are given high values and the rest are given the weight 0. That is done by using the step function in equation (6) to obtain

\[
f_{\text{hu}}(x, y) = f_s(x = \hat{I}_{ct}, y_1 = 0, y_2 = w_{\text{hu}}, k = 1/5, x_p = -25)
\]

where \( w_{\text{hu}} \) is a weight factor. In the second part, pixels with high SUV values get high values with the function

\[
f_{\text{suv}}(x, y) = \frac{I_{pet}}{t} w_{\text{suv}}
\]

where \( t \) is the SUV value of the aortic valve and \( w_{\text{suv}} \) a weight factor.

These two parts, \( f_{\text{hu}} \) and \( f_{\text{suv}} \), are weighted against each other where the highest HU value is scaled to \( w_{\text{hu}} = 1.2 \) and a SUV of the aorta is scaled to \( w_{\text{suv}} = 0.8 \). The highest of these two values is chosen as the link weight for each link. The link weights decrease further away from the SUV peak by the function

\[
f_d = \frac{||(x - x_0), (y - y_0)||_2}{20} \tag{8}
\]

where 20 is in mm and \( x_0 \) and \( y_0 \) is set by equation (7). The different factors that influence the s-links are put together according to

\[
source(x, y) = \max_{x \in S_x, y \in S_y} \left[ f_{\text{hu}}(x, y), f_{\text{suv}}(x, y) \right] w_{\text{DSO}} \frac{m_{SO}}{f_d(x, y) w_{\text{DSO}} + 1}
\]

where \( w_{\text{DSO}} \) is a weight factor for the distance term, which is set to 1.5. The constant \( m_{SO} \) is the maximum weight if a s-link. All weights and constants are summarized in the Table 3.

3.5.2 T-links

The t-links have a high value for pixels with HU far away from the approximated HU of the tumor. All the t-links increase in value further away from the SUV peak. This is done partly by the distance function \( f_d \) in equation (8), which is scaled to a value of 1.5 at 20 mm distance. The distance function is summed with a function \( f_{\text{hu-}} \) which has high values for pixels with a values close to \( \hat{I}_{ct} = -100 \). This is expressed by

\[
f_{\text{hu-}} = f_s(x = \hat{I}_{ct}, y_1 = 0, y_2 = w_{\text{hu}}, k = -1/2, x_p = -25)
\]

where \( w_{\text{hu}} \) is a weight factor of 0.8 and \( f_s \) is found in equation (6). The summation of the two factors is expressed in the function

\[
sink(x, y) = (f_d(x, y) w_{\text{DSI}} + f_{\text{hu-}}(x, y)) m_{SI}.
\]

where \( w_{\text{DSI}} \) is set to 1.5 as mentioned earlier and \( m_{SI} \) is the maximum value for t-links.
3.5.3 Summary

The previously described setup of the s- and t-links will give a segmentation which chooses pixels with good HU values and high SUV and discards pixels very far away from the center of the suspected tumors center.

<table>
<thead>
<tr>
<th>Source</th>
<th>Max value</th>
<th>Part</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$m_{So} = 80$</td>
<td>Good HU values, $f_{hu^+}$</td>
<td>$w_{hu^+} = 1.2$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High SUV values, $f_{suv}$</td>
<td>$w_{suv} = 0.8$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distance, $f_d$</td>
<td>$w_{dSo} = 1.5$</td>
</tr>
<tr>
<td>Sink</td>
<td>$m_{Si} = 80$</td>
<td>Bad HU values, $f_{hu^-}$</td>
<td>$w_{hu^-} = 1.5$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distance, $f_d$</td>
<td>$w_{dSi} = 0.8$</td>
</tr>
<tr>
<td>N-links</td>
<td>$m_n = 140$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Summary of the parameters used in graph cuts. By changing the parameters, the behavior of the algorithm is changed.

The n-links have one major role. The links must be weak where a possible tumor might have its boundary, which is seen in the CT by a slight change in intensity. Therefore, the weights of the n-links are high when the intensity of the two pixels are similar, but a slight difference makes the link strength drop quickly. The n-link strength between two pixels $p$ and $q$ is expressed by

$$n_{-\text{link}}(x_p, y_p, x_q, y_q) = f_s(x = |\hat{I}_{ct}(x_p, y_p) - \hat{I}_{ct}(x_q, y_q)|; y_1 = 0, y_2 = m_n, k = -1, x_p = 3)$$

where $f_s$ is the function in (6). The overall importance of the t-, s- and n-links is set by their maximum value. High n-links makes it more important to a pixel if its neighbors are object or background than what its t- and s-link values are. In other words, if a couple of pixels are set as object, other pixels in the vicinity will probably become object as well, if the n-links are strong. This will give smooth, rounded objects. Since that is favorable in this implementation, the s- and t-links have a maximum of 80 and the n-links have a maximum of 140, see Table 3. Expressed in terms from Section 3.1 the link strengths maximum values are

$$m_{So} = \max_{p \in P} R_p(1) = 80,$$
$$m_{Si} = \max_{p \in P} R_p(0) = 80,$$

and

$$m_n = \max_{p,q \in P} B_{p,q} = 140,$$

where $R_p$ is defined in equation (2) and (3) and $B_{p,q}$ in equation (4). The parameter $\lambda$ in equation (1) is changed by adjusting the ratio between the link’s maximum values $m_{Si}$ and $m_{So}$. The strength of the links might go beyond their maximum value since some weights are bigger than 1, SUV values in the PET image are occasionally larger than the threshold of the aorta and pixels can lie further away from the center than 20 mm.

All parameters are empirically determined and not based on measurements or studies.
4 Results

4.1 Snakes vs. Graph Cuts

Snakes was tested to segment lymph nodes in CT images as an alternative to graph cuts. The two methods are similar with a minimization of an energy function where the function has a regional and a boundary term where the regional term is an external force that is put together according to properties of the object to segment and the boundary term controls the shape of the boundary. It is not surprising that the two methods gave similar results.

The main problem with snakes is the computational time which is higher, and of course varies with the number of iterations. In this implementation snakes took approximately 1.5 s with 50 iterations while graph cuts completed on 0.2 s, both for one segmentation of varying size. If snakes would have been used as segmentation algorithm in the CAD system the computational time would have been at least 20 minutes, which is far too long. Compare with the time needed for the CAD system with graph cuts which is 5-8 minutes.

Despite the computational time, snakes has other more theoretical drawbacks. As mentioned earlier in Section 3.1 snakes finds the local solution where graph cuts finds the global. This makes snakes sensitive to the initial position of the curve where different curves may lead to different results. Another drawback is the iterations since it is hard to know how many iterations are necessary. Initial curves, far away from the border, or complex borders can result in a faulty segmentation if the steps are too few.

4.2 Experimental Results

To get a feeling of how heavy it is to work with PET/CT images the reader should know that the data from a PET/CT scan of the torso is up to 320x512x512 voxels for CT and 320x168x168 voxels for PET which is totally 200 MB of data. When every second PET and CT slice is deleted and the CT resolution reduced by a factor of two the CAD system completes in 5 to 8 minutes on a standard dual core 2.2 GHz computer. Because of this the analytical step of the CAD system which is possible to make in 3D is forced to be reduced to 2D.

The sensitivity of the organ segmentation algorithms is studied on 17 healthy patients. For organs in the PET image, the brain, bladder and heart, all parts of the organ that shows in the image must be included. No other structures may be included. For the trachea it must at least reach down to where it splits to two bronchi. The lungs must be separated into two lungs and the whole lungs must be included. As for the case of one faulty lung segmentation, the lungs were so dense that parts of the lungs were missed out. For the aortic valve, the whole valve must not be included, but at least 20-30 pixels must be correct. Of course no pixels are aloud to be found in other places that in the aorta. An example of the organ segmentation of the lungs, trachea and aorta is seen in Figure 11. All evaluations were done visually. None of the patients were used when developing the algorithm. The results are seen in Table 4.

The sensitivity of the detection and segmentation of malignant tissue was studied together with a physician at Sahlgrenska in Gothenburg. 5 new lymphoma patients were studied and the physician pointed out and segmented all pathological tissue in the patients. The result is presented in Table 5.
Table 4: Results from the organ detection and segmentations. A study on 17 healthy patients.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Percent correct detection and segmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>82.4%</td>
</tr>
<tr>
<td>Bladder</td>
<td>88.2%</td>
</tr>
<tr>
<td>Heart</td>
<td>76.5%</td>
</tr>
<tr>
<td>Trachea</td>
<td>88.2%</td>
</tr>
<tr>
<td>Lungs</td>
<td>94.1%</td>
</tr>
<tr>
<td>Aortic Valve</td>
<td>70.6%</td>
</tr>
</tbody>
</table>

Figure 11: An example of correct segmented lungs, trachea and aorta marked in a CT slice.
of 26 tumors were identified. Of those, 3 were not detected by the system at all. Mainly because of their locations which were in bone or lung tissue with very high resp. low HU values which were discarded as not being soft tissue. Every tumor was analyzed with graph cuts slice by slice and although the tumor was found, some slices were not found by the system, especially at the ends of the tumor. This reduces the sensitivity for detection from 88.5% to 81.4%. Of the tumors that were found and segmented, 40.0% of the total number of segmented slices were correct. If counting the total number of slices with pathological tissue, 30.8% were correctly segmented. By correct segmentation means no leakage to surrounding healthy tissue and no misses of tissue which was pathological in a visual inspection. In Figure 12 examples of correct and faulty segmentations are shown.

![Correct and faulty segmentations](image)

Figure 12: An example of a correct lymph node segmentation (left) and a incorrect segmentation (right) where muscle tissue has been included, marked with the green ring.

<table>
<thead>
<tr>
<th>Studied ratio</th>
<th>Percent correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of tumors found by system</td>
<td>88.5%</td>
</tr>
<tr>
<td>Percent of tumor slices, found by system</td>
<td>81.4%</td>
</tr>
<tr>
<td>Percent of found tumor slices segmented correctly</td>
<td>40%</td>
</tr>
<tr>
<td>Percent of all tumor slices segmented correctly</td>
<td>30.8%</td>
</tr>
</tbody>
</table>

Table 5: Results of the CAD system in a study on 5 patients with lymphoma.

The positive predict value for the system is very low, between 2-10%, which means that only 2-10% of the sites which the system claims to be positive actually were positive. That means that the goal is 100%. The main reason is the low threshold used, the SUV value of the mediastinal blood pool. A tumor can have such a low value, but is generally only malignant if there is any abnormalities in the CT image at the site.
5 Discussion

The CAD system for lymphoma is evaluated in two studies. The algorithms to find organs in PET and CT images are evaluated on 17 healthy patients. The mean success rate is 83.3%. The detection and segmentation of malignant tissue is studied on 5 lymphoma patients where the detection has a sensitivity of 81.4% and the segmentation is correct in 40.0% of the found tumors.

The segmentation with graph cuts which is currently done in 2D, would benefit from the use of 3D. Now, the segmentation is done separately for each slice which results in mismatch of the boundary between slices. It also results in some slices of the tumor being missed completely. That resulted in a lowering of the sensitivity from 88.5% to 81.4%. With 3D, the risk of missing slices would decrease rapidly. There is one possible drawback with 3D. When analyzing lymph nodes which are of around 10-20 mm when malignant, the slice thickness of a couple of millimeters is quite big. It is therefore suspected that the boundaries of the lymph nodes might be lost in the axial direction, making leakage to other slices a problem. The benefits or drawbacks are, however, not investigated in this work.

The algorithms for finding the organs are not perfect and the main reasons will be explained here. In the case of the brain, for most of the 17 patients the brain was not included in the images which sometimes had the effect that the algorithm pointed out other sites in the neck area as the brain. All in all the sensitivity of the brain finding algorithm is not reliable in this study because the low rate of brains in the images. The heart algorithm is stable and reliable but has one problem. In some patients the heart does not show in the PET images, resulting in the algorithm finding the spleen or other nearby organs. Both for the heart and brain, the algorithm tries to sort out the cases where there is no organ to find, but this is not completely fail safe. As for the trachea the main problem is when some patients have a very thin trachea wall which leads to a merging with the lung and the tracking of the trachea is lost. That would be solvable with a higher threshold, but that would also lead to the risk of the algorithm not finding its way all the way down to the splitting due to the narrower path. The solution is to have a variable threshold. Another problem with the algorithm is when it does not find a starting point, mainly because the patient has his or her arms on the chest. This causes problems only in very few cases. The lung algorithm failed only in one of the 17 patients where the lungs were very dense and parts of the lungs were lost. The algorithm with the worst sensitivity is the aortic valve detector. The sensitivity may be even worse for lymphoma patients because of the lymph nodes in the vicinity which may grow and cause a problem, see Figure 9 on page 31. If a malignant lymph node is included in the aortic segmentation, the SUV threshold will rise and pathological sites will be lost.

In the study with 5 patients from Sahlgrenska 3 of the 26 tumors were not found. This is because the algorithm sorted out peaks from the circle detector with a HU that was far away from soft tissue. In retrospect, this is incorrect because although the main purpose of the CAD system is to segment lymph nodes, other pathological tissue must not be overlooked. With that mistake corrected the sensitivity would probably rise from 88.5% to 90-95%.
5.1 Future Work

For future work, many of the algorithms to find organs need to be further developed to achieve a higher sensitivity. A more extensive study of the organ finding algorithms with 110 patients is currently in progress to determine the sensitivity and for PET also the specificity.

It would be interesting to investigate the difference between 3D segmentation and 2D segmentation with graph cuts. Will the suspected leakage problem have any effect? How will the overall sensitivity be affected?

In the description of the CAD system the system was said to measure size and SUV values on the found tumors, which is not implemented due to the time limit of the master’s thesis. This would not be hard to implement and would make the system useful in the future. The most interesting extension is to investigate if it is possible to compare scans of the same patient and get data such as shrinkage or enlargement of tumors and if the number of tumor sites has increased or decreased.

There is a third possible way to use graph cuts other than the 2D and 3D discussed earlier. As for now, graph cuts is done on a single site, i.e. a cut-out of the patients body. It may be possible to do graph cuts on the entire scan area at once. Leakage may become a bigger problem since it may be hard to raise the value of the t-links at a distance from the possible tumor, as described in Section 3.5. Moreover it also is hard to tell how the computational time will be affected.

There are two possible future developments for this work. First, if the sensitivity of the CAD system is high enough it may be used in clinical work with lymphoma patients. It may also be possible to develop a CADx system, i.e. including a staging of the patient. That would require analyzing the number of infected lymph node conglomerates\(^{16}\), determining if the disease is present on both sides of the diaphragm and if the spleen is involved. This requires a much better positive predict value than the current. The other possible future use is to develop an general CT segmentation tool for segmentation of organs using graph cuts. It can be used to measure size or mean and max SUV value for an organ. Segmenting tissue is extremely time consuming and clinicians would benefit from such a tool.

\(^{16}\)lymph node clusters
References


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