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Master's Thesis in Biomedical Engineering

Evaluation of Quantitative PET/CT Usage for Cancer Treatment

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March 23, 2016

Title

Evaluation of quantitative PET/CT usage for cancer treatment

Titel

Utvärdering av kvantitativ användning av PET/CT för cancerbehandling

Author

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Number of pages

126

Illustrations

Unless specified, created by the author or obtained from the Sectra image archive.

Keywords

PET/CT, SUV, Cancer treatment, PET/CT report, Prototype, PET/CT images

Sökord

PET/CT, SUV, Cancerbehandling, PET/CT-rapport, Prototyp, PET/CT-bilder

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Printed in E-huset

Lund 2016

Abstract

Cancer is a disease affecting practically the entire society in one way or another. A great effort is made to find a cure and positron emission tomography/computed tomography (PET/CT) has recently become a vital part to achieve this goal. The reason for this is because PET/CT provides an opportunity to obtain more tumor information than other techniques, which in turn could improve cancer treatments and increase the survival rate.

This thesis work examined how PET/CT is utilized for cancer treatment in Sweden and how the workflow for the examination can be simplified and improved. This was initially achieved by conducting a literature study where articles and research describing PET/CT and/or cancer treatment both in Sweden and in the world were investigated. Questions for interviews and a questionnaire were constructed based on this information. The result from the interviews and the questionnaire contained data regarding PET/CT and oncology, and how the physicians wish to utilize PET/CT images for cancer treatment in the future. This information was compiled and features were selected to be implemented in a prototype for a user interface for examining PET/CT images. The information will hopefully contribute to an improvement of the everyday life of the physicians and to the PET/CT images being analyzed more time efficiently. This can in turn shorten the investigation part of a cancer treatment and save more lives.

It could be concluded that PET/CT has great potential within the oncology area. The semi-quantitative uptake metric called standardized uptake value (SUV) could for example be developed further and its usage could be increased due to the interest in PET/CT. The disbelief in changes within the health care system was also clear and as a consequence it is vital to design products that are adjustable and have a high usability.

Sammanfattning

Cancer är en folksjukdom som på något sätt påverkar praktiskt taget alla i samhället. För närvarande pågår en kamp för att hitta botemedel och PET/CT har på senare tid blivit ett viktigt verktyg för att nå detta mål. Anledningen till det är för att PET/CT har möjlighet att få fram mer tumörinformation än tidigare och på så sätt både förbättra behandlingarna samt öka överlevnaden.

I denna rapport studerades det hur PET/CT används för cancerbehandling i Sverige. Detta uppnåddes initialt genom att utföra en litteraturstudie där artiklar och forskning som beskriver PET/CT och/eller cancerbehandling både i Sverige och i världen undersöktes. Frågor som lade grund för intervjuer och ett frågeformulär framställdes utifrån denna information. Resultatet från intervjuerna och frågeformuläret innehöll fakta om PET/CT och onkologi, samt om hur läkare önskar att använda PET/CT-bilder för cancerbehandling i framtiden. Denna information sammanställdes och egenskaper valdes ut för att implementeras i en prototyp för ett användargränssnitt till granskning av PET/CT-bilder. Informationen ska förhoppningsvis i slutändan bidra till att läkarnas vardag förbättras och att de mer tidseffektivt kan granska PET/CT-bilder. Detta kan i sin tur bidra till att utredningsdelen av en cancerbehandling förkortas och således att man kan rädda fler liv.

Slutsatser som kunde dras var att det finns mycket potential för PET/CT inom onkologi. Bland annat kan det semi-kvantitativa indexet SUV utvecklas ytterligare och dess användning öka. Det var även tydligt att det finns en misstro till förändring inom sjukvården och att det därför är avgörande att utveckla produkter som är anpassningsbara och har en hög användbarhet.

Preface

This Master's Thesis concluded nearly five years of studies to acquire a Master in Biomedical Engineering. The thesis work was conducted in Linköping, Sweden, at the main office of the medical systems company Sectra Imaging IT Solutions AB. The work commenced on the 19th of October and ended with the final presentation on the 23rd of March.

The main reason for conducting the thesis was to investigate the actual usage of PET/CT for cancer treatment in the health care of today and determine how this relates to the management described by literature and research. Quantitative and semi-quantitative uptake metrics, with a focus on SUV, were examined to identify the one or ones most frequently used by health care professionals and to assess which one or ones that are most suited according to literature.

It was also of interest to determine the relevant information to present when reviewing PET/CT images, and to comprehend when and where to display it for an optimal user experience.

Acknowledgments

Numerous people have been supporting me over the last five years and it would be impossible to thank them all. Even though, I would like to extend my deepest gratitude to the following people who contributed substantially over the last six months.

- Jacob Bernhard – Thanks for your knowledge and guidance.
- Magnus Cinthio – Thanks for all your formal and technical support.
- Family and friends – Thanks for always believing in me.
- Thanks to the health care professionals, engineers, professors etc. who provided help and information.
- Thanks to the employees at Sectra for your advice and encouragement.

Rebecka Henrysson

Lund, March 2016.

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List of Abbreviations

AC	Attenuation Correction
BMI	Body Mass Index
BSA	Body Surface Area
CMR	Complete Metabolic Response
CR	Complete Response
CT	Computed Tomography
DICOM	Digital Imaging and Communications In Medicine
EANM	European Association of Nuclear Medicine
EORTC	European Organization for Research and Treatment of Cancer
FBP	Filtered Back Projection
FDG	2-deoxy-2- ¹⁸ F-fluoro-D-glucose
FOV	Field Of View
FWHM	Full Width at Half Maximum
GTV	Gross Tumor Volume
HL	Hodgkin's Lymphoma
HU	Hounsfield Unit
IR	Iterative Reconstruction
LBM	Lean Body Mass
LOR	Line Of Response
MIP	Maximum Intensity Projection
MRI	Magnetic Resonance Imaging
NHL	Non-Hodgkin's Lymphoma
NSCLC	Non-Small Cell Lung Cancer
PACS	Picture Archiving and Communication System
PD	Progressive Disease
PERCIST	PET Response Criteria in Solid Tumors

PET	Positron Emission Tomography
PMD	Progressive Metabolic Disease
PMR	Partial Metabolic Response
PR	Partial Response
PVE	Partial Volume Effect
RC	Recovery Coefficient
RECIST	Response Evaluation Criteria in Solid Tumors
RIS	Radiology Information System
ROI	Region Of Interest
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SMD	Stable Metabolic Disease
SPECT	Single Photon Emission Computed Tomography
SUS	Skånes Universitetssjukhus
SUV	Standardized Uptake Value
TLG	Total Lesion Glycolysis
TNM	Tumor Node Metastasis
TOF	Time Of Flight
US	Universitetsjukhuset
VOI	Volume Of Interest
WHO	World Health Organisation

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1

Introduction

This chapter will provide a brief background to the studied problems, the purpose of the thesis, which questions it should answer, the selected limitations and the outline of the report.

1.1 Background

PET/CT is an imaging modality that provides both functional information, from the positron emission tomography (PET), and anatomical information, from the computed tomography (CT), that surpasses the amount and the quality of information from the individual modalities. PET/CT has potential to contribute greatly to improving cancer treatments as the disease can be detected earlier and the sensitivity for determining treatment response is high. Nevertheless, a problem with receiving vast information is to demonstrate it in a convenient way so the user can utilize the data to its full extent. As a consequence, a problem studied in this thesis was to determine what kind information the user actually wants to obtain, to optimize the evaluation process during a cancer treatment.

As stated above PET/CT has a potential for improving cancer treatment and saving millions of lives, which is vital since cancer soon will become the most common cause of death worldwide [2]. In order to use PET/CT efficiently, in a health care which is becoming increasingly burdened, quantitative and semi-quantitative measurements have been implemented with various results. The most commonly used semi-quantitative uptake metric is the standardized uptake value (SUV). With minimal effort SUV provides information regarding the amount of radioactivity in a tumor and therefore also if it is benign or malignant. However, this tool has been surrounded with considerable concern as it varies substantially with, for example, the physiological properties of the patient and the settings of the PET scanner. With an aim to increase the value of the quantification process during a cancer treatment, this reproducibility problem and how it can be addressed was one of the issues studied.

The importance of using PET/CT information is becoming gradually clear and the usage is thought to increase with 15-20 % every year in Sweden [3]. Increasing the quality of the information could truly improve the quality of care and life. In order to use this information to its full potential a contribution to the quantification and evaluation aspects of a cancer treatment is required, which this thesis aims to provide.

1.2 Purpose

The purpose of this thesis was to investigate the usage of PET/CT for cancer treatment in the health care of today, focusing on the situation in Sweden, and compare this to the result of a literature study describing the PET/CT usage according to articles and research. It was also of interest to understand how the PET/CT information is examined by various health care professionals, what kind of information they deem vital, as well as how, when and where it should be provided.

Quantitative and semi-quantitative uptake measurements were examined and described

with the purpose to determine the uptake metric or metrics most frequently used to quantify PET/CT imaging for cancer treatment. The focus was on SUV as this is the easiest and most widespread semi-quantitative uptake measurement. Other metrics were mentioned for comparison and to provide a complete image of the current situation described by articles, research and the Swedish health care system. If differences between the areas were discovered these were depicted along with the obstacles and the deficits which caused them.

After investigating a substantial amount of articles in the literature study and, as a consequence, regaining a great amount of information, interviews could be conducted and a questionnaire could be established and delivered to relevant health care professionals. The result from which constructed a basis for the final purpose of this report, to develop a prototype for a user interface in a program managing PET/CT images. The current viewer for the Sectra picture archiving and communication system (PACS) called IDS7 was used for inspiration and as a foundation to generate the prototype from.

In summary, the purpose of this thesis was to examine the quantification and evaluation processes surrounding PET/CT for cancer treatment and to contribute to an improvement of the user experience and the patient care.

1.3 Question formulations

The thesis was focused on answering the following questions:

- How is PET/CT used for cancer treatment in the Swedish health care of today?
- How is the usage of PET/CT for cancer treatment described by literature and research?
- Which quantitative and/or semi-quantitative uptake measurements are utilized and how?
- What kind of PET/CT information is of interest to present various health care professionals and how, when and where should it be displayed?

1.4 Limitations

Due to the vast amount of information in the area of PET/CT and cancer treatment a number of limitations had to be conducted.

As the thesis work was completed in Sweden and since it was of interest to gain as well as analyze information about the situation in Sweden, the focus of the thesis was on the Swedish health care system. Information regarding the general situation in the world is presented to enable comparison and to obtain a complete representation, but the major attention

was aimed at collecting, understanding, utilizing and discussing information regarding the PET/CT usage for cancer treatment in Sweden.

In order to exemplify the usage of PET/CT for specific cancer forms it was decided to only mention the cancer diseases where PET/CT often is used and has the highest positive impact. The reason for this limitation was that numerous cancers forms and treatment stages exist which are too extensive to discuss in one report, especially when the purpose of this thesis lies within another field of study. The cancer diseases selected were lung cancer, lymphoma, and head and neck cancer. These cancer forms were selected because of recommendations during the interview process and findings in literature.

An immense number of PET/CT tracers exist and occasionally, depending on which cancer type to explore, a specific tracer can be used to optimize the tumor presentation in the PET image. However, one tracer called 2-deoxy-2-¹⁸F-fluoro-D-glucose (FDG) is used more frequently than others [4] and therefore the thesis focused on the FDG-PET/CT imaging process. Hence, if no indication of FDG can be found in front of PET or PET/CT the intention is still FDG-PET or FDG-PET/CT.

1.5 Outline of the report

After the introduction in Chapter 1, Chapter 2, 3 and 4 portray the theory behind the entire report and the result from the literature study. These theory chapters have a main focus on PET/CT, SUV and cancer treatment respectively. Next, a description of the method used during the literature study, the interviews and the questionnaire, and the process of developing a prototype for a user interface in a program managing PET/CT images follows, see Chapter 5. Chapter 6 depicts the results from the literature study, the interviews, the questionnaire and the development of the prototype for the user interface. Chapter 7 contains the discussion of the result from each of the previously mentioned result parts, thoughts concerning ethical and social aspects, as well as possible future work. The final section of Chapter 7 contains the conclusions that were established based on the result and discussion. The report is concluded with a presentation of the references in the Bibliography and further information in Appendix A and B.

2

PET/CT theory

This chapter provides general information regarding other existing imaging modalities as well as background theory for PET, CT and the combination of the two, PET/CT.

2.1 Alternative imaging modalities

Several imaging modalities can be utilized to create medical images. The choice of imaging technique varies depending on which body part to depict, for example bone, soft tissue or tumors. All modalities have specific advantages and disadvantages that have to be taken into consideration by the health care professional when making the treatment decision [5].

Magnetic resonance imaging (MRI) utilizes magnetism and radio frequency signals to depict detailed images of the human body. By using different sequences it is possible to adjust the image result according to the body part of interest. Advantages compared to PET/CT are that it uses no ionising radiation and can provide diagnosing information for a variety of conditions. Disadvantages compared to PET/CT are that it can be a fairly noisy procedure and an MRI cannot be conducted in certain situations such as when a patient has a pacemaker [5].

Ultrasound uses high-frequency sound waves to construct an image of organs and soft tissue. Advantages compared to PET/CT are that ultrasound does not utilize any ionising radiation, it does not require the usage of a contrast agent and it can help diagnosing a wide range of diseases. Disadvantages compared to PET/CT are that the quality and interpretation of the image is highly user-dependent and it is sensitive to artifacts [5].

2.2 Computed tomography

CT can be seen as a development of the original radiography image where only one single projection was used from a stationary X-ray tube. In CT the X-ray tube rotates around the patient as it simultaneously reconstructs a complete image of the inside of a patient. Detectors on opposite sides of the X-ray tube register and measure the amount of radiation passing through the patient. The measured radiation amount is proportionate to the thickness and absorption rate of specific parts of the body [6].

Filtered back projection (FBP) is often used as an image reconstruction technique and the values in the image are converted to CT values by applying the Hounsfield unit (HU) scale, which in turn provides a distribution of the attenuation coefficients [7]. The CT image is usually displayed in gray scale and the CT values must therefore be converted to a gray scale, with a certain contrast optimization, before the final image presentation [6]. For an example of a CT image, see Figure 2.1.

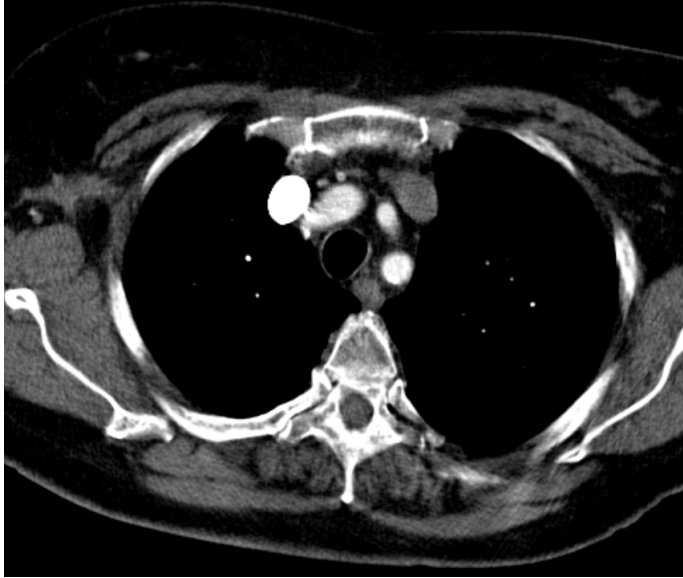


Figure 2.1: An example of a CT thorax image in the axial plane.

2.3 Positron emission tomography

PET imaging constructs functional images by using a non-stable radioactive substance which exhibits positive beta decay with a particle called a positron [8]. The radioactive substance is combined with a tracer, also known as a glucose analogue, in order for it to be attracted to certain parts of the body. The most frequently used radio-pharmaceutical is called FDG [4] and it is considered to be appropriate for PET as it has a convenient half-life and other useful features [9]. The radio-pharmaceutical can be administered to the patient either orally or intravenously and will after this point travel to and metabolise in specific parts of the body which could be of interest [6]. After being introduced to the human body the FDG will act as a glucose analogue and be transported by the glucose transport mechanisms. At this point the FDG will experience enzymatic phosphorylation to florodeoxyglucose-6-phosphate and be trapped in the cell as it radiates. The fact that the glucose metabolism in tumors and malignant tissue is higher than most normal tissue contributes to the FDG being able to identify tumors [10, 11]. An example of a PET image is displayed in Figure 2.2.

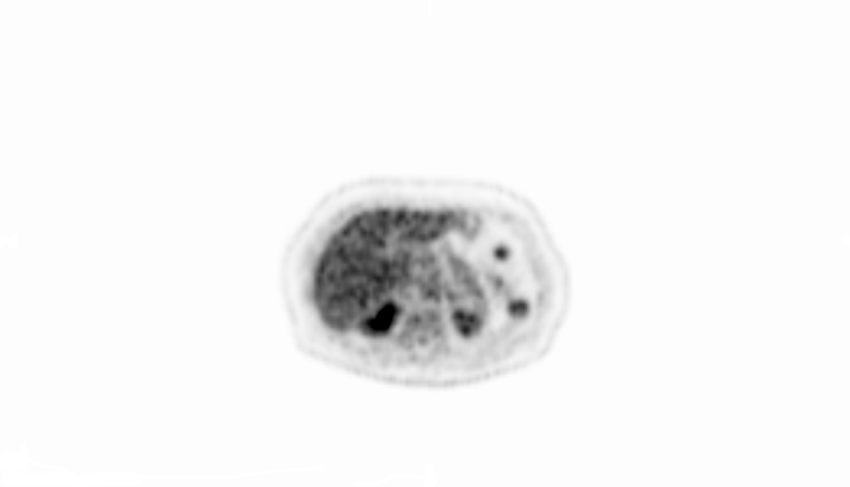


Figure 2.2: PET image of a thorax in the axial plane.

2.3.1 Annihilation

As the radio-pharmaceutical decays a positron will be emitted. This positron will squander kinetic energy by exciting and ionizing atoms until a point where it interacts with its anti-particle, an electron. The interaction process between an electron and a positron is called annihilation. The result of which produces two photons, or gamma particles, with the same amount of kinetic energy, 511 keV, in complete opposite directions, see Figure 2.3 [6].

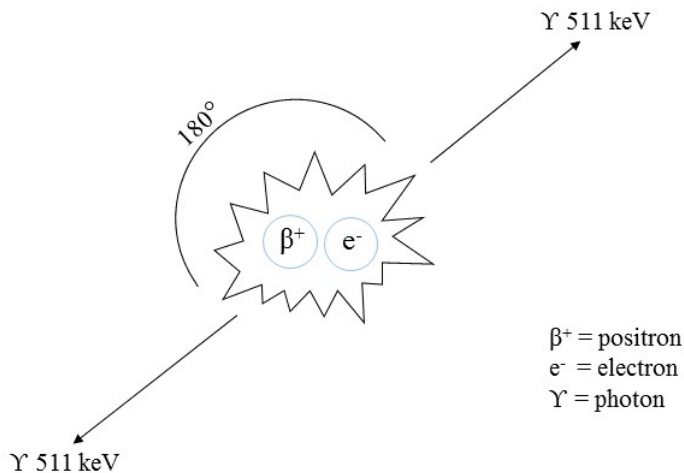


Figure 2.3: The annihilation process where a positron and an electron turn into two photons.

2.3.2 Coincidence detection

The photons from the annihilation process are registered by detectors in the PET scanner and possible trajectories are calculated in order to determine the original position of the positron. This process is called coincidence detection which means that if two electrical impulses were registered by two detectors within a certain time period these detectors could be seen as connected and that the positron was located somewhere on that line of response (LOR) when the annihilation occurred. The radioactivity is measured by counting the coincidence detections along a LOR and the total distribution of radioactivity can be established by constructing a parallel set of LORs [6].

2.3.3 Image reconstruction

Image reconstruction is the process where the raw PET data is transformed to an image which represents the relative radioactivity concentration. Corrections for errors such as attenuation, detector efficiency variation, scattered events and random events have often been applied before the actual image reconstruction process starts [12].

In order to present the raw PET data it is often stored as a sinogram. When using this approach the LORs are arranged in parallel subsets where each subset represent a projection angle. The actual image reconstruction process, see Figure 2.4, is commenced by using an algorithm of choice and numerous algorithms can be found by examining research articles [6].

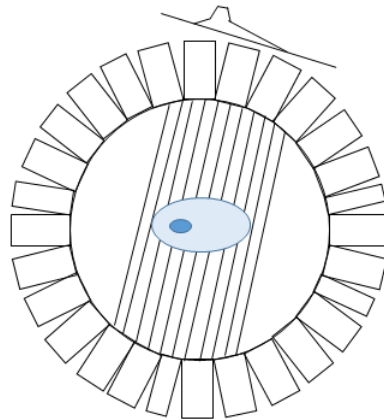


Figure 2.4: A parallel set of LORs is created in order to represent the radioactivity distribution in the body.

The most popular algorithm is often considered to be FBP as it is easy to implement, linear and fast. However, certain crucial disadvantages remain which has prompted the

development of the statistical or iterative reconstruction (IR) techniques where corrections for certain artifacts can be implemented in the reconstruction process [12, 13]. The IR methods are non-linear and have multiple parameters making them less predictable and well-understood than analytical methods such as FBP. The trade-off for image smoothing between noise and contrast applies to the IR as well as the FBP techniques. This means that an increase in smoothing will decrease the noise but also the contrast differences which in turn affects the SUV [12], which will be addressed in Chapter 3. A regularly used IR algorithm is ordered subsets expectation maximization, which has reached its popularity by accelerating the convergence of IR by updating the image more often and by having noise suppressing properties [12, 13].

2.3.4 Limitations

The quality of the PET image can be affected by several parameters such as scattered and random events. A scattered event is where photons lose energy and change direction but are still detected. The resulting LOR will therefore not contain the correct position of the annihilation which in turn contributes to an incorrect position of the radioactivity in the image. To minimize the influence of scattered events a shield called a septa can be placed in front of and behind the ring of detectors. A random event on the other hand consists of two detectors measuring two photons simultaneously but from different annihilations. In theory it is possible to measure three or four events instead of merely two since four photons leave the two annihilation reactions but the likelihood for this is small as photons often experience scattering. The rate of which a random event is detected is proportionate to the rate of which the detectors are detecting and the size of the time window. It is therefore of importance to have a time window that is small enough to discard false events but large enough to register true ones [6].

To reduce the effects from the limitations and errors in a PET image, a system with multiple detectors rings, called a multi-slice PET, has been implemented. Depending on if 2D or 3D is used the system will operate differently, but the general idea is that the accuracy of detecting true events will improve when adding several detector rings [6]. Another way of correcting the image for scattered events is to take the time of flight (TOF) information for each photon into consideration. This will reduce the amount of noise in the image and improve image quality as a decreased number of scattered events will be registered [14].

2.3.5 Spatial resolution

Compared to many other imaging modalities, such as CT or MRI, PET is often considered to be lacking in spatial resolution. Small lesions, with a size of 7 or 8 mm, or even 2 mm for the most advanced scanners [15], can be overlooked due to this limitation [8]. Factors limiting

the spatial resolution, to only mention a few, are positron range, i.e. when the location of the annihilation is detected instead of the emission, if the direction of the photons is not strictly opposite and the detector electronics [12].

In order to improve the spatial resolution the size of the detectors should be reduced since this will increase the chance of detecting a true event provided that the size is large enough for the event to be registered by the correct detector [6].

2.3.6 Attenuation

Attenuation is a process where photons, and coincidence events, are lost due to both scattering and absorption in the tissue [6]. Attenuation causes a photon to lose energy as it passes through the body and these effects are proportionate to the density and thickness of the tissue. Hence, the denser and the thicker tissue is the more it will attenuate [8].

One way to correct for attenuation is to create an attenuation map of the patient using germanium-68, which combined with the original emission image generates an attenuation corrected image. Instead of using this approach a CT image is often used to correct for attenuation in the PET image as it is more diagnostically valuable [16], see Section 2.4.1.

2.4 PET/CT

The combination of PET and CT was first introduced in 1992 and there were numerous reasons for developing such a hybrid. As CT provided anatomical images with high spatial resolution and PET generated functional images with an opportunity for early detection of abnormalities, it was only natural to combine the two for an improved image modality. The hybrid provided information by utilizing the strengths of one system where the other one was lacking which increased the value and accuracy of these anatomical and functional images [6]. For an example of a PET/CT image see Figure 2.5.

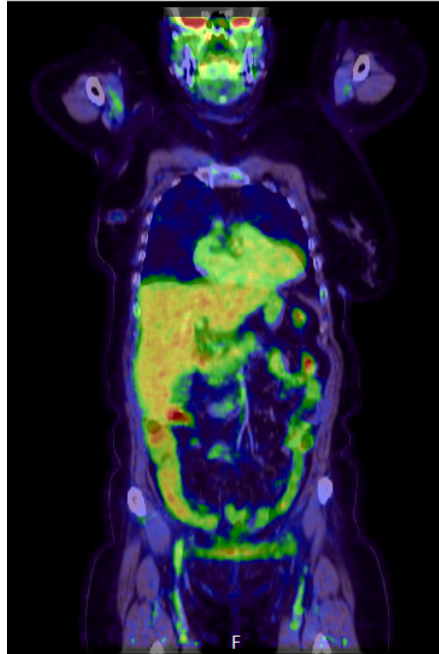


Figure 2.5: An example of a PET/CT image, depicting the patient from the skull to the mid-thighs.

The usage of PET is thought to increase the accuracy of the cancer diagnostic, which in turn contributes to a correct treatment selection and a reduced risk for over and under treatment. The demand for PET in oncology continues to increase because the method is being used more regularly and since it is used to assess more cancer diagnoses. As the standardized treatment courses (standardiserade vårdlopp) are introduced in Sweden during 2015 and 2016, PET and PET/CT will become vital parts of cancer treatments and of the radiation treatment planning. PET is at the moment a well-established modality for diagnosing head and neck cancer, and lung cancer, and the number of standard diagnoses for PET is expected to increase, especially for lymphoma and colorectal cancer [3].

Using PET/CT as a part of a health care process and cancer treatment is not without difficulty since two various workflows have to be synchronized, meaning the radio-pharmaceutical and the patient workflow. The radio-pharmaceutical has individual production times depending on the type to be synchronized and it is important to ensure that there is enough time to produce it and that the appropriate personnel are available. The half-life of the radio-pharmaceutical will affect the time period when the patient has to be ready for the examination and the camera has to be prepared during this time span as well. A PET/CT procedure could also be considered demanding since the personnel are expected to manage two different image modalities and feel comfortable doing so [3].

2.4.1 Attenuation correction

As mentioned in Section 2.3.6, attenuation correction (AC) of the PET data based on CT images is an important part of the PET/CT imaging process. The fact that the PET data can be corrected this way reduces the scanning time by a minimum of 40 % and the correction factors are considerably less noisy than for a standalone PET [17].

When conducting an AC the attenuation for each LOR is taken into consideration. The attenuation of a photon depends both on the energy of the photon and the density of the tissue, meaning that photons with high energy and tissue with low density will attenuate less [18]. Since the values of the AC is dependent of the energy of the photons it is important to scale the energy of the CT, of 70 keV, to the energy of the PET, of 511 keV. To do this a bilinear scaling function is implemented that depicts what PET value a certain CT value should correspond to [17].

The AC can be either measured or segmented, and the difference between the two is minimal except for lesions near the diaphragm where segmented AC can cause small errors. In order to improve the AC the CT could be gated identically to the PET. However, this is not often utilized as it leads to an increase in patient radiation [19]. When reviewing the PET images it is important to both display and inspect the image with and without AC. The reason for this is that the AC could have a negative effect on the image and therefore one has to identify artifacts caused by contrast agents, metal implants and/or patient motion in both images to determine the true data [9].

2.4.2 PET/CT quantification

PET/CT imaging has become a standard component for staging and diagnosing in oncology [12] and unlike many other imaging modalities such as CT, MRI and single photon emission computed tomography (SPECT), PET could be seen as quantitative. Quantitative means that the PET data can be transformed to represent the absolute radioactivity in the specified volume of interest (VOI) in all tissue and in a selected unit such as kBq/cm³ [15]. It can be beneficial to add PET data to CT data to enhance, simplify and increase the accuracy of the delineation of a primary tumor, especially for tumors located near areas where other imaging modalities are disturbed by artifacts [20].

Some corrections are required in order for the PET images to be useful for quantitative analysis, for example correction for random events, detector dead time and photon attenuation [15]. The potential value of a quantitative analysis of the PET/CT images is the highest if the measurement variance is small. The quantitative features can be used for measuring physiological properties such as blood flow and glucose metabolic rate [6] but then a VOI has to be defined. The VOI can be obtained in various ways such as manually, automatically or semi-automatically around any tissue of interest and will provide information about size,

volume and total activity etc. in this region [15]. A quantitative interpretation of the PET image is often acceptable, but to provide a semi-quantitative measurement of the amount of radioactivity in a certain area, the SUV can be utilized [8], which will be discussed in Chapter 3.

In summary, PET/CT can contribute substantially to the treatment of cancer by for example avoiding unnecessary invasive tissue biopsies and providing guidance for locating lesions for radiation treatment planning [12].

2.4.3 Future

The major technological advances are thought to occur in the imaging and computer technology as future scanners will have the ability to acquire the PET and CT signal using the same detectors. The image quality will continue to improve as the signal sensitivity increases and the reconstruction algorithms develop further, which in turn will shorten the imaging time and reduce the patient radiation dose. Implementing methods that utilizes TOF information to a greater extent will increase the signal to noise ratio as the information about the emission event becomes more accurate [1].

3

Standardized uptake value

This chapter will describe the theory behind the semi-quantitative uptake measurement SUV. A general introduction initiates the chapter which is followed by a description of the most commonly used SUV indexes, and concepts often used in cooperation with SUV. The chapter is concluded with detailed description of the limitations surrounding SUV and how it is recommended to take them into consideration for minimal influence.

3.1 Introduction

It is of great interest to determine the rate and/or total amount of FDG accumulation in tumors in a PET image. PET scanners are designed to measure the radioactivity concentration which is linked to the FDG accumulation. However, as this can vary from one person to another it is of interest to measure the relative tissue uptake, which is where SUV entered the picture over twenty years ago [19]. Two significant sources of variation when measuring the radioactivity concentration are the patient size and the amount of injected FDG, which the SUV is designed to compensate for [12].

The SUV is defined as [21]:

$$\text{SUV} = \frac{\text{Activity concentration in tissue}}{(\text{Injected activity})/(\text{Body size})} \quad (3.1)$$

Hence, SUV is an index that normalizes the concentration of the radioactivity with the injected activity and the body size. By dividing the measured activity concentration with the injected dose, a dose-independent index is generated. Next, by dividing the denominator with some measure of body size, such as body mass, body surface area (BSA) or lean body mass (LBM) [21], the SUV compensates for the fact that a smaller body has more competing muscle tissue for the FDG than a larger one [6, 15]. The combination of the division causes the SUV to be dimensionless when assuming that 1 ml of tissue weighs 1 g, depending on the measurement of body size [12]. In order to measure SUV a specific 2D or 3D region of interest (ROI) could be defined and positioned within a target. ROI will be discussed further in Section 3.3.

For clinicians using PET, SUV is a popular semi-quantitative measurement which can be assessed with ease in PET studies performed under physiological or pathological conditions. Despite it being a simple index, in the complex world of oncology and tumor biology, SUV has been deemed useful for diagnosis, prognosis, staging and response monitoring in PET/CT imaging [22, 23, 24]. When evaluating the initial response to therapy using SUV, clinical studies have shown that a decrease in SUV with 20-40 % indicates a tumor responding to treatment. Other studies have shown that decrease of 0.5 SUV is statistically significant of indicating a success of the cancer treatment and could be used to establish thresholds for future decisions [25]. With this said, it is important to be certain when deciding if the treatment is effective or not, and it is vital to understand the variables that have an impact on the accuracy of the SUV [21]. The SUV has the ability to increase the precision in diagnoses compared to visual assessment and the relative change in SUV over time can be used as a measurement of response to treatment [22]. However, some uncertainties still remain, which will be discussed further in Section 3.4, such as integration with the available clinical and instrumental data [23] and SUV should therefore be seen as a supplement to visual assessment [26].

Depending on the relative change in SUV, when determining treatment response, patients are categorized in various response categories. These categories include complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The classification of a patient according to a certain response category can be used to guide subsequent treatment decisions and to indicate a clinical outcome [27].

Since SUV was introduced several efforts have been made to reduce the variation of the index by implementing a more consistent patient preparation and data acquisition. However, differences in practical application of the imaging technique remain and therefore it is important to always consider the reproducibility of each specific imaging method to indicate a statistically significant change in the tumor [19]. Sources of variation and bias are for example introduced in the measurement of FDG accumulation and in the conversion of the image count data to SUV. Hence, even though some variability is removed by the normalization by patient size and injected FDG, SUV should not be exclusively relied upon for diagnostic purposes. It is important to understand the sources of bias and variance in order to stay in control and take them into consideration when interpreting PET images and constructing reports [12]. Despite CT images being somewhat limited as an indicator for cancer it is important to use the anatomic measurements provided by the CT when interpreting the PET image and the SUV, as it can be used as a reference standard [4].

The SUV can present a different resulting value depending on the method used to calculate it, such methods and indexes will be presented in Section 3.2. There is often a correlation between various SUV indexes and the variation for individual tumors could be substantial. These differences could contribute to the patient being categorized inconsistently and therefore it is important to determine the index that is best suited for response assessment and quantification of the treatment [27].

Westerterp et al. conducted a study of SUV variation with specific focus on multi-centre trials. Comparing the SUV with phantom data resulted in differences in quantification of approximately 30 % and varying the ROI contributed to a predictable change in SUV for both phantom and clinical data. The variation of SUV seemed to be affected by image resolution, ROI methods, segmented AC, acquisition mode and image reconstruction parameters, and therefore a standardization of acquisition, reconstruction and ROI was recommended for SUV quantification. It was also suggested that SUVs obtained at various institutes under different conditions should be compared by calculating the appropriate correction and calibration factors. However, assessment of treatment response of the same patient should be conducted using several scans taken by the same scanner and under identical scanning, image reconstruction and data analysis protocols at each institute [28].

3.2 SUV indices

Depending on the area of interest and image quality, among other things, it is possible to use various SUV indices, which will be described below.

3.2.1 SUV_{\max}

SUV_{\max} is defined as the voxel with the highest SUV within a specified ROI. Hence, this definition is independent of the ROI provided that the ROI includes the voxel with the highest SUV [21]. The definition is often required to be established for each lesion as a part of the study protocol or because it is clinically relevant, and it should be defined in the original reconstructed PET image [9].

SUV_{\max} is the most common index as the majority of health care professionals prefer to use it to analyze tumors in PET studies. The reason for this is because it is less observant-dependant and more reproducible compared to SUV_{mean} [21]. The advantages of SUV_{\max} are best utilized in PET images with high quality. For images containing much noise the robust index SUV_{peak} is recommended to use to assess the most metabolically active region of the tumor, and possibly the most clinically vital part, where SUV_{\max} otherwise is utilized. SUV_{\max} is also less affected by the partial volume effect (PVE), which will be discussed further in Section 3.4.5, and can be determined with high accuracy within a ROI as only one voxel has to be located [19]. Some studies have shown that the bias and variance for SUV_{\max} generally is lower than expected, often due to noise corrections introduced in the image reconstruction process. In addition, it has been demonstrated that SUV_{\max} can be a robust measurement for assessing response to treatment [12].

The reproducibility, i.e. the variation between two examinations conducted under standardized conditions, and the repeatability, i.e. the variation between two identical and successive PET scans of the same patient, of a PET study are considered to be vital properties to analyze. In a study by Lindholm et al. where repeatability and reproducibility were examined it was deemed that SUV_{\max} is a stable parameter from camera and computational perspectives [29].

A major disadvantage of SUV_{\max} is its high noise sensitivity and the fact that the bias seems to increase as the noise increases [19]. It is therefore often associated with uncertainty in quantification of the treatment response. The noise uncertainty can be reduced by using 3D PET acquisition, which is standard for most PET scanners, as it has an increased number of counts which improves the image quality [27]. At the moment the overall ambition for PET/CT studies is to reduce the patient radiation, but this will cause the image quality to decrease which in turn affects the SUV_{\max} negatively [19]. Concern has also been raised regarding the fact that SUV_{\max} only represents a small portion of a lesion which might not be a statistically reliable representation of the biology of the entire lesion [29].

3.2.2 SUV_{mean}

SUV_{mean} is defined as the mean SUV of all voxels within a specified ROI. By utilizing the value from several voxels it is less sensitive to noise but depending on the definition of the ROI, and the values included in the average can vary substantially. Hence, SUV_{mean} is sensitive to the delineation of the ROI and variation in intra- and inter-observation [21]. Due to these facts and the low reproducibility it is used less frequently than other SUV indexes. Using an optimal setting with no loss in resolution or uncertainty when defining the ROI, simply calculating the average SUV to obtain the SUV_{mean} could be seen as a reliable estimate. However, the problems with image noise and limited resolution in PET images causes a difficulty in defining the ROI which in turn contributes to the average being incorrect [12].

3.2.3 SUV_{peak}

SUV_{peak} can be seen as a hybrid between SUV_{max} and SUV_{mean} as it is defined as the local average SUV calculated from voxels surrounding the voxel with the maximum activity. Often a small fixed ROI is defined in the part of the lesion with the highest uptake. This index was developed to reduce the noise sensitivity of SUV_{max} while preserving the reproducibility. This has caused it to be considered as a more robust alternative to SUV_{max} , which can be seen as a special case of SUV_{peak} where only a single voxel is contained in the ROI [21, 27].

Even though SUV_{peak} could be seen as a more robust alternative to SUV_{max} , it is often associated with issues such as a non-uniquely defined ROI which in turn results in various treatment responses. Thus, it is important to compare the efficacy of SUV_{peak} and SUV_{max} when quantifying the treatment response [27]. Using SUV_{peak} is equivalent to smoothing the image and selecting the voxel with the highest smoothed value. This will cause the resulting value to be further from the true radioactivity concentration compared to SUV_{max} , especially in small lesions, which also has to be taken into consideration [21]. Small lesions are challenging to delineate because of the PVE, which will be discussed further in Section 3.4.5. Compared to SUV_{max} , SUV_{peak} depict a positive bias for small lesions which could be seen as a clear limitation. However, studies have shown that greater volume averaging can increase the reproducibility when the ROI is placed in the same location. However, this can be difficult to achieve manually and as a result a number of automated SUV_{peak} algorithms have been developed [19].

The robustness of SUV_{peak} can be additionally increased by using a population of tumors in the definition instead of only one. Hence, to calculate an average over several tumors could decrease the variation of SUV_{peak} and reduce the dependency in the ROI definition [27].

3.2.4 SUV_{ref}

The SUV indexes above do not take the variation of SUV caused by differences in scanner performance and reconstruction protocol into consideration, only the variation caused by body size and injected dose is addressed. These sources of variation can also affect the quantification using PET images and in turn its credibility in locating tumors. Kelly et al. therefore proposed a new SUV index called SUV_{ref} that would avoid the need for constraints in reconstruction to produce recovery coefficients (RC) in line with those constructed by older models, which negatively affects the ability to detect lesions. Instead the intention with SUV_{ref} was to utilize the improvements in image quality, scanner hardware and reconstruction technologies to reduce the non-biological effects on the SUV performance [30].

SUV_{ref} uses a phantom-optimized filter that is specific to a selected reconstruction protocol and applies it to the PET images. The filter is selected to minimize the variation in RCs of the activity concentration between images [30]. The RC is calculated by dividing the measured activity concentration by the known activity concentration, in a region constructed with phantoms, and it measures the ability of the imaging system to recover the true activity concentration in regions with varying activity concentrations [30, 31]. RCs can therefore be used to indicate clinical scanner performance when incorporating information about scanner resolution, sensitivity and accuracy of different corrections performed with the specified reconstruction parameters. The RCs for each lesion and reconstruction protocol is defined and compared to a set of reference RCs, and the root mean square error is calculated. This is repeated followed by a convolution of the original image with a Gaussian kernel with increasing FWHM. The kernel size which minimizes the root mean square error compared to the reference RCs is selected as the SUV_{ref} filter for the specific scanner and reconstruction protocol [30].

In order to compare the performance of SUV_{ref} with other SUV indexes, SUV_{peak} , SUV_{max} , and a combination of SUV_{ref} and SUV_{peak} called $SUV_{ref, peak}$ were defined. To determine the sensitivity of selecting the correct filter for the SUV_{ref} , non-optimal SUV_{ref} filters were applied. The result from the study showed that when applying an applicable SUV_{ref} filter, the variance of a set of data from different reconstruction protocol was lower than the data using the same protocol with SUV_{max} . Both the bias and variance were reduced when using SUV_{ref} , with a result of 1 % incorrectly identified tumors compared to 20 % when using SUV_{max} and 4 % when using SUV_{peak} . Using the combined index $SUV_{ref, peak}$ reduced the variance further and even though the chance for selecting a non-optimal SUV_{ref} filter is minimal, the effect of selecting the correct one was deemed significant. Hence, as SUV_{ref} reduces the reconstruction-dependant variation in SUV measurements, while utilizing the improved image quality due to advances in scanner technology, it is possible to rely more on quantitative comparison of PET images for monitoring treatment response [30].

3.3 Region of interest

The ROI, or occasionally the VOI [29], is utilized to define the activity concentration in a tumor which can be done either manually, automatically, semi-automatically or by using a fixed size that sample the tumor but do not intend to confirm the precise tumor boundary. Generally, the effects of shape, size and location of the ROI must be considered as they could have an effect on the quantitative analysis of the PET image [19, 22, 23, 32].

A ROI is frequently utilized to define the SUV_{peak} and during these occasions the ROI is denoted as ROI_{peak} . The definition of the SUV_{peak} varies greatly depending on the size, shape and placement of the ROI_{peak} . In the study by Vanderhoek et al. these parameters were varied to determine the effect a change could have on the SUV_{peak} [27]. The shapes circular and spherical were tested, with diameter sizes ranging from 7.5 mm to 20 mm. Other shapes that could have been of interest are square and cubic. The ROI was placed in two different locations: the center of the SUV_{max} and in the region with the highest uptake. It was discovered that in individual tumors the definition of the ROI_{peak} and changes made to it had a substantial effect. A change in size caused a higher variation of the SUV_{peak} than the shape or location did and the variation appeared to increase as the size increased. In other studies it has been identified that a change in ROI_{peak} could result in an average variation of $\leq 50\%$. It is important that the ROI_{peak} is large enough to exclude effects from noise, PVE etc. that influence SUV_{max} . But simultaneously, it cannot be so large that it includes considerable tumor uptake heterogeneity and voxels located outside of the tumor boundary. Considering this, a recommendation of a ROI_{peak} definition with a diameter of 1.2 cm in a spherical shape was defined in the response assessment system called PET response criteria in solid tumors (PERCIST) [19, 27], which will be discussed further in Section 4.7.1. Other useful ROI suggestions conducted by Boellaard et al. in The Netherlands Protocol were a 3D isocount contour at 41 %, 50 % and 70 % of the maximum uptake, with and without local background corrections [22, 33]. When using these ROIs, the SUV_{max} should always be reported. It has been shown that increasing the size of the ROI seemed to decrease the uncertainty of the SUV measurement [34].

Other factors that can affect the ROI are the reconstruction method, the amount of smoothing and the lesion to background ratio, and for tumors less than 3 cm in size PVE can also lead to errors in the measured SUV [12]. The shape of the ROI to define the outer boundary of the tumor should be affected by visual judgement and a characterization of the tumor heterogeneity [26].

3.4 Limitations

SUV measurements in general are limited by a great number of both biological as well as technical aspects, some of which will be discussed in the following section. To summarize these limitations see Table 3.1 and 3.2 and review them as an introduction to the section and its content [4, 12, 19, 21, 22].

Table 3.1: Examples of biological limitations of SUV measurements.

BIOLOGICAL	
Element	Description
PVE	
Patient preparation	
Tumor heterogeneity	
Tumor size	<i>Including leakage from nearby structures.</i>
Cell type	
Tumor avidity	
Other phenotype information	
Treatment effectiveness	
Patient motion	<i>Between the PET and the CT scan.</i>
Respiratory motion	
True tracer uptake	
Chemotherapy	<i>Disturbed renal function from chemotherapy can reduce the FDG clearance.</i>
Overlap between malignant and benign diseases	<i>Difficulties in deciding the correct threshold.</i>
Body size measurement	
Mass correction	
Blood glucose level	

Table 3.2: Examples of technical limitations of SUV measurements.

TECHNOLOGICAL	
Element	Description
PET scanner	<i>Malfunction and sensitivity.</i>
Reconstruction algorithm	
Filters	<i>Consider level of smoothing.</i>
Interobserver variability	
Scan duration	
Sinogram noise	
Image noise	<i>Consider the noise level as it is a cause of over half of all SUV_{max} variation.</i>
Measurement error	<i>Occurs in 30 % of SUV_{max} measurements.</i>
Correct data entry	<i>9 of 15 steps are constructed so that a technologist is required to measure, record and/or enter a value.</i>
Image reconstruction parameters	<i>Number of iterations when using IR, field of view (FOV), number of subsets, voxel dimension, certain scanner specific enhancements, detector modeling and TOF.</i>
Timing mismatch	<i>Between the scanner and the dose calibrator.</i>
SUV variability	<i>The variation is described to have a log-normal distribution rather than a normal distribution.</i>
Calibration errors	<i>According to the decay of the radio-pharmaceutical.</i>
Contrast material	

3.4.1 Body size calculation and mass composition

In order to normalize the SUV for body size and to calculate the average radioactivity concentration, the patient body mass is most commonly used. However, when using body mass the fact that the FDG accumulation is mass dependent is disregarded. In general heavier patients, who have a higher white body fat percentage, will have a higher SUV than patients with lower body mass. The reason for this is that muscle tissue is more metabolically active than fat which causes the FDG accumulation in the tumor to reduce as the uptake in muscle tissue increases. If the same amount of FDG has been introduced to a heavier and thinner patient, the heavier patient will exhibit a higher FDG uptake in the tumor as the amount of muscle tissue to accumulate FDG is lower than for the thinner patient. Studies have shown that the SUV for a heavier patient can be up to twice as high as for a thinner patient [21, 32]. It is also likely that a patient will lose body mass during the course of a treatment which can cause a change in the measurements of the SUV [21]. The variation in mass can cause a variation in the sinogram counts or noise which in turn result in bias. The noise effects can be diminished by smoothing but this will cause the PVE to have an influence. Another way to reduce this effect is to take the patient mass into consideration when determining which dose to administer [22].

To compensate for the change in body mass when calculating SUV two correction factors have been established to use instead of body size: LBM and BSA.

LBM can be calculated with both length, mass and gender as parameters using Equation 3.2 [9]:

$$\text{LBM} = \begin{cases} (9.270 \cdot \text{Body mass}) / (6.680 + 216 \cdot \text{BMI}), & \text{for male} \\ (9.270 \cdot \text{Body mass}) / (8.780 + 244 \cdot \text{BMI}), & \text{for female} \end{cases} \quad (3.2)$$

The body mass should be described in kg and the length in m, and the body mass index (BMI) is calculated by using the formula $\text{mass}/\text{length}^2$ [9].

It has also been discovered that LBM can be calculated by solely using the length of the patient by implementing Equation 3.3 [21]:

$$\text{LBM} = 48 + 1.06 \cdot (\text{Length} - 152) \quad (3.3)$$

The length should be specified in cm [21].

BSA is calculated as a combination of body mass and length by using Equation 3.4 [35]:

$$\text{BSA} = \text{Mass}^{0.425} \cdot \text{Length}^{0.725} \cdot 0.007184 \quad (3.4)$$

The mass should be expressed in kg and the length in cm [35].

Both SUV_{BSA} and SUV_{LBM} , the latter often also denoted as SUL [36], are less sensitive to mass changes than the SUV measurement when using body mass to normalize. SUV_{LBM} is on average closer to SUV_{max} than SUV_{BSA} but the fact that there is no well-established formula for calculating SUV_{LBM} contributes to it being inconsistent and varying from one study to another. It is therefore important, when monitoring a patient that does not vary significantly in mass, to be consistent in selecting which measurement to represent the body size with. It is also vital, when establishing the mass of the patient, that the same scale is used and that it is calibrated [21].

It is often recommended to use LBM to generate a SUV index independent of body size as this provides a more accurate and quantitative measure of the FDG uptake. However, when using any other body size calculation than body mass it is preferred to mention the SUV determined by using body mass as well [21].

3.4.2 Blood glucose level

Another biological factor that can affect the SUV measurement is the blood glucose level. The reason for this is that the FDG is in constant competition with glucose and the result of elevated glucose levels is that the FDG uptake in the cell will be reduced [21]. It has been shown that the blood glucose level has an inverse linear effect on the SUV measurement and therefore it is vital to take into consideration. Prior to a PET/CT examination the patient will be prescribed fasting and failure to comply with this will cause increased levels of FDG

in muscles as a result of the insulin increase after a meal. Consequently, a smaller amount of FDG will be available for tumor uptake and the SUV will be incorrect. Accordingly, the intake of calories or insulin is highly regulated in imaging protocols [12].

Some studies have shown that a correction of the SUV for blood glucose levels can be appropriate when monitoring the same patient during therapy. The reason for this is that it could provide a more stable SUV that is independent of variations in the blood glucose level. However, other studies have demonstrated no statistically proven advantage of applying a correction and one should contemplate the errors that such a correction could lead to, especially if the change in blood glucose levels between examinations is minimal [21, 25, 26]. For this reason a final recommendation is often that if the blood glucose level of a patient surpasses 11 mmol/L this patient should be rescheduled and corrections are not warranted [34].

If the SUV should be corrected according to the blood glucose level the following equation should be used [9]:

$$\text{SUV}_{\text{glu, LBM}} = \frac{\text{Act}_{\text{VOI}} \cdot \text{Gluc}_{\text{plasma}}}{(\text{Act}_{\text{administered}}/\text{LBM}) \cdot 5.0} \quad (3.5)$$

The distribution volume and body size normalization is calculated by using LBM, Act_{VOI} is the activity concentration measured in the VOI and $\text{Act}_{\text{administered}}$ is the net administered activity corrected for the FDG decay and for residual activity in the syringe and/or administration system. The measured glucose content, $\text{Gluc}_{\text{plasma}}$ is normalized for an overall population average of 5.0 mmol/L which causes the corrected and uncorrected value to be practically identical on average [9].

3.4.3 Uptake time

The SUV measurement will also be affected by the rate of glucose utilization. The clearance of FDG in normal and inflammatory tissue is faster than for malignant tissue which causes the time between injection and scanning to linearly affect the SUV. The reason for this is that the FDG in malignant tissue will increase over time and the longer the uptake time is the higher SUV will be measured. It is therefore recommended to have a constant uptake time for the same patient with an error marginal of ± 10 min [12, 21, 32].

3.4.4 Respiratory motion

The respiratory motion of a patient can affect the SUV, especially for images taken with a focus on the lungs and abdomen. The reason for this is that the CT scan, often used for AC of the PET image, can be obtained during a single breath hold but the PET acquisition takes minutes to complete and is acquired as the patient is calmly breathing. This in turn

affects the AC to be either over- or underestimated which can significantly influence the SUV calculation [21]. Studies have shown that respiratory motion can contribute to a 25 % underestimation and a 2-fold overestimation of the SUV for small lesions near the diaphragm. These errors generally decrease as the lesion size increases and/or the respiratory motion decreases [12].

It is also of importance to consider the breathing patterns from one CT scan to another as respiratory motion can cause image artifacts such as blurring and positional mismatch, which could lead to incorrect interpretation of the PET/CT images over several scans [12, 21].

To reduce the effect of respiratory motion it is important to use the same acquisition protocol for every scan with the same patient. Factors that otherwise can affect the respiratory pattern of a patient between a series of scans and complicate the measurement of true SUV changes are patient anxiety, breathing pattern coaching by the technologist and/or room ambiance [12].

3.4.5 Partial volume effect

The PVE describes the effect where an object, smaller than a few cm, has a measured activity concentration that is less than the true concentration value. This occurs due to two reasons: one voxel will represent a radioactivity from a volume that is larger than the volume of the voxel, and radioactivity from a small region will be measured from several neighboring voxels, both resulting in an incorrect representation of the activity concentration. As a result, a small source in the final image will be depicted as larger and less intense than it should be which leads to an underestimation of the maximum or mean activity and consequently a false SUV [12, 21]. Hence, the PVE leads to an increase in bias of the measured SUV as the size of the object in question decreases [12]. However, PVE has a positive effect on the variation of SUV_{peak} as it reduces the uptake heterogeneity of the tumor and a PVE correction should be expected to contribute to an increase in variation when using SUV_{peak} [27]. The PVE has a higher impact if the tumor volume changes rapidly and in such cases a correction should be contemplated in order to improve the accuracy of the SUV measurement [20, 22].

At the moment, the most frequently used approach for PVE correction is to approximate the tumor to a spherical volume which exhibits homogeneous tracer uptake and is located in a homogeneous background. A more advanced correction to improve the quantitative measurements can be established by using CT images and the true spatial distribution of the tracer, but this entails several challenges and it might not be worth the trouble [12, 18].

In order to measure the impact of the PVE, an RC can be utilized that describes the ratio between the measured SUV and the true SUV [12].

3.4.6 Scanner variability

The variation from one scanner to another is vital to take into consideration when using PET/CT for cancer treatment. The same patient should, to the greatest extent possible, have its pictures taken by the same scanner for the baseline as well as the follow-up studies. The reason for this is that scanners from various distributors and of different models could have distinctive physical properties, and acquisition and calibration factors. A major factor that differs from one scanner to another is the spatial resolution which in turn could affect the SUV measurement, especially if it is a small lesion because of the PVE. Factors such as various detector crystal dimensions, random correction options, TOF capabilities etc. may change the SUV. The PET scanner can also be affected by inherent blurring and this problem can be reduced by modeling the point-spread function response. However, this will only improve the contrast of small lesions and the variation in the SUV measurements will remain [21].

3.4.7 Reconstruction parameter changes

Several factors during the image reconstruction process can affect the SUV measurement and depending on the algorithm used for image reconstruction these parameters will also vary. Adams et al. conducted a study to test the effect on the SUV by varying the image matrix size, post-smoothing, FOV, size, TOF versus non-TOF reconstruction, number of iterations and image matrix placement, when using an IR technique. It was concluded that in order to reduce the variation between a series of scans the same reconstruction parameters should be used for the baseline study and all follow-up studies. The variation of the SUV measurements for smaller objects were higher but this could be reduced by implementing smoothing and local averaging at the expense of underestimating the true maximum value [21].

During the image reconstruction process it is recommended to select image matrix sizes and zoom factors so that the reconstructed voxel sizes are 3.0-4.0 mm in any direction. If a spatial filter is applied during or after the reconstruction this should not exceed a FWHM of 7.0 mm [9].

3.4.8 Calibration error and timing mismatch

As can be seen in Equation 3.1 the radioactivity concentration is highly important when calculating the SUV. In order to do this correctly the radioactivity has to be measured and corrected according to the radioactive drug, in this case ^{18}F [21]. Since ^{18}F decays to approximately 49.9 % of the initial activity over a period of 110 min, the SUV will be substantially underestimated if not corrected for this decay [1]. For the decay and decay time to be measured correctly the clocks of the dose calibrator and the PET scanner are

required to be in sync. The mismatch in timing between these two clocks has a nearly linear relationship to the SUV error and an error in timing could therefore result in considerable errors in the SUV measurements. The timing mismatch could also contribute to an error in the SUV because of the inconsistent uptake time, and corrections have to be conducted in order to account for the delay between the injection time and scan start time. An improper decay correction could cause an error of 6 % in the SUV measurements, even for a small drift in clock timing such as 10 min [12, 21].

When calculating the SUV both the injected activity and the measured activity is included and if there is an error in determining the calibration of the measured count rate to the true radioactivity concentration the SUV measurement will be affected. Furthermore, any activity remaining in the injection system could cause an error. The injected activity should therefore be measured with precise accuracy and any residual activity in the syringe, needle or tubing should be determined and subtracted from the original syringe activity to obtain the net activity that was administered to the patient. Additionally, it is of importance to regularly and accurately calibrate the dose calibrators according to a general one [21].

After the image reconstruction process the PET image does not specify the SUV, instead it is presented in units specific to the scanner, reconstruction method and reconstruction parameters. In order to convert the image to SUVs it is primarily required to estimate the scanner calibration factor, which can vary from one scanner to another. Using this calibration factor it is possible to first convert the image from scanner units to radioactivity concentrations and then to SUVs using Equation 3.1. An error in the dose calibration at this point could have a substantial effect on the calculated SUV and it has been suggested that at least 10 % of all dose calibrations have measurable effects due to mistakes during the calibration process and/or the patient-specific SUV calibration process. If both the injected dose and residual activity are accurately measured and incorporated no error will occur in the SUV calculation. However, by using inaccurate and incorrect measurements instead a median underestimation of the SUV of 2 % will be introduced [12].

A related error source is when extravasation of the dose occurs. This is when a fraction of the FDG is trapped in the tissue near the injection site, which in turn reduces the SUV. The best way to reduce this effect is to normalize the SUV according to a reference tissue such as the liver or the brain [12].

3.4.9 Interobserver variability

The variation of SUV measurements between users can be considerable, especially for SUV_{mean} as this has a high dependency of the size and the location of the ROI. Variation in SUV_{max} due to different ROI placements has been established in pre- and post-therapy images. The interobserver variability could be decreased by using documentation tools such as screen saves since this could reduce the inconsistency between images and therefore also

the positioning of the ROI [21].

Because of the presence of interobserver variability it is important to only compare the SUV from the same type of acquisition when monitoring treatment response, otherwise incorrect conclusions could be drawn [21]. However, efforts are being made to reduce the effect of acquisition protocols and scanner performance on the SUV measurements [30]. For quality control it could be useful to determine the SUV of the liver after completing every scan. The SUV of the liver should not differ tremendously if the images have been acquired correctly and a difference is a strong indication of scanner fault [21].

3.4.10 Noise level and smoothing

Several studies have shown that SUV_{max} , or the pixel with the maximum value, varies with different ROIs, tumor sizes and noise levels. It has also been established that by increasing the number of iterations in the image reconstruction protocol, the SUV will be enhanced since the noise level increases as the convergence improves. Therefore, images with a high noise level show positive bias for the maximum pixel within a sphere and the bias increases with the size of the sphere. Smoothing of the images will reduce the noise which will have a positive effect on the SUV, especially when using SUV_{max} . However, smoothing also contributes to a larger PVE which instead has a negative effect. With this said, it has been shown that the measured response is close to independent of noise, resolution and ROI method when using SUV ratios, which are common in some cases. This can be explained by the fact that most of these factors cancel each other out when calculating the ratio. In order to improve the images and the accuracy of the result even more, PVE corrections and smoothing can be applied, while taking the previously mentioned obstacles into consideration [22].

3.4.11 Thresholds

A threshold value of 2.5 for the SUV has long been popular to use for determining if a tumor is benign or malignant. However, the practice of using SUV thresholds for diagnosis is not widely accepted and therefore some caution should be exercised when using a threshold value. It has also been established that using such a definition could be completely invalid. The reason for this is that some benign infections or inflammatory processes could have a substantial FDG uptake with a high SUV and slowly growing malignant lesions could express minimal uptake with a low SUV. Another reason to be sceptical of using SUV thresholds that are established in one institution in another institution, is the fact that several institutional differences exist, such as diagnostic conservatism and specific methodology which can affect the SUV measurement. Hence, a threshold should never be taken from literature and used without validating the appropriateness since the SUV varies substantially

from one institute to another. It has also been discovered that the SUV exhibit a log-normal distribution rather than a normal one which should be considered when selecting a threshold to use [12, 22, 26].

The usage of thresholds could occasionally be valid such as when the uptake in the lesion does not differ greatly from the adjacent reference tissue or when the pre-test likelihood for malignancy is low. PERCIST utilizes different response thresholds to classify tumors in various categories, for example, PD/SD and SD/PR. PERCIST will be discussed further in Section 4.7.1. Thresholds can be established by utilizing population average response data and a unique threshold should be defined for every specific disease and its corresponding treatments. The size of the threshold is required to exceed the overall uncertainty associated with the SUV measure and as a result an SUV measure should be defined for each individual patient to determine their response to therapy using the pre-defined thresholds as guidelines [12, 27].

3.5 Recommendations

In order to manage the technical and biological factors affecting the SUV and to minimize the errors in the SUV measurements, several recommendations have been made, see Table 3.3 [4, 9, 12, 19, 21, 22, 25, 26, 30, 32, 34, 37, 38]. These recommendations were conducted to standardize the quantitative assessment of PET studies using SUV, to minimize the possibilities for human error and to facilitate comparison when determining treatment response, tumor staging etc. [21, 26].

Table 3.3: Recommendations for optimizing the accuracy and usability of the SUV.

SUV RECOMMENDATIONS	
Element	Description
Scanner	<i>Same one for baseline and follow-up studies, also use the same display station and document workstation for displaying and analysis. Important to maintain the calibration over time, especially when software and hardware changes occur. Specify scanner sensitivity.</i>
Protocol	<i>Same one for preparation, processing and analysis. Contemplate using the same CT protocol.</i>
Administered dose	<i>Measure residual activity in the syringe, needle and tubing system.</i>
Uptake time	<i>A minimum of 60 min and the same uptake time, \pm 10 minutes, should be used for each study. Increasing the uptake time further does not appear to be valid. Interactive scheduling software and flexible dispensing systems could ensure a constant uptake time.</i>
Acquisition and reconstruction technique	<i>Specified the one used, for example FBP, IR etc.</i>
Reconstruction parameters	<i>Same FOV, image matrix size (often 128 x 128 or 256 x 256), TOF, number of iterations and subsets, smoothing, using 2D versus 3D, slice thickness, acquisition time and image resolution. Document the settings used.</i>
Blood glucose levels	<i>Measure with reagent strips, should not surpass 11 mmol/L.</i>
Reference SUV	<i>Measure the SUV in the liver, cerebellum and/or blood for reference, reassure that it is within a normal range. Normal SUV in the liver lies between 1.0 – 3.0 and for a blood pool between 1.2 – 1.6, depending on the calculation method used.</i>
Patient mass	<i>Weigh the patient on a calibrated scale located at the facility of the study.</i>
ROI	<i>Use documentation tools to ensure consistency between baseline and follow-up studies.</i>
Record potential artifacts	<i>Blood glucose level, injected and residual doses, other unexpected events of relevance, respiratory motion etc.</i>
Reporting	<i>Use consistent and standardized analysis and reporting for SUV. User-friendly software could be utilized for correcting the report.</i>
Performance verification	<i>According to manufacturer instructions, evaluate calibration, AC, random coincidences correction, detector variation correction, scattered radiation correction, imaging reconstruction including smoothing, decay correction, manual clock synchronization, and dose calibration.</i>
Quarterly checks of PET/CT scanner	<i>Multidimensional phantom image stability verification, normalization stability verification and coincidence timing verification.</i>
Weekly checks of PET/CT scanner	<i>Detector dead time, energy calibration and amplifier gain.</i>
Daily checks of PET/CT scanner	<i>Normalization, coincidence timing correction, tube warming and CT calibration.</i>

Continuation on next page

Continuation of Table 3.3	
Element	Description
Patient instructions	<i>Fast six hours before study, encourage hydration and the patient should be warm before and during the examination. Patient compliance should be evaluated and the patient should be educated about the imaging process.</i>
CT parameters	<i>Document and/or measure rotation time, slice thickness, FOV, tube voltage, tube electric current, pitch, slice acquisition technology, tube rotation, collimation, table feed per rotation, inter-slice spacing, frame duration, and amount of iterations and subsets.</i>
Lesion size	<i>The lesion should preferably be large enough to neglect PVE and effects on the RC.</i>
PVE corrections	<i>Use corrections when appropriate.</i>
Patient comfort	<i>The patient should be comfortable and stress should be reduced as this could increase FDG uptake in muscle tissue and/or brown fat.</i>

3.6 Other quantitative methods

SUV is the most commonly used quantitative index in the clinic today, but other tools also exist. The reason for it being the most popular index is because it is easy to determine the radioactivity concentration and it requires less scanner time compared to other analyses which rely on dynamic acquisition of data [25]. Hence, several other methods have been developed and researched that provide more extensive and accurate information than SUV. These methods should be substantially simplified before being suitable for clinical use since an efficient workflow is compulsory in the health care system.

3.6.1 Tumor delineation

Several methods used for tumor segmentation have been described in literature but they are not yet implemented as a part of a clinical routine. Examples of these methods are contrast-oriented methods [22, 39, 40, 41], gradient-based methods [42], iterative methods [43] and fuzzy clustering methods [44].

The segmentation can be based on a threshold to determine which voxels to consider as tumor and which voxels to be regarded as normal tissue. Examples of such thresholds are a percentage of the SUV_{max} value or a constant added to the percentage of the SUV_{mean} value [9, 29, 45, 46, 47]. Thresholds tested for tumor delineation are 15-50 % of SUV_{max} where 40 % is the most commonly used. The FDG accumulation rate of the tumor and its heterogeneity can affect the result of threshold methods because of the binary approach [20].

Visual assessment could be regarded as a quantitative method. Studies have shown that

visual studies often perform better than automatic segmentation and they are both accurate and comparable. It is a simple method, since the boundary of a tumor is defined by the experience of the physician, and, as a consequence, visual assessment is the most clinically used segmentation method [20, 25, 46].

3.6.2 Tumor uptake metrics

Full kinetic modeling and Patlak analysis are two quantitative measurements often mentioned as a substitute for SUV. An advantage of using full kinetic, or compartment modeling, is that it can provide absolute information regarding the FDG accumulation rate or the glucose metabolic rate, meaning the amount of glucose metabolized per gram of tissue per unit of time. However, this requires a great effort from both the patient and the personnel since the FDG concentration in the arterial blood should be monitored which is not without difficulty. Studies have shown that the glucose metabolic rate represents various metabolic behavior better than for example SUV_{mean} and SUV_{max} [1, 18, 21, 48, 49].

Patlak analysis and dynamic PET studies can be utilized to assess the FDG influx constant provided that a transport in one direction between two compartments can be assumed. The influx constant can be described as the constant utilization of FDG, it is expressed in mL/100 g/minute [16, 50] and calculated by using Equation 3.6 [26].

$$K_i = k_1 \cdot k_3 \cdot (k_2 + k_3) \quad (3.6)$$

Each k is a different uptake rate in the various compartments of the model.

The influx constant can be used to calculate the metabolic rate of FDG by multiplying it with the blood glucose concentration [16, 50]. If the influx constant is not available the metabolic rate can be calculated according to Equation 3.7 [51].

$$\text{MrGl} = \frac{C_{\text{gl}} \cdot C_i^*(T)}{\text{LC} \int_0^T C_p^*(t) dt} \quad (3.7)$$

Here LC is the lumped constant which is set to 1 and assumed to be constant over time, C_{gl} is the blood glucose concentration, $C_i^*(T)$ is the tissue concentration of FDG in a region at the time T , and $C_p^*(t) dt$ is the plasma concentration of FDG as a function of the time t [51].

Studies have shown that a combination of Patlak analysis of FDG kinetics and dynamic PET acquisition can provide important and improved information. Using SUV to indicate the radioactivity concentration is easy and convenient but it does not take all important aspects into consideration, such as the variation in plasma clearance of the tracer and the rate of FDG uptake in the tumor, which can lead to errors. The study of Brun et al. showed that SUV had a poorer association with survival and that metabolic rate had a greater prognostic

value [16, 50, 51].

SUV and metabolic rate describes the metabolic activity per tissue gram and not the metabolic rate in the entire tumor. This limitation can be overcome by establishing the metabolic rate or the SUV within a lesion and multiplying it by its volume, in mL, which results in the total lesion glycolysis (TLG). Determining the tumor volume prior to treatment is often without difficulty as the tumor boundary is clear. During and after treatment the complexity factor increases as the contrast between the tumor and the background is reduced in the PET image. However, by combining PET and CT it is now possible to measure the tumor volume in the CT image and calculating the TLG by multiplying this volume with the SUV measurement, often SUV_{mean} , in the PET image. Combining information regarding the tumor volume and the FDG uptake to produce the TLG is only one of several approaches to utilizing morphological and anatomical information to improve the tumor response assessment [1, 18, 52].

4

Cancer treatment

This chapter describes how PET/CT can be a part of a cancer treatment. The chapter is commenced with a general introduction to PET/CT and its usage in the area of oncology. In the next part a detailed description of the PET/CT application is provided, in the world as well as in Sweden, by using three cancer types: lung cancer, lymphoma, and head and neck cancer. These cancer forms were selected based on the interviews conducted and based on the fact that PET/CT is most often used for diagnosing lung cancer, most often used for treatment response evaluation of lymphoma and a standardized treatment course has been developed for head and neck cancer in Sweden. The chapter is concluded with a description of classification and response assessment systems for oncology and how PET/CT contributes to these systems. Information about the classification system called TNM and the response assessment systems response evaluation criteria in solid tumors (RECIST) and PERCIST is provided.

4.1 Cancer treatment

The use of PET/CT has increased 10-fold in the United States between the years 2001 and 2010, and in some institutions it is the most frequently used nuclear medicine imaging modality. During the same time period the PET usage has increased 7-fold, from 250 000 to approximately 1.7 million examinations [53].

A cancer treatment includes various stages and PET/CT contributes with vital information to complete them. Examples of these stages are diagnosis, staging, recurrence, restaging, treatment response assessment and radiation treatment planning. Diagnosis is the part where the cancer is detected before confirming the disease. Staging occurs after the disease confirmation but before the therapy. Recurrence means that cancer has been discovered in a follow-up examination after treatment. Restaging occurs after the primary therapy or when recurrence has been confirmed. Treatment response assessment is conducted during or immediately after therapy. Radiation treatment planning occurs before the radiation therapy to define the target volume and dose. The result when using PET/CT for these stages vary depending on the stages and the cancer form. It has been shown that FDG-PET can improve the diagnostic accuracy for detecting distant metastases, restaging and recurrence for head and neck cancer, and staging of lymphoma, among others [54].

Other examples of the usage and the importance of FDG-PET was discovered in an economic model in England, which stated that it is cost-effective to use FDG-PET for patients with non-small cell lung cancer (NSCLC) and a CT node-negative result, but not for patients with a CT node-positive. It has been shown that PET/CT substantially alters the treatment for one in every five patients and could therefore have an impact on the overall patient management. PET and PET/CT is used for a variety of cancer diseases but the validity of using it for all decisions mentioned above has not been confirmed, thus it requires more research. In a study in England it was discovered that the clinical effectiveness was at its maximum when using PET/CT for staging NSCLC, restaging Hodgkin's lymphoma (HL) and staging/restaging colorectal cancer [54].

Other studies have shown that the accuracy of using FDG-PET/CT for staging is high for the cancer forms NSCLC [55], lymphoma [56] and head and neck cancer [57]. The patient sensitivity and specificity of PET/CT averaged at 93 % and 96 % respectively, which is considerably higher than the average for conventional imaging with a value of 52 %. It has also been discovered that PET/CT can be utilized to determine treatment response after a single cycle of chemotherapy [58], in the middle of the treatment and at the end of treatment [2, 59, 60, 61].

The previously mentioned decisions, such as cancer detection, staging, restaging and therapy response evaluation, were formerly only investigated using anatomical information. The anatomical information provides a framework to study tumor metabolism by using PET,

which is the main idea behind PET/CT, where both modalities contribute equally. PET plays a substantial role in deciding the patients who will benefit from surgery [62] and in defining targets prior to radiation therapy [63]. Another strength of FDG-PET is to evaluate response to therapy and by combining this information with measuring TLG [52] or total metabolic volume [64, 65], the prediction of therapy response will improve even further [59].

Vital information from the CT images of the PET/CT is for example the tumor size as this cannot be accurately defined using the PET due to its lack in resolution and the fact that the area that radiates is larger than the actual tumor size. This information is important for the T part of the TNM-staging, which will be discussed in Section 4.6.1, and for determining if the cancer has invaded adjacent tissue [66]. Tumor size is often used to define treatment response even though there are some limitations, such as the fact that a change in metabolism can occur prior to a change in size making it less sensitive [59].

PET/CT can additionally be used to differentiate a benign lesion from a malignant one, to search for an unknown primary tumor when metastases have been located and to identify the tumor that will provide maximum diagnostic information for a biopsy [9]. It can also be used to define prognosis when, for example, higher grade and less differentiated tumors have higher levels of FDG accumulation and more metabolically active residual masses, which often leads to a worse prognosis than by using another imaging modality [18, 21].

The most common usage of PET/CT is for tumor staging and it has a great amount of advantages compared to using PET alone. A newer area of application is to use PET/CT for treatment response evaluation and it has been suggested in several studies that investigating changes in FDG accumulation 2-3 weeks after the initiation of therapy could be correlated with reduction in tumor size and consequently patient survival. It could therefore be used to monitor the treatment response regularly to have the opportunity to change treatment if it should show no effect. This in turn reduces costs as well as unnecessary side-effects and increases the chance of reaching a curative treatment. A problem with using FDG-PET to evaluate therapy response is to find small amounts of tumor that may be present after a completed treatment. Studies have shown that to rectify this issue it is appropriate to wait 4-6 weeks after treatment end before making the patient undergo a new PET/CT, to be able to identify residual tumors. However, when using PET/CT during a treatment it is best to wait 2-3 weeks after the most recent cycle before doing a new PET/CT as this will ensure that the PET/CT is done as close to the next cycle as possible. The goal is to identify patients that do not respond to the current treatment and determine if it should be intensified or altered completely, to in some way help individualizing the treatment [1, 18].

As mentioned before, the result from a PET/CT could be used to determine a change in treatment and patient management, and the alteration can be conducted in four ways. It could be decided to give treatment or not, it can be determined if the treatment should be palliative or curative, and the third and fourth way describe changes in type or number of

clinical actions, which in turn can be depicted as either minor or major. A major change could for example be defined as a change in treatment type from chemotherapy to surgery. A minor change could be defined as removal or addition of treatments. PET is more associated with an upstaging change rather than a downstaging one, across all cancer forms, as the change from non-treatment to treatment compared to the opposite was 30 % and 8 % respectively [67, 68].

Some limitations have to be considered when using PET/CT for cancer treatment planning such as benign lesions could be associated with an increase in FDG accumulation and these could be separated from malignant ones by using SUV. However, this should perhaps not be done using specific threshold values such as 2.0, 2.5 or 3.0 since studies have shown that this only lead to a correctly identified lesion in 64 % of the cases [21, 69]. Another limitation is the fact that the image acquisition protocols and reconstruction parameters used vary substantially and require standardization. This will not be a process without difficulties as the technology and the algorithms used are constantly evolving, which could lead to standardized parameters quickly being outdated, and as PET scanners from various generations and manufacturers have a great amount of different properties to take into consideration. A suggested solution has been to always ensure that the measurements of activity concentrations using a phantom should be within specified limits [18].

A standardized imaging procedure could also simplify and increase the value of comparisons of semi-quantitative and quantitative image interpretation between different platforms and institutes. As a consequence guidelines have been developed which should be seen as recommendations to assist the physician when performing, interpreting and reporting results from a PET/CT examination for oncological purposes [9]. A challenge of the near future is to define standards to be used in international multi-center studies that also should address the issues surrounding the usage of different modalities and tracers in one study [70].

To summarize, PET/CT is one of the most established and advanced technologies as it provides both structural and functional information at a whole-body level. In the area of oncology this has practically limitless applications for diagnosing, staging and therapy response evaluation [59].

4.2 Lung cancer

PET/CT examinations have received an important role for quantitative analysis of lung cancer and NSCLC [18, 46]. Lung cancer causes more than 1.3 million deaths every year and NSCLC accounts for over 80 % of all primary lung tumors. The usage of FDG-PET/CT for NSCLC staging has increased and it has also been shown to completely alter or influence treatment decisions for the disease. International guidelines recommend that a patient assessment based on medical history, a physical examination, a chest or upper abdomen CT

scan, bronchoscopy and/or CT-guided biopsy should be conducted and a PET/CT should be performed on all patients with a possible curative outcome. The patients are classified in various stages ranging from I to IV, which will be discussed further in Section 4.6.1, and this will help determine an initial treatment such as surgery, chemotherapy or radiation treatment. Conducting a PET/CT could be considered a vital part of the staging process and as a result this has become standard. The PET/CT examination has an increased sensitivity, specificity and positive as well as negative predictive values compared to stand alone CT, which could sometimes be seen as the routine instrument for staging. However, the fact that using a PET/CT could delay the completion of the diagnosing process should be considered, especially in health care facilities which do not have immediate access to a PET/CT [46, 71].

The usage of PET/CT instead of CT has had a positive effect on the treatment planning stage due to the improved tumor volume delineation. The reason for this is that the PET images could present possible malignant tumors which would have been disregarded on a CT and it has been shown that using a PET/CT for manual tumor delineation reduces the interobserver variability. It could also provide a more accurate therapeutic ratio where an area with an increased activity would receive a higher radiation dose. This in turn will increase the management abilities of the radiation therapy while remaining within dose/volume constraints for normal tissue [72]. Hence, several studies have shown that the delineation of the gross tumor volume (GTV), which is the clinically defined tumor volume, clinical target volume, which is the GTV plus suspected microscopic spread, and the planning target volume, which is the clinical target volume plus a margin for movement and technical uncertainties, improve when using PET/CT instead of stand alone CT [46, 73]. For example, tumor coverage improved from 75 % to 89 % when going from a CT to a PET/CT and an alteration of the GTV and the planning target volume occurred in 52 % and 42 % of the cases respectively [74]. Merely using a CT scan for target volume delineation has been associated with over- or under-estimation of the tumor tissue. By including information from PET, the delineation volume could either be increased, if it had not been registered as malignant on the CT, or reduced by excluding non-tumorous structures. Automatic methods for tumor delineation have been discussed but a manual technique is still preferred as the size and shape of the GTV could vary considerably, which is managed by implementing detailed protocols. However, if an automatic method should be utilized it is recommended that it is adapted to the used system and every lesion should be defined separately [46].

A limitation that has to be taken into consideration when using PET/CT imaging, especially for lung cancer investigations, is the fact that the breathing pattern for the CT, which is relatively quick, does not immediately correspond to the breathing pattern during the PET, which can last for several minutes. Therefore, it has been recommended to use shallow free breathing during the acquisition of the CT scans [75] and for small lesions (< 1 cm) respi-

ratory gating or averaging should be used to improve accuracy [18, 76, 77]. Caution should also be exercised when examining patients with diabetes, as they can present false negative FDG accumulation due to high levels of "cold" glucose, and patients receiving chemotherapy as they can present false negative lesions due to a decreased glucose metabolism [46].

Three main diagnoses can be made within the lung cancer area and these are NSCLC, small cell lung cancer (SCLC) and solitary pulmonary nodule. PET/CT is mostly used for NSCLC as it can provide superior anatomical information and the staging can be improved compared to using a stand alone PET. The other two cancer types can be diagnosed and staged by PET but this is not recommended [54, 78].

4.2.1 Lung cancer in Sweden

The usage of PET/CT in the area of lung cancer has successively increased, and in some hospitals 50 % of all PET/CT examinations are correlated to lung cancer. PET/CT is expected to be used for primary diagnosis in 500 cases yearly and lung cancer is predicted to increase with 900 new cases every year [3]. This increase in usage is in line with the national guidelines where it is described that a PET/CT should be conducted for all patients with the possibility for a curative treatment. This has on the other hand contributed to an increase in investigation time and complexity, which are two aspects that have to be streamlined in order to be reduced. As the need for a more detailed diagnosis and treatment plan increased, not to merely separate NSCLC from SCLC, the demand and importance of a PET/CT examination increased as well. The purpose of the national guidelines was to provide a base for clinical actions and to enable conditions for an equal health care. Since lung cancer is a complicated disease the investigation, treatment and care should be based on knowledge, experience and understanding of the patient situation. A team has been established to form a standardized treatment course for lung cancer and it should come into effect in April 2016 [79].

Today lung cancer is almost as common for women as for men and in 2014, 3900 cases were diagnosed. A poor prognosis is common for lung cancer since most patients are diagnosed at a late stage of the disease. 15 % of patients in stage I and II can have surgery and 55-60 % are cured. However, patients with a spread disease in stage IV are often only given palliative treatment to impede disease progress and ease symptoms. 60 % of all NSCLC patients are in stage IV when diagnosed and the corresponding number for SCLC is 70 % [79]. The expected relative survival five years after diagnosis is approximately 13 % in Sweden, which makes it the most common cancer related cause of death for women and men. At least 80 % of all lung cancer cases are associated with smoking. Other factors such as occupation, air pollution, diet and genetics can also have an impact [80].

Patient symptoms for lung cancer could be coughing, pain or loss of breath, and after an initial clinical examination the patients should be examined by a lung X-ray. If this

shows pathological changes in the lungs, which occurs in 95 % of cases, a CT of the thorax and possibly abdomen is the next step, which will provide more detailed information than the standard lung X-ray as the resolution is better. Data has shown that more than 95 % of all patients expected to have lung cancer underwent a thorax CT. The CT will provide information for differential diagnosis and to map the anatomical distribution of the cancer. The next step will be to conduct a PET/CT if there is a prospect of curative treatment. PET/CT is a vital part to improve diagnosis and staging, and it can be used for treatment planning of radiation therapy. The usage of PET/CT varies greatly in Sweden which could be explained by the fact that not all hospitals have an easy access to PET/CT technology. However, as the method contributes to such a great increase in quality of care it should still always be conducted on patients with a need and a possibility to be cured. The purpose of the investigation is to define a diagnosis, map the tumor distribution and to assess the status of the patient with respect to the contemplated treatment [79, 80].

In order to determine if a tumor is benign or malignant from a CT image, it is possible to examine some specific properties. The density of the tumor can be reviewed by investigating the HU scale where a $HU < 147$ is often malign and a $HU > 164$ is often benign. Other factors to examine are patient age, smoking, tumor size (the bigger the higher risk for malignancy, < 3 mm 0.2 %, 4-7 mm 0.9 %, 8-20 mm 18 % and > 20 mm 50 %), edge (a benign tumor often has a smooth edge), calcification, appearance and growth (duplication time which means that a duplication is reached when the diameter of the tumor has increase with 30 %) [80].

As mentioned before, a PET/CT is always included in a lung cancer investigation if a curative treatment is possible, thus surgery at stage I and II, or chemotherapy at stage III. It is also used for staging, to map eventual metastases (especially distant ones) and guidance for the dose planning process of the radiation treatment. PET/CT has a high sensitivity and a negative predictive value of 85-95 % which means that the possibility for a malignancy on a negative PET/CT is low. However, some uncertainties remain since the method has a difficulty in separating tumor from inflammations or infections as they too can have an increase in FDG accumulation. It is also important to know that tumors with a reduced growing rate could present a negative result on a PET/CT due to the low metabolism and the FDG uptake. The positive predictive value is around 50 % and therefore it is vital to verify the result with morphological tests, if crucial for the treatment decision. The staging part of a lung cancer investigation has two purposes: to guide the physician when selecting the treatment and to assess the prognosis. It is also a vital part when evaluating the treatment response and the result of the treatment, especially when examining survival rate [80]. The TNM-classification is used as a base for the staging, which will be discussed further in Section 4.6.1.

4.3 Lymphoma

FDG-PET is seen as an appropriate modality when staging and evaluating treatment response for lymphomas. FDG-PET/CT has shown a particular positive effect on HL and high-grade non-Hodgkin's lymphomas (NHL), with an increase in accuracy compared to CT [1]. Lymphomas are a group of heterogeneous malignancies which origin from haematologic and lymphoid tissues. Staging is a vital part of the lymphoma investigation as this has a major impact on the treatment selection and can provide an indication of the prognosis. As mentioned previously, PET and PET/CT have become important parts of the staging process as these modalities contribute with more information than a conventional CT. The reason for this is that they have the ability to detect lesions which would have been disregarded on a CT, and PET/CT can help with detecting lesions that could not be identified using a CT. Some facilities have now selected to use PET/CT as a primary imaging examination and to only use other modalities in cases not suitable for PET. PET has a specificity of 90 % and sensitivity of 79-100 % for staging lymphoma [48, 54, 81].

Studies have shown that PET/CT and PET are superior in accurately defining treatment response in HL and high-grade NHL, and as a consequence it has been proposed to alter international guidelines to take this into consideration. It has been demonstrated that conducting a PET/CT after two or three treatment cycles can be useful when defining the future therapy direction and the long-term prognosis, particularly for aggressive lymphomas. The assessment of the treatment response has earlier only been defined by visual analysis which can be affected by interobserver variability. However, objective measurements such as SUV has been subjected to a great amount of suspicion and no evidence clearly suggest that analysis by using SUV is superior to a visual one. It would have been preferable to use a threshold value to distinguish a benign lesion from a malignant one but this has not yet been established. Being a semi-quantitative index, SUV is surrounded with considerable sources of variation, which in turn causes additional caution [1, 48, 54, 81].

In summary, the usage of FDG-PET/CT has a major effect on the investigation of lymphomas and the management of patients with lymphomas, but any diagnostic value has not been presented at this time. The staging and treatment response monitoring parts of a cancer treatment acquire an increase in accuracy by including PET information. It also contributes with valid prognostic value which allows for an accelerated risk definition [78, 81].

4.3.1 Hodgkin's lymphoma in Sweden

Malignant lymphomas are groups of tumors which origin from the cells of the immune system. The standard lymphoma has a great variation of histological and immunological sub-types with different primary sources and distribution patterns, making it a highly unpredictable disease. Since 2007 it has been established that the probability of survival is

considerably reduced as the age of the patient increases, but the survival within each age group continues to improve. It is expected to register an increase of lymphoma cases with 350 every year and PET/CT is predicted to be used for primary diagnosis in 140 cases yearly [3, 82].

It is not recommended to use PET/CT for diagnosing a lymphoma patient and it should instead be based in a biopsy according to the World Health Organisation (WHO) classification. The investigation process is commenced with a review of the patient history and a clinical examination, including blood tests. If curative treatment is expected, a PET/CT and a contrast CT can be conducted. In the case of a palliative treatment plan a diagnostic CT of the neck, thorax and abdomen should be performed instead. It is recommended to take biopsies of lesions where the FDG accumulation level were uncertain [78, 83].

PET/CT is often used in the process of defining targets for radiation treatment. As it is common to receive chemotherapy before radiation treatment the lymph nodes have often reduced in size which contributes to the PET/CT being highly important. It is recommended to perform the diagnostic examination and the dose planning CT simultaneously, and optimally a diagnostic PET/CT has been conducted in the treatment position [83].

As opposed to many other cancer types it is common to use PET/CT to assess the treatment response and result for lymphomas. It is recommended to evaluate the treatment after two cycles and after terminating the treatment of initially discovered tumors. According to the Cheson-criteria the treatment should be evaluated with a PET/CT examination after the complete termination of treatment. This examination should be conducted 3-4 weeks after the concluded chemotherapy and 6-8 weeks after completing the radiation therapy. Several studies suggest using PET/CT or PET early in the treatment course to determine prognosis and to review the treatment plan. If a PET/CT is performed after 1-2 cycles this should be assessed according to the Deuville-criteria which, for example, state that if the FDG uptake in a tumor exceeds the liver uptake then this tumor is considered to be positive [83].

It is common to have a residual tumor after completing treatment and if this tumor is > 2.5 cm it is recommended to perform a PET/CT, provided that the lesion has not been FDG-negative in a previous one. If the PET/CT is negative then the patient is considered to be remaining in complete remission, which means that there is no sign or symptom of the original disease. If no PET/CT was performed the patient is managed according to the program of complete remission unknown, which means that there still are some enlarged nodes. If the PET/CT is positive then a confirming biopsy is taken, which is also the case when partial remission has been confirmed [83, 84].

A CT of the neck, thorax and abdomen is often performed one month after the final treatment occasion, but this examination can be replaced with a PET/CT. The follow-up plan is generally five years long and during the first year the patient should visit a physician every third month, the second year every fourth month, the third year every sixth month and

during the fourth and fifth year it is sufficient to visit a doctor once a year [83].

4.4 Head and neck cancer

Head and neck cancer is defined by nine different categories, which each has a certain amount of sub-types and individual patient management plans. Head and neck cancer constitutes 3 % of all cancer cases in the United States and 55 000 people are affected each year where 12 000 die from it yearly. One common treatment used is radiation therapy which is not without difficulty as the tumors often are surrounded with vital and radio-sensitive organs such as the spinal cord. The treatment is also made more complex since most patients are diagnosed in the severe stages III or IV where the tumors are > 4 cm and have spread to regional lymph nodes [85]. Using PET to determine the metastatic invasion of lymph nodes could pose some difficulties due to the lack of spatial resolution. This could also affect the tumor delineation process which could lead to uncertainties of whether the tumor has infiltrated other structures or not. Thus, a PET with high spatial resolution that is specifically designed for investigating head and neck cancer could greatly contribute to an improvement in both staging and treatment [86].

Studies have shown that the usage of a PET/CT technology with a focus on head and neck cancer could register more information than a CT and therefore be able to display objects with decreasing sizes. It is also vital to consider that an improvement in representing FDG accumulation could improve the treatment of head and neck cancer. During the treatment planning process it is vital to, as mentioned previously, perform an accurate tumor delineation to determine tumor boundaries and active GTV. This in turn contributes to the ability of predicting relevant prognoses and treatment plans. It has been demonstrated that having a specialized PET and to use PET/CT could substantially improve staging and treatment as well as dose planning since, for example, uptake in structures with a size of down to 2 mm can be registered. The fact that an enhanced tumor delineation process can be implemented could reduce the radiation to sensitive tissue surrounding a tumor while retaining the curative dose to the tumor [86].

PET is often used for diagnosis since studies have shown that it has a superior accuracy compared to CT and MRI, as it detects 30 % of all primary tumors, including those not registered by other imaging modalities. The enhanced sensitivity also makes it appropriate to use for staging and restaging, and it could in some cases alter patient management. The target delineation process is often commenced with a physical examination followed by a CT or MRI. However, using PET or PET/CT instead has been proven to improve the definition of the GTV as these modalities have a slightly higher sensitivity of at least 80 % and specificity of at least 90 %. It has been shown that FDG-PET should not be utilized for predicting treatment response as it is not consistent, but it could be essential to perform a

PET or PET/CT for radiation treatment planning as this occasionally has an impact on the radiation volume [1, 45, 54, 78].

4.4.1 Head and neck cancer in Sweden

A standardized treatment course has been established for head and neck cancer in Sweden. The purpose of which is to ensure that cancer patients experience a well-organised and professional health care without unnecessary waiting periods, no matter where in Sweden one decides to seek for medical treatment. The standardized treatment course is based on the national guidelines for head and neck cancer [87].

Every year approximately 1 300 patients are diagnosed with head and neck cancer and this number is expected to increase with 250 new cases every year, where PET/CT is predicted to be used for primary diagnosis in 170 cases yearly. Head and neck cancer includes tumors in the lips, mouth, esophagus, larynx, nasal cavity and sinus, salivary gland and lymph nodes metastasis with an unknown primary tumor, which all have individual subtypes that vary in investigation, distribution, prognosis and treatment. Approximately 90 % of all patients receive a curative treatment and the observed five year survival is 57.3 %. The usage of PET/CT is expected to increase for investigation of unknown tumors and for dose planning purposes [3, 87, 88].

There are many known risk factors for head and neck cancer, such as tobacco consumption and smoking, and the majority of new cases are diagnosed with an advanced tumor progress, in stages III and IV. This could be explained by the fact that the symptoms are fairly vague and could often be correlated with other more common diseases, such as a cold or a sore throat. It can also be explained by that it is an unusual disease, only 2.3 % of all cancer cases, which can be difficult to examine in an ordinary health care center [87, 88].

The process usually begins at a primary care facility where the patient should be referred to an ear, nose and throat clinic if cancer is suspected. At this point it should be decided if the patient should receive care according to the standardized treatment course or not. When a malignancy could be expected a radiological examination should be conducted to detect and map the primary tumor and its position, distribution and invasion of nearby organs, and to depict changes and metastases (including possible distant ones) [87].

A PET/CT is relevant to conduct when a metastasis is located in the neck, for staging and to identify an unknown primary tumor, for staging of large tumors (stage III and IV), for dose planning, to identify remaining tumor or to discover recurring cancer if executed earliest 8-12 weeks after treatment (to reduce the risk of interpreting an inflammation as a tumor). It is beneficial to conduct a PET/CT as it can provide both anatomical and functional information to identify tumors, metastases and remaining tumors after surgery. It can also be used to distinguish physiological uptake from pathological and as it is a whole-body examination it can be utilized to detect connected tumors and distant metastases. However,

the patient is exposed to a great amount of radiation since both X-rays and radiating isotopes are used. All hospitals do not have immediate access to the technology and as the tracers have relatively short half-lives they demand a certain amount of logistics before being able to be used. PET/CT is not appropriate to use to investigate tumors and lesions < 1 cm as well as necrotic metastases since they are often difficult to define, which can lead to a false negative findings [73, 87].

Before establishing a final treatment plan it is vital to have a multi-disciplinary conference where a variety of health care professionals should meet and discuss the investigation. The investigation should have been conducted in such a detailed manor that a decision regarding treatment can be achieved during the multi-disciplinary conference. The investigation should be concluded in fourteen days, starting with the first visit at the ear, nose and throat clinic. It should be possible to perform a head, neck and thorax CT within six days, which applies for the PET/CT examination as well. The final treatment decision should be made after communicating with the patient so that it can be adjusted according to the wishes this person and hers or his family. The cancer is staged according to the TNM-classification system which is specific for each cancer disease. The treatment can consist of either surgery, chemotherapy, radiation therapy or a combination [73, 87, 88].

If the patient should receive radiation therapy then the first treatment is commenced with the creation of a fixed mask to ensure a consistent head position every time. A CT, MRI or PET/CT is then performed in the treatment position to provide an image for the physician to conduct target delineation on. This part can be optimized for head and neck cancer by using a small FOV and a doubled sampling time of the FDG during the neck part. The treatment is adjusted according to the target by using a dose planning system [73].

4.5 Reporting

The importance of a standardized PET/CT report has been discussed for a while as the reports can differ in format, content and quality. It has been suggested that each facility should implement a specific structure and language but studies still suggest that vital parts of the report such as indication, treatment history and comparison to prior imaging examinations, could not be found in 40 % of the reports. It is important for the health care professionals to have access to reports online and these reports should be well-structured and accurate to increase the time-efficiency. However, little has happened to the imaging reports over the last few decades which is a clear set back since the optimal standard PET/CT report changes with time. It has been suggested that the focus should be on implementing a standard language, structured format and a consistent content in the reports. This could be achieved by using software that creates, archives, transmits and displays reports, and by training new physicians to implement the standard and uniform report [1, 53, 89].

To standardize the report format a template could be used with a certain structure and headings according to anatomical and physiological terms often used. The terminology used should be consistent and the report should contain information about the clinical indication, anatomy, imaging findings, diagnoses and eventual uncertainties. The display of the electronic reports should also be considered to improve the readability and information transfer by for example using color coding and separating anatomical data [89].

A great amount of studies have been performed to evaluate which information a PET/CT or general radiology report should contain. It is often suggested that the information is presented in separated parts such as clinical history, findings and impression. A complete recommendation based on the literature study of this thesis can be found in Section 6.1. A request for the examination should be sent from the referring physician and this should include the clinical information necessary to determine if an imaging examination such as a PET/CT is valid and the medical questions to be answered. It is vital to have a PET/CT report with high quality to ensure correct use of the information and the continued success of the image modality. If the referring physician should receive a report which is confusing, the real important information could be disregarded. Guidelines for the content of a PET and PET/CT imaging report have been developed by the Society of Nuclear Medicine and Molecular Imaging, American College of Radiology and European Association of Nuclear Medicine (EANM) where each country has their individual interpretations and additions [9, 53].

A crucial part of examining the PET/CT images is to conduct comparisons with both previous PET/CT studies but also studies conducted with other imaging modalities. It has been identified that by comparing a current result with previous ones it is possible to decrease the number of misdiagnoses. Comparison could also be used to confirm certain results and to identify treatment response. The structure of the PET and CT findings could be either anatomical, ordered according to importance or a hybrid of the two. With anatomical it is meant that the findings should be depicted with head and neck first, followed by the thorax and finally the abdomen and pelvis. When using this model the findings of the PET and CT parts are described in the same anatomical section if the findings were located in both images. Order of importance implies that the findings should be presented according to the level of relevance for the patient care. The anatomical structure is often preferred by physicians as it is well-organized and it can be recognized from other imaging modalities. The report should also contain an impression part describing all relevant information in a clear way, as numerous physicians only read this part of the report, to conclude the report. An interpretation of the findings along with a diagnosis and possible differential diagnoses, with level of likelihood, should be provided. The reason for having such a clear impression and report with several predefined properties is to facilitate the communication process between the interpreting physician and the referring physician, as this might be the

only route of communication. However, emergent malignant findings should be conveyed orally without delay to avoid negative consequences for the patient. Many physicians, both interpreting and referring, have little training in reporting PET information which makes it even more important to have a distinct structure for everyone to follow. It is important to take into consideration the fact that by improving the quality and accuracy of the PET/CT report, the referring physician will be assisted which in turn leads to better patient care and management [1, 9, 53, 90, 91].

One study examined several PET and PET/CT reports and it was discovered that certain elements were mentioned in more than 90 % of the reports. These elements were the type or site of the cancer, name of the radio-pharmaceutical, the administered activity, the body region scanned, the date of previous PET and/or PET/CT examinations, the type and date of prior studies with other imaging modalities, the description of the location, the extent and intensity of the FDG accumulation (if abnormal) and the correlation of the abnormal PET findings with other results such as the ones from a CT when conducting a PET/CT [90]. For an example of a PET/CT report see Figure 4.1.

CANCER TYPE: SUSPICIOUS SOLITARY PULMONARY NODULE (SPN)**PATIENT NAME:** Jane Doe**MEDICAL RECORD NUMBER:** 000000**EXAMINATION:** PET/CT from base of skull to mid-thigh**EXAMINATION DATE:** 12 / 12 / 2012**CLINICAL HISTORY:** 70 year old female with 40 year history of smoking. CT scan showed enlarging 1 cm speculated nodule in the right mid-lobe without lymphadenopathy. PET/CT requested to search for malignancy.**COMPARISON STUDY:** No prior PET exams. CT chest dated 11/30/2012**TECHNIQUE:**

Approximately 60 min after the IV administration of 10 mCi of ^{18}F -FDG, PET images were obtained from orbits to mid-thighs using 3D acquisition. The patient's fasting blood glucose level was 120 mg/dL. The patient was positioned in the PET/CT scanner approximately 60 min after injection of the radiopharmaceutical. A CT scan from the orbits to upper thighs was obtained for attenuation correction and anatomical localization. Images were displayed in the axial, coronal and sagittal planes. Injection site was in the right antecubital fossa.

FINDINGS:

A 1 cm spiculated nodule is seen unchanged at the anterior aspect of the right middle lobe with intense FDG uptake (SUV_{max} 4.7). No other abnormalities are seen in the rest of the lung parenchyma. There is no FDG avid mediastinal or hilar lymphadenopathy.

No abnormal FDG uptake was demonstrated in the abdomen and pelvis.

There is normal physiological FDG uptake in the liver, spleen, adrenal glands, bone marrow, bowel, renal collecting systems and urinary bladder.

IMPRESSION:

Highly FDG avid enlarging spiculated 1 cm nodule in the right middle lobe is highly suspicious for malignancy. Biopsy is recommended. No evidence of metastatic disease.

Figure 4.1: Example of a PET/CT report sent from the interpreting physician to the referring physician [1].

Another aspect to consider is the fact that health care records are becoming increasingly accessible to patients, which is the case in the United States and Norway, and a goal for Sweden. As a part of this it is important to realise that the language in these reports should be understandable for everyday people and not only for health care professionals. The precise language needed to describe interpretations of imaging studies and possible diagnoses poses a problem for patients with an interest in reviewing their health care process. The study of Kvist et al. suggests a usage of automatic text simplifications as the report structure and content often is fairly consistent in Sweden. This study mentions that the general structure of an imaging report was: a heading or sentence describing the procedure and the method used, and an interpretation of the findings and their individual importance, with a plausible diagnoses in mind. Additional information provided in the report was dates, name of the physician, findings, examined body parts, procedures used and administration data. The

uniform structure supports the usage of a "translator" to simplify the report language to the level of a person without medical training [92].

4.6 Classification methods

Several classification methods exist to, for example, guide the physicians towards a certain treatment plan, to predict a plausible prognosis, to facilitate communication and to evaluate the quality of care. It was decided to focus on the classification method TNM as it was regularly mentioned in the articles examined during the literature study and in the interviews. PET/CT can be used as a support for this system but it is not a predefined part of the guidelines.

4.6.1 TNM

The TNM classification and staging system was developed approximately 50 years ago and it describes the anatomical distribution of the cancer. TNM is used for its ability to individually classify each tumor (T), lymph node (N) and metastasis (M), and to combine these elements for a specific staging of cancer types. The TNM staging system is regularly updated to new versions, where the most recent one is version 7, and each cancer type has a specific TNM system [93, 94].

The TNM staging provides information about the anatomical extent of the cancer and it is based on the correlation between treatment choice and survival chance, and the tumor, node and metastasis criteria. These criteria are based on the extent of the tumor at the primary site, whether tumors are present in regional lymph nodes or not, and if metastases can be found beyond the regional lymph nodes. Information provided by both imaging modalities, such as CT or MRI, and by pathological test results are therefore vital when determining the treatment plan, the prediction of prognosis and the evaluation of the treatment response. The cancer is classified prior to treatment, called a clinical TNM, and after the resection, called a pathological TNM [93, 94].

The T factor is often assessed by performing a thorax CT and this can in certain situations be complemented with an MRI. Due to the accuracy of these imaging modalities they can be utilized to evaluate tumor proximity to other structures. The T factor is generally divided into four parts (T1-T4) which correspond to the depth of the tumor invasion, tumor size, spread of the primary tumor and gross morphology, where a higher number is associated with a poorer prognosis. The N factor has at least two categories, starting with 0, and can determine therapy and prognosis when no distant metastasis can be found. The M factor also consists of a minimum of two categories and describes the presence of regional or distant metastases. PET could contribute to determining the M factor as it can define the

primary tumor as well as distant and local metastases in one examination with high accuracy compared to many other imaging technologies. The results from each category are then combined to form specific stages and these are constructed to ensure a correct and distinct survival rate. For example, the survival rate for stage I should be considerably higher than for stage IV. Hence, a certain combination of the T, N and M factors generates a specific stage, ranging from I to IV, which could provide indications for treatment and prognosis [11, 80, 93, 94].

A challenge with the TNM classification is knowing how to manage and incorporate information of a non-anatomical kind. These properties with substantial prognostic data could provide valid information if used appropriately. Thus, all prognostic factors should be evaluated and perhaps incorporated into the TNM classification system without removing any vital anatomic information [94].

4.7 Response assessment systems

In order to evaluate the treatment plan and treatment response it is popular to utilize response assessment systems. Based on the literature study and the interviews it was decided to focus on the systems called PERCIST and RECIST.

4.7.1 PERCIST

PERCIST is a fairly new system, published by Wahl et al. [95] in 2009, and it is solely based on the result from the PET or PET/CT technology. PERCIST was established to provide a basis for refining and validating quantitative measurements of FDG accumulation in tumors to define treatment response by using both functional and anatomical information. Instead of implementing discrete categorization PERCIST uses the percentage change in metabolism from the baseline study to follow-up studies to provide a continuous measurement of the activity in a tumor. In PERCIST it is recommended to use a threshold value of 30 % to differ between the categories and it should be considered using technical improvements to reduce effects of noise, reproduction of uptake periods within 15 minutes and other enhancements [1, 4].

The main idea is to use a fixed ROI with a size of 1 cm^3 , which is placed in the region with the highest FDG accumulation in the most metabolically active tumor in the patient during each PET/CT. The ROI does not have to be placed in the same tumor every time, instead it is encouraged to select the tumor with the highest metabolic activity as long as it was registered in the baseline study. The result from establishing the activity in one lesion at each PET/CT is used to indicate the disease status of the patient and the treatment response. To determine the treatment response SUV is used. It is recommended to normalize SUV

with LBM since research have shown that this will lead to fewer variations in the patient body size. In order to compare the SUV in the selected tumor with another patient specific value, a spherical ROI with a diameter of 3 cm is placed in the liver, which has a fairly stable SUV, to represent the background activity. It is not specified which SUV index to use but it is important to use the same one in every examination. The treatment response should be defined according to the four specified criteria. Complete metabolic response (CMR) is defined as a complete disappearance of the FDG uptake in both targets, and non-targets to a level less than or equal to the mean activity of the liver and so that the tumors cannot be distinguished from the background blood-pool. Partial metabolic response (PMR) is reached when the reduction of the selected SUV index is at a minimum of 30 % and an absolute decrease of SUV units of 0.8. Progressive metabolic disease (PMD) is considered when an increase of at least 30 % in SUV and absolute increase of 0.8 units is registered or if new lesions were located. Stable metabolic disease (SMD) is established when values between PMR and PMD is defined [1, 36, 96].

Treatment response evaluation has generally been conducted by using RECIST, which will be discussed further in Section 4.7.2. Instead of using the metabolic activity to define treatment response, changes in size based on a CT is utilized, which can have considerable limitations. Changes in size may take months to occur which causes opportunities to register early response for improving patient management based on possible success or failure, to be lost altogether. It has been shown that size measurements are highly correlated with patient survival but RECIST would be greatly improved if it was possible to incorporate metabolic, biologic and prognostic information in the criteria. Hence, assessing metabolic activity by using a PET/CT could provide a possibility for discovering early treatment response and therefore also quick treatment management. Studies have demonstrated that performing a PET/CT when the CT examination cannot detect any changes can be valid. It has also been indicated that PERCIST is consistent with RECIST 1.1 and PERCIST has a higher sensitivity in detection CMR and patients exhibiting progression. Another decision support system is the European Organisation for Research and Treatment of Cancer (EORTC) criteria and its correlation with PERCIST was evaluated in the study by Skougaard et al. [96]. In the study PERCIST was perceived as easier to apply due to its several predefined application aspects. Each category was defined in detail which caused PERCIST to be less prone to ambiguity and interobserver variability than the EORTC criteria. It was also concluded that quantification by applying PERCIST is required in order to continue improving cancer treatment and the usage of PET/CT [1, 12, 36, 96].

4.7.2 RECIST

RECIST was introduced in the year 2000 and revised in 2009, then called RECIST 1.1, which makes it a more established and utilized system than PERCIST [36]. However, it is

regularly discussed if a volumetric anatomical assessment or functional assessment should replace the entirely anatomical based assessment. To this date many health care experts do not find the standardizations using other image information sufficient to recommend an adjustment, apart from using FDG-PET imaging. It is also possible to use a PET/CT to determine the RECIST criteria provided that the diagnostic quality is comparable with a diagnostic CT [97]. A variety of the RECIST 1.1 version exist which are defined to comply with specific cancer diseases, such as modified RECIST for hepatocellular carcinoma [98].

The process of categorizing the tumors is commenced with defining them as either measurable or non-measurable. A lesion is considered measurable if it in one dimension, where the longest axis of the plane should be registered, is ≥ 10 mm in a CT scan and 20 mm in a chest X-ray. For a lymph node to be found enlarged and measurable it is required to be ≥ 15 mm in the shortest axis on a CT scan. For a lesion to be defined as non-measurable the longest axis is < 10 mm and a lymph node has to have a short axis with a size of ≥ 10 to < 15 mm. The baseline examination should preferably be conducted immediately after treatment start and with a maximum limit of 4 weeks after [97].

The method for assessing the results should be consistent from the baseline study to all follow-up examinations. The assessment should rather be based on the image results than clinical results, except for when the lesions cannot be evaluated in an image but in a clinical examination. Examples of assessment methods are chest X-ray, CT, MRI or ultrasound. In order to objectively define response and progression it is required to determine the general tumor burden at the baseline study and use this for comparing the result of the follow-up studies with. Only measurable lesions are defined as target lesions with a limit of five lesions in total and a maximum of two lesions per organ. The lesions should be selected with respect to their size (longest diameter if non-nodal), representation in multiple organs and the ability to be detected in several examinations. The sum of all target lesion diameters (longest for non-nodal and shortest for nodal) is calculated and reported, and it should be noted if lymph nodes are a part of the sum [97].

RECIST is divided into four response criteria in which the target lesions should be categorized. CR is defined as the disappearance of all target lesions for at least 4 weeks and the pathological lymph nodes, both target and non-target ones, must exhibit a minimum 10 mm reduction of the short axis. PR is when the sum of diameters has decreased with at least 30 % compared to the baseline study. PD is considered when there is at least a 20 % increase in the sum of diameters, where the smallest sum of all examinations is used for comparison. The sum must also display an absolute increase of 5 mm and if any new lesions have been discovered it is furthermore considered to be progression. SD is used when the decrease or increase of the sum is neither enough to qualify for being PR or PD, where the reference is the smallest sum yet registered [36, 97].

Even though the focus of RECIST is on the sum of diameters the individual size of each

target lesion should be registered at every examination. However, occasionally the lesions become too small for the radiologist to be comfortable in assigning a specific measurement and instead the lesion is reported as being "too short to measure". In these situations it is important to still enter a numerical value in the report. If the lesion is thought to have disappeared then the value 0 mm should be recorded and if the lesion is present but too small to assign a certain value then a default value of 5 mm should be entered [97].

RECIST is also divided in four response criteria in which the non-target lesions should be classified. These lesions should only be assessed when the study protocol specifies it. CR is defined as the disappearance of all non-target lesions and normalization to the level of the tumor marker. All lymph nodes is required to be non-pathological in size, meaning that they should be < 10 mm. Non-CR/Non-PD is considered when one or more non-target lesions remains and/or when the tumor marker levels continue to be above normal. PD is defined as the unequivocal progression of existing non-target lesions. This means that the discovery of a new target should not depend on the scanning technique, the imaging modality or findings expected to be something else than a tumor. A new lesion is not required to meet the measurable criteria in order to be legitimate, which is especially important when the baseline lesions demonstrate PR or CR [97].

Occasionally PET information can be utilized to compliment the CT scan, particularly when assessing progression. PET can be used to define new lesions and therefore to indicate that a certain category should be used. If the baseline FDG-PET is negative but the follow-up one is positive then a sign of PD based on the new lesion is present. If no FDG-PET was conducted at the baseline study and the follow-up PET is positive, this should be confirmed by performing a CT before assigning PD. If no new lesion is present on the CT then additional follow-up CT scans should be performed to determine if progression is present or not [97].

The best response is determined from the start of the study to the end of the treatment and it will depend on the findings of both target and non-target lesions with a consideration for the appearance of new lesions. The tumors should be re-evaluated based on the statements in the protocol and be adjusted according to the type and schedule of the treatment. The duration of the overall response is measured from the date of the CR/PR recording to the date when recurrent or PD is measured. SD is measured from the start of treatment until progression has been documented [97].

RECIST and PERCIST have been compared in several studies due to the fact that RECIST often is considered the "gold" criteria in CT evaluation, and because of the increasing popularity in using PET/CT and SUV to evaluate treatment response. Even though RECIST often is applied to evaluate treatment response it has some limitations since it completely relies on morphological changes. It has been demonstrated that PERCIST can be more sensitive and prognostic than RECIST and several studies have indicated that PET can detect

tumor changes during a treatment that would not be registered on a CT scan. The study of Ding et al. showed no significant differences between PERCIST and RECIST 1.1, and PET had a superior sensitivity in detecting CR and progression. The combination of PERCIST and RECIST could therefore provide more relevant information, which could improve the overall treatment response evaluation [36].

To summarize, several limitations have been discovered concerning the RECIST criteria. It could therefore be valid to implement a treatment based on PET/CT information as well, as this could be beneficial for the patient. It is thought that the usage of PET/CT in patient management during the entire oncological treatment process will increase over the next decade. The applications for PET/CT in the area of oncology will as a consequence become more detailed and specific by standardization of the image acquisition protocol, the reconstruction and the analysis, which will in turn probably result in an internationally approved treatment response criteria such as PERCIST [59].

5

Method

This chapter depicts the methods used to obtain the results in this thesis. The chapter will commence with a description of the literature study and go on to depict the process behind the interview and questionnaire results. The method behind the development of a prototype for a user interface concludes the chapter.

5.1 Literature study

The literature study could be seen as a vital part of the thesis as it contributed to all other parts. It provided and inspired questions for the interviews and the questionnaire, which in turn lead to the resulting prototype.

The literature study was commenced by a referral to specific articles from people with experience of the field. The references of each article were examined and this constantly provided new articles that could be of interest. The abstract of all articles was read to determine if the article contained essential information or not.

After reading an article, a summary of it was written in order to easily be able return to the article and collect relevant information.

When contacting experts in the field of PET/CT and cancer treatment, which will be described in the subsequent section, it was asked if these people could provide information or articles that could be interesting. Generally a certain website with applicable information was provided but occasionally specific articles were referred to as well.

In the writing process of the report, additional literature was required to answer questions or provide a ground for statements made. In these situations the literature was acquired by need and not as a specific part of the study.

The databases most used for this literature study were PubMed, Journal of Nuclear Medicine, National Oncologic PET Registry and LUBsearch.

The information from the literature study, which is described in the theory chapters 2, 3 and 4, was constantly compared and reviewed during the interview and questionnaire process to comment on the existing differences.

5.2 Interviews

In order to assemble people to interview, several different approaches were implemented. The process was commenced by contacting people recommended by Sectra and the supervisors of the thesis. Thereafter, suitable people for the interviews, such as professors in nuclear medicine, medical personnel operating in the area of nuclear medicine and radiology, scientists, people with a master of science in medical physics, presidents of applicable associations in Sweden (Svensk förening för bild- och funktionsmedicin, Regionala cancercentrum i samverkan and Svensk förening för klinisk fysiologi) etc. were contacted by locating their e-mail addresses online. The search was narrowed a bit by using survey from the national medical physics personnel meeting of 2014 [99]. This survey presented hospitals in Sweden that own and operate a PET/CT as well as the amount of PET/CT machines. Hence, it was decided not necessary to contact personal of a hospital that does not use a PET/CT. It was important to in the e-mail convey an interest of additional knowledge from

other people that could be even more applicable for the subject. This resulted in an increase of the contact list since several individuals recommended other people to contact.

People all over Sweden were contacted in order to achieve a full representation of the usage of PET/CT for cancer treatment in the health care of today. After receiving positive answers in general it was decided to focus the interviews to Linköping and Lund/Malmö. Linköping because Sectra is located there and Lund/Malmö since nearly 33 % of all PET/CT investigations in Sweden are conducted by Skånes Universitetssjukhus (SUS) [3]. All contacted people, including the ones in Lund and Linköping, received the questionnaire which contained questions mainly inspired by the result from the interviews.

The questions for the interviews were determined by the literature study where both articles describing PET/CT usage in general and for cancer treatment were used. Due to the great number of questions this generated, some questions were prioritized to manage interviews or parts of interviews which were time sensitive. The questions were not adjusted according to the area of expertise of the person to be interviewed. It was namely deemed too difficult to select the correct questions to remove as it was problematic to define the knowledge of the person prior to the interview. To review all the questions used in the interviews, see Appendix A.

To regain the most information possible from the interviews it was decided to record them, after asking the person to be interviewed for permission, and to take some notes to complement the recording.

5.3 Questionnaire

The interview questions and the result from the interviews were utilized as a basis for the questionnaire. The reason for this was to optimize the questions, and hopefully the answers as well, to acquire as much relevant knowledge as possible.

The questionnaire was created in Google Forms to facilitate the answering process for the participants and to provide a continuous overlook of the answers. It was initiated by a general information section about the person answering. It was not obligatory to enter a name, but it was compulsory to register location and occupation. The reason for this was that it could be of interest to differ between occupation and/or location when describing the results and when discussing them. Hence, it was interesting to compare the usage between hospitals and the health care professionals. It was also explained that if a person has no knowledge regarding a question it would be acceptable if no answer was provided. Additionally, it was encouraged that the participants passed on the questionnaire to people who they think could contribute with relevant information.

The questionnaire was separated into different parts depending on which area the questions addressed. This was to encourage the participants to move forward towards the end

and to complete the questionnaire, which was enhanced by adding a box at the bottom of every part depicting the progress. The answers were monitored continuously for some time to allow for as many people as possible to answer before establishing a result. To review the questions used in the questionnaire, see Appendix B.

5.4 Prototype of user interface

The process of developing a prototype for a user interface was initiated by examining the results of the interviews and the questionnaire. Several valuable features were extracted to form a list, which in turn was utilized as basis for the actual prototype. The user interface of the viewer in the Sectra PACS, called IDS7, was used as a foundation for the implementation process since it was of importance that the prototype complied with the current product.

During the entire process of developing the prototype the usability was considered. It was also of importance for it to comply with the current product to simplify the usage of a possible new one.

The program used for developing the prototype is called Balsamiq and it was selected based on a recommendation from a user experience expert. Due to the fact that only a limited number of features could be completed in one project, while still ensuring that the workflow could be easy to comprehend, several projects were created to depict the entire prototype. It varied if only one or numerous features were addressed in one project and this depended on the similarity of the features and their respective workflow.

After completing all projects, information to describe the usage and workflow was entered. The reason for this was to facilitate a future development process and to ensure that the correct feature is developed in the intended way.

6

Results

This chapter describes the result from the literature study, the interviews, the questionnaire and the development of a prototype of a user interface for examining PET/CT images. The result from the literature study consists of a suggestion for the complete content of a PET/CT report sent from the interpreting physician to the referring physician and how this can be compared with the referring report. The result from the interviews and the questionnaire is presented and reviewed to form a list of features to be implemented in the user interface prototype, which is the section that concludes the chapter.

6.1 Literature study

Since the content of the PET/CT report can vary substantially, the result of the literature study contains a compilation of several article suggestions [1, 9, 53, 90, 91].

The study identification part of a PET/CT report should contain the full name of the patient, the patient date of birth, the patient medical record number, the protocol name of the examination, the date and the time of the examination performance, the facility or location of the study, and the names of the physicians or other health care providers.

The clinical information section of a PET/CT report should provide general medical information about the patient, see Table 6.1.

Table 6.1: Content of the clinical information part of a PET/CT report.

CLINICAL INFORMATION	
Element	Description
Patient information	<i>Age, gender, length and mass. Should be determined before the FDG-PET/CT to compensate for mass loss.</i>
Patient therapy information	<i>Biopsy based or surgical pathology results, chemotherapy (including date of completion), radiation therapy (including date of completion) and treatment, oncology and medical/surgical history.</i>
Clinical indication for the study	
Reason for performing the study	<i>Diagnosis, search for unknown tumor, staging, restaging, therapy monitoring, evaluation, detecting tumor recurrence or selecting biopsy region.</i>
Specific question to be answered	
Summary of previous relevant diagnostic tests and imaging findings	
Diagnosis	
Cancer type and site	
Treatment history	<i>Brief review of previous and ongoing treatments.</i>
Date of last treatment	
Therapy	<i>Type and timing relative to PET scan.</i>
Clinical questions from referring clinician	
Additional medical or surgical history	<i>If relevant for PET/CT interpretation.</i>
Medications and/or devices	<i>Current and recently used.</i>
Renal Function	
Known patient reactions or complications	

The procedure part of a PET/CT report should contain information regarding the complete examination, see Table 6.2.

Table 6.2: Content of the procedure part of a PET/CT report.

PROCEDURE	
Element	Description
Type of PET/CT system	
Radio-pharmaceutical	<i>Name.</i>
Administration	<i>Dose (MBq and/or mCi), route, time, site and concentration.</i>
Significant dose infiltration	
Uptake time	<i>From injection to imaging.</i>
Blood glucose level	<i>mmol/L. Include date and time.</i>
Regulated non-radioactive drugs and agents	<i>Name, dose and route.</i>
Ancillary medications administered	
Precise body region scanned	
Position of the patient	<i>Supine or prone.</i>
Position of the arms	<i>Elevated or by the sides.</i>
CT technique	<i>Description of the protocol and the corrections used and if it was diagnostic, non-diagnostic or low-dose.</i>
CT contrast	<i>Oral, IV, allergies (signs, symptoms, treatment and response) and type of contrast (positive or negative).</i>
CT parameters	<i>kVp and mAs or patient radiation exposure estimate.</i>
Dosimetric parameters	
Additions or modifications to the standard PET/CT acquisition	
SUV	<i>State parameters (maximum, peak, mean, normalized to body mass, lean body mass etc.) and corrections.</i>
Limitations	<i>Small lesions (PVE), inflammatory changes, muscle activity, high blood glucose levels etc.</i>

The comparison section of a PET/CT report should depict information about the result of comparing the current examination with previous ones and with images taken with other modalities, see Table 6.3.

Table 6.3: Content of the comparison part of a PET/CT report.

COMPARISON	
Element	Description
Prior PET or PET/CT studies and reports	<i>Date, scanner, facility and different technique. State if no previous examination has been performed.</i>
Prior non-PET studies and reports	<i>Date, scanner, facility and different technique. Include digital imaging and communications in medicine (DICOM) data if possible. State if no previous examination has been performed.</i>
Other examinations performed on the same day as the PET/CT	
Correlations	<i>Prior PET and non-PET studies.</i>
Assessment of response to therapy	

The findings section should contain information regarding the result of the PET/CT examination, see Table 6.4.

Table 6.4: Content the findings part of a PET/CT report.

FINDINGS	
Element	Description
PET findings	<i>Described by anatomical site, by importance or by a hybrid method.</i>
Significant CT findings	<i>Described by anatomical site, by importance or by a hybrid method. Include relationship to pathological FDG accumulation.</i>
Incidental findings	
Quality of the FDG PET/CT study	<i>Limited due to motion artifacts, abnormal bio-distribution or tracer (muscles, brown fat), infiltration of tracer at the injection site, CT-artifacts etc. Identify factors that may compromise the sensitivity and specificity of the examination.</i>
Location, extent and intensity of the FDG uptake	<i>If abnormal and if it should be related to normal tissue. Should be defined as mild, moderate or intense compared to the background intensity, and explained with anatomical descriptors. The visual interpretation needs to be defined for each study protocol as well as incidental CT and PET findings. The SUV should be included.</i>
Correlation of abnormal PET findings with other results	
Size measurements	<i>Single transaxial diameter or in two/three orthogonal directions.</i>

The impression part of a PET/CT report should provide a summary of the result and a clear answer to the asked question, see Table 6.5.

Table 6.5: Content of the impression part a PET/CT report.

IMPRESSION	
Element	Description
State definite diagnosis	<i>Include staging assessment or estimate likelihood of diagnosis or conclusion.</i>
Possible differential diagnoses	<i>According to level of likelihood.</i>
Clinical issues	<i>When performed for monitoring therapy a comparison of the extent and intensity of the uptake may be summarized as metabolic PD, SD, PR or CR.</i>
Interpretation of the findings	
Recommendations for follow-up or additional studies	
Recommend repeat examinations	<i>To clarify or to confirm findings.</i>
Documentation of communication of urgent or emergent findings	
Documentation of communication of study findings to referring physician	
Clear identification of the study as normal or abnormal	
Address study question	
Date of dictation	
Date and time of transcription	

An example of a PET/CT report sent from an interpreting physician to a referring physician can be seen in Figure 4.1. The content of which can be compared to the report sent from the referring physician in order to request PET/CT imaging [1]:

- Part I provides information regarding the patient:
 - Patient name, medical record number, address and phone number.
 - Patient gender and mass (kg).
 - Date of study.
 - Insurance information, if possible.
- Part II provides information about the referring physician and other imaging studies:
 - Name, phone number and e-mail of the requesting physician.
 - Enter if a previous CT or MRI has been conducted or not. If yes, specify location and date.
 - Enter if a previous PET has been conducted or not. If yes, specify location and date.
- Part III provides information regarding the patient health:
 - Enter if the patient is diabetic or not. If yes, specify diabetic medications.
 - Latest fasting blood sugar.

- Allergy to contrast agents.
- Renal function.
- Creatinine level.
- Length (cm) and body mass (kg).
- Part IV indicates the study to be performed:
 - Enter if the studied region should be:
 - * Standard body study (skull base to proximal thighs).
 - * Special, meaning non-standard, body study.
 - * Whole body study (skull to toes).
 - * Head and neck cancer study (skull to thighs) or dedicated head and neck protocol.
- Part V specifies reasons for conducting a PET/CT and information affecting the interpretation:
 - Enter if the type of cancer has been histologically proven or if it is merely suspected.
 - For diagnosis, determine if a suspicious lesion is cancer, a pulmonary nodule or other (specify).
 - For diagnosis, detect an occult primary tumor.
 - Initial staging of confirmed and newly diagnosed cancer.
 - Monitoring response during treatment, chemotherapy, radiation therapy or other (specify).
 - Restaging after completion. Enter date of therapy, chemotherapy, radiation therapy or other (specify).
 - Suspected recurrence of previously treated cancer. Enter site of the suspected recurrence and what this assumption is based on.
 - Surveillance of a previously treated cancer in a patient with no known residual disease. Enter last date of treatment.
 - Enter other patient clinical information and specify instructions.

6.2 Interviews

A summary of the result from the interviews in Lund, at SUS, and in Linköping, at Universitetsjukhuset (US), can be found below. Each area of information specifies the city in which the information was gathered and from which occupational category. To review all

questions asked during the interview process, see Appendix A. The general opinion of each category is displayed below the name of the city, and if specific and relevant opinions were expressed by a certain health care professional, these are located below the general opinion. A total of nine people were interviewed and these individuals covered the occupational categories found below.

PET/CT in general

SUS Lund

The reason for conducting a PET/CT is to evaluate hyper metabolism and tumor distribution. Occasionally it is used to determine treatment response during treatment. Not all tumors exhibit hyper metabolism and therefore the usage of PET/CT is also a trade-off between the PET and the CT image, and the information they individually provide. It is desired to answer the question in the referral and reach an unbiased assessment. Prior to the PET/CT examination it is important to ensure that some preparations have been done such as the patient has been fasting and resting, and making a note of medicines and treatments that can affect the examination. A biomedical analyst prepares the patient for the examination, enters information to the radiology information system (RIS) and performs the examination. The PET/CT image can be affected by inflammations and infections where FDG also is accumulated. PET/CT is often used to investigate lymphoma, head and neck cancer, bowel cancer, lung cancer and malignant melanoma.

Nuclear medicine physician: A diagnostic CT (normal CT) or low-dose CT can be conducted. If there is actual ground for performing a PET/CT and it is available, the cost of the examination is not an issue. However, the cost could contribute to a hospital not buying any additional PET/CT machines. PET/CT contributes greatly when staging lymphoma, as a change in metabolism often occurs before a change in size.

US Linköping

A PET/CT is performed to locate and display the intensity of pathological FDG accumulation early in the investigation. Hence, there are three major areas of interest: 1. Locate and validate a tumor. 2. Examine the cancer distribution. 3. Evaluate cancer recurrence. The machine can be adjusted according to the suspected cancer disease and it manages corrections and such independently. PET/CT is only used on patients who have the possibility of being cured. PET/CT is also conducted to detect metastases, tumor heterogeneity and distribution but to perform it for follow-up during and after treatment is rare, except for lymphoma. Could be of interest to save and review PET and CT raw data in order to change the image protocol a posteriori. All false positives such as inflammations, infections and accumulation in the blood affect the PET/CT images and their interpretation. The risk for false positives is reduced as the time between injection and imaging increases. The reason for this is that FDG accumulation in tumors will continue to increase but it decreases in

other locations. PET/CT is most commonly used to investigate and diagnose lung cancer (50 % of all examinations), breast cancer and lymphoma. It is especially appropriate for cancer with random metastasis occurrences.

Radiochemical specialist: The Warburg-effect is studied when performing a PET/CT, which means that cancer cells have an increased demand for glucose to regain energy and as a consequence they have a higher glucose metabolism, which can be examined using a PET/CT. National electrical manufacturers association phantoms are used once every three months to ensure that the PET/CT operates correctly.

Medical physics expert: It is important that the patient has been fasting for six hours before the examination. The reason for this is to ensure an appropriate blood glucose level, which is always checked before the examination. A urine sample and a blood sample is also taken and compared. The PET/CT machine manages the corrections according to decay, the SUV calculation, DICOM information etc.

Biomedical engineer: There are camera protocols for each cancer diagnosis and these can be specified according to the requirements of the physician. A control of the PET/CT system is done regularly by the manufacturer every year. A downside with PET/CT is that it is four times more expensive than a CT.

Lung cancer clinician: PET/CT substantially changes the treatment course for every fifth patient. The distribution of the cancer is often higher than originally expected.

Oncologist: The information from the PET/CT helps when defining a target for radiation treatment. Instead of doing a PET/CT it is possible to do a CT or an MRI, but these modalities would not provide as much information, which, on the other hand, sometimes could be sufficient. If the tumor is not going to accumulate FDG then there is no point in doing an FDG-PET/CT.

PET/CT image management

SUS Lund

During the image management process it is of interest to relate the accumulation in a tumor to a reference (liver, blood pool etc.), examine the activity in metastases and compare it to the background, and grade the tumor activity after treatment. The user often wishes to adjust the intensity and intensity scale, alter the window depending on area of interest and manage the images and the report in one program, which should all be done in a time efficient way. Tumor size, volume and length, changes in SUV, number of metastases and if any new tumors have been formed, are properties in the images that are investigated. All three images (PET, CT and fusion) are examined individually and simultaneously, and compared with previous PET/CT images and images from other modalities. The images should be interlocked and the user should be able to adjust the visualization as it is highly individual as to how one wishes to display the images. All information is correlated for a total assessment,

which is tumor and somewhat patient specific. The images are examined by various experts, whose assessments are joined later in a report. Hence, the final assessment is based on type of change, location, correlation with information and experience of cancer behavior, among others. A probability assessment is conducted to distinguish the physiological processes from the abnormal ones.

Nuclear medicine physician: The images are not processed but measurements are performed. The ability to edit the window depending on the examined area would be appreciated. Wishes to have one system that manages everything, such as the image interpretation and the report writing. Should be possible to arrange the images according to the requirements of the user or at least the department. Important to be able to compare the PET/CT images with images from other modalities in a simple way.

Oncologist: No measurements are performed since the only thing to be done is to define the tumor. Important to be able to adjust the intensity of the image to determine what should be defined as high uptake and low uptake, and the relation between the two. Would be appreciated if all images appeared simultaneously along with the answer from the nuclear medicine physician. Another wish is for the images over a certain time period to appear to enable comparison. These images should be correlated so that if a specific area in one image is marked, then this area will appear in the other images as well, this also applies to images completed with other modalities.

US Linköping

To review the images from the PET/CT manufacturer specific programs are used. When examining the images it is of interest to adjust the SUV-scale, change the threshold of what SUV-values to depict (40 % of SUV_{max} or a fixed value), expose certain organs, rotate and adjust the gray- and color-scale. It would also be appreciated if it was possible to change how SUV is calculated, by for example using LBM or body mass. A nice feature mentioned was the ability to slide between the image being 100 % PET to 100 % CT. The images should be correlated so that when pressing an area in one image this area will be marked and appear in the other ones as well, including the maximum intensity projection (MIP) image. Interesting properties of the tumor is size, volume, SUV, FDG accumulation, quantity, intensity and length. The PET, CT, PET/CT and MIP images are examined separately and a result is achieved by weighing in the importance of each image and making a judgement call. This assessment could depend on the cancer form but mostly on the physician. The SUV should preferably be over 2.5 to indicate a clear malignancy. It is important to review the images in all planes: axial, coronal and sagittal. A radiologist generally reviews the images and the answer is read by a clinician/oncologist. Properties to investigate are tumor growing rate, size, distribution and SUV. To examine treatment response the number of lesions, their size and intensity are supervised.

Medical physics expert: Program features that are not utilized often can only be accessed

by workstations but features such as applying a VOI, calculating an uptake, changing a threshold and its effect on the SUV and the GTV, can be located on every computer. It would be desirable to have a direct contact with the PACS, such that the images and the patient journal are connected, and that the images are non-static, for the ability to conduct measurements. The radiologists otherwise select a certain image in one plane that is deemed the best one and this is the one that the referring physician has to work with.

Biomedical engineer: Important that the program complies with the DICOM conformance statement. The fusion of the images, threshold, accentuation of certain organs, rotation etc. are conducted on the workstation and not on the PET/CT managing station, to speed up the entire process. If the raw PET and CT data is saved it is possible to change the filter kernels, slice thickness, reconstruction method etc. later.

Nuclear medicine physician/radiologist: It is vital that all users have easy access to the systems and they should not, for example, only be available on one machine. It is necessary to examine all four images: CT, PET, fusion and MIP. It is not appropriate to use the fusion image for diagnostics. The reason for this is that a tumor can disappear in this image since it, for example, can be depicted as white in both the CT and PET image, which makes it error prone.

Lung cancer clinician: Clinicians use the image viewer in the PACS and the images are only reviewed, no measurements or image alterations are conducted.

Oncologist: It is possible to use a PACS with both static images and 3D images that spin around. No measurements, changes or interpretations are conducted since these are provided by the diagnosticians. The only thing that is conducted is the planning for treatment by examining locations with high activity. Important that all the images are in sync and they should show the same area automatically, including the dose-planning images from the CT.

SUV

SUS Lund

The usage of the SUV is minimal as the visual assessment and experience of the physician is deemed more reliable. It can provide some support occasionally. The SUV-scale is adjusted to visualize certain accumulations/intensities. A relative SUV, compared to a reference, could contribute with more information than an absolute value. The SUV can be found in the report sent from the diagnostician to the referring physician in Malmö but not in Lund. SUV can be useful for treatment response assessment for lymphoma, where the user examines the change in SUV and determines if the accumulation is higher or lower than normal (no absolute SUV is used). No information specific to the SUV is registered prior to the examination, but some information is provided as a part of the quality control, such as fasting time, blood glucose level, resting time, and medicines and treatments that can affect.

The SUV index most often used is SUV_{max} , perhaps SUV_{mean} . If the SUV should appear incorrect this can be investigated by accessing the DICOM tags explaining for example mass, length and accumulation time. A physician rarely changes the SUV, this is often done by a biomedical analyst. It would be appreciated to have the ability to see how the SUV was calculated. A valuable feature for a program to have is the ability to depict SUV_{max} in a volume.

Nuclear medicine physician: The assessment is mainly based on visual information and experience, not the SUV. However, a higher SUV increases the probability for the tumor being malignant. No threshold value of the SUV is used but it could be interesting to have a reference SUV, where the SUV in a tumor is compared to the SUV in the liver or the blood. It varies if the SUV-value is provided in the report and as a consequence it should be possible to access it with ease if it should not be present. Would have been nice to have a SUV threshold that actually works and contributes with information instead of uncertainty. SUV is mainly used for investigations and treatments of lymphoma to determine regression or progression. It would be interesting to see how the SUV was calculated, since it, at this point, is fairly complicated to check and change, if it is incorrect. The accumulation time, length and mass are often sources of SUV calculation errors. It would be nice to be provided with the SUV_{max} , both in one voxel and in a volume, instead of locating it manually.

Oncologist: SUV is not utilized as it does not provide any additional value. To use a numerical value as a threshold would have been convenient but this is not possible as it is too uncertain. Could be useful to compare the SUV in a tumor to a background SUV such as the liver or a blood pool. Does not understand the interest in SUV and the motivation behind researching it, as well as various SUV indexes. It is known to be semi-quantitative but it is questionable how quantitative it really is.

US Linköping

The SUV is used as a support to interpret cancer metabolism, which is weighed in along with the radiological result when investigating cancer. It can be used during a follow-up but this is rare. It is vital with experienced doctors who can utilize the objectivity of SUV. It can also be used for assessment of the cancer treatment and it is desired to compare the SUV in a lesion to a reference, such as the liver SUV. It can be used as a threshold between benign and malignant, the value of which depends on the cancer form. Properties measured with a respect to SUV are blood glucose level (should preferably not be over 8 mmol/L) and time between injection and imaging (should be 60 min \pm 5 min). The SUV index most often used is SUV_{max} . It can also be used as an average, where everything in an area that is > 2.5 or 40 % of SUV_{max} is included and then the average SUV in that area is calculated. SUV_{peak} is starting to be used, where 10-20 voxels are combined around the SUV_{max} voxel. However, at this point in time the doctors do not know how to interpret the SUV_{peak} value and what it could entail. Hence, presently no information is gained by using SUV_{peak} . If the

SUV is incorrect, it can be adjusted by investigating the used mass, time etc. in the DICOM tags.

Radiochemical specialist: A ROI is defined and both SUV_{max} and how it varies within the ROI is examined. The SUV-value is not provided in the report from the interpreting physician to the referring doctor.

Medical physics expert: The opinion about SUV seems to be separated and some might think that it is a bit unnecessary. If the body is completely homogeneous then it has a SUV of 1 and it is difficult to distinguish malignant from benign if the increase is minimal. Clear thresholds are used to define a malignant tumor according to a certain SUV. The index used in Linköping for SUV is most often SUV_{peak} and sometimes SUV_{mean} .

Nuclear medicine physician/radiologist: It should be possible to vary the parameters that affect the SUV, such as LBM or body mass. The program should be able to follow a specified SUV to depict a volume and this volume should be adjustable by the user. A basic scheme to interpret and use SUV exists for many cancer forms. SUV_{max} is the most frequently used index and SUV_{mean} is practically never used. SUV can be utilized to distinguish cancer from inflammation, as the SUV in an inflammation decreases after a while but the SUV in a tumor remains on the same level for a longer period of time. The blood glucose level should be below 8 mmol/L, otherwise the examination is not performed. However, there are exceptions, such as when the patient has travelled a long way, when the patient is diabetic (the insulin level and administration is highly regulated) or when the PET/CT is emergent. It is helpful to use an objective and measured value as a support when investigating a suspected cancer disease.

Lung cancer clinician: A high SUV could contribute to the patient receiving chemotherapy as an additional treatment. High SUV in the primary tumor and a low SUV in the lymph nodes indicate that the cancer has not spread. SUV can be used for treatment response evaluation for some cancer forms that cannot be assessed with radiological information, but this is not common.

Oncologist: The interpretation of the SUV from the diagnostician is used more than the actual value.

Other quantitative information

SUS Lund

Metabolic rate is another known quantitative index but it is too complicated to use as it is required to take blood tests continuously to monitor the radioactivity in the blood. It could provide an indication of the FDG accumulation rate of the tumor, which in turn indicates aggressiveness. Manual tumor segmentation is often preferred as the user can decide where the edge of the tumor is and thereby provide the opportunity for the user to select the margin. Automatic segmentation is not generally trusted in PET as it is hard to define edges when

a great amount of radiation could have spread beyond the tumor boundary, which results in an incorrect size and volume. Segmentation is particularly used for radiation treatment preparation. It would also be desirable if it provided a possibility to transfer a ROI from one image to another for comparison.

Nuclear medicine physician: It is not without difficulty to use a PET image to define tumor boundaries, since radiation/accumulation could have spread making the measured size and volume incorrect. Deauville-score is a quantitative scale used by radiologists to determine regression or progression in lymphoma and could be used for treatment decisions.

Oncologist: Something similar to SUV called the Likert-scale can be used to grade the accumulation, it is a kind of internal comparison. A true quantitative measurement can be conducted by using metabolic rate. However, this is not without difficulty as one is required to perform several blood tests or carry out a dynamic FDG-PET. The reliability of automatic segmentation is low and therefore it is not trustworthy. It is better to define the tumor boundaries manually, since health care professionals are aware of the limits of PET and can take them into consideration. A margin is determined and added to the original tumor boundary, and the size of which depends on the diagnosis and the risk of malignancy.

US Linköping

Other quantitative indexes are percent injected dose per gram and compartment modeling. Segmentation is merely used for radiation treatment and surgery, where a specific margin is manually selected. Could be of interest to automatically segment a volume and then be able to affect its margin. This for CT and not for PET because of the lacking image resolution and other error sources in the PET image. Could use seeding models for segmentation which start in the SUV_{max} and spread until they reach a specified limit. Could also be of interest to select a certain SUV-value as a threshold and receive a volume by enhancing all pixels \geq this value. For both of these methods it is important to select an appropriate threshold to terminate the algorithm. If a completely spherical VOI is used this will often cause errors, especially when several tumors are located close to each other.

Radiochemical specialist: A quantitative index could be percent injected dose per gram. The common margin for segmentation is 0.5 cm when using it for surgery or radiation treatment, but this can vary depending on proximity to sensitive organs etc. A ROI can be determined either manually by the physician or automatically, however physicians rarely trust the automatic one.

Medical physics expert: Urine and blood samples could provide additional information for a kinetic model and for compartment modeling to be established. Segmentation can be done manually with a VOI using seeding algorithms. This means that the health care professional defines the voxel with the highest uptake and the algorithm starts to increase from this point until reaching a specified terminating value.

Assessment and treatment

SUS Lund

PET/CT is rarely used for evaluation of treatment response during treatment (except for lymphoma) and it is even rarer to use it after treatment for, e.g., follow-up examinations. The primary disease suspicion is based on general patient health and test results. In some cases a regular examination is conducted but this depends on the preferences of the physician and the form of cancer.

Nuclear medicine physician: A probability assessment is always performed during an investigation and it is of interest to determine what aspects could be seen as physiologically normal and what deviates. Several PET/CT examinations are performed over time to determine treatment response, especially for lymphoma, and it is of importance to examine if the SUV has changed and how, the size of the tumors, number of metastases etc.

Oncologist: It is difficult to perform a PET/CT for tumor follow-up or treatment response evaluation due to the lack of resources and time. The cost is often higher than the benefit, except for lymphoma. A CT is often done to determine if the cancer has been cured. To determine treatment response it is more suitable to examine a lymph node, test results and overall patient health. Important to take all images into consideration and determine the one that depicts the most valuable information, especially when the information is contradicting. The nuclear medicine physician, radiologist and oncologist/referring physician should meet more frequently to discuss each other's problems and expectations.

US Linköping

Usually the CT image is used for evaluation but this is not specified in any regulations, instead each hospital constructs its own follow-up schemes. For research, the follow-up protocol is more regulated and detailed. A PET/CT can be conducted but this is very rare as other examinations often is sufficient, such as a CT or a general patient examination. This evaluation is often done every other or third month and then reduced if no apparent issues are suspected. As a rule, only one PET is performed during a cancer investigation and this in the beginning to locate all metastases.

Medical physics expert: To assess treatment response, the SUV-values from several examinations are compared. If something else can be used for treatment response evaluation this is preferred but otherwise PET/CT is used. For example, a cancer diagnosis which is prone to form metastases should be monitored by using a PET/CT, otherwise it might not be necessary. The follow-up examination is usually performed a few weeks after the treatment.

Nuclear medicine physician/radiologist: When selecting treatment it is important to listen to the patients and listen to their intentions and wishes. The benefit should always be weighed against the risks or the side effects. A CT is usually performed during the follow-up examinations instead of a PET/CT. The reason for this is that when the PET has been used to create an initial map of the tumors they can be monitored using a stand-alone CT.

Lung cancer clinician: The imaging part of a lung cancer investigation is usually initiated by performing a lung X-ray, then a CT and finally perhaps a PET/CT. It could be useful and more time efficient to occasionally skip the CT step but this is generally not the case. The CT is mostly used due to the lack of PET/CT machines and the fact that a PET/CT is four times more expensive than a CT.

Guidelines and classification systems

SUS Lund

A system used for classification of the cancer is the TNM-scale, which only uses CT information such as size, and pathology information, and no information regarding the metabolism. PET facilitates the process but it is not a part of the actual classification system. The TNM is assigned either by an oncologist or a surgeon, often on a multi-disciplinary conference where all information, such as images and test results, is provided. RECIST is used to define treatment response and different stages for it. PERCIST is not used at the moment as it does not provide any additional value. RECIST is mostly used for research but occasionally for clinical purposes as well.

Nuclear medicine physician: PERCIST could be used for research purposes but this is rare. Both RECIST and PERCIST could be utilized to a greater extent in the future if it is shown that they have clinical value for cancer treatments.

Oncologist: No system takes the metabolism into consideration but this does not affect the result substantially as changes in the metabolism do not impact the treatment decision. RECIST is being used and it should be seen as a requirement. Not sure that measuring percentage decline, such as in PERCIST, is a reasonable way to determine treatment response.

US Linköping

The TNM-system is based on all information such as images, pathology and general patient examinations and tests. Before treatment a clinical TNM, cTNM, is established, and after treatment a post-TNM, pTNM, is defined and compared with the cTNM for evaluation purposes. Another pTNM, where the p stands for PET, can be conducted where the final result is completely based on the PET image, but this is rare. A corresponding rTNM, based on radiology, also exists and it is a bit more popular than pTNM. Hence, TNM is used for staging the tumor based on its size, growing rate, if it has grown into nearby organs, if there are adjacent lymph nodes or any fluid etc. PET is used as a support for the staging but is not included in the actual system. The staging is usually conducted on a multi-disciplinary conference where diagnosticians, oncologists and referring clinicians meet to discuss the staging and the treatment options. The tumor type is also decided but PET/CT does not contribute with any information. It is also possible to classify based on if the SUV in the tumor is below, between or above the SUV in the liver and the diaphragm. WHO (system for evaluating general patient health) and Deauville-score are two other systems used during

a cancer investigation and treatment. RECIST 1.1 is used for treatment response evaluation but not PERCIST as no one understands it. RECIST 1.1 determines the treatment response based on measurements of the longest side of the tumor in the axial plane, except for lymphoma when the shortest side is measured. RECIST is often used as a part of research studies and the protocol in the study determines which version to use. The radiologists conduct the measurements for RECIST and the oncologists determine the stage of the treatment response.

Nuclear medicine physician/radiologist: The Deauville-score can be used for staging lymphoma. During an assessment it is common to start with the CT image and continue by reviewing the PET image to see if the SUV is above or below 2.5.

Lung cancer clinician: Several classifications are conducted during an investigation and they are continuously corrected as more information is provided. Staging provides an understanding of the tumor distribution. The WHO-criteria, among others, is used for treatment response evaluation. RECIST is used for evaluating cancer treatments in research studies and it is rarely used clinically due to the fact that it is too time consuming.

Oncologist: The TNM-classification is a vital part in determining the treatment course. When deciding the M part it is important to investigate the distant metastases, meaning metastases distributed along the lymph system. When using RECIST it is crucial to review the same tumors every time.

PET/CT report

SUS Lund

A radiologist provides the CT information and a nuclear medicine technician provides the PET information, which are summarized in one report in the end. The report should contain a background, indication of the examination, an assessment of the primary diagnosis and an answer to the asked question. The oncologist can review the images and then write an assessment for the radiation treatment. A report template is always utilized to ensure a report appearance that is independent of the writer. It is important to have a clear question to ensure that an appropriate and accurate answer is obtained.

Nuclear medicine physician: The report could contain a summary of the referral if the referral is not provided. The referring physician prefers that the interpreting physician provides a clear interpretation that might be incorrect compared to never providing an interpretation at all. In Lund, a reporting template is used to ensure that the same information is located in the same area and described in the same way and order every time.

Oncologist: It is important to receive a distinct answer to the asked question. The images are examined to distinguish tumors from false positives. There is no need for a specific SUV-value but it is required to know if the uptake was elevated or not and if it was reactive or pathological. No specific answer is written by the oncologist, only an assessment

for the radiation treatment.

US Linköping

The report includes conclusions based on patient background, images, test results, experience of the interpreting physician and the probability for malignancies. The first part of the report illustrates the CT-findings anatomically by starting with the neck, then the thorax and lastly the abdomen. Then the PET-findings by starting with the primary tumor and working outwards to the lymph nodes and metastases, including the locations and intensities. The report is concluded with a summary of the two and an interpretation of the results. It is important to provide specific answers to the referred questions. The information in the report should be so distinct and defined that the referring clinician can determine the most appropriate course of treatment. The report contains all information for the ability to reconstruct the image information at a later point in time and to be able to compare it with prior data and images. The report also includes SUV-values for everything abnormal and unexpected findings are mentioned explicitly. It could be of interest to save the raw data of the PET and CT in order to be able to alter the reconstruction parameters later, if this should be desired. Everything is also well documented in the DICOM-tags and in the referral system. All information, such as the reason for the examination, questions to be answered and the findings, is entered to an examination database for research which is an examination database for research and quality control.

Medical physics expert: The SUV-value is always provided in the answer to the referring physician.

Lung cancer clinician: The clinician can interpret the images even before receiving an assessment from the radiologist. The main interest is to examine the intensities and during this process it is vital to recall the fact that 25 % of everything that glows are false positives.

Future

SUS Lund

There will probably be an increasing need and demand for PET/CT in the future as it can provide vital information for an additional number of cancer diagnoses. There will be a development of drugs and tracers that are more treatment and cancer/tumor specific. The health care will be optimized by centralization, stricter rules and more comparisons for a higher quality of care.

US Linköping

The usage of PET/CT will increase as it can be performed to investigate additional cancer forms. The value of conducting a PET/CT will probably extend from being focused on the investigation part to providing information for treatment response assessment as well. The amount of tracers will increase as they become more tumor specific and can separate tumor from inflammation. The treatment will become more personalized and targeting by, for

example, increasing the use of immunotherapy. The treatment decision will also be more influenced by tumor type and size and the degree of cancer differentiation, which is a part where SUV can be highly useful. As the accuracy in distinguishing tumor from healthy tissue the radiation treatment will be improved.

Medical physics expert: It is expected to see an increase in hybrid technologies and improvements of the hardware and electronics.

Biomedical engineer: Screening and a more prevention based approach to certain risk groups will perhaps be implemented. The PET/CT system will be used to its full capacity as it today can provide far more information than what actually is being utilized.

Nuclear medicine physician/radiologist: SUV will be vital in the future to individualize each treatment. It will be possible to regain more information about each tumor to target its weaknesses.

Lung cancer clinician: The use of PET for treatment evaluation will be greater and immunotherapy and targeting treatment will be considered vital.

Oncologist: The radiation treatment could be improved when the accuracy of the PET/CT increases. This because the definition of the tumor will improve which means that the radiation can be delivered in a way that the tumor is the only thing that will be affected, no normal tissue. This in turn will contribute to an increase of the radiation dose since it will be concentrated to the tumor which increases the chance of survival.

6.2.1 Reporting

During the interviews, information regarding the report processes was regained. As a preparation for the PET study the patient is required to answer several questions and enter some information. The information to be entered is mass, length, blood glucose level, PET camera, accumulation time and current medicines. The questions included were:

- Are you pregnant?
- Are you breast-feeding?
- Do you have any blood diseases?
- Do you have diabetes? If yes, have you been through an operation or a biopsy within the last two months? If yes, which operation and where in the body? When?
- Have you been through radiation treatment? If yes, specify the date of the last radiation treatment.
- Have you received chemotherapy? If yes, specify the date of the last chemotherapy.
- Do you have any ongoing or recent infections? If yes, where and what?
- Do you have a chronic inflammatory disease? If yes, where and what?

The report from an interpreting physician to a referring physician should be brief and merely contain the most vital aspects of the PET/CT examination. The report should contain:

- Name of the study.
- Name of the tracer.
- Description of the accreditation, if possible.
- Manufacturer and model of the PET scanner.
- Description of the CT protocol.
- Body region scanned.
- Correlation with previous other studies, if possible, including date. If not possible this should be explained as well.
- Comparison with previous PET studies, if possible, including date. If not possible this should be explained as well.
- Description of the result. If a low-dose CT was conducted, the result of the PET and CT could be combined. If a diagnostic CT was performed, the result description should be separated.
 - The CT findings could be described anatomically, starting with the findings in the neck, then the thorax and finally the abdomen.
- The locations where a measurement has been conducted should remain in the image but the measured number should be located outside the image. The measurements should be conducted according to the RECIST 1.1. criteria. Meaning, the longest side for every tumor, except for a lymph node where the shortest side should be measured.
- All locations of interest should be marked in the image.
- If a tumor is small, mark it with an arrow or a line.
- A general and brief assessment of the result.
- Summary of the assessment with a clear interpretation that answers the questions in the referral.
- Description of unexpected findings of relevance.
- Name of the interpreting physician.
- Date of the study.

When writing the report, a template of regularly used words should be utilized in order to simplify the interpretation process for the referring physician. It is also preferred if the

interpreting physician submits a definite diagnosis instead of the referring physician being forced to interpret to establish a diagnosis. For an example of a report mentioned above, see Figure 6.1.

POSITRON EMISSION TOMOGRAPHY (¹⁸F-FDG)

(by Swedac accredited establishment according ISO/IEC 17025, acc. nr. 1309)

Camera: GE Discovery 690

FDG-PET, with low-dose CT, from below groin to the base of the skull.

Correlation has been made with thorax and abdomen CT, 10-13-2014.

Result: No previous FDG-PET for comparison. Substantial hyper metabolism can be observed corresponding to enlarged lymph node in connection to the left head bronchus. In connection to a. pulmonalis a substantial hyper metabolism corresponding to enlarged lymph node is observed and a minor hyper metabolism corresponding to lymph node immediately to the anterior. No hyper metabolic foci are observed in the lung parenchyma. Substantial FDG accumulation is observed occasionally in the colon in the small pelvis – physiological/reactive? No hyper metabolic foci are observed in the abdomen/pelvis otherwise or within visualized parts of the skeleton.

Assessment: Lymph nodes suspected for malignancy in mediastinal. No certain primary tumour detected.

11-13-2014, Some One

Figure 6.1: Example of a PET/CT report sent from an interpreting physician to a referring physician.

As a supplement to the above described report, another report is written containing all information about the examination, see Table 6.6. This report is then sent to a database used for research and quality control.

Table 6.6: Content of a PET/CT report sent to a database for research and quality control.

PET/CT COMPLETE REPORT	
Element	Description
Name of the clinician	
Social security number of the patient	
Name and address of the patient	
Date for the PET/CT	
Referring hospital	
Interpreting clinician	
Clinic	
Diagnosis	
Radio-pharmaceutical	
Blood glucose level	<i>In mmol/L.</i>
Administered activity	<i>In MBq, and provide the time for the injection and the time for the imaging as well.</i>
Patient mass	
Questions to be answered	<i>Diagnostic, staging, investigate treatment response or RT-planning.</i>
If a prior PET/CT has been conducted	
If the patient is part of a research study	
If the examination protocol is abnormal	
PET findings	<i>Brown fat, accumulation in large vessels, lymph node metastasis in the mediastinum, other lymph node metastasis, adrenal metastasis, brain metastasis, liver metastasis, skeleton-vertebra metastasis, other distant metastasis, active tumor, inactive tumor or relapse. If an unexpected finding was discovered this should be described along with which of the findings it was. If the patient case was interesting this should be stated along with an explanation as to why.</i>

6.3 Questionnaire

A total of 29 people answered the questionnaire. The occupational categories covered by these people were professor, chief physician, physician, operations manager, radiologist, chief physician of oncology, research engineer, radiology nurse, radio chemist, medical physicist, nurse, biomedical analyst and department manager. These health care professionals operated from hospitals in Uppsala (Akademiska sjukhuset), Örebro, Göteborg (Sahlgrenska), Linköping, Eksjö (Höglandssjukhuset), Lund (SUS), Malmö (SUS), Umeå, Växjö, Stockholm (Karolinska), Huddinge (Karolinska) and Gävle.

PET/CT in general

The reasons for performing a PET/CT are staging and diagnosis prior to making a treatment decision, evaluating therapy/tumor response, tumor investigation, treatment follow-

up, distinguish malignant tumors from benign ones and inflammations, dose-planning and target definition for external radiation treatment, primary cancer investigation to exclude a metastatic disease, discover primary tumors (rare), evaluate tumor distribution, evaluate recurrent disease, TNM classification and determine lesions exhibiting FDG accumulation.

Recommendations and guidelines from national and regional health programs, EANM and the health authorities are used as guidance for when to perform a PET/CT and the physician concludes the final decision. Some hospitals conduct a PET/CT to investigate specific cancer diseases such as lung cancer, colorectal cancer and HL. Other hospitals perform a PET/CT when it is recommended by local guidelines. The national health programs specify guidelines for both the investigation and the treatment process for various cancer diagnoses, and when a PET/CT should be performed. Examples of when the guidelines recommend performing a PET/CT are when the primary tumor is larger than 3 cm and when the patient can be cured. In other cases, the decision is based on pathological results as well as physician experience, and it is vital to only conduct PET/CT when there is a valid reason.

Obstacles for performing a PET/CT are the cost for the referring clinic (should not be a problem in a rich country such as Sweden), pregnancy, a high blood glucose level, claustrophobia, the patient not being capable of remaining still in the camera due to pain or anxiety, poor renal function or allergies to contrast agents (when a contrast agent is intended to be used for the CT), lack of biomedical analysts, the waiting time is too long (depends on the region since some regions have far better access), the fact that PET/CT is used even though it is not mentioned in the recommendations for the specific cancer disease (this is avoided to refrain from causing queues), the lack of camera time (a camera can manage approximately 10 patients per day), the access to PET/CT physicians, biomedical analysts and nurses with the proper knowledge, the lack of access to a PET/CT camera and the lack of cyclotrons to produce the FDG.

PET/CT information

Practically all physicians consider the same information from a PET/CT to be interesting: it is desired to investigate the pathological FDG accumulation and the consequences this could have for the patient. The information provided by the CT part is vital for the overall examination. It is important that the asked question is clear so that the interpreting physician understands it and can answer it. The original hypothesis is then confirmed or discarded. As the information often is discussed at joint conferences, the overall result is the same even though various physicians are interested in different things. It is highly individual how the images are examined, for example nuclear medicine physicians might prefer to start with the PET image and confirm with the CT image, but a radiologist prefer the opposite order. The interpreting physicians quickly learn what the clinicians consider interesting, especially if the asked question is clear.

The programs used for examining the PET/CT images should be simple and have a low error risk. The user should be able to:

- Distinguish malignant uptake from benign and metastases from a primary tumor.
- Relate PET findings to morphological findings.
- Perform SUV and volume measurements in the PET image.
- Manage the settings of the color scales with ease.
- Dynamically change the slice thickness.
- Conduct a dynamic multi-plane reconstruction.
- Use an adequate and user friendly quantification model.
- Define the VOI and the ROI by using different geographic figures (circle, sphere, rectangle and cube) manually and by a predefined percentage of the SUV_{max} .
- Compare the current examination with previous images and images taken with other modalities.
- Utilize both automatic and manual tools where the automatic tools should be easily modified manually.
- Use good filters and CT as well as PET windowing.
- Review the axial, sagittal and coronal planes for the CT, the PET, the MIP and the fusion images.
- Decide the layout of the images.
- Conduct attenuation measurements in the CT image.
- Utilize tools for analysis of dynamic data.
- Compare lesion uptakes with normal references.
- Save and export key images and data.
- Visualize in both 2D and 3D.
- Examine the images using both SUV and radioactivity counts.
- Conduct trend analytics between examinations.
- Transfer a ROI or a VOI drawn in the CT image to the PET image.
- Rescale the image according to the specified SUV scale.
- Zoom in and out with ease.
- Measure the length and the area of the tumors.
- Measure global metabolic activity.

- Conduct visual analysis.
- Examine tumor distribution.
- Display dynamic and static information regarding the radio-pharmaceutical.

The software utilized to review the PET/CT images should provide analytical tools, be stable, correct and quick, require few button clicks, enable the use of key combinations, utilize user specific and created display protocols, operate with PACS and RIS (to review previous examinations and to ensure that the correct patient is examined), enable easy access to image extraction for presentations and publications, and provide an opportunity for correlation of the PET/CT results with radiology. The analytical tools used in the program should be available for both the performing physician and the referring physician, and the referring physician should have access to raw material in order to conduct more advanced measurements and settings. It would also be beneficial if the referring physicians could receive education regarding refinements that can be conducted during the image examination process. The PET/CT images are primarily examined visually and then semi-quantitatively by using SUV_{max} and size measurements. Clinicians often review the images when a patient is visiting as they are not interested in merely reading a radiology answer.

The images are examined according to the preferences of the user. For example, the user can start with the CT images, then examine the PET images and finally review the fusion images, or start with a review of the MIP images, then examine the images from the bottom to the top, one slice at a time. The interpreting report could be constructed by the nuclear medicine physician and the radiologist reviewing the images together and then writing a common interpretation, or by one individual if this person masters both imaging modalities. Another example is if two reports are written separately by each physician and then joined in one report, which is sent to the referring physician. Important that the interpreting physicians have knowledge regarding the disease in question, such as cancer and specific cancer forms, to be able to conduct a correct and adequate analysis.

SUV

The usage of SUV is relatively established, which can be seen in Figure 6.2, but the degree of usage and the approach can vary substantially.

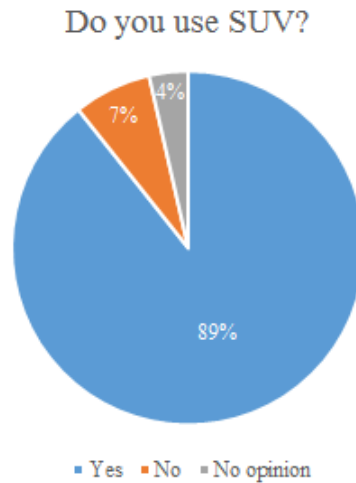


Figure 6.2: Presentation of the answers to the question: "Do you use SUV?". 89 % answered yes, 7 % answered no and 4 % had no opinion.

SUV is used to evaluate the uptake in a lesion compared to normal tissue, which vary depending on the diagnosis, to characterise tumors and follow-up cancer treatment in scientific studies together with CT information, to support the visual assessment, to conduct a relative judgement as the absolute values are rarely utilized (the SUV in the lesions are related to the SUV in the liver or blood, to each other or to lesions from the same patient but acquired during different examinations), to assess lesions suspected to be cancerous, to evaluate treatment response in lymphoma, to grade uptake as slightly, moderately or considerably elevated or not elevated, to characterize some cancer diseases (primary tumor when lung cancer is suspected), to distinguish a malignant lesion from a benign one (some malignant lesions could have low SUV and some benign could have high), to facilitate the probability assessment, to indicate the metabolic activity and to confirm a malignant suspicion.

It is important to be experienced and have a critical view when using SUV, to avoid exaggerating its possibilities. Some physicians state that SUV have a limited value and everyone using it should be aware of its limitations.

Each hospital decides if the SUV should be present in the report sent from interpreting physician to the referring clinician. The absolute SUV is generally mentioned in the report but occasionally the value is merely seen as a representation of an increase in metabolism and used to provide an indication of the intensity in the uptake. It is rare to not mention it at all but this occurs as well. The reason for it not being mentioned at all is because the physicians do not regard the absolute SUV as relevant since it varies a lot which could lead to an unclear report. Some physicians solely mention it when it is relevant, to for

example indicate a difference between two uptakes, and otherwise it is not provided as it can be incorrectly interpreted or even make the assessment process more difficult. If the referring physician is asking for the SUV it will always be provided. Some doctors are more interested in the interpretation of the SUV, such as if the uptake is elevated or not, rather than the actual value. No information about the factors that can affect SUV is provided in the report in general. However, the interpreting physicians are aware of the variations sources and can locate information about them if required. General information is entered in the report written before and during the actual examination, as a part of the examination data. When the data differs radically from normal these factors can be mentioned in the final report as well. Factors affecting the SUV that could be mentioned in a report are the blood glucose level (especially if it was high), the amount of injected activity and the patient length and mass. Data documented in RIS are blood glucose level, fasting time, injection time, camera time, bed position and information regarding treatments, biopsies, surgeries and inflammations.

A great amount of physicians are not aware of how the SUV is calculated, meaning the formula being used. Generally the imaging modality seemed to conduct the calculation by using a standard equation. The result of the calculation would be incorrect if the wrong data or no data has been entered, which is easily noticed since the SUV becomes highly deviant. If it is incorrect it can be corrected by a biomedical analyst.

Obstacles for using SUV are the limited clinical value, that the SUV differ depending on the PET scanner, the user has to be aware of its limitations in order to be able to use it, which not all are, and the fact that it has to be interpreted with some critic.

Instead of using SUV one can use visual assessment, provide information explaining if the uptake was high or not, use the Deauville-criteria for lymphoma or utilize the Likert-scale. However, SUV is definitely the most popular index to use for clinically assessing PET/CT images in clinical practice.

The tumor boundaries are rarely marked clinically but it would be seen as an advantage if a user friendly automatic or semi-automatic segmentation program existed, especially to improve the size assessment. The segmentation should not be constructed in the PET images since the image resolution is too poor. However, if the segmentation is based on a threshold, such as a percentage of the maximum SUV or a specified value, the PET images can be used to delimit the pathological uptake. Automatic segmentation would be considered a helpful support in the target definition and dose-planning parts of the radiation treatment. The segmentation could be conducted manually or automatically in the CT image and then be transferred to the PET image. Some say that automatic segmentation does not contribute with any information due to the great impact of error sources. If the program provides a segmentation option it should be able to do it both manually and automatically in all images.

Concept grading

The concepts presented in this section were selected based on the result from the interviews.

The relevance of SUV, metabolic rate, the Likert-scale and the Deauville-criteria for cancer treatment and/or interpretation of PET/CT images can be found in Figure 6.3, where 1 represented non-relevant and 5 represented highly relevant.

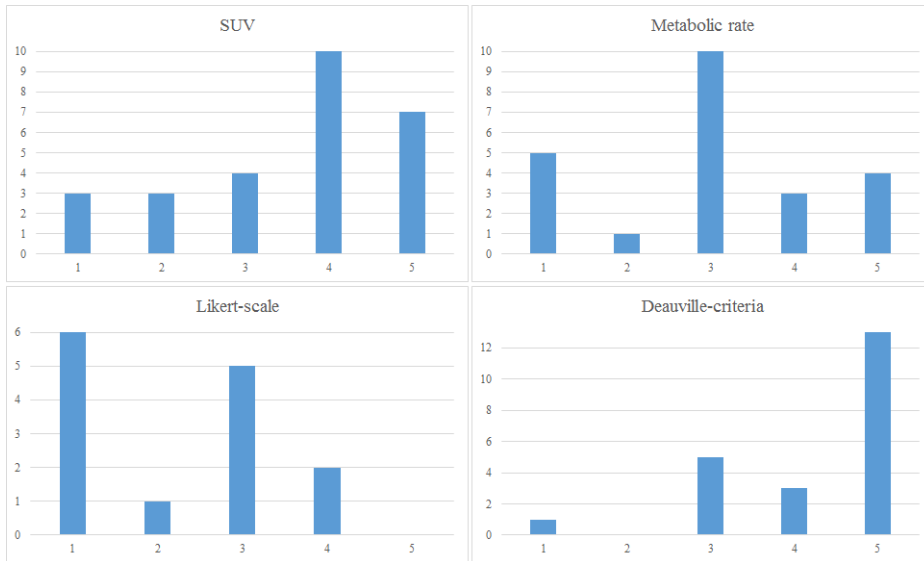


Figure 6.3: Presentation of the result regarding the relevance of SUV, metabolic rate, the Likert-scale and the Deauville-criteria for cancer treatment and/or the interpretation of PET/CT images. 1 represented non-relevant and 5 represented highly relevant.

The interpretation of the SUV is more important than the actual value and it can be used to grade the uptake. SUV could have a limited clinical value which should be considered. It can be utilized to distinguish malignant lesions from benign ones since a low SUV indicate a low probability for malignancy.

Metabolic rate can be used in research studies but this is relatively rare. It is important to be able to connect the SUV to glucose metabolic rate to improve the quantification. Metabolic rate provides a more accurate interpretation of the metabolism than SUV.

The Likert-scale can be used for an objective assessment of the uptake level.

The Deauville-scale is regularly used for evaluating lymphoma and the clinicians wish for it to be provided. It is visually based and describes the distribution of the lymphoma in a way that is significant for the treatment choices. Can be used to assess the therapy response for lymphoma.

The relevance of the TNM-system, the WHO-criteria, the PERCIST-criteria and the RECIST-criteria for cancer treatment and/or the interpretation of PET/CT images, can be found in Figure 6.4, where 1 represented non-relevant and 5 represented highly relevant.

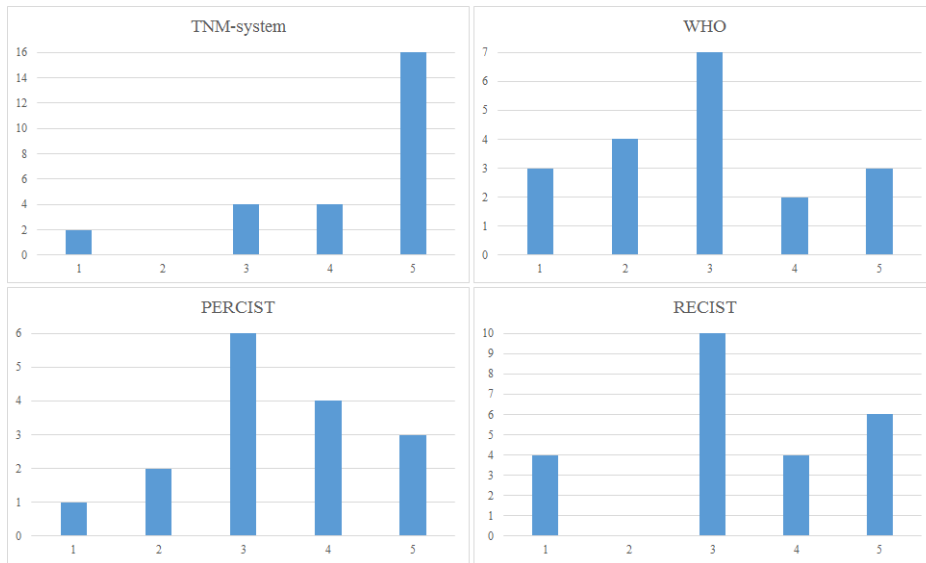


Figure 6.4: Presentation of the result regarding the relevance of TNM-system, WHO, PERCIST and RECIST for cancer treatment and/or the interpretation of PET/CT images. 1 represented non-relevant and 5 represented highly relevant.

The TNM-system contributes with vital information for the treatment plan and can provide prognostic information. The PET/CT report could present an indirect N- and M-classification due to its information content. TNM is a part of the quality control and it provides a staging of tumor diseases as it describes the disease distribution in a standardized way. The PET/CT report should contain enough details for the clinician to conduct a TNM-staging.

WHO is used to understand the patient status and for a clinical assessment of the patient's general well-being. WHO is not directly connected to PET/CT but it is still an important part of the entire cancer treatment process.

PERCIST is not used and some say that it has no clinically value while others claim that it could be useful in clinical studies.

RECIST is used differently depending on the diagnosis and research project. It is important to use during response evaluation in oncology and this during group studies, not on individual patients. It could be of importance that the same physician performs all the RECIST measurements to reduce the variation, which can be high. A complete RECIST assessment would be nice to use clinically but it is often too time consuming, complex and, as mentioned previously, it exhibits inter-individual variation.

Cancer treatment information

The information of interest during a cancer investigation process is the number of tumors, if they are new or old and if they show progression or regression, tumor aggressiveness, size, location, growth rate, duplication time and distribution, treatment goals, data description, both according to anatomical and functional information, patient response to treatment, both radiological and clinical, and possible patient side effects.

TNM is used to define and classify tumors. PET/CT contributes with guidance regarding the primary tumor, the cancer distribution and eventual biopsy locations, to improve the diagnosis and staging. The international association for the study of lung cancer provides guidelines to define the tumor type, and national health programs and the standardized treatment courses contain information regarding general treatment guidelines and recommendations.

PET is rarely used for treatment evaluation but when it is used the SUV and the FDG accumulation are investigated. The evaluation process is different depending on the tumor and the diagnosis. Visual assessment is used for evaluation and SUV as well as other measurements provide support. The cancer disease most frequently evaluated by PET/CT is lymphoma. The pathological uptake and the percentage reduction/increase of SUV_{max} can occasionally be examined. A CT is more frequently performed during a treatment evaluation than a complete PET/CT. For example, a CT can be conducted every 6-10 weeks while a PET/CT is only performed if the cancer treatment cannot be evaluated by using any other imaging modality, which is often the case with lymphoma. A CT is often conducted one month after the last treatment course to evaluate response, provided that certain factors indicate that a CT would be valuable. The evaluation process is different depending on if the treatment is curative or palliative.

The tumor activity is evaluated over time by using SUV and size (mm) assessments, meaning a complete evaluation of the PET uptake and the CT findings. PET/CT examinations are saved in PACS and documented with the report/answers in RIS. The result of the evaluation process is reported as progression, regression or stationary disease. For example, the lung cancer investigation process is started in the clinic, then a lung X-ray is completed if needed and finally a CT. A PET/CT is rarely performed after the CT.

The PET/CT report should contain information about the radiological properties of the tumors and the metabolic activity, the amount of metastases, a clear formulation of the assessment of the PET/CT result, the FDG accumulation, the tumor distribution, if the tumors are invading other organs, an anatomical description of the CT findings, if progression or regression is present, the PET findings, a summary of the patient disease, all findings and the tumor distribution presented with a description tool such as TNM, the answer to the asked questions, the locations exhibiting hyper metabolism, a separation of reactive and pathological metabolism, if a lesion is benign or malignant, infection/inflammation sites,

the size and distribution of the primary tumor, present lymph node metastases and their size, new metastases, distant metastases, SUV and specific problems that occurred during the examination which could affect the interpretation and/or the conclusions.

RECIST is used to evaluate treatment response but most often in clinical research studies and not in the clinic. The most popular evaluation methods used are visual assessment with a supporting SUV or visual assessment of the CT in combination with size measurements. The Deauville-criteria is utilized for lymphoma. PERCIST can occasionally be used in research studies.

Future

The progress of the PET/CT can clearly be depicted by the change at the hospital in Växjö. The examination was first conducted in 2003 on lung cancer patients, and during 2009 they introduced a PET/CT bus which was used twice a month. In 2014 they got their own system which is utilized once a week.

The number of PET/CT examinations is expected to increase, especially with the introduction of national guidelines for 19 various cancer diseases in 2016. The usage of PET/CT in Umeå increase with 15 % every year which result in a duplication of the usage every five years.

The increase in PET/CT usage could be explained by the fact that it will be used more frequently for already established cancer diseases but also by it being used for more cancer diagnoses. It will also increase because of the standardised treatment courses and due to the need of early therapy evaluation since the new treatments will be expensive and a patient cannot receive them unless they have a proven effect. As the amount of PET/CT machines increase it will probably be possible to perform a PET/CT earlier in the investigation process and perhaps even skip the CT step. PET/CT could be used to a higher extent to evaluate treatment response. The treatment will probably become more patient and tumor specific by using tumor targeting treatment tracers. Hence, the resources will have to increase to meet the expanding need for PET/CT examinations.

6.4 Prototype of user interface

6.4.1 Feature lists

The result from the interviews and the questionnaire was examined to establish two lists with valuable features to be implemented in a prototype for a user interface of a program displaying PET/CT images. The lists contained the following features, where the features marked in bold were selected to be implemented in the prototype as they were deemed more relevant and did not exist in the current software:

Interviews:

- The images should be linked to the patient journal in PACS.
- General patient information should be presented when desired.
- Information regarding the examination such as preparations, image protocol etc. should be presented when desired.
- The report sent from the interpreting physician to the referring clinician should be presented when desired.
- The referring report should be presented when desired.
- The program should ensure that the machine has been calibrated and give feedback regarding the result of the calibration such as approved, failed etc.
- **The user should be able to provide information for the RECIST or the PERCIST guidelines.**
- **If available, the TNM-staging should be presented when desired. The TNM-staging used should also be explained as this can vary depending on the cancer disease.**
- It should be possible to access a report template and write a report while reviewing the images.
- It should be possible to present all three or four images (CT, PET, fusion and MIP) and various combinations of them.
- It should be possible to present images taken with other imaging modalities.
- It should be possible to present previous PET/CT images.
- **The user should be able to decide the layout of the image presentation.**
- The images should be interlocked, meaning that if something happens in one image the same thing occurs in the other ones as well.
- **It should be possible to slide from displaying an image that is 100 % CT to 100 % PET, with the percentage presented.**
- It should be possible to present PET images taken with another tracer than FDG.
- **It should be possible to review the images in all planes: axial, sagittal and coronal.**
- **The SUV_{max} -value of each tumor should be displayed when desired.**
- **Information regarding all tumors should be presented in a list when desired.**
- **The user should be able to select which segmentation method to be used: automatic, 40 % of SUV_{max} , fixed value or SUV_{peak} .**

- **The user should be able to select which SUV index to be depicted, meaning SUV_{max} , SUV_{mean} , SUV_{peak} or SUV_{ref} for example.**
- **It should be possible to examine and change how the SUV was calculated and with which values.**
- **The SUV of the background, such as the liver or a blood pool, should be displayed to enable comparison.**
- **The changes in SUV between examinations should be depicted by displaying the absolute value and the visual change over time.**
- **An indication of whether a tumor is malignant or benign should be presented when desired. The threshold SUV-value used for the indication should vary depending on the cancer disease.**
- **It should be possible to assign an area as a tumor, a false positive or a false negative.**
- **The tumor size, length, area and volume should be displayed when desired.**
- **The number of metastases should be displayed when desired.**
- **It should be possible to access the DICOM tags easily.**
- An indication of whether something is physiologically normal or a deviation should be presented when desired.
- **It should be possible to assign a tumor as an unexpected finding.**
- It should be possible to adjust the intensity and intensity scale.
- It should be possible to adjust the gray and color scale.
- It should be possible to alter the window depending on area of interest.
- **It should be possible to use both automatic segmentation, that can be manipulated manually, and manual segmentation. If a certain margin is specified this should be taken into consideration in the automatic segmentation.**
- It should be possible to apply a VOI or a ROI.
- When a VOI or a ROI is applied in one image it should be possible to transfer it to the other images as well.
- It could be of interest to depict probable tumors in one color and probable false positives in another.
- It could be of interest to display the most recent date of manual calibration when the user hovers over the feedback information from the calibration.

- **It could be of interest to slide from displaying 100 % of the first PET/CT examination and its images, to 100 % of the most recent PET/CT examination and its images.**
- It could be of interest to indicate the uncertainty of the SUV.
- It could be useful to add a note explaining what information to provide to the RECIST or the PERCIST guidelines.
- **It could be valuable if the program is adapted to the user. For example, if a certain user is logged in which always wishes to start the assessment with the CT image and then move on to the other ones, this should be the default setting.**

Questionnaire:

- The user should be able to relate the PET findings to morphological findings.
- **The color of the segmentation presentation should change depending on the color scheme selected.**
- **The user should be able to assign a tumor as new, distant, lymph node and/or primary.**
- The user should be able to select a dynamic change of the slice thickness (dynamic MPR).
- The user should have easy access to the raw image data, which is saved in an .IMA-format.
- The user should be provided with information regarding the global metabolic activity when desired.
- The user should be able to decide if radioactivity counts or the SUV should be presented.
- The user should be able to use key combinations to access features.
- The user should be able to conduct trend analyses between examinations.
- The user should be able to transfer a VOI or a ROI defined in the CT image to the PET image.
- The user should be able to export images for presentations and publications.
- **The user should be able to compare tumors with each other.**
- It could be valuable if a report program could enable several physicians to write in the same report simultaneously.
- The percentage reduction/increase of a tumor should be presented when desired.

6.4.2 Implementation

Some figures depicting the result from the prototyping process have marked areas in them. These areas should only be seen as a representation of a tumor and should not be mistaken for an actual one.

The user should be able to change the image from being 100 % CT to 100 % PET and visualize the entire process. The user should be presented with the selected percentage by using the mouse pointer in the image and it should be possible to select a specific value on the scale. See Figure 6.5 to review the result. The color of the dot, which is used for visualization of the selected PET/CT percentage, was chosen to match the Sectra profile colors.

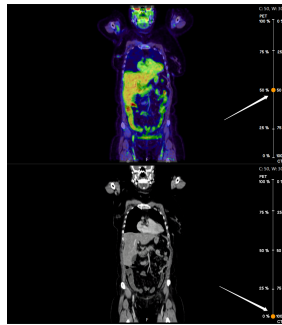


Figure 6.5: Presentation of a PET/CT image being changed from being 100 % CT, the bottom image, to 50 % PET and 50 % CT, the top image, with the selected percentage visualized to the right.

The user should be able to provide information to the RECIST and the PERCIST guidelines. By selecting either longest or shortest, a corresponding distance is automatically measured in the specified area. The user can measure a distance manually by selecting manually and then conducting the measurement. After establishing a distance this can be added to the report to review tumor response according to the RECIST or the PERCIST guidelines. To review the result, see Figure 6.6.

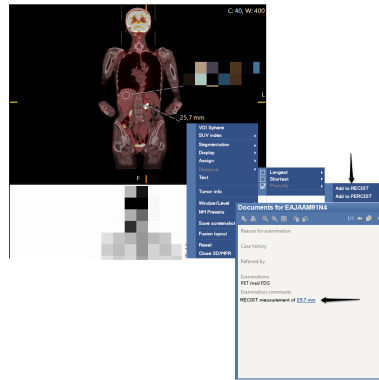


Figure 6.6: A RECIST distance is measured in the image and entered to the report.

The user should be able to decide the layout of the image presentation. The initial configuration is presented in the image to the left in Figure 6.7. The same setting but with added image data is displayed in the middle image. The final configuration, selected by the user, is depicted in the image to the right. The user should be able to rearrange the image layout according to preference and move them back to the original location.

The user should be able to review the images in all planes: axial, sagittal and coronal. The buttons marked in blue, see Figure 6.7, represent the plane that have been selected for the specific image stack. The user should be able to change the selected plane independent of the image location and the image layout at any point in time.

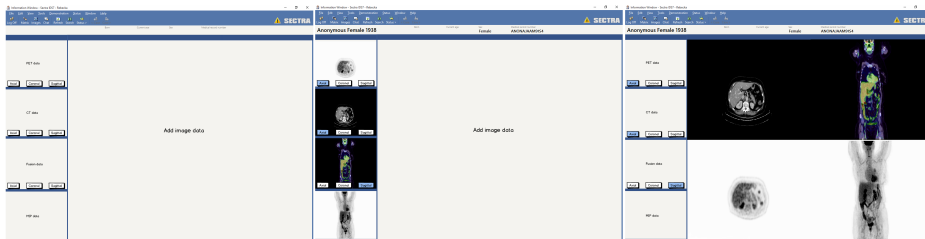


Figure 6.7: The user can decide the presentation layout of the images. The image to the left depicts the initial setting without image data, the image in the middle presents the initial setting with image data and the image to the right displays the final selected layout. It is also possible to decide which plane to depict each image in, meaning axial, coronal or sagittal.

The user should be able to review the result of the TNM-staging after it is established. Information regarding the TNM-system used for the specific cancer disease should be available if desired. To review the result, see Figure 6.8.

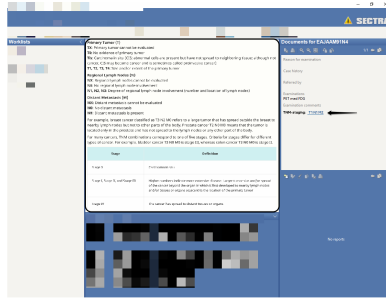


Figure 6.8: Visualization of the TNM-staging along with a description of the TNM-system used.

The user should be able to select which segmentation method to be utilized: automatic, 40 % of SUV_{max} , fixed value or SUV_{peak} . The user is required to select a VOI or a ROI before being able to conduct the segmentation. The reason for this is that the algorithms for the final three segmentation methods have to locate the SUV_{max} voxel within a certain VOI or ROI before being able to perform the segmentation. The automatic segmentation can theoretically be conducted before assigning a VOI or a ROI but it is definitely easier to do it afterwards since the user at this point has indicated a certain area of interest where the segmentation should occur. To review the result, see Figure 6.9.

The colors of the segmentation presentation should change depending on the color scheme selected for the image, to ensure that the segmentation always is clear and visible.

The user should be able to select which SUV index to be depicted, meaning SUV_{max} , SUV_{mean} , SUV_{peak} or SUV_{ref} for example. The information regarding a tumor, such as the SUV index or the volume, should only be displayed when the mouse pointer hovers over the tumor and if the specific properties have been selected for presentation. If the user decides for the information to be present at all times then it should be possible to alter the location of the information area.

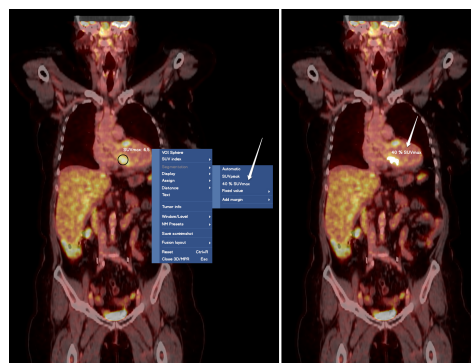


Figure 6.9: The user can select which segmentation method to use and in the image to the right the setting 40 % of SUV_{max} has been selected.

The user should be able to apply both an automatic segmentation, that can be manipulated manually, and a manual segmentation. If a certain margin is specified then this should be taken into consideration when defining the automatic segmentation of the tumor boundary. To review the result, see Figure 6.10.

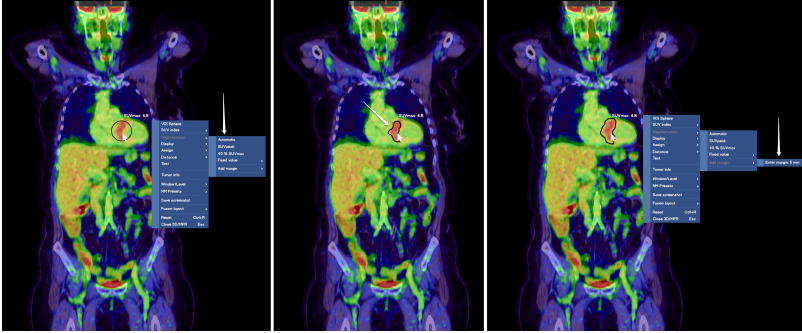


Figure 6.10: After assigning a VOI or a ROI, the tumor boundaries can be automatically located. The user can add a margin afterwards if this should be desired.

To enable comparison with previous PET/CT images, the change in SUV between examinations should be depicted by displaying the absolute value and the visual change over time. To review the result, see Figure 6.11. The user should regain information regarding the currently presented image by examining the scale to the left and this should also facilitate the selection of an image to display.

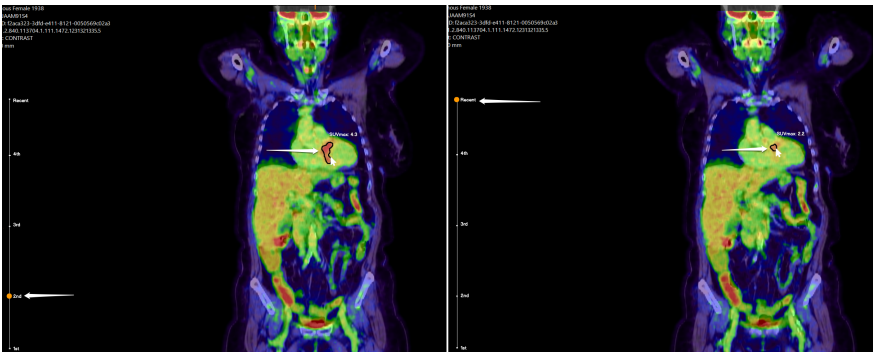


Figure 6.11: The therapy progression/regression is visualized by displaying the change in absolute SUV_{max} and the segmented area. The selected examination to be presented is depicted to the left in both images.

The user should be able to decide what to represent the background activity with and in this example the liver was selected. To review the result, see Figure 6.12. The SUV of a certain background activity should be displayed to enable comparison. The VOI or the ROI in the liver disappears when a background SUV has been assigned. The reason for this is

because this area is not of interest anymore and to reduce the risk for mistaking the area for a tumor.

The user should be able to review and alter how the SUV was calculated and with which values, the result of which can be seen in Figure 6.12. It should also be effortless to access and examine the DICOM tags.

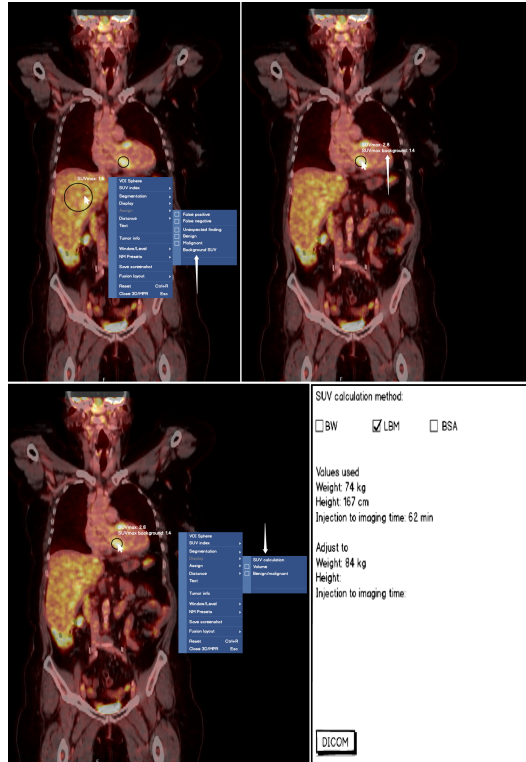


Figure 6.12: The user can assign a background SUV, such as the liver. It is possible to examine the values selected for the SUV calculation as well as the formula used and change these properties.

An indication of whether a tumor is malignant or benign should be presented when desired. The threshold SUV used for the indication should vary depending on the cancer disease. To review the result, see Figure 6.13. The user should be able to define an area as a tumor, a false positive, a false negative or an unexpected finding, and display the information when desired. The tumor size, length, area and volume should be presented when these properties are of interest. The user should be able to automatically add tumor information to the report when this data has been assembled.

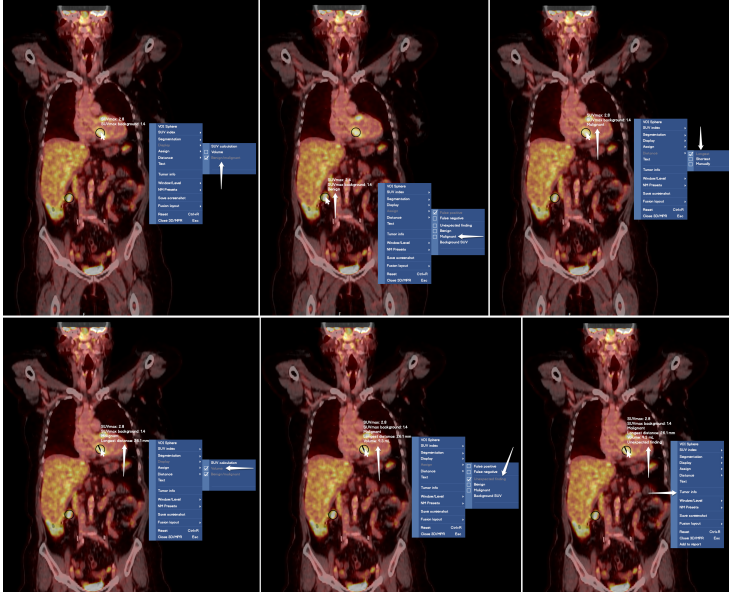


Figure 6.13: The user can apply automatic and disease dependant thresholds to determine if a tumor is benign or malignant, display the tumor volume, assign a tumor as benign, malignant or an unexpected finding, determine a certain distance manually or automatically and examine a collection of the established tumor information.

A menu suggestion was established containing all features mentioned above but displayed in a new layout, see Figure 6.14 and 6.15.

The user should be able to decide if the menu should be present at all times or merely when it is of interest, such as when the mouse pointer is moved to the area. If the second choice is selected then the menu should appear on all sides to reduce the mouse travelling distance.

Colors are used to indicate different sections such as information regarding tumors, which have buttons displayed in blue, and images, which have buttons depicted in orange. These specific colors were selected to coincide with the Sectra profile.

The user should be able to select a ROI, the circle or the square, or a VOI, the sphere or the cube, and drag it to a location of interest. The pen should be utilized when the user wishes to define the VOI or the ROI manually. If a VOI or a ROI is defined in one of the images, such as the CT image, this should be automatically transferred to the other images as well. The color of the VOI or the ROI should be adapted to the selected image color scheme in order for it to always be distinct. The user should be able to manipulate the shape of the VOI or the ROI after positioning it.

The user is required to mark the VOI or the ROI in which information is going to be gathered and presented, and subsequently it is possible to, for example, establish a distance or display an SUV. The specified information appears in the vicinity of the selected infor-

mation. The user should be able to decide if the information should be displayed at all times or solely when the mouse pointer hovers over the tumor. The user should be able to alter the location of the information area if it should be present continuously.

The top five parts in Figure 6.14 have the same basic structure. The first variation of this basic structure can be found in the sixth and seventh part. The placement of the SUV and Segmentation buttons have been switched to ensure that all volume or area related buttons are in the proximity of each other. All tumor related buttons, except for VOI/ROI, Tumor info, Add text and Add info to report, have been disabled and will remain in this state until a VOI or a ROI has been defined. The Tumor info button should be disabled if no tumor information has been added.

The second variation of the basic structure can be found in the bottom four parts in Figure 6.14. At this point the user is required to press the buttons Display, Assign and Distance in order to reach their respective actions. The options to assign a tumor as new, primary, distant or a lymph node have been added. The user can access the DICOM tags by pressing the DICOM button.

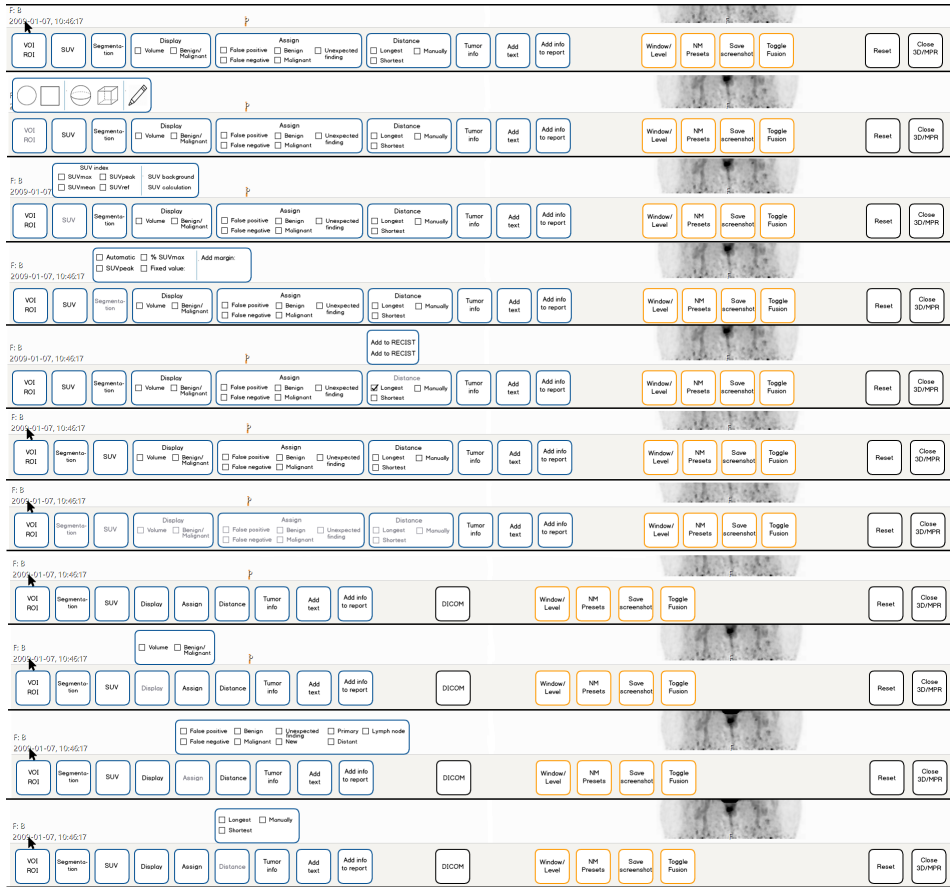


Figure 6.14: A menu suggestion containing all previously mentioned information. The first five parts display the primary version of the menu. In the following two parts the buttons for the segmentation and the SUV have been switched, and some buttons have been disabled. In the four final parts the menu content has been minimized and the user is required to press the button in question in order to reach the desired action. A button to present the DICOM tags has also been added in the four final parts.

Three options were established to represent the result of pressing the Tumor info button and the user should be able to decide which option to use, see Figure 6.15. In the image to the left the tumor information appears in a list above the Tumor info button. In the image in the middle the tumor information is presented next to the tumors of which the information concern. In the image to the right both previous options are utilized. The tumor information in the list is correlated to a tumor by using color coding. The colors should be selected to accentuate both the tumor and the correlation clearly.

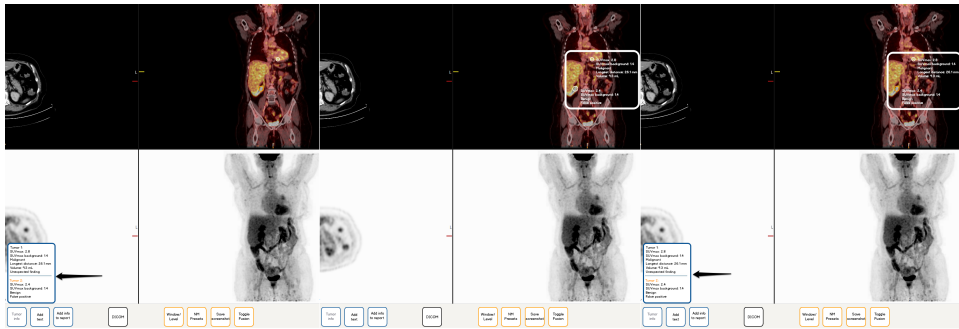


Figure 6.15: Three options were developed to represent the result of pressing the Tumor info button. The user could either display a list containing the information, which can be seen in the image to the left, depict the information next to the tumors, which is presented in the image in the middle, or both, which is illustrated in the image to the right.

7

Discussion and conclusions

The chapter contains the discussion of the thesis. The four major areas to be discussed are the results, the method, ethical and social aspects, and future work. The main focus will be on discussing and evaluating the results, meaning all parts mentioned in Chapter 6. The final section of the chapter presents the conclusions that could be drawn based on the result and the discussion.

7.1 Results

The chapter is commenced with a discussion regarding the results of the literature study, the interviews, the questionnaire and the development of the prototype. The result from the literature study depicted the great amount of information a PET/CT report could contain and the differences between a referring report and a report sent from the interpreting physician to the referring physician.

The result from the interviews and the questionnaire presented a vast diversity of how to examine PET/CT images but the information of interest was practically identical. It was also clear that the opinion regarding the relevance of SUV is relatively consistent throughout Sweden, but some still consider it to be close to useless while others regard it to provide vital information for a cancer treatment.

The result of the development of the prototype contained a substantial number of features but only a few was selected for implementation. Practically every user presented a unique feature that they considered important for the examination of PET/CT images, which has to be taken into consideration when developing products for the health care system.

7.1.1 Literature study

The process of finding relevant articles was easy due to the fact that adequate search engines and websites were utilized. Most articles could be deemed appropriate since they were cited in a great number of other articles.

The result of the literature study could possibly have been improved if the focus had been on only using recent review articles to ensure that the information was up to date. However, it was continuously of great importance to critically examine each article to establish an acceptable quality.

The general opinion regarding the PET/CT examination compared to a conventional CT is that it provides substantially more information, which in many cases have been deemed useful. It differs from one case to another if this increase in information actually is valid. Occasionally it could be vital to compare information from two modalities which is also an advantage of the PET/CT since this is provided to begin with.

The fact that the PET/CT modality is relatively new and that changes in the health care system generally occurs slowly, could be seen as explanations as to why the usage of the PET/CT has only begun to increase over the last few years. The number of PET/CT examinations increased with 82 % during 2014 compared to 2013 and it is expected to continue to increase with 15-20 % yearly [3]. The usage could definitely increase further but a major limitation seems to be the lack of resources in the health care system and the fact that a PET/CT examination is not always deemed necessary, even though it could provide additional information.

Everything surrounding the SUV seems easily affected by variation and a major contributing factor is the human one. A focus should be on reducing all uncertainties as this could lead to an increase in trust of the so called objective and semi-quantitative value. Another observation made after the literature study and during the interview process was the fact that the general opinion of SUV is somewhat more positive in the literature and research compared to one expressed by clinical users. There is a considerable interest in improving the quality of the SUV and several articles have been written to explain this need. However, some users express thoughts regarding how unnecessary this process is and that focus should be on other more important aspects. The opinion is divided but more and more people seem to go from thinking that SUV is a "silly useless value" to a "smart uptake value". But research is required to reduce the uncertainty of the SUV and several parameters can be improved.

Other quantitative methods exist but they are generally too complicated or unknown to be used clinically. A reason for the hospitals not using other quantitative tools is because the major effort is spent on utilizing already familiar methods. Another reason is that there is little time to obtain new knowledge, which, as a result, is considered to be superfluous instead. An example of this is PERCIST and the fact that this concept seems to be relatively established in the articles examined in the literature study but health care professionals are oblivious of its existence since there is no requirement in knowing. As a consequence it could take some time before an actual need for another index than SUV emerges. Other quantitative indexes could provide more relevant information and in a more detailed way reflect the true uptake, but at the moment they are too complicated and time-consuming to be used clinically.

Specific guidelines exist for every country and cancer disease regarding how the entire investigation and the evaluation process should proceed. These guidelines can be adjusted according to the opinion of the physician and they should always be seen as a support during the entire process. It could perhaps be useful to implement a clearly defined standard which ensures that the health care is independent of location and economy. However, this could in turn contribute to the physicians feeling limited which should preferably be avoided.

In order to reach a health care that is optimized, physicians should always have access to everything needed, provided that the requirements are considered reasonable. At the moment this is not possible to achieve due to the lack of resources in both personnel, equipment and finance. The lack of resources cannot be influenced by the health care professionals, as these decisions are beyond their control.

The guidelines for cancer investigations, treatments and evaluations are constantly revised to remain relevant. However, the health care could perhaps be improved further if the guidelines actually were revised to recommend the optimal patient management, and course of care, instead of merely focusing on recommending actions that are appropriate with the

current resource situation.

7.1.2 Interviews

A discussion regarding the amount of interviews and respondents to the questionnaire is considered vital since these aspects could have a substantial impact on the final result. The amount of interviews and respondents could be considered sufficient but it is not without difficulty to determine when enough is enough. As a consequence, this limitation should be kept in mind when reviewing the result, discussion and conclusion.

It was very interesting to experience the fact that people both in the same occupational category and in different ones have a various understandings regarding several health care concepts. For example, people can express the complete opposite opinion even though they work at the same hospital. As a consequence, it is of great importance to conduct a complete assessment of the situation and evaluate different statements depending on the profession and experience of the person in question.

Another observation made during the interviews was that it is highly individual how physicians and hospitals wish to operate, which indicates that a certain flexibility is required in all products. It is also vital to speak the same language as the interview subjects, meaning that some words could have a different implications depending on the background of the person in question. It was very clear that some words could be interpreted completely differently by a physician than by a student, which in turn contributes to the result being incorrect. Another important discovery was that the health care personnel is fairly limited in their knowledge and it is easy for them to be specialized in a certain area while knowledge about other subjects is inferior. As a consequence it could be relatively easy for them to disregard contributing information from other areas and one might not be as inclined to absorb information that is not directly related to their field of expertise. This is another aspect to have in mind when designing and marketing products for the health care system.

When comparing the result from the literature study to the result obtained during interviews it can be concluded that both areas are fairly consistent and compatible. It was however apparent how far back and slow the health care system is compared to other sectors. In practically all other professional fields it is important to focus on utilizing the most recent technology and everything new is not questioned to the same extent as in the health care system. The health care does not trust anything unless it has been established as reliable several times, which definitely makes sense since human lives are at stake, but it could also hinder possible development. It would definitely be interesting to consider a health care that is more prone to accept new technologies and reflect on how much change this could lead to. This could perhaps also to some extent contribute to an increase in biomedical companies and research since a more positive attitude towards development and change is perceived from the health care.

Even though the articles in the literature study in general were consistent with the information regained during the interview process, one thing differed substantially. The articles presented a great usage of SUV with a need and interest in further research for improvement. This was on the contrary not the impression from the interviews, where the usage could be described as relatively positive but still hesitant. SUV could be used to support a theory but other aspects such as visual information was deemed more important. Occasionally some physicians presented a negative attitude towards SUV while others were more positive. This is also an indication of the importance of conducting a complete investigation to regain a full picture of the situation. For example, if only personnel working at the same hospital were interviewed the impression would have been far different than if another hospital had been the target for the interviews.

The desire to use PET/CT is high but the access is at the same time limiting. The reason for performing a PET/CT must therefore be well-motivated which could perhaps contribute to some patient cases being disregarded since the reason for performing the examination was not sufficient. The areas of interest in the images are everything with an increased intensity and their distribution. However, it was mentioned at several occasions that the PET/CT images in fact can be used to regain much more information than the ones utilized today and at a earlier stage discover cancer diseases which often go undiscovered due to the lack of symptoms.

A clear obstacle surrounding the PET/CT examination is the fact that several health care professionals are involved in the entire cancer investigation, treatment and evaluation processes. These people are required to meet and discuss each case which could be difficult to manage in a time efficient way since the health care system is very pressured at the moment. This is definitely something that could be improved and facilitated in the future.

The main interests regarding the PET/CT images are consistent at several hospitals but physicians present a particular concern for various features. This is an indication that a software program managing PET/CT images has to be versatile and able to present information according to the specifications of the physician. This will in turn increase the usage of the product and the chances for the user to utilize it correctly. The physicians are of course interested in acquiring as much information as possible which later can be screened to only depict the vital data. The most logical alternative would perhaps be if the software had been adjusted according to each physician or group of physicians at the same department. An alternative could be that the software acquires information as it is being used to continuously adapt to its users to ensure minimal extra effort.

The measurements of interest vary from one health care professional group to another which should be taken into consideration when developing a new product. Some physicians might be interested in conducting measurements and edit the images by for example changing the contrast and the selected window, while others are focused on comparing the images

and analyzing them visually.

One opinion that was mentioned several times was the fact that a system managing both images and reports would have been appreciated. The reason for this is that it could possibly reduce error sources since there is a risk at the moment that the report concerning one patient can be depicted along with the images for another one. The process of regaining a complete overview of the patient status would also be simplified by accessing and displaying images taken with other imaging modalities and from previous examinations. It is common that the physicians use a report software that display images but they are static, meaning that no alterations or changes can be made, which hinder the investigation process instead of facilitating it.

A general opinion regarding the image management process is that a highly adaptable product is desired, which take interesting factors, that should be investigated, into consideration. To use automatic and objective methods, provided that the quality of the result is acceptable, which can be manipulated manually, is also something to regard as valuable. These products could be used during a transition period from a health care solely controlled by physicians to one more based on objectivity and efficiency where doctors only focus on treating patients rather than sifting out healthy ones.

As mentioned before, the usage of SUV differs greatly from one hospital to another, where for example one hospital only uses it for supporting a visual assessment where another utilizes it to the extent of distinguishing malignant from benign. Another observation is that the more interested the user is in using SUV the more adjustments are conducted, such as the body size measurement in the calculation, which area to depict in the image etc.

Another aspect to discuss concerns the usability of SUV considering its great variance. This has created a certain hesitance towards using SUV since the actual information content can be debated. With this said, it does not seem to contribute to substantial damage when using additional information to support an assessment, especially if it clearly indicates a specific diagnosis. Experience is a considerable asset for physicians but it could also lead to some subjectivity which an objective index such as SUV could remedy. In the future it could definitely be considered valuable to use SUV for an initial screening to distinguish healthy patients from sick ones, who the physicians should focus on.

SUV varies greatly depending on a number of parameters but according to the articles examined in the literature study this can in many cases be completely remedied or at least improved, but this fact is not utilized in the health care. It could be that they are not aware of these techniques or that they do not have the time or energy to implement them. Various body size measurements, the blood glucose level and the time between injection and imaging seem to be taken into consideration occasionally and the machine manages changes due to the decay of the tracers, but practically nothing else is of concern. Both the usage and the actual SUV would probably be improved if further parameters and correction possibilities

had been taken into consideration. Many of the corrections could most likely be completed automatically by the software program after the examination, demanding no extra time from the clinicians. It could therefore also be valuable if the corrections to be made can be selected by the physician depending on the result, tumor type and patient, among other things. Hence, the possibilities with SUV should be examined to increase and improve its usage in the future.

It seems to be of interest to use another quantitative index than SUV but at the moment there is no index that is easy enough to be used clinically and as a consequence SUV has to do for now. There is a risk of SUV being challenged if another index came along providing more information with less uncertainty while being as easy to use. However, since the evidence burden in the health care system is high it will probably take several years before a new index is established clinically.

It is not without difficulty to analyze PET/CT images since knowledge regarding both imaging modalities is considered to be a prerequisite. This is something that could be taken into consideration when developing a product by, for example, implementing features that facilitate the assessment process for the physician. Another aspect of importance is the fact that everyone involved should contribute with clear descriptions of their interpretations. If anyone does not meet this requirement then it will lead to excess work for people subsequent in the treatment chain. Since the complete assessment of the investigation and the treatment choice is discussed at a multi-disciplinary conference it would probably be valuable if this process could be simplified and easier to perform. For example, there could be a time line explaining where in the investigation process the patient is, to enable continuous assessments, and a possibility for conducting the conference virtually.

Some concepts are relatively established in Sweden such as the TNM-staging, which also is an example of a system that is used clinically, while other ones merely is used for research purposes, such as RECIST, or not at all, such as PERCIST. If these guidelines would have been used clinically it would probably been appreciated but there is not enough time or knowledge at the moment. This process could be simplified by implementing software properties that facilitate, and if the guidelines to be used is standardized. This would probably also contribute to a more equal health care since everyone would be included by the same guidelines and systems. The health care could also be improved as the quality of care could be managed at a higher level.

PERCIST was generally not recognized during the interview process and if it was it still was not used due to the fact that there is no demand for it. PERCIST has existed for a few years now but since the actual value in using it has not been established there is no need to use it. Hence, there has to be a high demand in order for the health care system to take the time to comply.

To reduce the number of errors and misconceptions many hospitals have standardized

the appearance of a PET/CT report. The template does not have to be officially declared and instead it could be implemented instinctively as everyone merely write reports in the same way. It would probably facilitate substantially if an official template had been declared for all hospitals in Sweden. This would not only simplify the process of developing products for report management but also aid interpretations and management of reports between hospitals.

In general, the PET/CT usage is thought to increase as more cancer diagnoses can be established using metabolic information. Since practically everyone assume that the usage will increase it seems reasonable to expect that the information from the PET part will be further implemented in classification systems and such, where today only the CT data is utilized. The metabolism is a clear contributing factor during a cancer investigation, making it a natural component in the official process. A reason for it not being an established factor at the moment could be due to the fact that PET has not existed as long as CT and it has therefore not contributed with as much significant information, but this is not the case anymore. If the usage of the metabolism information is thought to increase it could be assumed that the SUV usage will increase as well. As a consequence, it is vital to develop a product that can manage SUV to the expected extent when this period arrives.

Another clear opinion is that the treatment will go from being general to more patient and tumor specific. It is therefore important to be able to use all the additional information and to visualize it in an informative and efficient way. Since the information content is expected to increase greatly it could be of interest to zoom into an image to examine the tumor heterogeneity, the tumor distribution etc., which is an aspect that the image management software should be able to comply with.

7.1.3 Questionnaire

The general opinion of the result from the questionnaire is that the usage of PET/CT for cancer treatment is highly diverse. The usage seems to be very individual and specific to a certain occupational category or hospital.

The knowledge and the lacking demand from the clinicians could clearly limit the development of new quantitative indexes. The reason for this is that the interpreting physicians will only provide the required information to ensure a high time efficiency, not more and not less. Hence, the demand from the clinicians should increase to facilitate improvements in the health care system. The most frequently used SUV index today is SUV_{max} but the interpretation could perhaps be improved further if another index is used, such as SUV_{peak} . However, due to the lack of interest from the clinicians to obtain new knowledge regarding these indices the situation might never change. It may even be required for the guidelines to completely change before an actual improvement in the SUV usage could occur.

The number of PET/CT machines and the access to them clearly limit the usage of

PET/CT. Some regions do not have any access at all, resulting in them referring patients to other regions which cause queues and related issues. The hospitals are constantly required to prioritize the patients which probably is not the best system and does not provide the best health care. Another interesting aspect regarding the lack of PET/CT machines is the fact that when these hospitals actually acquire a PET/CT they have no assumptions or bias regarding the usage. It is often easier to teach someone something completely new instead of trying to change an already established workflow. When this occurs it is highly important to utilize previously obtained knowledge and alter it to produce a system that operates as optimal as possible.

Another issue at the moment with the PET/CT is the fact that it is expensive and, as mentioned in Section 6.2, it costs approximately four times more than a CT. This could cause it not to be used even though it could contribute with a great deal of information that could affect the patient treatment. However, it is important to consider the fact that the result from a PET/CT can contain more important information which in turn could contribute to another treatment that would have been selected if only a CT would have been conducted. This could save the health care system and society a immense amount of resources since the proper treatment could be performed immediately.

The amount of required qualities in a program managing PET/CT images is substantial since all users desire and demand various properties. Due to the vast potential amount it is vital to examine which properties that are most important and implement these, as it is not possible to provide them all. It could perhaps also be of interest to present an ability for each user or department to select which properties to use and adapt the software accordingly. This leads to a program with high flexibility and that is completely adjustable according to the requirements of the users.

It could also be of interest to provide an opportunity to display additional information regarding each step in a cancer investigation and treatment. The reason for this is that several guidelines and methods exist, such as Likert, Deauville and SUV, and this can occasionally cause confusion regarding which one that is being used and what information it contains. Physicians will probably find it helpful and interesting to be educated in how to utilize each program and its functions to their full capacity, especially in the image management part. At the moment one could get the impression that numerous physicians and occupational groups are not aware of the possibilities existing in current software, which is a clear disadvantage. Since the investigation and interpreting part of a cancer treatment can be improved, the resulting therapy response and final outcome could also be enhanced.

Due to the fact that several physicians often construct and examine the same report, a program should be developed that could provide a time efficient way for numerous physicians to write and assess a report simultaneously. This will reduce the investigation and interpreting processes of a cancer treatment, since reporting is a substantial part of them

both, which will contribute to the patient receiving a treatment faster.

The usage of SUV appears to be relatively established, which can be seen in Figure 6.2. With this said, some of the physicians still state that they never use SUV which is very interesting. It could therefore be extremely insightful and valuable to investigate the reason for these distinguished opinions and to observe a discussion between two physicians with complete opposite opinions and listen to their arguments.

The trust in PET and its measurements could occasionally be considered as minimal due to biological and technological limitations, such as patient motion, incorrect SUV, attenuation, measurement precision and resolution. Therefore, it is vital to make the users aware of these limitations and to provide information regarding them and an opportunity for them to be corrected. The error sources in the CT are more established and understood and as a consequence it could be useful to focus the interpretation of the CT images and merely use the PET information as a support, which is often the case today. However, as time proceeds the knowledge and experience regarding PET will increase and the resulting interpretation can be based more on the metabolic information rather than solely on size measurements.

It was very interesting to review the results from the concept grading section because of the fact that it occasionally varied considerably, which can be seen in Figure 6.3 and 6.4. The concepts were selected based on the result from the interviews and the result from the questionnaire clearly depicts the importance of conducting a completely covering study when investigating interesting properties for the health care. Some concepts might only be familiar to a small number of people, which all consider them to be extremely important, while others do not recognize them at all, which was the case for the Likert-scale. Hence, certain information can indicate one result but this does not have to be the entire truth. Instead every claim has to be validated and confirmed in order to avoid a misrepresentation.

7.1.4 Prototype of user interface

A great amount of features were presented during the interviews and in the result from the questionnaire, and it was therefore difficult to determine which ones to implement in the prototype. The final feature list was established based on the following criteria: several people should have stated a need, the feature was not already implemented in the current software and the feature appeared relevant based on the information from the literature study.

Both before and after implementing the prototype in the software it is important to conduct several user test as these could provide additional vital information to improve the product further. It is especially important to conduct user test on the new menu as this differs greatly from the original design, which could lead to a substantial change for the users. During the user tests it is of importance to have a group containing several relevant users working at various hospitals all over Sweden. Otherwise, there is a risk of obtaining a mis-

representation of the general opinions as some users consider the same things relevant and these are the only ones being asked.

When designing a new product it is central to consider the usage of colors. Not all users might have the ability to display colors which could completely ruin the intention of a product. It is therefore important to be able to depict the information in various ways such as by using dotted or continuous lines. Colors can also be used to construct groups and it is vital to consider that various colors can provide different associations [100].

Another important aspect to recognize is the fact that users, particularly health care professionals, consider the opportunity to conduct changes and manipulate the images manually almost as a requirement. As a consequence, it is central to provide a software that the user feels comfortable in operating and to enable alteration alternatives whenever reasonable.

In Figure 6.5 it is vital to contemplate when to display the percentage menu, meaning if it should be present at all times or if the user should be required to move the mouse pointer to the side closest to the fusion image for it to appear. An optimal solution would probably be if the user can select the preferred option but otherwise one can assume that the second option is the best as this would disturb the image reviewing minimally. It could also be of interest if the selected percentage only appear when the user wishes to examine it. It could additionally be interesting to implement an area where the user can enter a value of a certain mixture, which the image then can be adjusted according to. One box could be assigned to the PET percentage and another one to the CT percentage, and the percentage in both should change if the user alters the percentage by using the computer mouse in the image.

In the prototype displayed in Figure 6.7 it could be valuable to implement a solution which adapts to the user. For example, if a certain user is logged in who always wishes to start the assessment with the CT image and then move on to the other ones, this should be the default setting. It could also be valuable if the user or a department could save several predetermined image layouts to select from. The areas depicting the original location of each image stack could be smaller to provide more space for the actual image reviewing and since a large area might not be needed to understand the purpose. It could perhaps even be valid to remove the area when the layout has been selected and for it to only be displayed when the user wishes to alter the layout setting. It could be relevant to add an area for other purposes such as writing a report, examining images taken with other imaging modalities or regaining information about the RECIST guidelines. The latter would especially be valuable when the user is supposed to add measurements according to the RECIST or the PERCIST guidelines, see Figure 6.6. This would ensure an efficient and effective usage of the software. The user should be able to reset the images to their original location, which could be of interest to achieve either by physically moving them by using the mouse pointer or perhaps by right clicking on the image to immediately send it back.

The automatic segmentation in Figure 6.9 could for instance be accomplished by using

seeding algorithms. It should be contemplated if the segmentation should be present at all times or merely when the mouse pointer hovers over the tumor. It is highly important that the user always has the possibility to manually alter the automatic segmentation. This is particularly vital at the moment since a lot of scepticism surrounds automatic segmentation. The fact that the user can manipulate the result could definitely increase the usage and the reliability of the result.

It could be of interest to display the percentage change between examinations in addition to the absolute SUV and the visual change, see Figure 6.11. It has also been contemplated when the menu containing the information regarding the examinations should be displayed. It is probably the most appropriate if the user can decide that she or he wishes to compare the current examination with previous ones and at this point all previous examinations will appear along with the menu. When displaying previous examinations it is vital to distinctly depict the fact that an image is a previous one and not the most recent one since this otherwise could cause confusion if one image stack is old but all the other ones are recent.

The menu suggestions in Figure 6.14 were constructed with the intention for it to be easy to add new features, by for example adding a completely new row. This could perhaps reduce the image space but if the user decides to only display the menu when it is of interest the impact would be relatively small. If the user wishes to display the menu constantly the problem could be solved by only showing one row at a time and adding arrows to move between the various rows. Another fact that has been contemplated is the mouse distance that the user is willing to travel in order to reach the menu. One could find it less time efficient to be forced to move the mouse pointer to the sides of the page every time compared with merely right clicking. However, a benefit of placing the menu at the sides of the page is that the user always can locate the desired action with ease. With this said, the mouse travelling distance is still definitely something that has to be investigated in the future. The user should be able to enter a fixed value to perform the segmentation according to and a margin to alter the segmentation by. However, it could perhaps be made more clear that these areas enable an opportunity for the user to enter a value, which at the moment could be considered a bit ambiguous. It could also be of interest to display the Add margin part as disabled before having selected a segmentation since it should not be possible to add a margin before having a segmented area. Figure 6.15 depicts how the tumor information should be presented. The user should be able to select the presentation of hers or his choice and if the information should be present at all times or solely when it is of interest. It could be valuable to display the tumor information beside each tumor constantly as this enables comparison of the tumors, which also can be achieved by reviewing the tumor information list.

7.2 Method

The content of all sources was compared whenever possible to confirm that the information was authentic. It was additionally of great importance to constantly examine all sources critically and question the information content. A certain purpose was defined for the thesis and it was vital to locate sources which both presented a positive and negative attitude towards this purpose. The reason for this was to ensure that the obtained result contained a complete representation of the situation and the research concerning the area, and to reduce the potential impact of bias towards a specific opinion.

The method for performing the literature study could possibly have been improved by focusing on certain sources and articles, and on them having a high quality instead of utilizing a large quantity. However, the information of each article was definitely deemed appropriate and the fact that numerous articles were investigated could also be seen as a strength since this contributes to a wider representation of the research. The result from the literature study could perhaps also have been improved by merely focusing on locating exceptionally relevant articles such as review articles.

A major part of the result was based on the interviews and the questionnaire which probably would provide the same result if equivalent questions would have been asked within a reasonable time period. The reason for assuming this is because the opinions of the physicians change with time due to the development in the area but it takes a while for these alterations to occur. The questions asked were constructed based on the result from the literature study and if other articles had been studied perhaps other questions would have been established, which in turn could provide another result. With this said, the impression from the articles was that they represented the current situation relatively well and that approximately the same result would have been concluded.

The design of the prototype was essentially based on three things: the result from the interviews and the questionnaire, the current product called IDS7, and my opinions and experience. If another person had completed the thesis work the result would probably be different since several aspects are prone to variation, such as the questions and the interpretation of the result. The variation could potentially be reduced by utilizing numerous iterations of user tests and alike before establishing the final prototype. The feedback from each iteration would improve both the result from the questions and the final prototype. However, one could conclude that an amount of variation sources exist since the person performing the thesis work determines which decisions to be made and these differ from one person to another. Hence, everything from which articles to be read to how the information from the interviews is interpreted could vary depending on the person in question, which is something to consider when examining the result from this thesis.

The reasons for selecting the questions for the interviews and the questionnaire have

previously been discussed. It is likewise important to reflect on how the questions were asked since this could affect the final result. It was very important to deliver the questions in a neutral way and not to affect the people answering by subconsciously stating personal opinions. Occasionally suggestions for answers had to be presented since the person being interviewed had a hard time understanding the question or did not know how to answer it, but this was preferably avoided to ensure that a true opinion was obtained. A small number of the people answering the questionnaire expressed that the questions could be considered as too general which in turn could affect the quality of the result and potential conclusions. This opinion was definitely kept in mind while reviewing the results and establishing the prototype.

Another aspect to discuss regarding the method behind the interviews and the questionnaire is the number of people answering these questions. The result could perhaps have been improved and statistically assured if a greater number of health care professionals had answered. With this said, it was concluded that an acceptable number of people was reached in order to represent the general opinion in Sweden.

The program used for developing the prototype is called Balsamiq. The resulting prototype could potentially have been improved if another program had been used since Balsamiq had some clear limitations regarding for example how detailed the appearance of the prototype could be managed, which functions it could represent, how the workflow could be regulated etc. The process of developing the prototype would also perhaps have been simplified if another program had been used since one was required to implement a great amount of workarounds in order for the features to be presented correctly. Using another program could have resulted in a prototype with a more modern constitution as the appearance alternatives in Balsamiq were fairly limited.

Conducting several user tests could definitely have improved the resulting prototype since the feedback would have been utilized to create a prototype which was more adjusted to the needs and demands of the users. The reasons for not performing any user tests were that a further development of the prototype would probably been required and because of the lack of time to properly analyze the results from the user tests and implement them in a new version of the prototype.

7.3 Ethical and social aspects

The thesis can have an impact on and relates to several social aspects since it has a clear connection to cancer and how PET/CT can be a part of the cancer treatment. Nowadays practically no one can state that they have not been affected by this disease and by contributing to an improved investigation process and treatment one can truly affect the society, which this thesis could be considered doing.

An increase of the PET/CT usage can contribute to earlier cancer diagnoses and the overall resources can be utilized more efficiently, meaning for example the finances and the personnel, since irrelevant investigation steps can be skipped. Hence, it could be possible to reduce the lack of resources and/or utilize the current capital to its maximum to optimize the health care system. At the same time it is important to consider the fact that an increase in PET/CT examinations could lead to an increase in cancer cases due to high patient radiation doses. The risk is particularly elevated for young people since the cancer has a longer time to develop.

The introduction of the standardized treatment courses could be expected to have a great impact, both from an ethical point of view and a social one. They have a long-term potential of providing an equal care for everyone and to ensure that all patients should have the same access to treatment regardless of where in Sweden they live. However, the standardized treatment courses can initially lead to issues since not all diseases have an established treatment course and this could contribute to an increase in waiting time for these patients, which is not acceptable. It is also vital to ensure that the physicians feel comfortable and not limited during the process of introducing the standardized treatment courses since the latter could lead to a deterioration of the health care, which is not tolerable from either an ethical or a social perspective. The long-term goal is, as previously stated, to reach an equal health care system and this is significant from a social perspective since the resources can be managed more efficiently, and from an ethical perspective as everyone literally will receive an equal treatment. One could also imagine that the quality of care will improve since the possibilities for documentation as well as quality assurance and control increase.

Hopefully, this thesis could be seen as a contributing factor to improving the usage of PET/CT for cancer treatment and provide information for a long-term progress of patient management and survival.

7.4 Future work

SUV is becoming more and more popular and several factors indicate that this development will continue in the coming years. However, numerous articles state that more research is required before health care professionals can utilize this semi-quantitative index to its maximum capability. SUV could be seen relatively established index, which can be seen in Figure 6.2, and it would be very interesting to conduct a similar examination in a few years to determine its progression or possibly regression.

A number of features, information and opinions regarding the usage of PET/CT for cancer treatment have been presented, which can be utilized by Sectra for further development of the current products. These factors can also be used as guidance for creating products which meet actual demands and this in a way that is appreciated and user friendly.

It would be interesting to research and discover additional features that are desired by health care professionals. This in order to facilitate and improve the investigation and the interpretation parts of a cancer treatment even further. Conducting user tests have been mentioned in previous sections and this could definitely be seen as future work. A great amount of information could probably be determined by testing the prototype on real users to regain information regarding how intuitive it is. After completing enough iterations of user tests and when the prototype has reached its optimum quality, it would be appropriate to implement the entire prototype or parts of it in the current viewer of the Sectra PACS.

An important factor that should be improved in the future is the fact that physicians in general present an attitude towards change that is relatively negative. Doctors are by default fairly hesitant to utilizing new products since they in the past often have discovered that these products are everything but user friendly. User experience is therefore important to take into consideration when designing new products and one should focus on clearly exhibiting the positive properties of a product and the fact that it is easy to use. It is significant to truly reach the costumer and understand their needs in order to produce a product that facilitate their everyday work, which could be a future goal to achieve with this prototype.

It would also be interesting to compare the Swedish health care system to health care systems in other countries, such as the United States or the United Kingdom. It could be discovered that health care professionals are more positive to change in these countries. If this is the case it would be highly valuable to determine why and how this was reached in order to achieve such a situation in Sweden as well.

7.5 Conclusions

The information regained during the literature study did not differ considerably compared to the information acquired during the interview and the questionnaire processes. With this said, the health care system exhibits a slow development which leads to a great difference between the areas of interest for research and what is actually used clinically.

The area of PET/CT and cancer treatment is one with immense potential and one where practically everyone involved believe in a positive development in the future. The demand for further SUV research in order for it to be improved is clear and the interest in developing additional quantitative indexes for clinical use is substantial. The quantitative or semi-quantitative uptake metric most frequently used to examine PET/CT images is SUV and the index most common to discuss is SUV_{max} , which explicitly indicate the considerable interest in reducing the hesitance towards SUV.

A great divergence exists in the health care system regarding how PET/CT images should be examined. The reason for these differences could be due to exceedingly individual physician preferences and the fact that various hospitals have distinct possibilities,

meaning for example the finances and the access. As a consequence, it is important to develop a solution which is highly adaptable according to the needs and the desires of the users. The purpose for this thesis of developing a prototype containing features of relevance could be considered achieved but if these features are presented in the most user friendly way possible is yet to be discovered by conducting user tests.

This thesis report could hopefully be utilized to facilitate the situation for physicians in general and for those who interpret PET/CT images for cancer treatment in particular. The consolidated information in the report should construct a basis for further development of current program software to ensure that true requirements are addressed. The everyday work for a physician is characterized by stress and the pressure of performing properly. The quality of care could therefore definitely be improved if a product could help with reducing these factors and one could in the long run contribute to saving a substantial number of patient lives.

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Appendix

Appendix A contains the questions asked during the interview process, where the questions marked in bold were prioritized in time sensitive situations.

Appendix B depicts the questions in the questionnaire which was sent out to various health care professionals and experts in the fields of PET/CT and/or cancer treatment.

A Interview questions

PET/CT generellt

1. Vad har ni för uppgift inom PET/CT och cancerbehandling?
2. Hur går en PET/CT-undersökning till?
3. **Vad mäter operatören och vad får man från maskinen?**
4. **Hur ofta kalibreras maskinerna? Finns det något som varierar angående detta så som hur ofta, olika på olika maskiner? Jämförs maskinerna med varandra?**
5. **Vilken information anser ni vara viktig och oviktig från en PET/CT?**
6. Hur mycket informeras patienten om innan och vad innehåller informationen?
7. **Om inte PET/CT skulle användas, vad använder man då och varför?**
8. **Vad är anledningen till att man gör en PET/CT? Bedöma behandling, bedöma cancertyp mm? Vilka indikationer behövs för att det ska vara värt att göra? Finns det riktlinjer för när en PET/CT ska användas?**
9. Vilka patienter får genomgå en PET/CT-undersökning?
10. **Om man ska fokusera på vissa cancerformer för FDG-PET/CT, vilka skulle det vara?**
11. I vilka fall används PET/CT?
12. Hur kan PET/CT påverka behandlingen och vilka alternativ man väljer?
13. Har ni någon rekommendation på hur jag kan hitta information om hur PET/CT används som en del av en cancerbehandling?
14. **Vad är resultatet av en granskning av en PET/CT-undersökning? Vilka program används för detta och hur gör man?**
15. **Vad får man ut från en PET/CT och vilka steg behöver man gå igenom för att få fram ett resultat? Vilka faktorer är man intresserad av? Vad vill man ha och inte ha?**
16. **Hur skulle du säga att beskrivningen av användningen av PET/CT för cancerbehandling skiljer sig i verkligheten jämfört med det som beskrivs i artiklar?**

PET/CT-kvantifiering

1. Står SUV-mätning med i rapporten? Alla gånger? Om nej, varför inte?
2. Används SUV för karakterisering av cancer och behandlingsutvärdering på något sätt? Hur används det?
3. **Vad finns med i rapporten angående SUV? Blodglukosnivå, tid mellan injektion och bildtagning, patient i vila, etc.?**

4. **Om SUV används, vilket i så fall? Max, mean, peak o.s.v.? Om inte, vad används istället?**
5. Är SUV-mätningar beslutsgrundande?
6. **Hur beräknar man SUV? Blir det alltid rätt och märker man att det blir fel, hur i så fall? Vill man kunna ändra värdet och se hur det är beräknat?**
7. **Förstår man vad SUV innebär? Behöver man ha någon utbildning i detta, är man begränsad på något sätt? Finns det några hinder för att använda SUV fullständigt?**
8. Används SUV tillsammans med någon annan information? T ex blodvärde, volymmått och liknande?
9. Finns det riktlinjer för hur SUV ska användas eller är det upp till varje enskild individ?
10. **Om inte SUV används, vad använder man för begrepp eller index för att bedöma cancer?** Förutom visuell tolkning. Exempel på saker som kan bedömas är respons på behandling, malign eller benign, planering inför strålbehandling etc.
11. **Vilken metod är vanligast för att segmentera ut en tumör? T ex isocontours.** Vad använder man för verktyg för att segmentera ut en tumör? T ex, sätter någon ut en markering baserat på visuell information eller använder man automatisk segmentering? Om automatisk, vilken?
12. **Vet du för vilka cancerformer som man använder SUV? Eller hur man kan ta reda på det?**
13. **Hur granskar man en PET/CT-undersökning? Vem granskar, t ex gör en nuklearmedicinare och radiolog det var för sig eller gemensamt?**
14. Får man någon specifik utbildning för PET/CT? Har ni någon utbildning för både PET och CT eller bara för en?
15. Hur granskas bilderna? Var för sig som PET och CT eller PET/CT?
16. **Hur granskar man när man kollar på fusion-bilden PET/CT? Vilka verktyg används och vilka egenskaper vill man ha/få reda på?**
17. Vilken information vill alla personer i behandlingsstegen ha? T ex, vad vill nuklearmedicinaren och radiologen veta jämfört med klinikern? Vad är det enskilda behovet?
18. I ett program som hanterar PET/CT-bilder, vad vill man att det ska innehålla för information och hur ska denna presenteras?
19. Hur vill man visualisera att ett område är markerat, t ex med färger, visst SUV? Vilken information vill man få presenterat?
20. Vilken information vill användarna ha, vad tolkas och förväntas? I vilka steg vill man se denna information, och var och när vill man få reda på vad?
21. **Hur ser man på en aktiv tumörvolym?**

Cancerbehandling

1. **Vad tycker du om att standardiserade vårdförlopp ska införas? Positivt/negativt, varför?**
2. Hur ser behandlingsförloppet ut från början till slut? Har du något exempel?
3. **Vad har man för allmänna riktlinjer för att definiera och klassificera en tumör och hur används PET/CT?**
4. **Hur bedömer man om en tumör ska behandlas och hur väljer man behandlingsalternativ?**
5. **Hur följer man tumöraktivitet över tid och hur rapporteras det? RECIST, PERCIST?**
6. **Vilka mätningar är av intresse under en tumörbehandling? Växttakt, aggressivitet, dubleringstid, metastasering etc.?**
7. **När görs en utvärdering av behandlingen och hur avgör man om den fungerar?**
8. Vilka behandlingskriterier finns och varierar de beroende på kroppsdel, tumörtyp, sjukhus etc.?
9. När gör man en ny undersökning och används andra modaliteter än PET/CT då? Varför?
10. Hur bedömer man att cancer är botad och finns det gränsvärden för detta?
11. Gör man uppföljningar efter att cancer anses vara botad?
12. **Används PERCIST eller vilken form av beslutsstöd använder man?**

Rapport

1. **Hur tycker du att en PET/CT rapport ska se ut? Hur ser den ut? Kan jag få se en?**
2. **Vem granskar en rapport som beskriver en cancerbehandling och hur vill man optimalt göra det? Vilka hinder finns för detta?**

Framtiden

1. Vilka förändringar vill du se till morgondagens cancervård?
2. Vilka riktlinjer för cancerbehandling och tumöruppföljning kommer finnas i framtiden?
3. Hur kommer PET/CT användas i framtiden?

B Questionnaire

PET/CT generellt

1. Vad är anledningen till att man gör en PET/CT på ert sjukhus?
Bedöma behandling, bedöma cancer typ etc.
2. Finns det riktlinjer för när och hur ni ska använda en PET/CT? Vilka?
3. Finns det några hinder för att göra en PET/CT?
Kostnad, tillgång etc.

PET/CT-information

1. Skiljer det sig från en läkare till en annan vilken information i PET/CT-bilden man är intresserad av? Hur?
T ex. nuklearmedicinaren är kanske inte intresserad av alls samma information som onkologen.
2. Vilka egenskaper tycker ni är viktiga hos ett program som används för att granska PET/CT-bilder?
Vilka verktyg vill man ha, vilka mätningar vill man göra och hur vill man att allt ska visualiseras? etc.
3. Vilken sorts information/faktorer är ni intresserad av från en PET/CT? Hur ska denna information presenteras?
Kunna göra mätningar, justeringar, förstärkningar etc. Var, när och hur vill man få reda på vad?
4. Hur granskar ni bilderna från en PET/CT-undersökning?

Standardized uptake value SUV

1. Använder ni SUV?
Ja, nej eller ingen åsikt.
2. Hur använder ni SUV?
Karakterisering av cancern, behandlingsutvärdering, bedöma benign/malign etc.
3. Står SUV-mätningen med era rapporter?
Varför? Varför inte?
4. Vad finns med i er rapport som berör SUV?
Glukosnivån i blodet, patienten vilade, patienten fastade etc.
5. Hur beräknar man SUV på ert sjukhus och blir det alltid rätt? Om inte, märker man det och hur kan det justeras?
6. Finns det några hinder för att använda SUV?

7. Om SUV inte används, vad använder ni då för kvantifiering av PET/CT-bilderna?
8. Har ni något intresse av att markera tumörens gränser för att urskilja den från normal vävnad?
Antigen automatiskt eller manuellt, i PET-, CT- och PET/CT-bilden.

Begrepp

1. Hur skulle ni gradera följande begrepp, från 1 till 5, baserat på hur relevanta de är för cancerbehandling och/eller tolkning av PET/CT-bilder? 1 är inte relevant och 5 är mycket relevant.
SUV, Metabolic rate, TNM-skalan, Likert-skalan, Deauville-skalan, PERCIST, RECIST och WHO
2. På vilket sätt är de relevanta eller inte relevanta?

Cancerbehandling

1. Vad tycker ni om att standardiserade vårdlopp införs under 2015/2016?
Bra, dåligt eller ingen åsikt.
2. Vilken information är ni intresserad av under en tumörbehandling?
Växttakt, aggressivitet, dubbleringstid, metastasering etc.
3. Vilka allmänna riktlinjer finns för att definiera och klassificera en tumör och hur används PET/CT för detta?
4. När gör ni en utvärdering av behandlingen och hur avgör ni om den fungerar?
Nämn gärna om och hur PET/CT och/eller SUV påverkar detta.
5. Hur följer ni tumöraktivitet över tid och hur rapporteras det?
6. Vad tycker ni att en PET/CT-rapport ska innehålla för information? Vad innehåller den?
Syftar på den rapport/svar som skickas från nuklearmedicinaren och/eller radiologen till den remitterande läkaren.
7. Använder ni PERCIST och/eller RECIST? Om inte, vilka standarder används för beslutsstöd?
Syftar då både på bedömning av behandlingsrespons under behandling och eventuell uppföljning efter avslutad behandling.

Framtiden

1. Hur tror ni att framtiden kommer se ut för cancerbehandling och PET/CT?
Nämn gärna detta specifikt utifrån ert användande.