POSITRON EMISSION TOMOGRAPHY WITH 2-DEOXY-2-[^{18}F]FLUORO-D -GLUCOSE IN PATIENTS WITH THYROID DISEASES

Running title:

FDG PET IN THYROID DISEASES

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“Truth is a constant variable”

William J. Mayo

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PREFACE

"The gap between good enough and perfect never closes"

This work started in 2004 during a ten-month PET training program in the Department of Radiology, Division of Nuclear Medicine, at the Mayo Clinic in Rochester, Minnesota, USA. During numerous short and extended visits to Rochester throughout the following years, research protocols have been discussed and modified, data have been collected and updated, abstracts for international meetings and manuscripts have been discussed with my co-authors, corrected and improved, and important friendships have developed. I am particularly thankful for all support, valuable scientific advices and help in planning and writing protocols and manuscripts by my great PET mentor and main supervisor at the Mayo Clinic, Professor Val J. Lowe. Important advices and excellent proof reading have been given by Dr. Mark A. Nathan, and together we were the co-winners in the MD/Scientist category for the 29th Annual Western Regional Chapter Meeting, Society of Nuclear Medicine, Vancouver, BC, Canada, October 21-25, 2004, with the oral abstract presentation "The value of ^{18}F-FDG PET in patients with residual or recurrent medullary thyroid cancer".

I have spent numerous twelve-hour working days at the Mayo Clinic together with my co-author and friend Dimitrios Karantanis, reading PET scans, preparing for the next day´s PET examinations, preparing teaching files, and working on our research projects. During our frequent lunches at Jimmy John´s Gourmet Sandwich bar across the street from the Charlton Building, we read the following phrase written on the wall: "*The gap between more and enough never closes*". We soon modified the saying to "*The gap between good enough and perfect never closes*". An important breakthrough during the writing of this thesis came on the day I actually realized that the gap between good enough and perfect writing never closes!

My special interest in thyroid cancer started in 1983 when I as a fresh resident in the Department of Clinical Biochemistry, Nordland Central Hospital, Bodø, Norway, learned about thyroid diseases including thyroid cancer from Erling Saltrøe, MD, the head of the department. He is a very knowledgeable physician, and from whom I also learned the importance of scientific humbleness. One year spent under the skillful supervision of Professor Kjell Rootwelt at the National Hospital in Oslo in 1989 has also been important for

my professional and scientific maturation. My very first international publication as a first author was in close collaboration with Professor Kjell Rootwelt.

My interest in PET started in 1992 during a four-month nuclear medicine training program in the Department of Nuclear Medicine at the University of Washington Medical Center in Seattle, Washington, under the inspiring supervision of one of the great international pioneers in the field of nuclear medicine, Professor Will B. Nelp. At the University of Washington I also became acquainted with Greg Wiseman, MD, an oncologist and a nuclear medicine resident. Some years later, he was appointed to a position as a staff member in the Department of Nuclear Medicine at the Mayo Clinic in Rochester. He was an important reference for me when in 1996 I applied for a 12 month fellowship at Mayo Clinic. During my fellowship at Mayo Clinic in 1997 / 1998, Professor Joe C. Hung was my supervisor in radiopharmacy research, and he gave me valuable education in international presentation technique and in preparation of international publications.

A short history has to be told: At a dinner for congress participants held in a film studio in Beverly Hills during the 74th American Thyroid Association (ATA) Annual Meeting in Los Angeles in October 2002, I happened to be sitting next to a bald, white bearded American in his early sixties. He was curious to learn where my strange English accent came from and what I was working with. The ATA Annual Meeting is primarily a congress for endocrinologist working with thyroid diseases and many of the participants were at that time not familiar with PET scanning. I told him about my interest in thyroid cancer and PET imaging and I asked him whether he knew about PET-scanners. He responded promptly: “Sure, I am the one who invented the PET scanner!” He was Professor Edward Josef Hoffman from the University of California Los Angeles! Together with Michael Phelps he designed and built the first PET scanner in 1973 at the Washington University, St Louis, MO.

Support and contributions from my friends and colleagues at the Norwegian Radium Hospital have been very important to me during my work with this thesis. Particularly, my work in the hospital´s thyroid cancer program has been a valuable source of inspiration and friendship. The program has been under the skilful leadership of one of my two main supervisors and co-author, Professor Trine Björo. My close collaborator, the thoracic surgeon Lars H. Jørgensen, has on occasions invited me to assist him during reoperations of lymph node metastases in the neck and upper mediastinum, and I have learned that metastatic lymph nodes easily identified on FDG PET/CT are not necessarily easy to remove by surgery even for as skilled a thyroid surgeon as he is. In 1999 Lars and I established the hospital´s weekly

multidisciplinary thyroid cancer meeting. From Eva Sigstad, MD, and Krystyna Kotanska-Grøholt, MD, I have acquired valuble knowledge on thyroid cytology and histopathology, and from Arne Heilo, MD, I have acquired valuble knowledge on ultrasound examinations of the thyroid gland and neck lymph nodes.

I have appreciated numerous valuable suggestions from my ingenious colleague, close friend and second main supervisor, Tore Bach-Gansmo, MD, PhD. I am a late evening writer, and I have called him numerous times close to midnight to discuss my writing. I am sorry that I never assimilated that he usually goes to bed a couple of hours before I normally do. Professor in medical physics, Arne Skretting, has greatly contributed to my understanding of PET physics, which has been very important for me, both for my work with this thesis as well as for my past, present and future work with PET in general. I have very much enjoyed our research collaboration on SUV measurements and the partial volume effect, or what he prefers to call the phenomenon: “intensity diffusion”. Arne Skretting and my previous supervisor at the Norwegian Radium Hospital, Magne Aas, MD, PhD, have contributed with valuable and creative suggestions during my work on individual papers and on the preparation of this thesis.

It has been very encouraging during the writing of this thesis to recognize that our articles have been cited in international guidelines on thyroid cancer, in international reputable textbooks on PET, and in numerous articles in international medical journals. However, irrespective of the encouraging recognition of the published articles and irrespective of all valuable support and contributions from numerous colleagues and friends in the USA and in Norway, my most valuable support and source of inspiration has been my three children Martin, Katrine, and Andreas.

Nesbru, Norway, January 2011,

Trond Velde Bogsrud

ABBREVIATIONS

ATC	anaplastic thyroid carcinoma
CEA	carcinoembryonic antigen
CT	computed tomography
Ct	calcitonin
DTC	differentiated thyroid carcinoma
^{18}F	Fluorine-18
FDG	2-deoxy-2 [18F]fluoro-D-glucose
FDG PET	PET with FDG
FNAC	fine needle aspiration cytology
FTC	follicular thyroid carcinoma
keV	kilo electron volt
MIP	maximum intensity projection
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
NOPR	National Oncologic PET Registry
PET	positron emission tomography
PET/CT	combined (hybrid) PET and CT
PTC	papillary thyroid carcinoma
RAI	Iodine-131
SUV	standardized uptake value
SUVmax	maximum standardized uptake value
Tg	thyroglobulin
TgAb	thyroglobulin autoantibody
TOF	time-of-flight
TPOAb	thyroid peroxidase autoantibody
TSH	thyroid stimulating hormone (thyrotropin)
TSHRAb	thyrotropin (TSH) receptor-stimulating antibody
US	ultrasound

LIST OF PAPERS

I. Karantanis D, **Bogsrud TV**, Wiseman GA, Mullan BP, Subramaniam RM, Nathan MA, Peller PJ, Bahn RS, Lowe VJ. **Clinical Significance of Diffusely Increased ^{18}F-FDG Uptake in the Thyroid Gland.** J Nucl Med 2007; 48: 896-901.

II. **Bogsrud TV**, Karantanis D, Nathan MA, Mullan BP, Wiseman GA, Collins DA, Kasperbauer JL, Strome SE, Reading CC, Hay ID, Lowe VJ. **The value of quantifying ^{18}F-FDG uptake in thyroid nodules found incidentally on whole-body PET/CT.** Nucl Med Commun 2007; 28: 373-381.

III. **Bogsrud TV**, Hay ID, Karantanis D, Nathan MA, Mullan BP, Wiseman GA, Kasperbauer JL, Reading CC, Bjøro T, Lowe VJ. **Prognostic Value of ^{18}F-Fluorodeoxyglucose-Positron Emission Tomography in Patients With Differentiated Thyroid Carcinoma and Circulating Antihyroglobulin Autoantibodies.** Nucl Med Commun 2011 (in press).

IV. **Bogsrud TV**, Karantanis D, Nathan MA, Mullan BP, Wiseman GA, Kasperbauer JL, Reading CC, Hay ID, Lowe VJ. **^{18}F-FDG PET in the Management of Patients with Anaplastic Thyroid Carcinoma.** Thyroid 2008; 18: 713-719.

V. **Bogsrud TV**, Karantanis D, Nathan MA, Mullan BP, Wiseman GA, Kasperbauer JL, Reading CC, Bjøro T, Hay ID, Lowe VJ. **The Prognostic Value of 2-Deoxy-2-[^{18}F]fluoro-D-Glucose Positron Emission Tomography in Patients With Suspected Residual or Recurrent Medullary Thyroid Carcinoma.** Mol Imaging Biol 2010; 12: 547-553.

1. INTRODUCTION

"To books we turn to learn of the past, opinions of the present, and prognostications of the future." William J. Mayo, 1936.

The use of positron emission tomography (PET) in oncology has been reviewed by a number of authors (Rohren et al. 2004, Juweid and Cheson 2006, Podoloff et al. 2009, Weber 2009). PET imaging of the distribution of fluorine-18 (^{18}F) labeled 2-deoxy-D-glucose (2-deoxy-2 [^{18}F]fluoro-D-glucose; FDG), is established as a powerful tool for staging and restaging of a wide range of cancers, for detection of cancer recurrence, for discrimination between residual or recurrent disease and scar, and for detection of occult cancer in patients with metastases from an unknown primary. PET with FDG (FDG PET) is increasingly used in radiation therapy planning and in early prediction of treatment response (Weber 2005, Weber 2009, Weber 2010). The large potential of PET as an early predictor of therapeutic response in development and evaluation of new drugs is discussed in an invited perspective article by Larson and Schwartz (2006).

With the recent widespread and rapidly increasing use of PET in clinical practice and its important impact on patient management, correct interpretation and reporting of the PET findings are fundamental (Coleman et al. 2010). Knowledge of the typical findings on PET for the individual cancer types and the normal response to different therapies is mandatory for the physicians who interprete the PET scans. A thorough knowledge of normal uptake, distribution and excretion of FDG, normal variants in activity distribution, artifacts, and potential pitfalls is essential for correct interpretation of FDG PET. These fundamental aspects of the PET interpretation are reviewed and discussed by a number of authors (Bogsrud et al. 2006, Bogsrud and Lowe 2006, Shreve et al. 2009, Lin and Alavi 2010b, Liu et al. 2010).

The standard scanning length for oncologic PET is from the base of the skull to the proximal thighs and is commonly called "whole-body scan". With the increasing use of PET, unexpected findings outside the anatomical region of primary interest present a growing challenge (Agress and Cooper 2004, Ishimori et al. 2005, Wang et al. 2007, Beatty et al. 2009, Liu et al. 2010) (Figure 1). Most incidental abnormalities are benign and are correctly diagnosed by experienced readers (Wang et al. 2007). Incidental findings considered as possibly malignant are found in 5-12% of whole-body PET scans. In lesions with adequate follow-up malignancy is confirmed in 20-60%. Most of these synchronous primary cancers

detected incidentally on FDG PET are stage I or II diseases for which a cure is often achievable. Thus, assessment of an accurate etiology of an incidental finding is important.

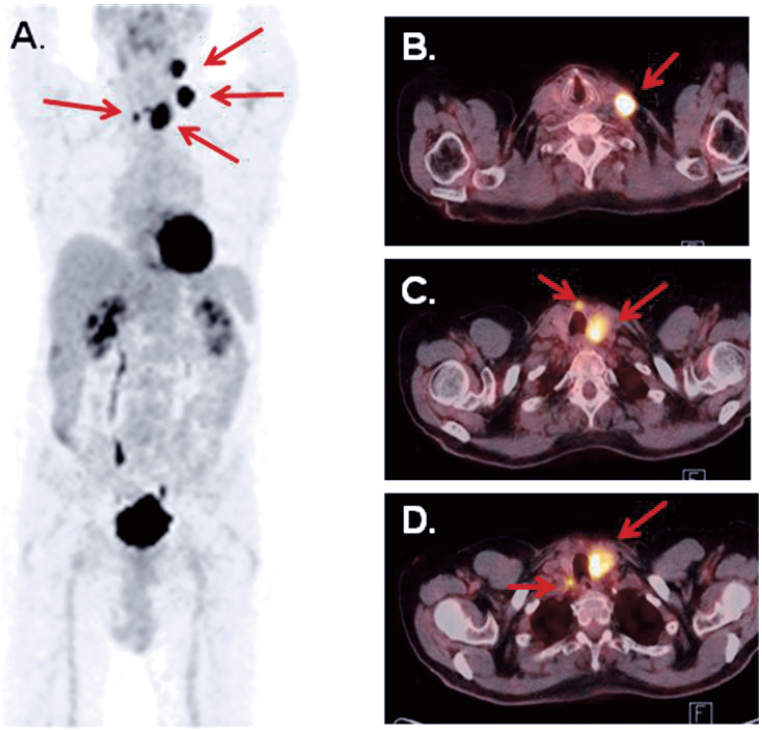


Figure 1. Whole-body FDG PET/CT of a patient with colorectal cancer. Indication for the PET scan was restaging after surgery and chemotherapy. **A:** Maximum-intensity projection (MIP, PET-only). There is no evidence of residual or recurrent colorectal cancer. However, there are incidental findings of several foci of high FDG uptake in the neck (arrows). These foci were confirmed histopathological to be aggressive metastatic papillary thyroid cancer. Physiological FDG uptake in the heart and normal excretion in the urinary tract are seen. **B-D:** Transaxial PET/CT slices show high FDG uptake in the primary thyroid cancer and in metastatic lymph nodes (arrows).

A frequent incidental finding on whole-body FDG PET is focally or diffusely increased FDG uptake in the thyroid gland (Yasuda et al. 1998, Cohen et al. 2001, Kang et al. 2003).

The use of PET in patients with cancer has a significant impact on patient management. According to data from 40 863 PET studies collected by the National Ongologic PET Registry (NOPR) in USA, when intended management was classified as treatment or non-treatment, physicians changed their intended management for 38% of the patients on average based on the results from PET scanning (Hillner et al. 2008b). The patients included in the NOPR had a cancer type or an indication for a PET study not previously covered by the Centers for Medicare and Medicaid Services (CMS). Overall, physicians changed their

management for 37% of the patients across the full spectrum of its potential uses (Hillner et al. 2008a). The impact of PET on physicians intended management was consistent across cancer types (Hillner et al. 2008b). Particularly, for patients with thyroid cancer, physicians changed their intended patient management in 35% of the cases according to data collected from 1131 patients registered in the NOPR (Hillner et al. 2008b, Barry Siegel personal e-mail communication October 6 and 7, 2009).

2. POSITRON EMISSION TOMOGRAPHY

2.1 What is PET

PET is a nuclear medicine imaging modality able to image and quantify biological processes at a molecular and cellular level applying positron emitting radionuclides (radioactive isotopes) or radiopharmaceuticals labeled with such radionuclide. Molecular imaging is the visualization, characterization, and measurement of biological processes at the molecular and cellular level in humans or in other living systems. PET is the prototype of molecular imaging (Mankoff 2007, Peterson and Manning 2009). In The National Institute of Health´s Molecular Imaging and Contrast Agent Database (MICAD) (2010), approximately 820 agents are listed of which about 600 are radiotracers and the vast majority of these are PET tracers.

2.2 Basic PET physics and technology

Basic PET physics and technology for non-physicists are excellently reviewed by a number of authors in articles and textbooks (Rohren et al. 2004, Jadvar and Parker 2005, Saha 2005, Phelps 2006, Pichler et al. 2008, Mawlawi and Townsend 2009, Turkington 2009). When a positron (β^+ particle) is emitted from a radioactive nucleus it will, after a very short travel, lose its kinetic energy and collide with its antiparticle, an electron. In the collision the rest masses of the two particles will fuse and be transformed into electromagnetic energy according to Albert Einstein´s law of energy preservation ($E=mc^2$), in the form of two 511 keV photons emitted in opposite directions (very close to 180º apart). The fusion of the positron-electron pair is called annihilation. It is the 511 keV annihilation photons that are collected by the PET detector, not the positrons per se.

Positrons from different radionuclides will carry different kinetic energy. The higher the kinetic energy the longer the positron will travel before its annihilation with an electron. Fluorine-18 (^{18}F), the most commonly used radionuclide in clinical PET, as well as in PET research, has a max β^+ energy of 0.63 MeV and an average travel rage in soft tissue with respect to the nucleus of 0.64 mm (Jadvar and Parker 2005). Oxygen-15 (^{15}O), which in the form of ^{15}O-water is used clinically and in research to measure blood flow and perfusion, has a max β^+ energy of 1.72 MeV and an average travel range of 2.01 mm.

The travel range is also highly dependent on the tissue density. The travel range will, for example, be about three times longer in lung tissue compared to ordinary soft tissue. Particularly for the emitters of positrons with high kinetic energy, the relatively long range in tissue is one factor that limits the spatial resolution power of the PET image.

When the 511 keV photons hit the PET detector, the energy is transformed to light, just like in a conventional gamma camera, a phenomenon called scintillation (Rohren et al. 2004, Jadvar and Parker 2005, Saha 2005, Phelps 2006, Turkington 2009). Thus, PET is a scintigraphic imaging modality. In modern PET scanners the detectors are arranged in several rings (ring detectors). PET detector rings are formed by individual scintillation crystals organized in blocks. A typical block may consist of 13x13 crystals. A ring of such 13x13 crystal blocks thus forms 13 individual crystal rings. A set of photomultiplier tubes, typically 4 in number, is attached to each block. Photomultiplier tubes transform light into electric signals. Based on information about the intensity of the electric signal from each individual photomultiplier, a processor determines which crystal was hit and how much energy was deposited. Scattered low energy photons are excluded by the use of energy threshold settings.

Only the pairs of annihilation photons that hit the two detector crystals in the detector rings within a very narrow time window, called the coincidence window, are accepted. Light and all forms of electromagnetic radiation travel at a speed of 30 cm/ns (299 792 458 m/s) in vacuum, and the coincidence window is typically around 5 ns or less. This detection principle is called coincidence detection. The line between the two crystals which are hit is called the line of response (LOR), along which the radioactive decay is assumed to have happened. Millions of LOR registrations form the basis for the mathematical reconstruction of the image volume associated with one longitudinal field of view (bed position).

Last generation PET cameras not only detect annihilation photons within a very narrow time window, but are also able to measure the time difference between the hits of a pair of annihilation photons within the coincidence window. This ultra-short time difference, actually about 0.5 ns, can be used to shorten the LOR and thus improve the reconstruction of the true activity distribution. This principle, called time-of-flight (TOF), has improved the image quality (Phelps 2006, Pichler et al. 2008, Mawlawi and Townsend 2008, Turkington 2009).

In planar x-ray studies and in CT the attenuation of photons (x-rays) is the basis of the image formation. In PET, however, the distribution of the radiopharmaceutical in the body is

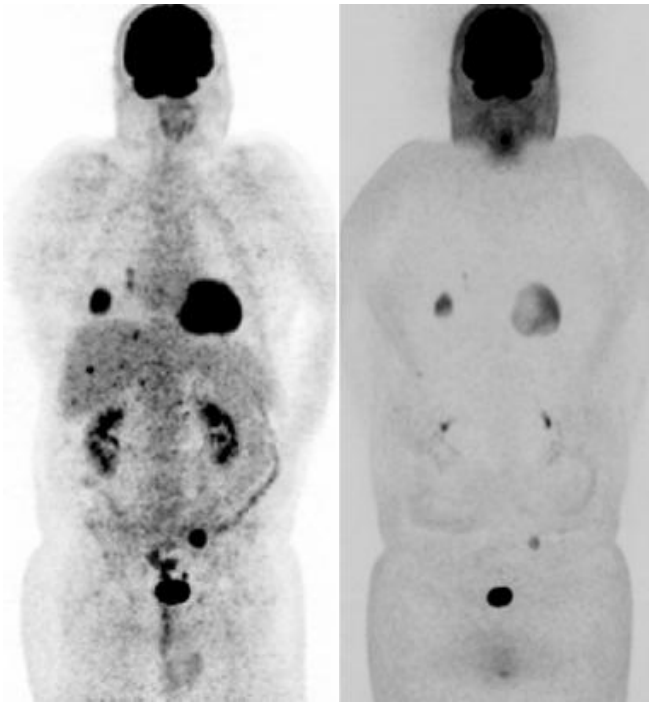


Figure 2. Metastatic disease. FDG PET/CT maximum intensity projections (MIP, PET-only). **Left:** CT attenuation corrected PET images. **Right:** Non-attenuation corrected PET images. **Left and right:** The CT attenuation corrected images show more malignant lesions and more intense uptake in the lesions compared to non-attenuation corrected images.

the basis of the image formation and any tissue attenuation of the photon flux reduces the image quality and makes quantification impossible. Therefore, correction of errors due to loss of photons by tissue attenuation is needed in PET (Jadar and Parker 2005, Saha 2005, Phelps 2006, Turkington 2009). In modern PET scanners attenuation correction is performed by applying the attenuation properties of the tissues derived from images obtained with the integrated CT scanner (PET/CT) (Figure 2).

The combination of small scintillation crystals organized in ring detectors and coincidence detection makes the spatial image resolution of PET scanners much higher compared to conventional gamma cameras. The spatial image resolution is, however, still far inferior to CT and magnetiv resonance imaging (MRI). An automatic, simultaneous co-registration of high-resolution CT images and low-resolution PET images in combined PET/CT scanners has proved to be very useful in precise lesion localization (Beyer et al. 2000, Kluetz et al. 2000, Saha 2005, Turkington 2009). Standard procedure for PET scanning

in most centers world-wide is integrated low dose, non-contrast enhanced CT for attenuation correction and anatomical co-registration.

2.3 PET radiopharmaceuticals

PET radiochemistry and radiopharmacy, including a description of the most commonly used radiopharmaceuticals for clinical PET and for PET research are comprehensively reviewed by Vallabhajosula (2009a, 2009b). A unique characteristic of PET is the possibility of labeling numerous biological compounds and drugs by substituting a stable nuclide of Carbon (C), Oxygen (O), or Nitrogen (N) in the molecule with the corresponding positron emitting radionuclide Carbon-11 (^{11}C), Oxygen-15 (^{15}O), or Nitrogen-13 (^{13}N) without changing the compounds biochemical or biological behavior. In a number of compounds a hydrogen atom or a hydroxyl group can be substituted with ^{18}F without any significant change in their biologic behavior.

Some other radionuclides commonly used in PET are Copper-64 (^{64}Cu), Gallium-68 (^{68}Ga), Rubidium-82 (^{82}Rb), and Iodine-124 (^{124}I) (Vallabhajosula 2009b, Vallabhajosula 2009c). With a few exceptions, *e.g.* ^{68}Ga and ^{82}Rb, which are produced as daughter nuclides in a generator, the positron emitting radionuclides used in PET are cyclotron produced (Saha 2009). The physical half-life of ^{18}F is 110 minutes, which allows for transportation to the PET-site within a couple of hours from the FDG production site. For most other radionuclides with shorter physical half lives an on-site cyclotron is needed. For example, the second most commonly used positron emitting radionuclide, ^{11}C, has a physical half-life of 20 minutes, and ^{15}O has a physical half-life of 110 seconds. The cyclotron production of PET radionuclides and the production of radiopharmaceuticals contribute considerably to the high cost of PET studies.

The most commonly used radiopharmaceutical in both clinical PET and in PET research is ^{18}F-labeled 2-deoxy-D-glucose; 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) (Rohren et al. 2004, Juweid and Cheson 2006, Saha 2009, Wahl 2009b, Vallabhajosula 2009a, Vallabhajosula 2009c) (Figure 3). FDG will be further discussed in the next chapter. Examples of other radiopharmaceuticals used in clinical oncologic PET are ^{11}C- or ^{18}F-labeled choline for patients with prostate cancer, ^{68}Ga-labeled somatostatin receptor analogues and ^{18}F-labeled 3,4-dihydroxy-6[^{18}F]-phenylalanine (FDOPA) used in patients with neuroendocrine tumors, and ^{18}F-NaF as a promising agent for detection of bone metastases.

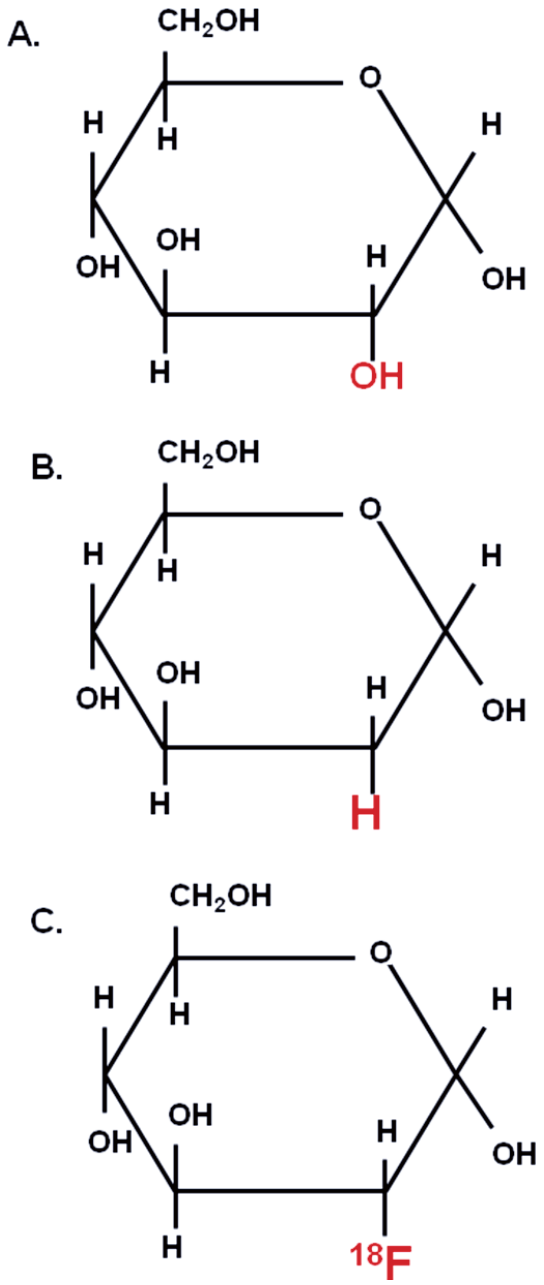


Figure 3. A. D-Glucose. **B.** 2-deoxy-D-Glucose. **C.** 2-deoxy-[^{18}F]fluoro-D-Glucose (FDG). FDG is the most commonly used radiopharmaceutical both in clinical and in PET research.

^{18}F labeled 3-[^{18}F]-3-deoxythymidine (FLT) and ^{18}F labeled 1-(2′-deoxy-2′-[^{18}F]fluoro-β-D-arabinofuranosyl)thymin (FMAU) have been used to image cell proliferation (Dunphy and Lewis 2009, Hicks 2009, Vallabhajosula 2009c, Weber 2010).

Not only glucose metabolism and DNA-synthesis are increased in malignant cells. Amino acid uptake and protein synthesis are increased as well. Carbon-11 labeled ([^{11}C]methyl)-L-methionine (MET) is the most commonly used amino acid tracer for PET imaging (Dunphy and Lewis 2009). Other amino acid PET tracers are the ^{18}F-labeled L-tyrosine analogue *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) and recently *O*-([^{18}F]fluoro-methyl)-D-tyrosine (FMT).

^{18}F-labeled fluoromisonidazole (FMISO), ^{18}F-labeled [^{18}F]fluoro-5-deoxy-α-D-arinofuranosyl-2-nitroimidazol (FAZA) and ^{64}Cu-labeled [^{64}Cu]Copper(II)-diacetyl-bis-(N4-methylthiosemicarbazone) (CuATSM) are used for imaging hypoxia and various ^{11}C-, ^{64}Cu-, ^{124}I and ^{18}F-labeled radiopharmaceuticals are available for imaging angiogenesis and apoptosis (reviewed in Dunphy and Lewis 2009, reviewed in Lapi et al. 2009, reviewed Piert 2009, reviewed in Vallabhajosula 2009c).

2.4 2-deoxy-2-[^{18}F]fluoro-D-Glucose (FDG)

PET with ^{18}F-labeled D-Glucose (2-deoxy-2-[^{18}F]fluoro-D-Glucose; FDG) is reviewed in a number of journal articles and textbooks (Oehr 1999, Rohren et al. 2004, Wahl 2009b, Vallabhajosula 2009a, Vallabhajosula 2009c). In FDG the hydroxyl group on carbon-2 of D-glucose is substituted with ^{18}F (Figure 3). The binding between the fluorine and the carbon atom in FDG is even stronger than the binding between the carbon and hydrogen (the C-H bond) in deoxyglucose: thus FDG is a very stable molecule (Vallabhajosula 2009a). FDG shares the same cellular uptake mechanism as glucose, and there is a competitive cellular uptake between FDG and glucose. When inside the cell, FDG is like glucose phosphorylated to FDG-6-P catalyzed by the enzyme hexokinase (Wahl 2009b). Hexokinase is the rate-limiting enzyme in the glucose metabolism, and thus, the FDG uptake reflects the intracellular hexokinase activity. To express it in a molecular imaging term: the molecular imaging probe FDG targets the cellular hexokinase activity (Vallabhajosula 2009c). In glucose-6-P the

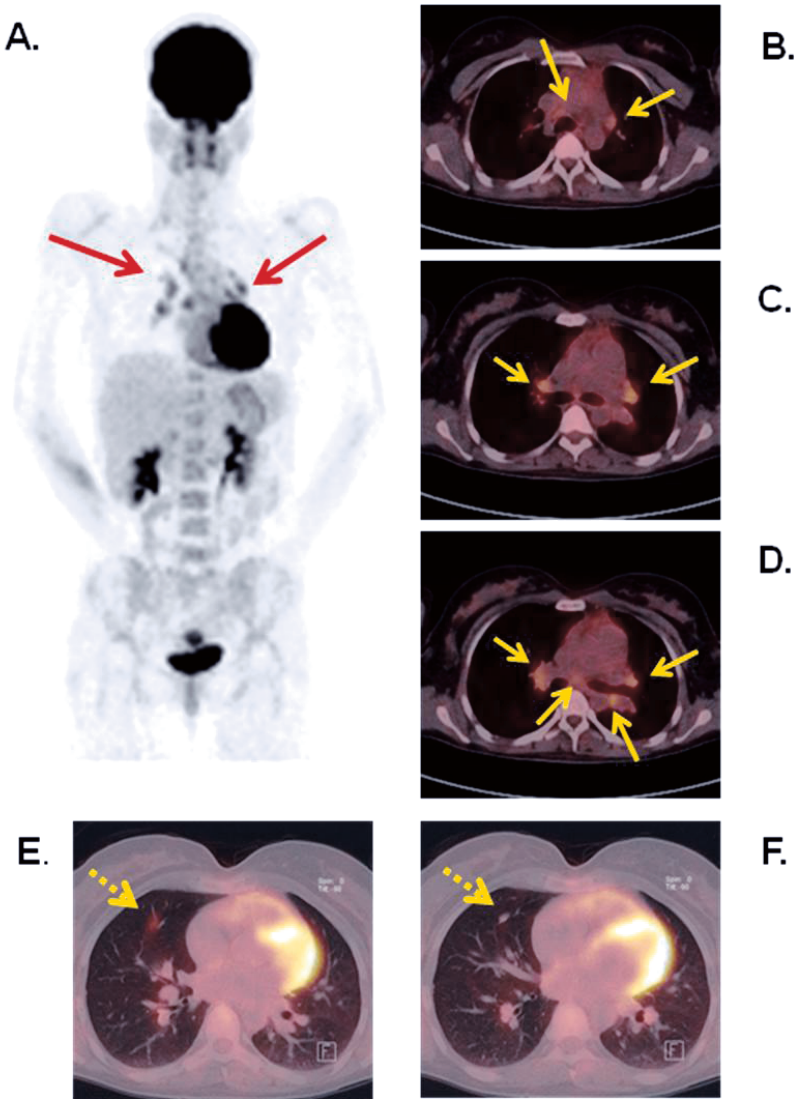


Figure 4. Young female with a 2.2 cm PTC treated with total thyreoidectomy, central and left lateral modified lymph node dissection and subsequent radioiodine ablation. Lymph node metastases histological confirmed in 13 out of 30 removed lymph nodes. Six months after radioiodine ablation Tg=1.2 µg/L after thyroxine withdrawal. Contrast-enhanced CT done in an elsewhere institution showed enlarged mediastinal lymph nodes and a solitary lung nodule considered suspicious for lymph node and lung metastases. The patient was referred to the Norwegian Radium Hospital for repeated radioiodine treatment. A FDG PET/CT was performed. **A.** The enlarged mediastinal lymph nodes (red arrows) show increased FDG uptake clearly seen on maximum intensity projections (MIP). **B-D**. Transaxial PET/CT shows increased FDG uptake in the mediastinal lymph nodes (yellow arrows). **E.** Localized FDG uptake (dotted arrow) in the right upper lobe. **F.** The localized FDG uptake does not match the lung tumor (dotted arrow) because of respiratory movement during PET aquistion (PET and CT misregistration). The pattern of the increased lymph nodes was more consistent with sarcoidosis than of metastatic thyroid cancer. Endobronchial ultrasound (EBUS) guided FNA confirmed cytological chronic granulomatous inflammation consistent with sarcoidosis. The lung tumor was consistent with sarcoidosis as well based on the CT findings.

hydroxyl group in the C-2 position is essential for further metabolism. Since FDG-6-P lacks this hydroxyl group, the molecule is not further metabolized. Since there is no active or passive transport of FDG-6-P across the cell membrane (no leakage), FDG is trapped within the cell (Vallabhajosula 2009a).

In most cancer cells the cell membrane glucose transporter GLUT-1, as well as the glycolytic rate-limiting enzyme hexokinase-1, are increased manyfold (Oehr 1999, Wahl 2009b). Furthermore, the rate of dephosphorylation catalyzed by the enzyme phosphatase is low in most malignant tumor cells. The higher the glucose uptake and hexokinase activity the more FDG is trapped in the cell. However, the increased FDG-uptake is not specific for cancer cells. FDG-uptake is also high in tissue with a high glucose metabolism such as the brain. Furthermore, increased FDG-uptake is seen in inflammations (e.g. thyroiditis) and infections, after surgery and radiation therapy, in reactive bone marrow, and in thymic rebound (Zhuang and Alavi 2002, Israel 2009, Liu et al. 2010) (Figure 4). FDG PET is routinely used not only in oncology, but also to some extent in neurology, cardiology and in rheumatology as well (Zhuang and Alavi 2002, Saha 2005).

2.5 SUV measurements

PET imaging is used not only for detection of lesions or regions with increased radiopharmaceutical uptake above normal but also involves quantification of the uptake. A unique property of PET is the capability of quantifying the activity concentration of an injected radiopharmaceutical in any (voxel) localization in the body. Juweid and Cheson (2006) have reviewed the usefulness of quantification of FDG uptake in differentiation between benign and malignant tumors, in differentiation between inflammatory tissue and residual or recurrent cancer, for monitoring cancer therapy, and for predicting outcome. For some cancer types including thyroid cancer, the intensity of the FDG uptake may reflect the aggressiveness of the tumor (Minn et al. 1988, Wang et al. 2000).

Most clinical research studies published on FDG PET involve measurements of FDG uptake. The most accurate quantification of FDG uptake is based on kinetic modeling. Kinetic methods, however, are too complicated and require too long of an acquisition time to be performed in a clinical practice and are too cumbersome even for most research projects (Carson 2005, Shankar et al. 2006).

A more common approach is to compare tissue uptake to the injected activity. A larger patient will have a larger distribution volume compared to a smaller patient and on average lower tissue uptake per unit injected dosage. Body weight, body surface area, or lean body mass are used to correct for differences in patient size. The most commonly used measure for FDG uptake both clinically and in research, is the standardized uptake value (SUV). The use of SUV has been reviewed by a number of authors and discussed in a number of consensus recommendations (Saha 2005, Shankar et al. 2006, Wahl 2008a, Boellaard 2009, Boellaard et al. 2010). The SUV is defined as the tissue activity concentration C_t (MBq/g) as determined in a chosen region (ROI) or volume of interest (VOI) relative to the injected activity ID (MBq) corrected for decay of the radionuclide multiplied by the body weight (g):

$$SUV = \frac{C_t(MBq/g)}{\frac{ID(MBq)}{weight(g)}}$$

SUV can also be corrected for body surface area or lean body mass (the mass of the body minus the fat). SUV corrected for weight or lean body mass is unit less. SUV corrected for body surface area relative to standard body surface area (1.73 m^2) will be unit less as well.

Most commonly the SUV is measured as SUVmax, which represents the FDG uptake in the voxel with the highest uptake within the chosen region (ROI) or volume of interest (VOI). Typically, SUVmax of blood background one hour after FDG injection is 1-2, normal liver 2-3, and normal brain cortex 12-15. The SUVmax is easily accessible on any PET work station. After the injected activity and patient weight have been entered into the computer, SUV is automatically calculated for a manually chosen region or a volume of interest. SUV, however, is affected by a number of factors such as body habitus, blood glucose level, as well as acquisition and reconstruction parameters. Particuarly when SUV is used in clinical research involving serial studies of individual patients, a strict standardization is mandatory. Unreliable SUV measurements are an important limitation of clinical studies and are a problem particularly in retrospective and in multicenter studies. Keyes (1995) has published an article on the sources of errors in SUV measurements with the title “SUV: standard uptake or silly useless value?”

2.6 The history of PET

"The development of positron emission tomography (PET) has attracted many strong personalities, great scientists, and businessmen, many of whom have dedicated their entire lives to this technology" (Nutt 2002).

The history of PET has been reviewed by a number of authors (Brownell 1999, Jones 2002, Nutt 2002). The very first report on the use of positron emitting radionuclides in medical sciences seems to be a work by Tobias et al. (1945 cited in Jones 2002). His group studied the elimination of ^{11}C-labeled carbon monoxide (CO) from the body with reference to the possible conversion of CO to CO_2. The first publications on medical imaging by the use of positron emission were two independent articles on localization of brain tumors imaged with ^{15}O published in 1951 (Jones 2002, Brownell 1999, Nutt 2002). The history of the first patient ever diagnosed with a brain tumor by positron emission was published in Time Magazine on April 5th, 1954. The patient was a seven year old girl. After the brain tumor was localized it was successfully removed by surgery.

In 1970 David Chesler (1971) applied a filtered back projection (FBP) algorithm image reconstruction for the first time ever for three-dimensional PET or CT data after registration of coincidences on a dual head camera system called PC-I (Brownell 1999). His research group called their computed tomographic technique "positron emission tomography".

A further important step forward in PET technology development was the introduction of PET scanners with ring detectors in 1973 (Brownell 1999, Nutt 2002). In the following years Michael E. Phelps and Edward J. Hoffman, at Washington University, St. Louis, MO, built their PET-scanners named PETT I, PETT II and PETT II ½. PETT was an acronym for *positron emission transaxial tomography*. These scanners had ring detectors, coincidence detection, attenuation correction, and image reconstruction based on an FBP algorithm (Phelps 1975 cited in Nutt 2002). The radiopharmaceuticals used in the beginning of the PET development were ^{11}C-glucose for glucose metabolism, ^{15}O water and ^{13}N ammonia for blood flow and ^{18}F-NaF for bone scan (Brownell 1999, Nutt 2002). Fluorine-18 labeled D-Glucose (FDG) was developed in the mid-seventies (Phelps et al. 1979, Brownell 1999, Nutt 2002). Important for the further development and expanded use of PET imaging not only in research but in clinical uses as well was the introduction of commercial compact medical cyclotrons designed for PET facilities in the mid-eighties (Nutt 2002).

The next important step forward was the introduction of PET scanners with integrated CT. The integration of a CT in PET scanners sped up and improved the attenuation correction important for PET imaging. Furtheremore, the co-registration of PET images lacking anatomical details with anatomical high resolution CT-images tremendously improved the diagnostic accuracy. In Time Magazine on April 4th, 2001, there was an article with the title "The Winning Combination" where the the integration of PET and CT in the same imaging system was described (Jaroff 2000).

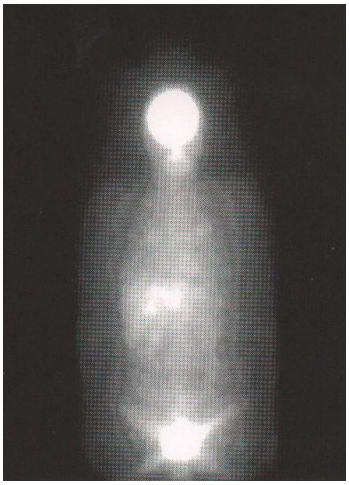
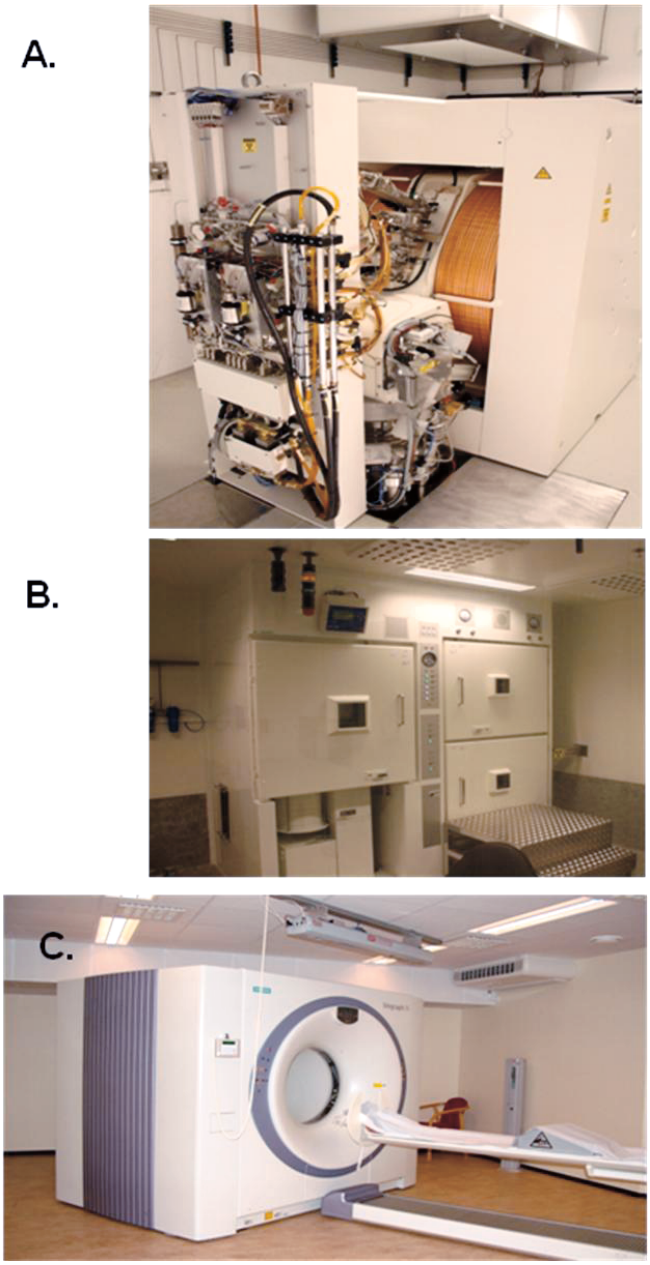


Figure 5. The very first FDG whole-body scan performed in Norway (Unversity Clinic the Norwegian Radium Hospital, 1992). A tomographic technique was not available, and the study was performed as a pilot experiment as a regular scan on a standar dual-head gamma camera with a high energy collimator. FDG was delivered by air transportation from Copenhagen. The image quality was severely affected by collimator septal penetration and scattered photons, and no further experiments were performed.

2.7 PET in Norway

The very first medical imaging in Norway based on detection of annihilation photons from a positron emitter occurred as early as in 1972 (Prof. Arne Skretting and Magne Aas, MD, PhD, personal communication August 2009). After injection of the bone seeking radio-pharmaceutical ^{18}F-NaF produced at Institute for Energy Technology, Kjeller, Norway, one patient was imaged on a rectilinear scanner with a high-energy collimator. The equipment used was not suited for detection of the high energy 511 keV annihilation photons and no further experiments were conducted.

The very first FDG whole-body scan performed in Norway was in 1992 (Prof. Arne Skretting and Magne Aas, PhD, MD, personal communication January 2010). Tomographic



Figur 6. A: The cyclotron at Oslo University Hospital (PETtrace 6, GE Healthcare Technologies). **B:** The clean room with the hot-cells for FDG production (Stacked Synthesis Cell SB2S, right, and Dispensing Hot Cell, left, Van Gahlen by Siemens Healthcare). **C:** The PET/CT scanner at Oslo University Hospital, The Norwegian Radium Hospital (Biograph 16, Siemens Healthcare).

technique was not yet available, and the study was performed as a pilot experiment on a standar dual-head gamma camera with a high energy collimator (Figure 5). FDG was

delivered by air from Copenhagen, Denmark. The image resolution was poor and no further experiments were performed.

The first camera used for PET-scanning in Norway was a modified dual-head gamma camera with dedicated electronics that made coincidence detection possible (Adac Vertex Plus MCD, ADAC Laboratories Inc, Milpitas, CA, USA). Measurements of photons transmitted through the body from a Caesium-137 line source (transmission scan) were used to generate the tissue attenuation maps that were applied for attenuation correction. The camera was installed at the University Clinic the Norwegian Radium Hospital (DNR), Oslo, in May 1998. ^{18}F was supplied from the cyclotron at the Department of Physics, University of Oslo, and FDG was synthesized at The Institute for Energy Technology, Kjeller, Norway. From year 2000 gamma camera PET images were digitally fused with diagnostic CT images at a Hermes work station (Hermes Medical Solutions, Stockholm, Sweden) at DNR.

The very first PET imaging in Norway with a dedicated PET scanner took place on May 27th and 28th 2003. A mobile PET scanner was rented from International Health Care Group in the Netherlands as a part of a PET promotional action towards the Norwegian Health Authorities.

The first dedicated combined PET/CT scanner (Siemens Biograph 16, Siemens Medical Solutions USA, Inc., Knoxville, TN, USA) in Norway was installed at DNR in August 2005 (Figure 6). By the end of 2010 there were 5 PET/CT-scanner installations in Norway; 1 in Bergen and 4 in Oslo. In addition to these permanently installed PET/CT-scanners, a mobile PET/CT scanner is operating one day every second week at the University Hospital of Northern Norway, Tromsø.

3. THYROIDITIS AND THYROID NODULES

Normal FDG uptake, measured as SUV, differs between various organs (Bogsrud and Lowe 2006, Liu et al. 2010). As discussed in chapter 2.4, FDG-uptake is in general high in tissue with high glucose metabolism, such as the brain. The cardiac uptake varies with the energy substrate available. With high blood glucose and high insulin level the myocardial FDG uptake will be high. The FDG uptake in a normal thyroid gland is low, consistent with the assumption that free fatty acids are the main source of energy in thyroid cells (Field 1974, de Groot 1996). Increased FDG-uptake is not specific for cancer cells, but it is also seen in a number of benign conditions with increased glucose metabolism including in oxidation of brown fat, in a number of benign tumors (i.e. Warthin´s tumor of the parotid gland), in fibrous dysplasia, in uterine fibroma, and in various inflammatory conditions (Zhuang and Alavi 2002, Israel 2009, Liu et al. 2010).

Diffusely or focally increased FDG uptake in the thyroid gland caused by benign thyroid disease is a relatively frequent incidental finding in persons examined with whole-body PET for non-thyroidal diseases (Gordon et al. 1997, Yasuda et al. 1998, Cohen et al. 2001, Kang et al. 2003). The following sub-chapters provide a brief description of the most common benign thyroid diseases that might be associated with focally or diffusely increased FDG-uptake on PET imaging.

3.1 Thyroiditis

Thyroiditis is an acute or chronic inflammation of the thyroid gland. Thyroiditis may be asymptomatic or associated with thyroid swelling, tenderness or pain, and the thyroid function may be disturbed temporarily or permanently (Pearce et al. 2003). The different types of thyroiditis are listed in table 1.

Thyroiditis is potentially relevant to PET imaging as acute and chronic inflammation in general are known to show increased FDG uptake (Zhuang and Alavi 2002, Israel 2009, Liu et al. 2010). The most relevant thyroiditis for FDG PET imaging may thus be Hashimoto thyroiditis (chronic autoimmune thyroiditis, chronic lymphocytic thyroiditis). Hashimoto thyroiditis is the most common thyroiditis and the most common cause of hypothyroidism (Pearce et al. 2003). This type of thyroiditis is characterized by bilateral diffuse enlargement of the thyroid gland and high blood levels of thyroid peroxidase autoantibodies (TPOAb). On histology, the gland typically shows widespread lymphocytic infiltration, lymphoid germinal

Type	Etiology	Symptoms	Remarks
Hashimoto´s thyroiditis (chronic lymphocytic / autoimmune thyroiditis)	Autoimmune	No tenderness or pain	Chronic. Most common cause of hypothyroidism
Painful subabcute thyroiditis	Viral infection?	Tenderness	Destruction-induced thyrotoxicosis followed by hypothyroidism and returning to normal thyroid function after 4-6 months.
Painless sporadic thyroiditis (silent thyroiditis)	Autoimmune	Small, diffuse, very firm goiter	Thyrotoxicosis or hypothyroidism
Painless postpartum thyroiditis	Autoimmune	No tenderness or pain	Destruction-induced thyrotoxicosis followed by hypothyroidism and returning to normal thyroid function after 4-6 months.
Suppurative thyroiditis	Infection	Painful swelling, fever	Normal function. Thyrotoxicosis and hypothyroidism may occur.
Radiation thyroiditis	Radiation	Tenderness and pain	Destruction induced thyrotoxicosis frequently followed by hypothyroidism.
Drug induced thyroiditis	Side effects of a drug	No tenderness or pain	(litium, amiodarone, interferon alpha, interleukin-2, sunitinib) Hyperthyroidism possible, but normal thyroid function or hypothyroidism more common
Fibrous thyroiditis (Riedel´s thyroiditis)	Unclear	Patients may have neck discomfort	Chronic. Autoimmune or primarily a fibrotic disorder?

Table 1. Classification and characteristics of thyroiditis.

centers, and oncocytic metaplasia of the thyroid epithelium (reviewed in Lloyd et al. 2002). The disease may also be focal in an otherwise normal gland. Thus, Hashimoto´s thyroiditis is relevant to FDG PET not only in diffusely increased FDG uptake but also in focally increased uptake. Thyroiditis induced by anti-cancer drugs is also relevant to FDG PET imaging. An

example is thyroiditis induced by the tyrosin kinase inhibitor suntinib (Sutent®, Pfizer, New York, NY, USA) (Mannavola et al. 2007).

Sarcoidosis and tuberculousis in the thyroid gland are uncommon conditions potentially relevant to PET imaging as both active granulomatous inflammations and infections demonstrate high FDG uptake (Lloyd et al. 2002, Zhuang and Alavi 2002).

3.2 Graves´ disease

Graves' disease is the most common cause of hyperthyroidism. The disease has an autoimmune pathogenesis characterized by the presence of circulating long-acting thyroid stimulating autoantibodies against the thyrotropin receptor (TSH receptor autoantibody, TSHRAb) (reviewed by Davies 2000). Diffusely increased FDG uptake has been reported in patients with Graves´ disease supposedly caused by increased glucose uptake and phosporylation by hyperactive thyrocytes (Boerner et al. 1998, Chen et al. 2007).

3.3 Thyroid nodules

The epidemiology of thyroid nodules is reviewed in an article on thyroid nodules in The Lancet by Hegedüs (2004) and by Cooper et al. (2009) in the 2009 Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. A palpable thyroid nodule is found in approximately 1% of males and 5% of females in iodine-sufficient geographic areas and is more common in iodine deficient areas.

Palpable thyroid nodules are a diagnostic challenge because such nodules are relatively common but less than 5% will be malignant. The most common benign nodules are cysts and colloid nodules. The most common malignant nodules are papillary thyroid carcinoma. To rule out or confirm a suspicion for malignancy of a thyroid nodule, fine needle aspiration cytology (FNA), preferably ultrasound guided, is the diagnostic procedure of choice according to international recomendations (Cooper et al. 2009, Layfield et al. 2009). Even more challenging, however, is the incidental finding on ultrasound of a non-palpable thyroid nodule, which has a reported prevalence as high as 67% according to a review by Tan et al. (1997). The controversy about the need to evaluate these incidentally found small nodules in the absence of risk factors for thyroid cancer is reviewed by Iyer et al. (Iyer et al. 2010).

The identification of papillary thyroid carcinoma (PTC) by FNA has been reviewed by LiVolsi et al. (2004), by Baloch and LiVolsi (2008), and by Cibas (2010). FNA can identify PTC with a high degree of certainty. Minimally invasive follicular carcinoma, however, cannot be differentiated from follicular adenoma on cytologic specimens.

The diagnosis is based on histopathological demonstration of microscopic capsular invasion with or without infiltration of blood vessels (LiVolsi et al. 2004). The diagnosis of minimally invasive follicular carcinoma vs. follicular adenoma is difficult with low reproducibility even in histological samples studied by experienced pathologists (Hirokawa 2002). Diagnostic hemithyroidectomy is usually needed to be able to differentiate between minimally invasive follicular carcinomas and benign lesions. Kaplan (2000) has reviewed the evaluation of thyroid nodules by needle biopsy. It is a problem that as many as 70% of indeterminate lesions on FNA appear to be benign, and there is a need for improved diagnostic procedures to reduce the high number of futile diagnostic hemithyroidectomies.

Many benign as well as malignant thyroid nodules show increased FDG uptake on PET (Bloom et al. 1993, Cohen et al. 2001, Van den Bruel et al. 2002, Kang et al. 2003). Toxic adenomas are also reported to show high FDG uptake, likely caused by increased glucose metabolism of the hypermetabolic thyrocytes (Gianoukakis et al. 2003).

4. THYROID CANCER

The use of PET in patients with thyroid cancer is reviewed by a number of authors and recommendations are given in various international guidelines (Cooper et al. 2009, Kloos et al. 2009, Podoloff et al. 2009, Heston and Wahl 2010). The use of PET depends on the stage and type of thyroid cancer. This chapter gives a brief overview of the different types of thyroid cancer, prognosis, treatment and follow-up strategies.

4.1 Classification and prevalence

Thyroid cancer is a relatively rare cancer representing only about 2% of all cancers in the USA (Hundahl et al. 1998). Burke et al. (2005) found an annual incidence of 9 per 100 000 in women and 5 per 100 000 in men in a population based study in Olmsted County, Minnesota, from 1935 to 1999. It is notable that a large proportion of the population in Olmsted County is descended from Norwegian and Swedish immigrants. Microscopic papillary thyroid carcinomas (PTC) are, however, frequently detected incidentally on ultrasound and on autopsy with an incidence reported as high as 36% in a publication from Finland (Harach et al. 1985, Iyer et al. 2010). It is believed that most thyroid microcarcinomas do not progress into clinical cancer (Baudin et al. 1998).

Thyroid cancer epidemiology and prognostic variables, pathology, clinical features, and treatment have been studied or reviewed by a number of authors (Høie et al. 1988, Are and Shaha 2006, You et al. 2006, Pacini et al. 2010, Sipos and Mazzeferri 2010). Papillary (PTC), follicular (FTC) and anaplastic thyroid carcinomas (ATC) are thyroid follicular cell derived cancers. PTC and FTC, including oncocytic variant of FTC (Hürthle cell variant) are classified as differentiated thyroid carcinomas (DTC). PTC accounts for about 75% and FTC for about 10% of all thyroid cancers. The vast majority of PTC is classic PTC, while the follicular variant of PTC (FVPTC) accounts for about 10% of PTC. Less common variants of PTC are tall cell variant, columnar cell variant, solid or trabecular variant, clear-cell variant, diffuse sclerosing variant, and oncocytic variant (LiVolsli et al. 2002). The most common form of FTC is the minimally invasive variant. Less common forms of FTC are oncocytic (Hürthle) cell variant of FTC, clear cell variant, and the widely invasive FTC (Sobrinho Simões et al. 2002). The incidence of follicular cell derived thyroid carcinomas has increased about 2.4-fold the last 30 years, an increase only partly explained by improvements in diagnostic tools (Sipos and Mazzeferri 2010).

Medullary thyroid carcinomas (MTC) arise from the parafollicular calcitonin producing cells (C cells) located between the basal layer and the thyroid follicular cells. Medullary thyroid carcinoma accounts for about 4% of all thyroid cancer. Poorly differentiated (insular carcinoma) and anaplastic (undifferentiated) thyroid carcinoma together account for less than 5% of thyroid carcinomas.

Primary thyroid lymphoma accounts for 1-3% of all primary cancers in the thyroid gland (Pedersen and Pedersen 1996, Wang et al. 2005, Basu et al. 2009). Primary thyroid lymphoma is most frequently limited solely to the thyroid gland (stage IE). The risk of thyroid lymphoma is reported to be increased about 70-fold in patients with Hashimoto's thyroiditis.

Clinically detected metastases to the thyroid gland are rare. Carcinoma of the breast, cervix uteri, colon, esophagus, kidney, lung, neuroendocrine tumors, and squamous cell carcinoma have been reported to metastasize to the thyroid gland (Nakhjavani et al. 1997, Nixon et al. 2010).

4.2 Clinical manifestations

The most common clinical presentation of thyroid cancer is an asymptomatic, palpable, solitary thyroid nodule (Reinwein 1989 cited in Reiners 2005). Less commonly seen are enlarged neck lymph nodes, and even rarer are symptoms from bone metastases, hoarseness, dysphagia, cough or dyspnea. For anaplastic carcinoma and thyroid lymphoma, the typical clinical manifestation are a rapidly growing thyroid tumor (Pedersen and Pedersen 1996, Wang et al. 2005, Are and Shaha 2006, Cornett et al. 2007).

4.3 Prognosis

DTC is among the most curable of all human cancers with a 10 year survival over 98%, while anaplastic thyroid carcinoma is one of the most aggressive and lethal human cancers with most patients dying within a year from the primary diagnosis (Samaan et al. 1992, Mazzaferri et al. 1994, Hay et al. 2002, Are and Shaha 2006, Cornett et al. 2007, Hay et al. 2010). FVPTC seems to perform clinically similar to classic PTC, except for the diffuse follicular variant which seems to be more aggressive with more frequent pulmonary metastases (Lin and Bhattacharyya 2010). There are, however, a number of controversies related both to the diagnosis and to the prognosis of FVPTC (Sobrinho-Simões et al. 2010). More aggressive variants of PTC are tall cell variant, columnar cell variant, solid and

trabecular variant, clear-cell variant, diffuse sclerosing variant, and oncocytic variant (LiVolsi et al. 2004). Oncocytic variant of FTC and particularly widely invasive FTC are associated with less favorable prognosis compared to classic minimal invasive FTC (Sobrinho Simões 2004, Sipos and Mazzaferri 2010). It has recently been reported that a somatic point mutation in the gene for the B-type Raf kinase, $BRAF^{V600E}$ is associated with a more aggressive tumor and a higher risk of recurrence in patients with PTC (Kebebew et al. 2007, Lupi et al. 2007). Testing for this mutation may be useful for selecting initial therapy and for follow-up monitoring. The cell proliferation activity marker Ki-67 labeling index may also be used as a prognostic indicator in PTC to discriminate beween patients with expected disease free survival (Ki-67<1%) and patients with expected poor prognosis (Ki-67>3%) (Ito et al. 2010).

Even if the risk of death is very low, PTC and FTC are reported to recur in 13-30% of the patients according to studies of larger patient populations (Mazzaferri et al. 1992, Samaan 1994, Hay 2002, Hay 2010, Lin HW 2010). However, these studies were initiated or conducted more than 20 years back in time, before ultrasensitive Tg measurements, high resolution US, high resolution multi-slice CT, MRI and PET were available. One might speculate whether a large proportion of the recurrences reported in these early studies were in fact, residual disease that today would have been detected postoperatively, or represented metastatic disease that would have been detected during preoperative US.

FTC of minimal invasive type has an excellent prognosis, while widely invasive variants frequently develop distant metastases and have a more unfavorable prognosis (Heffess and Thompson 2001). FTC, with capsular invasion only, has such an excellent prognosis that it is questioned whether these tumors actually are cancers (van Heerden et al. 1992). The vascular invasion is the most important criterion for the diagnosis of minimal invasive FTC. Minimally invasive FTC with limited vascular invasion has a good prognosis, but develops distant metastases somewhat more frequently than PTC.

In general, unfavorable prognostic indicators for DTC are advanced age, large tumor, extrathyroidal extension, lymph node metastases in patients 45 years or older, vascular invasion, and distant metastases (Samaan et al. 1992, Mazzaferri et al. 1994, Hay et al. 2002, Bilimoria et al. 2007, Sipos and Mazzaferri 2010). The type of primary treatment is also important for the outcome. Residual or recurrent disease with increased FDG-uptake on PET seems to be an independent negative prognostic indicator (Wang et al. 2000, Robbins et al. 2006).

Papillary and medullary thyroid carcinomas frequently present an early spread to regional lymph nodes, while follicular cancers rarely do so (Witte et al. 2002, Grant et al. 2010, Sipos and Mazzaferri 2010). In fact, regional lymph node metastases are found in as many as 80% of patients with PTC at the time of diagnosis, but the prognosis is still excellent, at least in patients younger than 45 years of age (Samaan et al. 1992, Mazzaferri et al. 1994, Hay et al. 2002, Davies and Welch 2010, Grant 2010, Hay et al. 2010, Sipos 2010, Lin and Bhattacharyya 2010).

Anaplastic thyroid carcinoma is one of the most aggressive cancers in humans. The median survival for patients with localized disease is 8 months and only 3 months for patients with metastatic disease according to reviewes by Are and Shaha (2006), and by Cornett et al. (2007). Poorly differentiated (insular carcinoma) has a prognosis intermediate between DTC and anaplastic thyroid carcinoma (Sobrino Simões et al. 2004b, Sipos and Mazzaferri 2010).

Medullary thyroid carcinoma usually has an indolent course, even in patients with elevated calcitonin and minor residual disease (Boostrom et al. 2009, Pacini et al. 2010). However, the overall prognosis is less favourable than for DTC. Hundahl et al. reported a 98% 5-year survival for stage I and II, 40% 5-year survival for stage IV, and overall 10-year survival of 75% based on 2002 TNM classification (Hundahl et al. 1998). Boostrom et al. (2009) found 82% survival in stage IV patients with MTC based on the 2002 TNM staging criteria, vs. 46% with the 1997 criteria. They suggested that the 2002 TNM staging criteria for MTC are inadequate particularly for stage IV cancer.

4.4 Treatment

Surgery and thyroxine therapy are the primary treatment of DTC (Samaan et al. 1992, Mazzaferri et al. 1994, Hay et al. 2002, Bilimoria et al. 2007, Cooper et al. 2009, Grant et al. 2010, Hay et al. 2010). The initial surgical approach has the greatest impact on prognosis. Adjuvant radioiodine ablation is used primarily in patients with PTC and FTC with intermediate or high risk of recurrence and particularly in patients with high risk for thyroid cancer related death. The use of radioiodine ablation in low risk patients is highly controversial, and the issue is reviewed and discussed by a number of authors (Hay et al. 2002, Hay et al. 2008, Cooper 2009, Hay et al. 2010). In a recently published study on 215 children and adolescents with PTC treated at the Mayo Clinic during 1940 through 2008, the difference in outcome after surgery alone and after surgery followed by radioiodine ablation to the endpoints of locoregional recurrence and distant metastases were not statistically

significant (Hay et al. 2010). Ultrasound guided percutaneous ethanol injection seems to be a valuable treatment option for patients with limited cervical nodal metastases from papillary thyroid cancer (Lewis et al. 2002, Lim et al. 2007, Kim et al. 2008).

According to the Medullary thyroid cancer: management guidelines of the American Thyroid Association, and the recommendations of the National Comprehensive Cancer Network, surgery is the only curable treatment of medullary thyroid cancer (Kloos et al. 2009, Tuttle et al. 2010). Ethanol injection may be used not only in patients with DTC but possibly in patients with MTC as well.

Cytotoxic agents are used infrequently in DTC and MTC but may be used in selected patients with aggressive disease (Sherman 2010b). Targeted cancer therapies such as tyrosine kinase inhibitors used experimentally in aggressive, progressive, inoperable metastatic DTC and MTC are reviewed by Sherman (2010a) and by Chougnet et al. (2010). The use of external beam radiation (EBR) in patients with thyroid cancer has recently been reviewed by Powell et al. (2010). Data on the efficacy of EBR are conflicting (Powel et al. 2010, Biermann et al 2003). According to the American Thyroid Association management guidelines, in addition to the patients with anaplastic thyroid carcinoma, EBR should be considered only in patients who have locally advanced and unresectable neck disease (Cooper et al. 2009).

In patients with anaplastic thyroid carcinoma, external beam radiation and concomitant combined chemotherapy, followed by surgery if the tumor can be completely removed, constitute standard therapy (Are and Shaha 2006, Cornett et al. 2007). Based on a study of 25 patients with ATC, a research group at the Mayo Clinic in Rochester, MN, showed that an aggressive treatment with combined intensity-modulated radiation therapy (IMRT), radiosensitizing (docetaxel) and adjuvant chemotherapy (doxorubicin) improved outcomes in patients with stage IVA and IVB locoregionally confined ATC (Foote et al. 2010). Overall survival at 1 year was 70% and at 2 years was 60% compared to <20% at 1 year following conventional treatment.

4.5 Follow-up

Serum thyroglobulin (Tg) measurements performed either on thyroxine therapy or during TSH stimulation and neck ultrasound are the primary and standard follow-up procedures for DTC according to international recommendations (Mazzaferri et al. 2003, Torlontano et al. 2004, Schlumberger et al. 2004, Cooper et al. 2009). Not only the Tg level

itself but the trend over time should be considered as well (Huang et al. 2006). When suspicious or indeterminate neck lymph nodes are detected on US, US guided FNA and Tg measurement in washout fluid should be performed (Sigstad et al. 2007, Sipos 2009). When distant metastases are suspected, chest CT and MRI of liver, brain and bone marrow, whole body radioiodine scan complemented by SPECT/CT, and FDG PET will be appropriate choices for further treatment planning.

Calcitonin (Ct) and carcinoembryonic antigen (CEA) are sensitive tumor markers and should both be used to monitor MTC according to the Medullary thyroid cancer: management guidelines of the American Thyroid Association (Kloos et al. 2009). Neck ultrasound, chest CT and MR of the liver are standard imaging procedures in follow-up of patients with MTC.

The follow-up strategy for patients with anaplastic and other aggressive thyroid cancers has been reviewed by several authors (Are and Shaha 2006, Cornett et al. 2007). The strategy will depend on the extent of residual disease following the completion of primary treatment.

5. PET AND THE THYROID GLAND

5.1 The history

The very first publication on PET in patients with thyroid disease seems to be an article by Frey et al. (1985) on the use of Iodine-124 (^{124}I) PET. The first publication on FDG PET in patients with thyroid disease seems to be an article from the PET research group in Turku in Finland by Joensuu and Ahonen (1987). Although the article was a case report of three patients with metastatic thyroid cancer, a number of key observations were made: They reported findings of metastases that accumulated ^{131}I but not FDG, metastases that accumulated FDG but not ^{131}I, and metastases that accumulated both FDG and ^{131}I. One patient with iodine avid metastases to the lungs and bone was treated three times with radiodine and was given additional palliative external radiation to the lungs. The radioiodine uptake ceased in most of the metastases after the treatment. However, the disease progressed. A subsequent PET-scan showed increased FDG-uptake in the radioiodine negative metastases, but no uptake in some lung metastases that were still radioiodine positive. The authors suggested that metastases that retain FDG might be more aggressive than metastases that trap iodine. The PET studies were all performed with the patients on thyroxine. They considered, however, that thyroxine might have an effect on the FDG uptake in thyroid cancer. They concluded that: "*FDG scanning may be useful in the follow-up of patients with advanced thyroid carcinoma, because it may reveal metastases that do not accumulate ^{131}I that therefore should be treated with external radiotherapy or chemotherapy rather than with radioiodine.*"

The following year, Joensuu et al. (1988) reported on FDG uptake in the thyroid gland in 14 patients with benign or malignant thyroid tumors. They reported that the FDG uptake was intense in anaplastic thyroid carcinoma and in Hürthle (oncocytic) cell carcinoma, but only low to moderate in PTC. Furthermore, they found that FDG not only accumulated in malignant thyroid tumors but in some benign tumors as well. They concluded that the value of FDG scanning in the preoperative diagnosis of thyroid malignancy was limited. Despite the fact that the number of patients studied was low, their conclusions and suggestions have since been validated by other authors based on studies on larger patient populations.

5.2 Incidental finding of increased FDG uptake in the thyroid gland

5.2.1 *Diffusely increased FDG uptake*

As already discussed in chapter 3, the FDG uptake in a normal thyroid gland is expected to be low based on the assumption that free fatty acids are the main source of energy in thyroid cells (Field 1974, de Groot 1996). The assumption is supported indirectly by studies of cell cultures of thyrocytes (Hosaka et al. 1992, Haber et al. 1997). The glucose transporter protein GLUT-1 responsible for insulin independent increased FDG-uptake in most malignant tumors including thyroid cancers, is not detectable in normal thyroid cells. Other glucose transporter proteins are low in normal thyrocytes as well.

Diffusely increased FDG uptake in the thyroid gland has been reported as an incidental finding on whole body FDG PET in 1-3 % of the subjects examined with whole-body PET for non-thyroidal diseases or for cancer screening (Yasuda et al. 1998, Kang et al. 2003, Kim et al. 2005). Some authors state that diffusely increased FDG uptake in the thyroid gland may be a normal variant (Gordon et al. 1997). Physiological increased uptake in intrinsic laryngeal muscles may have been misinterpreted as thyroid uptake in studies performed using older PET systems without integrated CT. More recently most authors suggest that diffusely increased uptake is primarily associated with autoimmune thyroiditis (Yasuda et al. 1998, Kang et al. 2003, Kim et al. 2005). Diffusely increased FDG uptake in the thyroid gland has also been reported in patients with active Graves´ disease and in patients with subacute thyroiditis (Boerner et al. 1998, Kang et al. 2003).

When the work on this thesis started, only two studies on patients with diffusely increased FDG uptake in the thyroid gland had been published (Yasuda et al. 1998, Kang et al. 2003). During the data collection period a third study was published (Kim et al. 2005). In none of these studies was the FDG uptake quantified and correlated to TSH-levels or to the level of thyroid peroxidase autoantibody (TPOAb). In none of the studies was PET with integrated CT used. Furthermore, only 1 of these 3 studies included a control group of patients (Yasuda 1998).

5.2.2 *Focally increased FDG uptake*

Focally increased FDG uptake in the thyroid gland has been reported as an incidental finding on whole body FDG PET in 1-2% of patients examined for non-thyroidal cancer or in healthy individuals who participated in cancer screening programs (Cohen et al. 2001, Kang

et al. 2003). In the study by Cohen et al. (2001) 7 out 15 patients with an incidental finding of a thyroid nodule with increased FDG uptake on PET had a thyroid malignancy, while in the study by Kang et al. (2003) 4 out of 15 patients had a thyroid malignancy. Papillary thyroid cancer was the most frequently reported form of malignancy. There have also been some case reports on hypermetabolic nodules being solitary toxic adenomas (Gianoukakis 2003). However, it has not been clarified whether or not quantification of the FDG uptake measured as standardized uptake value (SUV) can be used to differentiate between benign and malignant lesions (Bloom et al. 1993, Umeatsu et al. 1998, Cohen et al. 2001, Kang et al. 2003, Kresnik et al. 2003).

5.3 FDG PET in patients with differentiated thyroid cancer

5.3.1 *Radioiodine negative, Tg positive patients*

Several authors have conducted meta-analysis of the value of FDG PET in radioiodine negative patients with DTC and a number of authors have reviewed the role of PET in patients with thyroid cancer (Leboulleux et al. 2007, Robbins and Larson 2008, Dong et al. 2009, Chao 2010, Heston and Wahl 2010, Ma et al. 2010, Miller et al. 2010). Most clinical research on FDG PET and the thyroid gland has been performed on DTC patients with a negative post-therapy radioiodine scan, persistently elevated or rising blood levels of thyroglobulin (Tg), and negative thyroglobulin autoantibodies (TgAb). This scenario remains the main indication of FDG PET in thyroid cancer according to the most recent American Thyroid Association management guidelines (Cooper et al. 2009). Neck ultrasound (US), US guided FNA, measurements of Tg in blood and in wash-out fluid from lymph nodes during FNA, as well as chest CT are the methods of choice in the initial work-up of patients with suspected residual or recurrent DTC (Sigstad et al. 2007, Leboulleux et al. 2007, reviewed in Francis and Schlumberger 2008, Grant et al. 2008, Cooper et al. 2009, reviewed in Sipos 2009). FDG PET is an expensive imaging procedure. The procedure seems to be most useful in patients with aggressive residual or recurrent DTC when conventional imaging is negative or indeterminate, or when there is an incongruity between a high Tg blood level and more modest findings on conventional imaging (Leboulleux et al. 2007, Grant et al. 2008, Robbins and Larson al. 2008, Cooper et al. 2009).

The neck is the most frequent site of residual or recurrent DTC and neck US seems to be the single most important imaging procedure (Grant et al. 2008, Cooper et al. 2009). Patients with persistent high blood level of Tg have frequently been through multiple extensive neck surgeries with the result of scarring and modified anatomy. CT, MRI and US

are often unable to discriminate between malignant foci and scar tissue. Localized FDG uptake in the neck can help to direct US guided FNA, help the surgeon to choose the most appropriate surgical procedure or to choose between surgery and ultrasound guided ethanol injection. Furthermore, FDG PET can be used as a guide for radiation therapy planning in patients with aggressive residual neck disease.

Grant et al. (2008) demonstrated that FDG PET added valuable information to high resolution neck ultrasound in only 3 out of 30 patients who underwent surgical re-exploration after FDG PET scanning. A limitation of their study was that the Tg levels in the patients included were relatively low, indicating a small tumor burden. FDG PET sensitivity seems to correlate with thyroglobulin blood level. The sensitivity is low in patients with Tg level <10 μg/l (Leboulleux et al. 2007). However, a short Tg doubling time is probably important as well. FDG PET is recommended primarily in patients with stimulated Tg>10 μg/l and particularly if Tg shows an increasing trend. Not only will the volume of the metastases affect the FDG-uptake, but also the location and degree of differentiation.

An additional potential limitation of the study by Grant et al. (20008) was that almost all of the patients were on thyroxine suppressive therapy at the time of the PET scan. Thyroxine withdrawal or the use of rhTSH (thyrotrophin alfa; Thyrogen®, Genzyme, Cambridge, MA, USA) is by many authors a recommended pretreatment for FDG PET in patients with DTC (Moog et al. 2000, Petrich et al. 2002, van Tool et al. 2002, Chin et al. 2004, Deichen 2004). However, the clinical benefit of this marginally improved sensitivity has not been proven (Cooper et al. 2009, Leboulleux et al. 2009).

Feine et al. (1995) introduced the term “flip flop” to describe the pattern of either ^{131}I or FDG uptake in metastases from thyroid cancer, when DTC dedifferentiates the ability to concentrate iodine declines and the ability to concentrate FDG increases. However, as reported by Jonesuu and Ahonen (1987), some metastases accumulated both FDG and ^{131}I. Our own limited experience indicates that the response to radioiodine treatment for tumors with both high FDG and high radioiodine uptake is very good (Figure 8). In addition to locating residual and recurrent disease, there is good evidence that increased FDG uptake on PET is an independent prognostic indicator for increased risk of cancer-specific death in patients with advanced PTC and FTC (Wang et al. 2000, Robbins et al. 2006). Wang et al. (2000) studied 125 high-risk patients with DTC with known residual or recurrent disease.

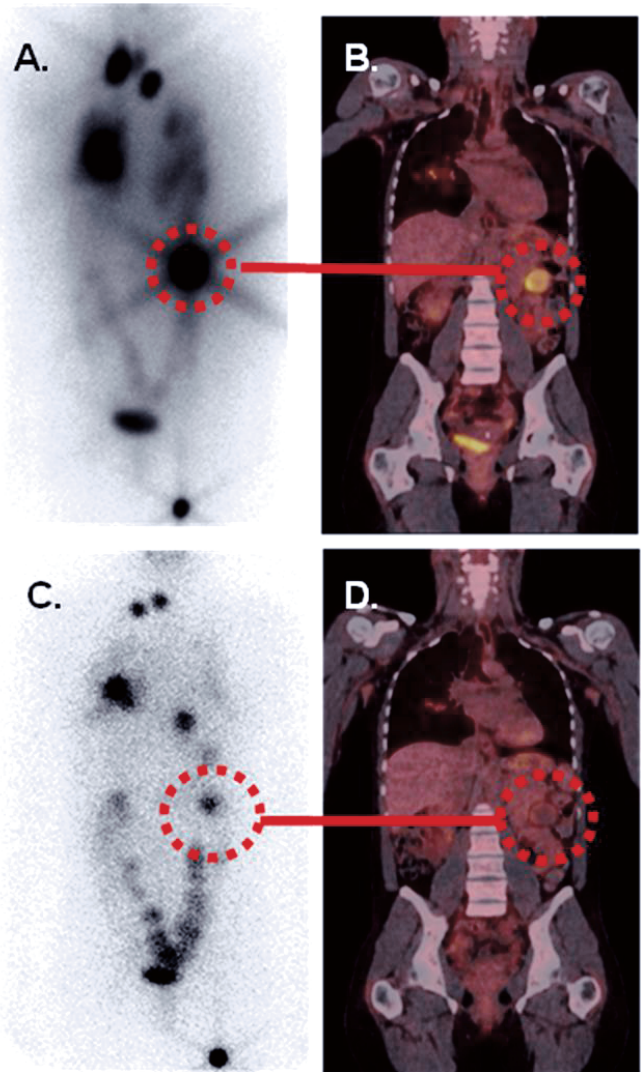


Figure 7. Young female with metastatic PTC. FDG PET/CT was performed on the same day but before a therapeutic radioiodine dosage was given after stimulation with recombinant human TSH (rhTSH). **A:** Planar post-therapy radioiodine scan: intense radioiodine uptake in numerous metastases in the neck, lungs, left kidney, and in the left thigh. Physiological intestinal accumulation and urinary tract excretion of FDG. **B:** Coronal FDG PET/CT image: the metastases to the the left kidney (encircled), neck, most of the lung metastases, and the metastasis to left thigh showed intense uptake of both radioiodine and FDG. **C:** Second planar post-therapy scan 6 months later. The radioiodine uptake in all the radioiodine avid lesions has decreased. **D:** Coronal FDG PET/CT image before the second therapeutic radioiodine dosage. All lesions with previously intense uptake of both radioiodine and FDG showed nearly resolved uptake. The lesion in the left kidney is encircled in the figure. Intense uptake of both FDG and radioiodine may predict good response to radioiodine.

Fourteen of the patients died during a 41 months follow-up period. The authors demonstrated reduced survival in patients with FDG avid tumors. Survival was significantly correlated with quantified uptake (maximum standard uptake value, SUV), suggesting that tumors with the highest metabolic activity have the most potential for rapid growth. Survival was further related directly to the total volume of FDG avid tumors. The larger the volume, the shorter was the survival time. Multivariate analysis demonstrated that the single strongest predictor of survival was the FDG avid tumor volume.

Robbins et al. (2006) studied the prognostic value of FDG PET in 400 patients with residual or recurrent DTC. Multivariate analysis showed that only age, the FDG uptake measured as maximum standardized uptake value (SUVmax), and the number of FDG avid lesions correlated with survival. They found that a positive FDG PET, by itself, was associated with a 7.3-fold increased risk of thyroid cancer specific death.

Treatment with radioactive iodine has been shown to reduce recurrence and mortality for high-risk patients with DTC (Mazzaferri et al. 1994, Hay et al. 2002, Hay et al. 2010). Survival is higher in patients with metastases that concentrate radioiodine than in patients with metastases that do not concentrate iodine. Wang et al. (2001) retrospectively compared the tumor volume with the intensity of the FDG uptake in 25 patients with metastatic DTC both before and on average 12.9 months after treatment with ^{131}I. The authors concluded that high-dose ^{131}I therapy had little or no effect on the size of FDG avid metastases from thyroid cancer.

Oncocytic (Hürthle) cell carcinoma is an uncommon variant of FTC and an even less common variant of PTC. The tumor type may seem to be somewhat more aggressive than DTC in general. Radioiodine ablation improves outcome in high-risk patients with DTC. However, oncocytic cell carcinomas frequently show low radioiodine accumulation, and radioiodine ablation is thus not an option in these patients. Several studies have shown that oncocytic cell carcinomas show intense FDG-uptake on PET indicating that patients with this variant of thyroid cancer might undergo FDG PET as part of their initial staging and periodically thereafter to search for occult recurrence when circulating Tg is persistently elevated (Plotkin et al. 2002, Lowe et al. 2003, Pryma et al. 2006).

5.3.2 *Patients with DTC and circulating thyroglobulin autoantibodies*

Follow-up of patients with DTC and circulating TgAb represents a particular challenge. The presence of circulating TgAb will interfere in the laboratory Tg-assays,

making the Tg measurements unreliable. Spencer and LoPresti (2008) have reviewed the insight of the laboratory technology in measuring Tg and TgAb. Tg may be falsely increased or decreased depending on the laboratory method used to quantify Tg (Spencer et al. 1998, Chung et al. 2002, Spencer 2004, Spencer et al. 2005). Immunometric assays, the most commonly used laboratory method, are prone to underestimate Tg. In fact, when using immunometric Tg-assays, Tg is commonly undetectable in TgAb-positive patients (false-negative Tg) despite significant leakage of Tg from residual thyroid tissue. In addition, the Tg response to TSH stimulation is commonly blunted or completely absent. Consequently, Tg measurements require adjunctive TgAb measurements to assess for possible analytic interference. It is important that referring physicians are aware of how the presence of TgAb may influence Tg measurements.

The problem with TgAb is common in patients with DTC. Spencer et al. (1998) found increased TgAb in 25% of patients with DTC, compared with a 10% incidence in the general United States population (Hollowell et al. 2002). After successful total thyroidectomy with or without radioiodine treatment or after surgical removal of metastatic lymph nodes, TgAb levels decrease progressively and typically become negative within a few years given the absence of any residual thyroid tissue (Chiovato et al. 2003, Gorges 2005). A number of studies have shown that persistently increased TgAb and particularly increasing levels indicate residual or metastatic disease (Spencer et al. 1998, Chung et al. 2002, Spencer et al. 2008, Pedrazzini et al. 2009). TgAb measured serially using the same laboratory method may be used as a surrogate tumor marker in TgAb-positive patients (Spencer et al. 1998, Spencer et al. 2005).

The value of FDG PET in radioiodine negative DTC patients with circulating TgAb was not studied. It is an open question whether FDG avid metastatic lesions on PET in these patients may have the same prognostic implication as reported for radioiodine-negative, Tg-positive DTC patients without increased TgAb.

5.4 FDG PET in patients with medullary thyroid carcinoma

In patients with MTC, FDG PET has been compared to conventional imaging and to other nuclear medicine procedures in a number of studies (Brandt-Mainz et al. 2000, Diehl et al. 2001, Szakáll et al. 2002, de Groot et al. 2004). These studies indicate that FDG PET may be a useful complement to neck ultrasound, CT of the chest and abdomen, and MRI of the liver and bone marrow in patients with suspected residual or recurrent disease based on

elevated calcitonin levels after primary surgery. All of these early studies concluded that FDG PET is a promising tool in the management of patients with MTC, locating more lesions compared to other imaging modalities. The more aggressive the MTC, the better FDG PET performed compared to other imaging modalities.

As already discussed discussed, there is strong evidence that increased FDG uptake on PET is an independent prognostic indicator for increased risk of progressive disease and cancer-specific death in patients with advanced DTC (Wang et al. 2000, Robbins et al. 2006). However, no studies have been published on the potential prognostic value of FDG PET in patients with MTC.

5.5 FDG PET in patients with anaplastic thyroid carcinoma

To our knowledge the use of ^{18}F-FDG PET in patients with ATC has not been systematically studied and only a few pertinent case reports have been published (Jadvar and Fischman 1999, Kresnik et al. 2003, Poppe et al. 2004). A highly malignant cancer like ATC is expected to show intensely increased FDG-uptake and FDG PET might thus be useful to determine the extent of disease, to differentiate between scar and residual disease after completion of chemoradiation, and for early detection of recurrent disease. If the FDG uptake in ATC is as high as might be expected, FDG PET/CT may be used to determine the target volume in radiation therapy planning and FDG PET may be used for interim prediction of final treatment effect. However, because of insufficient data on FDG PET in patients with ATC, routine use of FDG PET has not been established and its utility in staging and follow-up of this patient group has been debated.

6. AIMS OF THE THESIS

The aim of this thesis is to contribute to the field of FDG PET in benign and malignant diseases of the thyroid gland. This is attempted by exploring:

1) the prevalence and clinical significance of an incidental finding of diffusely increased FDG-uptake in the thyroid gland on whole-body FDG PET in a large group of patients with cancer of non-thyroid origin (paper I)
2) the potential value of SUV-measurements in differentiation between benign and malignant thyroid nodules with increased FDG-uptake found incidentally on whole-body FDG PET (paper II)
3) the potential prognostic value of FDG PET in post-treatment radioiodine negative patients with DTC with elevated circulating TgAb (paper III)
4) the potential value of FDG PET in staging, restaging, detection of residual or recurrent disease and prognostification in patients with anaplastic thyroid carcinoma (paper IV)
5) the potential prognostic value of FDG PET in patients with medullary thyroid carcinoma (paper V)

7. MATERIALS AND METHODS

7.1 The patients

The studied subjects were all patients who had been examined, treated or both at the Mayo Clinic, Rochester, MN, USA. The vast majority of the patients were Caucasian American citizens. A large proportion of the population in Minnesota and neighboring states are descendants from Scandinavian immigrants. There is no overlap of subjects included in the individual studies.

7.2 The Institutional Review Board

For all studies a Minimal Risk Protocol was prepared, and all these protocols were approved by the Mayo Foundation Institutional Review Board (IRB). All included patients had consented to have their clinical data used for research purposes.

7.3 PET and PET/CT

The ^{18}F was produced at the Mayo Clinic using a PETtrace Cyclotron (GE Medical Systems, Inc, Milwaukee, Wisconsin, USA), and the FDG was synthesized with the standard automated Hamacher method. All patients had been fasting for at least 6 hours before injection of FDG. Blood glucose was measured just before FDG injection to ensure that it was low enough. The standard procedure in the Mayo Clinic is to reschedule the scan for patients with a blood glucose value greater than 11 mmol/l (200 mg/dl) if achievable.

The PET imaging was performed on a GE Advance PET scanner (GE Medical Systems) or on an integrated PET/CT scanner (Discovery LS; GE Medical Systems). PET images from the base of the skull to the proximal thighs were obtained between 1 and 1.5 h after intravenous injection of 740 MBq of FDG, applying a two-dimensional acquisition mode with 5-min duration per bed position. Emission data were corrected for scatter, random events, and dead time losses using the manufacturer's software. Full width at half maximum of the Gaussian smoothing filter applied in reconstruction was 8 mm. The image pixel size was 4.25 mm, displayed in a 128×128 array. These collected data were reconstructed using the default iterative reconstruction applying two iterations and 28 subsets.

For the integrated PET/CT scan, nonenhanced CT images were acquired with a helical mode with a detector-row configuration of 4×5 mm, a high-speed mode (pitch 6:1), a gantry rotation of 0.8 s, and a table speed of 30 mm per gantry rotation, 140 kVp, and 120 mA. The 5-mm-thick transaxial CT images were reconstructed at 4.25-mm intervals (transaxial) for fusion with the transaxial PET images.

The PET or PET/CT studies and written reports for all included patients were retrospectively reviewed by two experienced PET readers (Trond Velde Bogsrud and Dimitrios Karantanis). In case of discrepancy, a third experienced PET reader reviewed the study and a consensus was reached. The PET or PET/CT interpretations were based on the study of maximum intensity projection images, and on transaxial, coronal, and sagittal reconstructed slices. PET or PET/CT images were always compared side by side with contrast-enhanced CT images, and, when available, with other relevant imaging procedures including written reports from US examinations of the neck. The PET or PET/CT findings were compared against the overall findings on US, CT, MRI, results of blood analyses, cytological and histopathological examination, and clinical examinations at the time of the PET scan and on follow-up. When in doubt about a finding on CT or MRI, a radiologist or an experienced radiology resident was consulted. All laboratory testing of blood samples, cytology and histopathology were perfomed at Mayo Medical Laboratories. The FDG uptake was quantified as maximum standardized uptake value (SUVmax) based on body weight. A circular region of interest with a fixed diameter of 1.5 cm was placed over the visual hottest part of the hypermetabolic lesions and the uptake was automatically quantified.

8. SUMMARY OF THE PAPERS

8.1 Summary of paper I:

Clinical Significance of Diffusely Increased ^{18}F-FDG Uptake in the Thyroid Gland.

All patients with diffuse high FDG uptake in the thyroid gland as an incidental finding on whole-body PET examined at the Mayo Clinic, Rochester, MN, USA, from November 2004 through June 2006 were prospectively enrolled. Patients with a history of thyroid cancer were excluded. The FDG uptake was quantified as maximum standardized uptake value (SUVmax). The patients were followed for any subsequent clinical, ultrasonographic or laboratory evaluation of thyroid status. Clinical information was reviewed retrospectively for any past history of thyroid disease. The group of patients with diffuse high FDG uptake was compared to a control group of patients with no thyroid uptake matched for age and sex. This group was included to determine the proportion of benign thyroid disease in patients with no thyroid FDG uptake.

In the study period, 4732 patients without a history of thyroid cancer underwent whole body FDG PET/CT on an oncologic indication. Diffusely increased thyroid uptake was found in 138 patients (3%). Four of these patients denied access to their data for research purposes and one patient received no care other than the PET/CT scan at the Mayo Clinic. Thus, 133 patients with available data were included.

Thirty-eight of the 133 patients (29%) did not have any further work-up for thyroid disease, most likely because of the serious nature of their primary cancer.

Sixty-three of the 133 patients (47%) carried the diagnosis of hypothyroidism, autoimmune thyroiditis or both before undergoing the PET/CT scan, and 56 of those patients (89%) were already receiving replacement therapy with thyroxine.

Thirty-two of the 133 patients (24%) had no prior history of thyroid disease and were examined for thyroid disease after the PET/CT scan. Nineteen of those 32 patients had either subclinical or overt hypothyroidism. On the basis of the laboratory results, thyroxine replacement therapy was instituted in 12 of those 19 patients. In the remaining 13 patients, either TSH was normal or US did not show any sign of thyroiditis and these patients were considered to be without any thyroid disease.

There was no statistically significant correlation between SUVmax and the TSH-level (P=0.089), or between SUVmax and the level of thyroid peroxidase autoantibodies (TPOAb) (P=0.675).

In the control group of patients without diffusely increased FDG uptake in the thyroid gland, only 13 out of 133 patients (9.8%) had a history of hypothyroidism or autoimmune thyroiditis.

Conclusion: **An incidental finding of diffusely increased FDG uptake in the thyroid gland on whole-body PET/CT was associated with chronic autoimmune thyroiditis with or without the presence of hypothyroidism. The intensity of the FDG uptake was neither suggestive of the degree of the hypothyroidism nor correlative with the level of TPOAb.**

8.2 Summary of paper II:

The Value of Quantifying ^{18}F-FDG Uptake in Thyroid Nodules Found Incidentally on Whole-body PET/CT.

All patients with focal high FDG uptake in the thyroid gland as an incidental finding on whole-body PET/CT examinations at the Mayo Clinic, Rochester, MN, USA, from May 2003 through May 2006 were prospectively enrolled. Patients with a history of thyroid cancer were excluded. The FDG uptake was quantified as maximum standardized uptake value (SUVmax). The size of the lesions was measured as the largest transaxial diameter (cm) on transaxial PET/CT images based on the FDG-uptake.

Incidentally detected focal high uptake in the thyroid gland was found in 79 out of 7347 (1%) consecutive patients. Two of the patients denied access to their data for research purposes, and 77 patients were included in the study.

Based on the results from previously published studies, the finding of a FDG hot nodule was always reported as a possible primary or secondary thyroid cancer and an ultrasound evaluation with possible fine-needle aspiration cytology (FNA) was recommended for further follow-up. The referring physician decided which of the patients with the finding of an incidental hot nodule should have a follow-up procedure.

An adequate follow-up was performed in 48 of the 77 patients (62%). Probably because of advanced primary cancer with extensive metastases, poor prognosis or advanced

age, the remaining 29 patients had no follow-up of the thyroid finding despite the recommendation in the PET-report. US without concomitant FNA was defined as adequate follow-up when the radiologist determined the finding to be conclusive. Otherwise US-guided fine needle cytology or biopsy, or histopathology if the patient underwent surgery, were defined as adequate follow-up.

A benign etiology was confirmed in 31 out the 48 patients (65%) with adequate follow-up. In 15 patients (31%) malignant etiology was confirmed. In addition, in two patients cytology was suspicious for Hürthle cell carcinoma and follicular thyroid carcinoma, respectively, but no final histologic confirmation was performed. Thus, 17 out of 48 patients (35%) had malignancy confirmed or findings on cytology highly suspicious for malignancy.

We did not find any statistically significant difference between the SUVmax for the malignant, the benign, and the no follow-up group. Based on ROC analysis the best cut-point for SUVmax between benign and malignant lesions was 6, which resulted in a sensitivity of 69% and a specificity of 61% in our dataset. Thus the SUVmax does not discriminate any better than by random chance.

Conclusion: **In our group of patients with focal high uptake in the thyroid gland as an incidental finding on whole body FDG PET/CT, SUVmax did not discriminate between benign and malignant lesions. Regardless of the SUVmax value, an incidental finding of a focal high uptake in the thyroid gland should be reported as a possible primary or secondary thyroid cancer and an ultrasound evaluation with possible FNA is recommended for further follow-up.**

8.3 Summary of paper III:

Prognostic Value of ^{18}F-Fluorodeoxyglucose Positron Emission Tomography in Patients With Differentiated Thyroid Carcinoma and Circulating Antithyroglobulin Autoantibodies.

We searched the patient database at Mayo Clinic, Rochester, Minnesota, USA, from August 2001 through December 15, 2004 for the records of all patients with DTC who were referred for FDG PET. During the study period, 235 FDG PET scans were performed on 185 patients with DTC. Eighteen of these patients (9.7%) had an increased blood level of TgAb at the time of the PET-scan. Follow-up information was unavailable for 1 patient, who

was not included in further analysis. Thus, 17 patients were included in the study. Combined PET/CT was performed in 3 patients, and PET-only was performed in 14 patients.

The PET or PET/CT studies and written reports for all included patients were retrospectively reviewed. The PET findings were compared against the overall findings on US, CT, MR, cytology, histopathologic examination, and clinical examination to determine the status of the disease. The patient's blood levels of Tg, TgAb, and TSH at the time of PET and during follow-up were also noted. Further, follow-up information including findings on clinical examination, diagnostic imaging, and cytologic and histologic results, were collected through December 19, 2009.

All patients had total thyroidectomy with central neck compartment lymph node dissection. Most patients had had unilateral modified lateral lymph node dissection, and most patients had surgery more than once. All patients except 1 had one or more radioiodine ablation procedures. All patients except two were, at least once, found to be Tg negative / TgAb positive during TSH-stimulation or after thyroxine withdrawal in connection with radioiodine therapy or a diagnostic radioiodine whole-body scan.

In 12 patients, residual or recurrent disease was confirmed to be present at the time of PET. PET results were true-positive in 10 of these 12 patients and false-negative in 2. In 8 of the 12 patients with confirmed residual or recurrent disease, the increased TgAb level persisted during the follow-up period. In all of these 8 patients the disease progressed, and 3 of these patients died of thyroid cancer during the follow-up period. In 2 of the 12 patients with confirmed residual or recurrent disease, TgAb disappeared 6 and 4 months after reoperation, respectively. Both patients had further disease recurrences and slow progression, but TgAb levels remained negative. Two of the 12 patients with limited recurrent neck node disease received ethanol injections as treatment for metastatic neck lymph nodes, and TgAb levels decreased in both.

In 5 of the 17 patients, no residual or recurrent disease was found either at the time of study inclusion or on follow-up. FDG PET was true-negative in all 5 patients. In 4 of these 5 patients, TgAb level went from positive to negative spontaneously within a median time of 18 months (range, 4-36 months). In one patient the increased TgAb level persisted without any evidence of residual or recurrent disease on follow-up for 68 months.

Conclusion: FDG PET may seem to have the same prognostic value in radioiodine negative patients with DTC and persistent TgAb as those reported for TgAb

negative, radioiodine negative DTC patients with increased Tg levels. A negative FDG PET result was associated with the absence of active disease and disappearing TgAb over time. FDG-avid residual lesions were associated with aggressive disease, poor outcome and persistently increased TgAb levels. Persistently increased blood levels of TgAb may be associated not only with residual disease, but may also indicate unfavorable prognosis.

8.4 Summary of paper IV:

^{18}F-FDG PET in the Management of Patients with Anaplastic Thyroid Carcinoma.

All patients with confirmed anaplastic thyroid carcinoma imaged with FDG PET (1 patient) or PET/CT (15 patients) at the Mayo Clinic, Rochester, MN, USA, from August 2001 through March 2007 were studied with a further follow-up period through October 2007. The intensity of the FDG-uptake was measured as maximum standardized uptake value (SUV_{max}) for all primary tumors and all recurrences, for the regional and distant lymph node metastases with the highest FDG uptake, for the lung metastases with transaxial diameter >1 cm with the highest FDG uptake, as well as for other lesions suspicious for distant metastases.

The PET findings were compared to the overall findings on other imaging modalities (US, CT, MRI, plain films and bone scan) lesion by lesion. Primary tumors, recurrent disease, and lymph node metastases were confirmed by cytology and when surgery was performed by histology. According to this comparison, the PET findings were characterized as true-positive, false-positive, true-negative, and false-negative. Furthermore, any change in the treatment plans as a direct result of the PET findings as documented in the clinical notes was recorded.

PET showed intense FDG-uptake in all primary tumors, in all confirmed recurrent tumors, in all confirmed lymph node metastases, in all confirmed bone metastases and in a confirmed single metastasis to an adrenal gland. In three of the five patients with lung metastases the lesions were too small (<3 mm) to be characterized by PET.

PET was false-positive in two patients: a confirmed inflammatory jugular chain lymph node in one patient and a confirmed wound infection in another showed increased FDG uptake erroneously interpreted as suspicious for residual disease.

All the patients who died during the follow-up period had PET positive metastatic disease after completion of primary treatment. All 3 patients without evidence of residual disease by the end of the follow-up period were PET negative after completion of treatment.

In 4 patients there was a major change in the planned treatment as a result of the PET findings, and in an additional four patients the clinical records indicated a direct supportive impact of the PET findings on the patient management. Thus, in 8 of the 16 patients the medical records reported an impact of the PET findings on the clinical management of the patients.

Conclusion: ATC demonstrated intense uptake on FDG PET images. In 8 of the 16 patients the medical records reported an impact of the PET findings on the clinical management of the patients. A negative PET-scan after completion of therapy may be indicative of extended survival. PET may improve disease detection and has an impact on patient management in patients with ATC relative to other imaging modalities.

8.5 Summary of paper V:

The Prognostic Value of 2-Deoxy-2-[18F]Fluoro-D-Glucose Positron Emission Tomography in Patients With Suspected Residual or Recurrent Medullary Thyroid Carcinoma.

The study included all patients with MTC examined with FDG PET or PET/CT at the Mayo Clinic, Rochester, MN, USA, from October 1999 through March 2008. Twenty-nine patients with MTC were included. All patients had had a total thyroidectomy and central neck compartment lymph node dissection performed. All patients except one had had one or several lateral neck dissections performed on one or both sides. Residual or recurrent disease was subsequently suspected on the basis of elevated blood levels of CEA, non-stimulated calcitonin, or both.

The PET or PET/CT studies and written reports for all included patients were retrospectively reviewed. The PET findings were compared against the overall findings on US, CT, MR, cytology, histopathologic examination, and clinical examination to determine the status of the disease. According to these comparisons, the PET findings for each patient were characterized as true-positive, false-positive, true-negative, or false-negative. The blood levels of calcitonin and CEA were also noted. Furthermore, follow-up information including

findings on clinical examination, diagnostic imaging, blood levels of calcitonin and CEA and cytologic and histologic results were collected through March 2008.

PET was positive in 14 patients: true-positive in 13 and false-positive in one. PET was negative in 15 patients; true negative in 14 and false-negative in one.

Follow-up information was available for 12 out of 14 patients with confirmed clinical residual or recurrent disease with either true-positive (13 patients) or false-negative (1 patient) PET findings. The average (SD) follow-up time for these FDG PET positive patients was 37 (25) months (range, 1-86 months). During this follow-up period, 6 of these patients died from metastatic disease, 4 had disease progression, while 1 was in stable condition with a constant high calcitonin level of 3400 pmol/L (12000 pg/mL).

Follow-up information was available for 12 of 15 patients without evidence of clinical residual or recurrent disease with either true-negative (14 patients) or false-positive (1 patient) PET findings. The average (SD) follow-up time for these FDG PET negative patients was 44 (25) months (range, 3-94 months). Eleven of these patients had no evidence of disease during follow-up. A metastatic neck lymph node was detected in one patient after 3 years. After the metastatic lymph node was surgically removed, there was no further evidence of clinical disease during a further follow-up period of 34 months.

The calcitonin blood levels for patients with confirmed positive findings on any imaging study [median 2103 pmol/L (7250 pg/mL); range 226-14692 pmol/L (780-50662 pg/mL)] were statistical significantly higher than for patients with negative findings [median 275 pmol/L (948 pg/mL); range 1.3-1595 pmol/L (4.4-5500 pg/mL)] (P=0.003).

The CEA blood levels for patients with confirmed positive findings on any imaging study (median 13.8 µg/L; range 3.0-577 µg/L) were not statistically different from those with negative findings (median, 8.0 µg/L; range 0.5-177 µg/L) (P=0.31).

The calcitonin doubling time (median 10 months; range 3-42 months) was significantly shorter in patients with positive findings on any imaging study compared to patients with negative findings (median 62 months; range 11-infinity) (P<0.001). Sufficient data to calculate CEA doubling times were not available.

Conclusion: FDG PET had a high prognostic value in patients with residual or recurrent MTC. Patients with elevated calcitonin but negative FDG PET had indolent disease, while patients with positive FDG PET had more aggressive disease with a less favorable prognosis.

9. DISCUSSION

9.1 Methodological and technical considerations

9.1.1 *PET, PET/CT with low-dose CT or PET/CT with contrast enhanced CT*

In the studies published in paper I and II all the patients were examined with a PET scanner with integrated CT (PET/CT). In the study published in paper III, 3 out of 17 patients were examined with PET/CT. In the study published in paper IV, 14 out of 16 patients were examined with PET/CT. In the study published in paper IV, 17 out of 29 patients were examined with PET/CT. The remaining patients in these studies were examined with PET only. No oral or intravenous CT contrast agents were used for the exams. The low dose CT was performed during normal breathing and used for attenuation correction and anatomical correlation. PET or PET/CT images were always compared side-by-side with a previously performed contrast-enhanced CT, and when available, with other relevant imaging procedures including written reports from neck US examinations.

According to a meta-analysis performed by Dong et al. (2009) for most studies in which the performance of PET has been evaluated in patients with thyroid cancer the PET examinations have been performed with PET without integrated CT. The main advantage of the integration of CT in PET scanners is faster and more accurate correction of tissue attenuation of photons compared to correction based radionuclide transmission scans used in the past. For these purposes low-dose CT without contrast enhancement was used. PET/CT image fusion results in more accurate anatomic lesion characterization compared to PET-only as well as improved diagnostic accuracy in most cancers including residual and recurrent thyroid cancer (Beyer et al. 2000, Kluetz et al. 2000, Zoller et al. 2007, Palmedo et al. 2006, Nahas et al. 2006, Shammas et al. 2007, Miles 2008).

Nahas et al. (2006) demonstrated that FDG PET/CT provided additional information compared to conventional imaging that directly influenced the patient management in 22 of 33 patients (67%) with papillary thyroid carcinoma.

PET scanners have limited spatial resolution and it is well known that tiny lung metastases <5 mm are too small to be characterized by PET (Dietlein et al. 1997, Hung et al. 2003, Palmedo et al. 2006). However, lesions too small to be characterized by PET may well be detected on the low-dose CT in combined PET/CT, particularly when a proper lung filter is applied in reconstruction of the chest images.

Zoller et al. (2007) have reported an improved diagnostic accuracy of PET/CT compared to PET-only for patients with differentiated thyroid cancer. Forty-seven PET/CT scans were performed in 33 radioiodine negative DTC patients with increased Tg. An experienced radiologist interpreted the CT scans without information of the PET results. An experienced nuclear medicine physician interpreted the PET scans (PET-only) without information of the CT results. Increased FDG uptake in residual or recurrent disease was detected in 35 of 47 scans (74%). CT was helpful in differentiation between local thyroid bed recurrences and metastatic lymph nodes and in differentiation between tumor uptake and brown fat uptake. Furthermore, CT provided useful detailed anatomical information of tumor extension. PET was helpful to differentiate between scar and residual or recurrent tissue in the thyroid bed and PET detected distant bone metastases missed by CT. PET was also useful in differentiation between enlarged inflammatory lymph nodes and metastatic lymph nodes.

CT has a far better spatial resolution compared to PET and small lung metastases will be missed on PET. Zoller et al. (2007) reported that only 26 regions with lung metastases were detected by PET compared to 41 on the CT. Thus, small lung metastases missed by PET were detected on the CT in the hybrid PET/CT scanning. This was also the case in 3 patients included in our study on patients with ATC (paper IV). Even if small lesions will be detected on the integrated low-dose CT, lesions below about 5 mm (depending on the activity concentration) are too small to be characterized on PET because of underestimation of the uptake intensity caused by the physical phenomenon called intensity diffusion (partial volume effect) and image noise. This physical phenomenon of intensity diffusion is discussed in sub-chapter 9.1.3.

Palmedo et al. (2006) have studied the use of PET/CT compared to side-by-side interpretation of PET and CT in patients with DTC. Integrated PET/CT added useful information to side-by-side interpretation of PET and CT in 17 out of 23 patients with suspicious findings on FDG PET. They concluded that by precisely localizing tumor tissue, image fusion by integrated PET/CT was clearly superior to side-by-side interpretation of PET and CT-images.

Choi et al. (2006) suggested that CT attenuation patterns or calcification in the integrated low dose CT images together with quantified FDG-uptake measured as SUVmax might be useful in the differentiation between benign and malignant thyroid nodules found incidentally on FDG PET/CT. Seventy patients with a focally increased FDG uptake in the thyroid gland found incidentally on FDG PET/CT were studied. They found that

accompanying diffusely increased FDG uptake, a very low CT attenuation, or no discernible thyroid nodule on CT favored a benign etiology irrespective of the intensity of the FDG uptake. When they combined CT and PET criteria, the area under the receiver operator curve (ROC) of PET/CT for characterizing focal thyroid lesions was significantly increased from 0.70 for SUVmax alone to 0.88 for combined patterns.

In a study by Nam et al. (2007) the intensity of the FDG uptake measured as SUVmax, type of calcification seen on CT, CT attenuation and their combination failed to discriminate between benign and malignant nodules. When we planned our study on thyroid nodules with increased FDG-uptake found incidentally on PET/CT, we did not consider the use of low-dose CT-findings for purposes other than attenuation correction and anatomical co-registration. To discriminate between malignant and benign thyroid nodules, US and US guided FNA are the methods of choice according to several reviews and according to the 2009 American Thyroid Association guidelines (Cooper et al. 2009, Sipos and Mazzaferri 2009, Lew et al. 2010). Neither contrast enhanced CT nor MRI are able to discriminate between malignant and benign lesions unless surrounding tissue is infiltrated. Micro-calcification typical for malignancy is seen on US but not seen on CT.

Yi et al. (2005) suggested that their somewhat higher prevalence of hot nodules (4.3%) compared to previous studies using PET could only be attributed to the use of PET/CT. They claimed that PET/CT depicts focally increased FDG uptake better than PET alone does. Their apparently higher prevalence may, however, be within the range of statistical uncertainty. Our experience is that thyroid nodules with increased FDG uptake are best detected on the maximum-intensity projection PET-only images (MIP images). Fused transaxial, sagittal and coronal images are however, helpful in locating the lesions precisely.

Modern PET-scanners have integrated multislice CT and are capable of performing state-of-the-art diagnostic CT with contrast enhancement. However, there is so far no general agreement upon the optimal use of contrast enhanced CT integrated in PET and there is no consensus about standardization of PET/CT protocols (Wong et al. 2006, Boellaard et al. 2009). One concern about the use of contrast enhanced CT integrated in PET/CT is the high patient radiation dose (Brenner and Hall 2007). A diagnostic CT should not be added routinely but considered only when strongly indicated.

The use of contrast enhanced CT integrated in PET/CT in patients with thyroid cancer is not established. Only a few prospective studies on other cancer types have evaluated the additional clinical value of contrast enhanced CT compared to PET/CT with low-dose CT

(Pfannenberg et al. 2007, Rodríguez-Vigil et al. 2006, Yoshida et al. 2009). These studies all found a good correlation between contrast enhanced full-dose CT and non-contrast enhanced low-dose CT. They concluded that routine use of contrast enhanced CT in PET/CT was not justified. For the vast majority of the patients examined with PET/CT you will not know until after the interpretation of the PET/CT whether a contrast enhanced CT is really indicated or not.

The strongest argument against routine use of contrast-enhanced CT integrated in PET/CT is found in the initial results from the National Oncologic PET Registry (NOPR) in the USA based on data from 22 975 PET studies (Hillner et al. 2008a). The most common strategy if PET had not been available, accounting for 41% of the cases (9 518 patients), was alternative imaging. In these cases, the post-PET strategy continued to call for additional imaging in only 6% (552) of the patients. In 47.6% of the cases (4530 patients) the strategy was changed directly to a new or major alteration in therapy, in 37.2% (3540 patients) to watching or supportive care, and in 9.5% (904 patients) to biopsy.

A precise co-registration between PET and CT is mandatory for an accurate attenuation correction and for an accurate anatomical correlation. However, a perfect contrast enhanced CT for chest and abdomen depends on deep inspiratory breath-hold. PET imaging of chest and abdomen takes about 12 minutes and breathing during the examination is obviously needed. Unless acquisition during respiratory gating is performed to ensure perfect co-registration between PET and CT in combined PET/CT, CT imaging needs to be performed during normal breathing or possibly better, in expiratory breath-hold (Fin et al. 2008) (Figure 8). However, expiratory breath-hold for the about 15 seconds needed for a 16 slice CT to perform a chest study is difficult to carry out for many patients. Important to be aware of is that in most studies where the additional clinical value of contrast-enhanced CT compared to PET/CT with low-dose CT has been studied, the contrast enhanced CT and the PET fused with low-dose CT have been evaluated side-by-side rather than truly integrated (Pfannenberg et al. 2007, Rodríguez-Vigil et al. 2006, Yoshida et al. 2009). In none of the studies has PET/CT with low dose CT plus contrast enhanced CT been compared to PET/CT with low dose CT plus an available prior contrast enhanced CT performed within the last 3-4 months.

Despite the evidence that the use of contrast enhancement for CT imaging when doing PET/CT is less important, radiologists and nuclear medicine phycicians in Europe are expecting that the proportion of CT with contrast-enhancement as an integrated part of

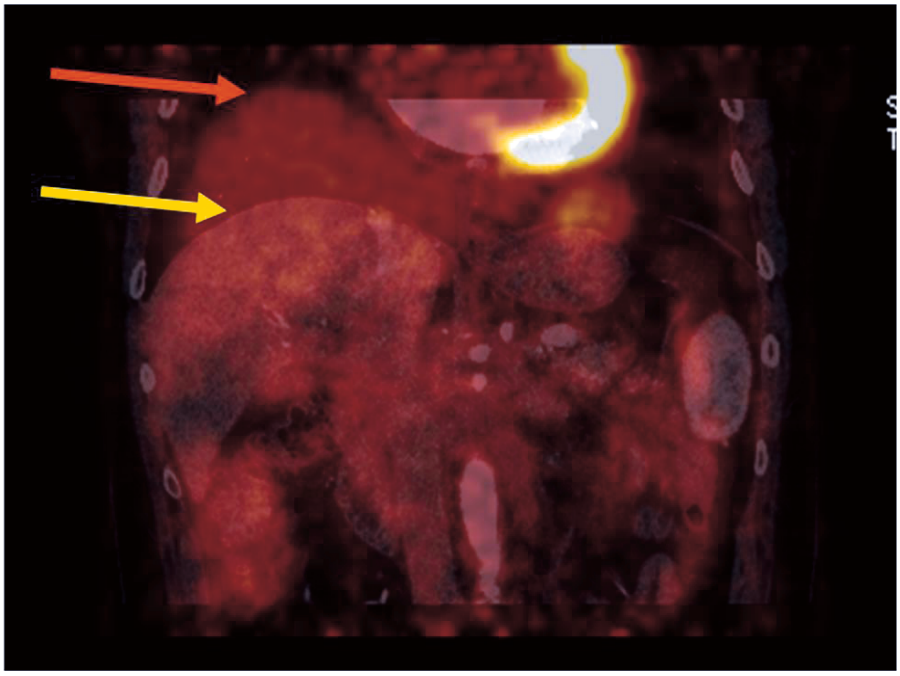


Figure 8. FDG PET/CT with contrast-enhanced CT: misregistration between contrast-enhanced CT performed during deep inspiratory breath-hold and PET images acquired during normal breathing. Red arrow indicates upper liver surface on PET and yellow arrow indicates liver surface on CT. Misregistration may result in serious image misinterpretation.

PET/CT will increase in the future (Cuocolo et al. 2009).

One promising use of PET with integrated contrast enhanced CT is in target volume determination in radiation therapy planning of various cancer types (Bannas et al. 2010). Cancers located low in the pelvis and in the head and neck region are ideal for the combination of PET and optimized contrastenhanced CT because of the minimal effect of respiratory movements, while respiratory movements will result in misregistration between PET and CT particularly in the chest and abdomen. The promising use of PET/CT in target volume determination in radiation therapy planning of head and neck squamous cell carcinomas, lung cancer and cervix uterine cancers is reviewed by a number of authors (de Ruysscher and Kirsch 2010, Haie-Meder et al. 2010, Troost et al. 2010). The potential use of PET/CT with integrated contrast enhanced CT in target volume determination in radiation

therapy planning in patients with anaplastic thyroid carcinoma and other aggressive thyroid cancers has not yet been explored.

There are high expectations for the emergence of PET/MRI. In PET/MRI the integration of PET and MRI is possible with the simultaneous acquisition of PET and MRI datasets (Hicks and Lau 2009, Wehrl et al. 2009, Pichler et al. 2010). However, combined PET/MRI is complicated and challenging to develop compared to the PET/CT system, and considerable progress must be made before such systems will be routinely used clinically for whole-body imaging (Hicks and Lau 2009, Wehrl et al. 2009, Pichler et al. 2010).

Seiboth et al. (2008) performed digital image fusion of FDG PET and MRI images performed on separate scanners using dedicated software (Hermes MultiModality^{TM}, Hermes Medical Solutions, Stockholm, Sweden) on 34 patients with thyroid cancer. PET/MRI was compared to PET, MRI, US, ^{131}I scan, and CT. Fused PET/MRI provided information that altered the treatment plan in 16 of 34 patients (46%) and provided additional information that confirmed the treatment plan in an additional 12 of 34 patients (36%). The authors concluded that PET/MRI fusion can be a useful tool in surgical planning, radioactive iodine therapy decision, and determining the level of follow-up necessary for each patient.

9.1.2 *FDG uptake and SUV measurements*

"When you cannot express it in numbers, your knowledge is meager and unsatisfactory".

Lord Kelvin.

In papers I, II and V we quantified the FDG uptake as SUVmax normalized to the body weight. For SUVmax calculation we used a circular region of interest (ROI) with a fixed diameter of 1.5 cm placed over the visually hottest part of the region of interest. The size and position of the ROI may influence the SUV measurements. If the hottest voxel is not included in the ROI or if the tumor is small, SUVmax will be under estimated (see paragraph 8.1.3). Using a volume of interest (VOI) most of the sources of error in the selection of ROI will be eliminated. Statistic variations may also influence the SUVmax.

In study III and V we did not quantify the FDG uptake. The criteria for PET interpretation in paper III and V was the presence of localized, pathologically increased uptake clearly seen on the MIP images as well as on PET/CT fused images not attributable to normal FDG uptake or physiological variations.

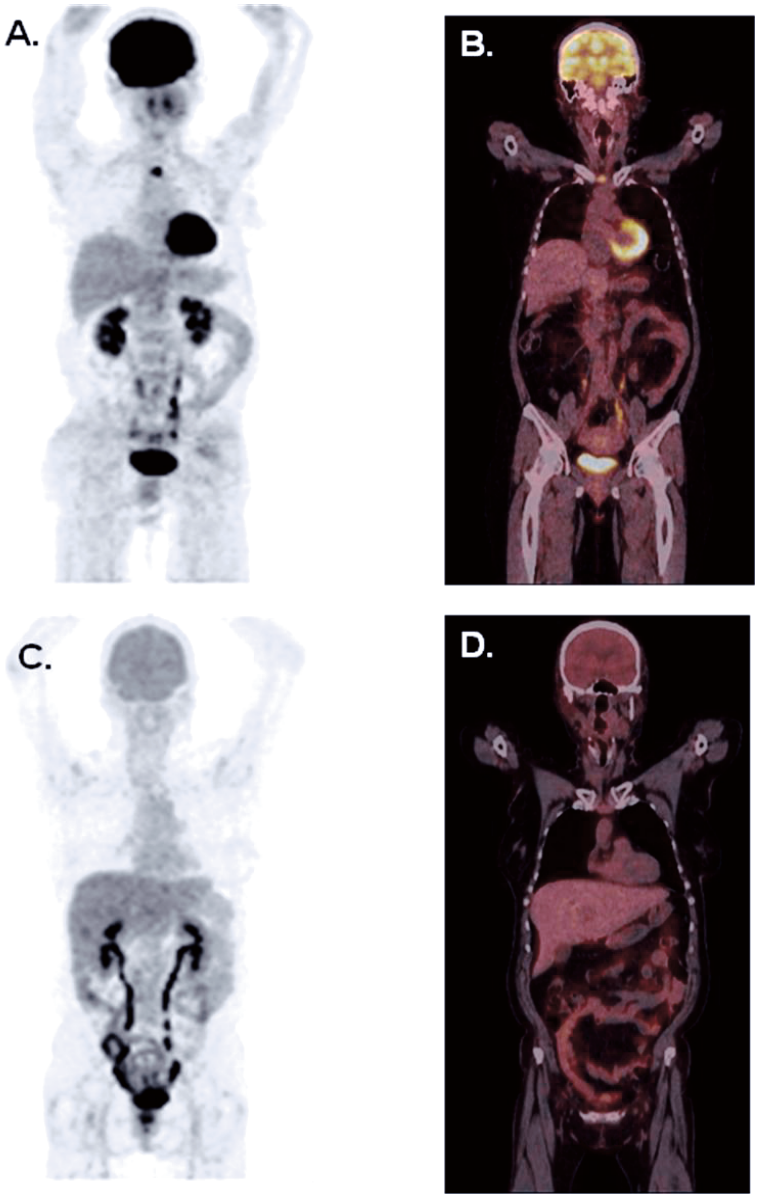
The mean voxel value SUV (SUVmean) instead of the SUVmax is recommended by some authors for serial measurements (Krak et al. 2005, Nahmias and Wahl 2008). SUVmean is critically dependent on both the size and the position of the ROI or VOI (Keyes 1995, Soret et al. 2007). In our study on patients with diffusely increased FDG uptake in the thyroid gland (paper I) we compared SUVmax and SUVmean in 21 patients, and we found a strong correlation between the two SUV measures (P<0,0001). We concluded that uptake measurements done with either SUVmax or SUVmean would have yielded similar results.

In study I, II and IV, measured SUV were normalized to body weight, the most commonly used normalization factor for variations in body habitus. Obesity was common in the populations studied in all of our papers. In oversized patients the fraction of body fat is increased compared to normal sized persons and SUV normalized to body weight will be overestimated because fat has low FDG uptake during fasting. SUVmax corrected for body surface or lean body mass (the mass of the body minus the mass of fat) is less affected by increased body fat and has been suggested used by some authors and consensus groups (Zasadny and Wahl 1993, Kim et al. 1994, Shankar et al. 2006, Wahl 2009a, Boellaard et al. 2010). In one study SUV normalized to body weight was 70% higher in a 100 kg person compared to a 50 kg person (Kim et al. 1994). Thus, in obese patients FDG uptake in lesions will be higher compared to identical lesions in patients with minimal body fat. However, the potential advantage of body surface and lean body mass is only valid in fasting patients. In non-fasting patients with increased insulin level the FDG uptake in fat will increase and SUVmax corrected for body surface or lean body mass will be underestimated. Several studies have shown that normalization of SUV to weight, surface area and lean body mass yield similar results in therapy response monitoring and most clinical trials use SUVmax corrected for body weight (Stahl et al. 2004, Couturier et al. 2006, Vriens et al. 2009).

Serial SUV-measurements in the same patient on the same PET-scanner, however, have been shown to be reproducible, both in normal tissue as well as in malignant tumors (Paquet et al. 2004, Nahmias and Wahl 2008, Velasquez et al. 2009). This is important because of the frequent need to follow cancer patients with PET serially (Nahmias and Wahl 2008). When serial scans are performed, the same time from injection to imaging is mandatory. In many malignant tumors the FDG-uptake will continue to rise even later than two hours after injection, whereas many benign tumors will reach a plateau within half an hour (Wahl and Henry 1992, Shankar et al. 2006). Important exceptions exist, *e.g.* sarcoidosis in which the uptake in affected lymph nodes may seem to continue to increase beyond one

hour after FDG injection. The glucose metabolic rate in most cancers does not depend on the plasma insulin level. The FDG uptake in tissue competes with blood glucose level (Lindholm et al. 1993, Langen et al. 1993). In a hyperglycemic condition the FDG uptake is reduced by competitive carrier-mediated uptake with high plasma glucose level; FDG is competitively displaced by high plasma glucose (Langen et al. 1993). The brain uptake is also independent of insulin. During hyperglycemia the cortical brain uptake may be an indication of the significance of possible competive uptake between FDG and high blood glucose (Figure 9). This will, however, not be valid in patients with large tumors, extensive disease or both with particulary intense FDG uptake in whom the brain FDG uptake will be ousted by the tumor uptake.

The FDG uptake in breast cancer tumors in rats was, in one study, reduced to about 50% at high glucose concentrations, assummedly caused by competitive replacement of FDG by the high blood glucose (Wahl and Henry 1992). In contrast to tumor uptake, FDG uptake and glucose metabolic rate in fat and muscles will be increased when stimulated by insulin in hyperglycemic conditions. Furthermore, increased muscle and fat uptake may result in reduced contrast between tumor and soft tissue and reduce the quality of the PET study. Thus, FDG PET studies may be unreliable in non-fasting patients and in hyperglycemic patients with diabetes mellitus type 1. The problem is somewhat different in patients with diabetes mellitus type 2 because of peripheral insulin resistence. In hyperglycemic patients with diabetes mellitus type 2, there will not be high uptake in fat and muscles, however, the cortical brain uptake will be low because of competitive FDG replacement of high blood glucose (Figure 9). Non-insulin dependent tumor uptake is likely low as well. However, because the muscle and fat uptake is low, the scans look nicer than in hyperglycemic non-diabetic patients or in hyperglycemic patients with diabetes mellitus type1 shortly after insulin administration. Some authors have suggested that hyperglycemia deteriorates the quality of the PET scan mostly in rapid onset hyperglycemia and less in chronic hyperglycemia with little effect on tumor uptake. Tumor uptake was reduced by only 10% in chronic hyperglycemia reported by one group (Torizuka et al. 1997). In a recent work by Rabkin et al. (2010) on FDG PET in patients with hyperglycemia, diabetes mellitus itself did not affect the diagnostic accuracy in patients with cancer but hyperglycemia did. Consensus groups in Europe and the United States have suggested that SUV may be corrected for elevated blood glucose levels for PET studies used in clinical trials and particularly in multi-center studies (Shankar et al. 2006, Boellaard et al. 2010). Glucose correction is, however, not yet



Figur 9 A-B: Female with DTC and increased Tg. Negative neck US and chest CT. FDG PET/CT identifies metastatic lymph node in upper anterior mediastinum (region VI). Blood glucose 5.4 mmol/L. **A:** Maximum intensity projections (MIP; PET-only). Normal brain intensity, frontal cortex SUVmax=15. Blood background SUVmax=2.1. **C-D:** Female with rectal cancer and diabetes mellitus type 2. Reduced FDG uptake in the brain caused by competetive uptake of high blood glucose 18.7 mmol/L. Tumor uptake was probably correspondingly reduced. FDG uptake in fat and muscle is typically low as well because of peripheral insulin resistance.

established as a clinical tool.

As a routine in clinical oncologic PET imaging at the Mayo Clinic, all of our patients had been fasting for at least 4 hours and blood glucose level was always measured before the FDG injection. When we collected the data for patients included in our studies, we did not register the measured blood glucose levels. However, we intend to do so in future studies, particularly when SUV measurements are being included. For non-diabetic patients the blood glucose level should be <6.7 mmol/L, and in diabetic patients <11.1 mmol/L. For concentrations above these limits the study should normally have been rescheduled if reasonably possible. However, in some patients the study may still have been performed despite higher blood glucose, particularly in patients with diabetes mellitus type 2.

9.1.3 *Intensity diffusion (partial volume effect)*

Due to the inherent physical characterstics of the PET-detector, properties of the reconstruction algoritm and application of post-reconstruction smoothing filters, the image of a point source shows a spread distribution (Keyes 1995, Soret et al. 2007, Skretting 2009, Skretting et al. 2010). This spread distribution pattern is known as a point spread function. If a point source is reconstructed with sufficiently small voxels, the distribution will show a Gaussian distribution. The full width at half maximum (FWHM) of this Gaussian function is usually 5-8 mm and reduced to 3-4 mm in the newest generation of PET-scanners. Obviously, the intensity of a point source that should have been assigned to only one small voxel seems to have diffused into neighboring voxels (Skretting et al. 2010). Since the total intensity of a point source is given by the number of β^+-emissions detected, the intensity in the central voxel of the point source distribution is significantly reduced. This phenomenon is reviewed by Soret et al. (2007). As the most commonly used term for this phenomenon, partial volume effect, is somewhat of a misnomer in nuclear medicine, the term *intensity diffusion* has been suggested used instead (Skretting 2009). In other words, intensity diffusion is the phenomenon of diffusion of image intensity from small sources of activity into a reconstructed image volume larger than the physical size of the source. Intensity diffusion will also exist on the edges of all sources independent of size. If a source is large, the diffusion of intensity will level out, and the effect of intensity diffusion will be seen only on the edges. The intensity diffusion effect does not only result in intensity diffusion out of a lesion, but also in diffusion of intensity into a lesion from surroundings with higher activity concentration is important (e.g. overestimation of intensity in small liver cysts). The intensity diffusion results in underestimation of the visual impression of the FDG intensity as well as the SUV in small tumors, and the effect is highly significant for tumors <1.5 cm even with

modern PET scanners (Soret et al. 2007, Skretting 2009, Srinivas et al. 2009, Skretting et al. 2010). The smaller the size the more pronounced the intensity diffusion effect (Figure 8). This underestimation adds increased errors to those caused by biological properties.

In the study on the value of quantifying FDG uptake in thyroid nodules found incidentally on whole-body PET/CT (paper II), 18 of the benign and 13 of the malignant nodules were smaller than 1.5 cm. The SUVmax measured in these nodules were consequently underestimated caused by the intensity diffusion effect. However, there was no significant difference between the average size of the benign (1.7±1.0 cm, range 0.5-4.7 cm) and the malignant nodules (1.3±2.0 cm, range 0.6 – 2.0 cm) (P=0.54). From this observation we concluded that the impact of the intensity diffusion effect should have been similar in both groups and the SUVmax values for the group of benign and malignant nodules could be compared. This conclusion also assumes that the FDG was evenly distributed within the tumors in the two groups. If the average or median size of the tumors in one of the groups in our thyroid nodule study had been significantly smaller compared to the other group, a difference in SUVmax could have been caused by the intensity diffusion effect. In the case of this scenario, a correction for difference in tumor size could have been used. We only considered the difference between the groups, not the absolute values, furthermore, did we not compare the SUV values with other studies.

The important impact of the lesion size on SUV has not been taken into account or discussed at all in a number of studies. Some authors have reported the finding of a correlation between SUV and tumor size, even though this correlation is most likely strongly influenced by the intensity diffusion effect (Kim et al. 2007, Bae et al. 2009, Zhai et al. 2010). Intensity diffusion applies not only to tumor size but to tumor shape and the FDG-distribution within the tumor as well. In the article on FDG PET in the management of patients with anaplastic thyroid carcinoma (paper V) we reported the SUVmax of the hottest lung metastases >1cm. In the same article we reported the SUVmax for metastatic lymph nodes. We did not report the sizes of the lymph nodes. The relation between SUV and lymph node size is more intricate than assumed valid for solid lung metastases or phantom studies using spheres with homogeneous FDG uptake.

The use of recovery factors to correct for underestimation of measured intensity in small tumor volumes has been suggested by some authors (Hickeson et al. 2002, Soret et al. 2007, Srinivas et al. 2009). The simplest method is to multiply the measured SUV with the inverse of a calculated or measured recovery coefficient (RC). The recovery coefficient is

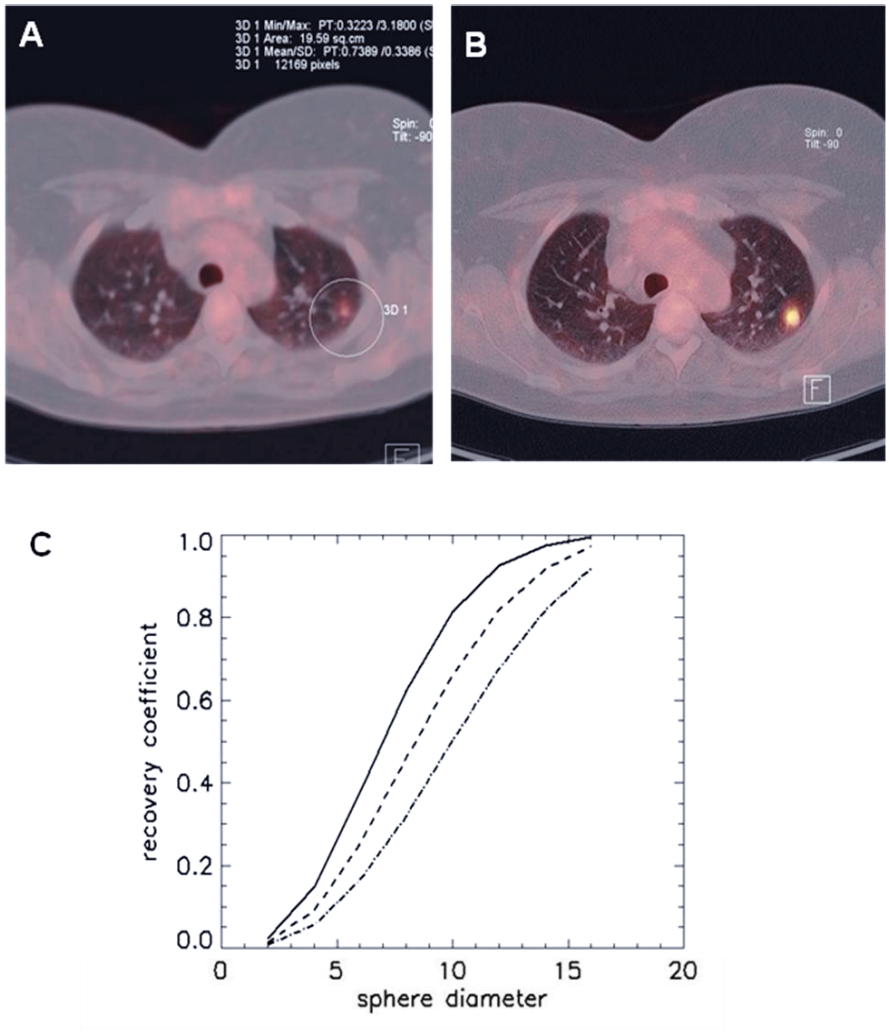


Figure 10. Example of intensity diffusion in FDG PET/CT. **A:** Solitary metastatic lung lesion with increased FDG uptake is seen in left upper lobe (encircled). Axial diameter 0.7 cm. SUVmax=3.2. SUVmax is underestimated because of small size (intensity diffusion). **B:** Follow-up FDG PET/CT 18 months later. The tumor has increased in size to 1.6 cm. SUVmax=8.4. **C:** Graph shows recovery coefficient *vs.* tumor size for spherical tumors with homogeneous uptake (FWHM 2, 3.5, and 5 mm, respectively). Applying a recovery factor (0.35) read out of the diagram (dash-dotted right curve) to the FDG-intensity of the smaller tumor gives SUVmax=9.1. Thus, the metastasis has increased in size but not in uptake per volume unit.

the ratio between the measured maximum image intensity inside an object with homogeneous distribution of activity and the ideal image intensity which the same activity concentration

creates inside a larger object. The RC can be theoretically calculated based on assumptions on tumor geometry and knowledge of the point spread function.

The true intensity corresponds to the intensity in the central region of a large object (diameter >5 cm) with the same activity concentration homogeneously distributed. The size of the tumor can be measured from CT. However, if a small tumor has a non-uniform FDG distribution or a shape different from the one assumed by the recovery factor method (typically a sphere), the correction factor cannot be used directly. For example, in metastatic lymph nodes the metastasis may not occupy the entire lymph node and a volume correction based on the lymph node volume may result in an underestimation of the corrected SUV. Srinivas et al. (2009) established a look up table for partial volume correction of spherical lesions and applied recovery coefficients from the table to a cohort of 17 patients with biopsy proven lung cancer. Mean SUVmax was 7.0 for 64 lung lesions with an average diameter of 2.5 cm. After partial volume correction the mean SUVmax was 15.5.

By applying partial volume corrections the corrected intensity will be equal to or less than the ideal intensity depending on the distribution of the activity within the volume. If the intensity distribution within the source is homogeneous the corrected intensity will correspond to the true intensity while the corrected intensity will be lower if the activity is non-homogeneously distributed.

As discussed in chapter 8.1.1, small lung metastases missed by PET may be detected on the CT in hybrid PET/CT scanners. This was the case in 3 patients with ATC (paper V). The patients had numerous lung metastases <3 mm detected on the low-dose CT. Our study showed that primary tumors as well as metastases from ATC demonstrated intense FDG uptake. It is likely that those small lung metastases also had high FDG uptake, however, the uptake was substantially underestimated due to intensity diffusion as well as blurring caused by respiratory movement during PET imaging. Lesions <3-5 mm are in general too small to be characterized by PET. However, when the visually observed intensity and measured SUV are high, the finding is a true positive finding. The uptake intensity will still be underestimated. Low uptake in small tumors may be a false negative finding. In the article on ATC the SUVmax reported for lung metastases was measured in the hottest lesion >1 cm. Even in lesions 1-1.5 cm the intensity diffusion effect is present, dependent on the post-reconstruction smoothing filter applied, although less pronounced compared to smaller lesions.

In paper IV on FDG PET and MTC, we did not report the SUV. The PET interpretation was exclusively based on visual detection of localized uptake above surrounding tissue not attributed to normal uptake or physiologic variations. The intensity diffusion phenomenon does not only affect SUV measurements but also equally involves visual impression. Thus, even if SUV quantification was not used, the lesion size should still have been reported.

Most PET studies include SUV measurements. A number of system characteristics and parameters used during scanning and image reconstruction will affect the intensity diffusion effect and consequently influence the SUV measurements. In studies where SUV measurements are included, these parameters have to be specified. A single measurement of the effective spatial resolution (the combined effect of the intrinsic resolution and smoothing applied) would enable calculation of the contrast recovery coefficients for different sizes of homogeneous spherical tumors (Skretting et al. 2010).

9.2 Incidental finding of increased FDG uptake in the thyroid gland

9.2.1 *Diffusely increased FDG uptake*

In a number of studies on incidental finding of increased FDG uptake in the thyroid gland both focally and diffuse uptake are included. Only a few articles present data exclusively on diffusely increased uptake, and it seems that only the study by Yasuda et al. (1998) has included a patient control group.

We found diffusely increased uptake in 138 out of 4 732 patients (3%). The percentage is similar to what Yasuda et al. (1998) reported (3.3%) for healthy persons included in a cancer screening program. The percentage is numerically somewhat higher than reported in other studies, however, the differences may not be statistically significant (Kim et al. 2005, Kang et al. 2003, Are et al. 2007). It is uncertain whether the exclusion of patients with any prior history of benign thyroid disease from these latter studies may have accounted for any possible significant differences.

In a recently published work, Tateishi et al. (2009) studied the FDG PET scans of 146 females with advanced breast cancer receiving systemic cancer treatment. Bilateral increased diffuse uptake in the thyroid gland was found in 29 (20%). The authors concluded that the uptake represented active inflammation caused by chronic thyroiditis. The high number of patients with diffusely increased thyroid uptake was consistent with the evidence of increased incidence of thyroid disorders in women with breast cancer (Reinertsen et al. 2009).

Hypothyroidism is shown to be increased in women after multimodal treatment for stage II/III breast cancer. Unintended radiation to the thyroid gland during radiation of breast and axilla may be a contributing factor.

Our conclusion is consistent with other studies: diffusely increased FDG uptake is strongly associated with chronic thyroiditis (Yasuda et al. 1998, Kurata et al. 2007, Chen et al. 2009, Tateishi et al. 2009). One limitation of our study, like most other similar studies, was the lack of cytologic or histologic confirmation (Yasuda et al. 1998, Kang et al. 2003, Kim et al. 2005). In only 4 out of our 138 patients, US-guided FNA was performed and in all 4 the finding was consistent with chronic thyroiditis. For the remaining patients the standard of reference was the presence of thyroid peroxidase autoantibodies (TPOAb) supported by characteristic echo pattern on US. The clinically most important thyroid autoantibodies are TPOAb, anti-thyroglobulin (TgAb), and thyrotropin receptor-stimulating antibodies (TSHRAb). TPOAb is associated with chronic autoimmune thyroiditis and with hyper- or hypothyroidism (Hollowell et al. 2002). TgAb alone in the abscense of TPOAb is generally not associated with thyroid disease. TSHRAb is associated with Grave´s disesase (Davies 2000).

We did not report the result of any follow-up PET scan. Yasuda et al. (1998) reported that 14 of the 36 included patients underwent two or more repeated PET scans during the following 1-2 years. Persistent diffusely increased FDG uptake was observed in 13 of these 14 patients, supporting the anticipated etiology of a chronic disorder in most of the patients. Tateishi et al. (2009) showed that the increased FDG uptake persisted in patients who received thyroxine treatment. This observation is consistent with findings on repeat thyroid biopsies in 601 patients with autoimmune thyroiditis performed by Mizukami et al. (1992) at intervals of up to 20 years; the thyroid histology in patients with chronic lymphocytic thyroiditis showed little alteration over time.

Out of 133 included patients in our study, 56 were already on thyroxine therapy. Thyroxine replacement therapy was instituted in 12 patients based on results of blood samples analyzed as recommended in the PET report. Two additional patients had subclinical hypothyrodism. Secondary changes in FT4, FT3 and TSH caused by serious non-thyroidal illness were considered but decided unlikely in any of the patients. Thus, 68 out of 133 patients (51%) had hypothyrodism and needed thyroxine. There was no statistical significant difference in the intensity of the FDG-uptake between patients on thyroxine or in hypothyroid patients not yet on replacement therapy.

In patients with DTC with a prior history of hypothyroidism caused by chronic thyroiditis, radioiodine uptake will be low in thyroid remnants. Radioiodine treatment may be ineffective in ablation of residual hypofunctioning thyroid tissue but may still be effective in treating metastases. For radiologists and nuclear medicine physicians reading PET scans, it is important to be aware that residual thyroid tissue in a patient with a history of chronic thyroiditis will accumulate FDG. Thus, in DTC patients with a prior history of chronic thyroiditis and hypothyroidism a finding of increased uptake in the thyroid bed on FDG PET scanning, even after one or more treatments with radioiodine, may represent benign residual thyroid tissue. Such increased FDG uptake in residual inflammatory thyroid tissue has to be differentiated from increased uptake in post-surgical inflammation.

In our paper we suggested that the increased FDG uptake seen in patients with autoimmune thyroiditis may not only be caused by uptake of lymphocytes, but may be related to other intrathyroidal processes as well. The suggestion was based on the lack of correlation between TPOAb levels and SUVmax. However, the reasoning may be wrong. As already discussed, repeated thyroid biopsies in 601 patients with autoimmune thyroiditis performed by Mizukami et al. (1992) at intervals of up to 20 years showed little alteration in thyroid histology, even in patients treated with thyroxine. We know that in fibrotic tissue the cell density is low with slow proliferation, and FDG uptake is likely to be low. There is good evidence that chronic autoimmune thyroiditis preceedes atrophic thyroiditis, however, only very few patients with chronic thyroiditis develop atrophic thyroiditis (Hayashi et al. 1985). Furthermore, TPOAb commonly decreases during thyroxine therapy. The mechanism of diffusely increased FDG in chronic autoimmune thyroiditis is most likely mainly contributed to FDG-uptake in activated lymphocytes. Hypothyroidism, increased TPOAb and low FDG uptake may be associated with atrophic thyroiditis rich in fibrotic tissue resulting from a burned-out chronic inflammation.

Are et al. (2007) reported that 2 patients with diffuse FDG uptake had thyroid malignancy. Kurata et al. (2007) reported that 1 of 25 patients with diffuse FDG uptake had PTC detected as a nodule on US. Although not described explicitly in the papers, it may seem that the carcinomas detected in those 3 patients were incidental findings detected on US in glands with diffusely increased FDG uptake caused by chronic thyroiditis. Among 152 patients with diffuse thyroid FDG uptake reported by Bae et al. (2009), 31 patients underwent an ultrasound examination and thyroid nodules were found in 14 of these. In 4 patients the nodules were indeterminate on US and FNA was performed. Cytology was benign in 2

patients, indeterminate in 1, and PTC was found in 1. The patient with indeterminate cytology was operated and follicular carcinoma was confirmed on histopathology. The two malignancies were incidentally detected on US in a gland with increased uptake caused by chronic thyroiditis.

The prevalence of malignancy in nodules with increased FDG-uptake in a thyroid gland with both diffusely and focally increased uptake has been studied by Kurata et al. (2007). Diffusely increased FDG-uptake in the thyroid gland was detected in 29 out of 1626 healthy subjects included in a cancer screening program. In 4 of those 29 patients with diffusely increased uptake, an incidental finding of a focally increased uptake was detected. Two of these 4 nodules were PTC. It is probably wise to perform FNA liberally in incidentally found nodules with increased FDG uptake included in patients with both diffusely and focally increased uptake in the thyroid glands.

In patients with an incidental finding of diffuse uptake in the thyroid gland on FDG PET without any known history of thyroidits or hypothyroidism, a clinical evaluation of the neck should be performed, and FT4, FT3, TSH, TPOAb and possibly TSHRAb should be analyzed. An US examination should be considered as well. We did not find any significant correlation between the intensity of the FDG uptake in the thyroid gland and TSH level, and therefore even mild uptake should not be ignored. While diffusely increased uptake in the thyroid gland in the vast majority of the patients is associated with thyroiditis, the possibility of thyroid lymphoma or even anaplastic thyroid carcinoma should be kept in mind.

A number of drugs are known to alter thyroid function, and some drugs may induce inflammatory thyroiditis. Thyroiditis induced by drugs is relevant for FDG PET imaging as diffusely increased thyroid uptake may occur. Amiodarone, litium, interferon alfa, and interleukin-2 are examples of drugs that may induce thyroiditis (Pearce et al. 2003). The tyrosine kinase inhibitor sunitinib (Sutent®, Pfizer, New York, NY, USA) is a multi-targeted receptor tyrosine kinase (RTK) inhibitor approved by the FDA for the treatment of renal cell carcinoma (RCC) and gastrointestinal stromal tumor (GIST) and is also used experimentally in a number of different cancers types including inoperable, progressive, metastatic both differentiated and medullary thyroid carcinoma. A common side effect of sunitinib is thyroiditis (Mannavola et al. 2007). Thyroiditis with hypothyroidism may possibly occur with any tyrosine kinase inhibitor.

Combined PET/CT was used in all of our patients with diffusely increased FDG-uptake in the thyroid gland. The CT was used only for attenuation and anatomical

coregistration. We did compare the findings on PET with linear attenuation correction coefficient measured as Hounsfield units (HU) in the tissue on CT. In a recently published study by Han et al. (2010), CT density was studied in 56 patients with diffuse FDG uptake in the thyroid gland and in a group of 56 control patients without increased FDG uptake. Even if HU on CT were closely related to FDG uptake, we cannot see that the CT findings added useful information to the FDG uptake.

9.2.2 *Focally increased FDG uptake*

While diffusely increased FDG uptake is strongly associated with thyroiditis and the probability of malignancy is very low, solitary nodules have a high risk of being malignant, most frequently PTC (most likely because this is the most common thyroid cancer). Shie et al. (2009) have published a systematic review of articles on focally increased FDG uptake in the thyroid gland incidentally identified on FDG PET with confirmed diagnoses based on cytology, histology or on long time follow-up. Eighteen articles published from 1998 through 2007, including our own, met the inclusion criteria of this review. Among 55 160 patients, 571 (1.0%) had an incidental finding of a thyroid nodule with increased FDG uptake. Among 322 patients with confirmed diagnoses, 200 (62%) were benign, 107 (33%) were malignant, and 15 (5%) were indeterminate. PTC was the most frequent malignancy (82%). These average numbers correspond to the numbers found in our study: we found thyroid nodules with increased FDG uptake in 1.1%, 15 (35%) of the nodules with adequate follow-up were malignant, and 12 of these 15 were PTC (80%). Later articles have further supported the validity of these numbers (King et al. 2007, Nam et al. 2007, Salvatori et al. 2007, Kwak et al. 2008, Chen et al. 2009, Bae et al. 2009, Eloy et al. 2009, Jin et al. 2009). There is substantial support of the notion that an incidental finding of a nodule with high FDG uptake in the thyroid gland on PET should be reported as a possible primary or secondary malignancy and further evaluation with US and possible FNA should be recommended.

What remains unclear is whether SUVmax may be useful in discriminating between benign and malignant nodules. We did not find any statistical significant difference in the SUVmax between benign and malignant nodules. Our study does not support the notion that SUVmax above some given value can predict thyroid malignancy or a value below a given limit may exclude malignancy. Based on ROC analysis the best cut-point between benign and malignant lesions in our study was SUVmax=6, which resulted in a sensitivity of 69% and a specificity of 61%. In fact, the SUVmax for our dataset did not discriminate much better than by random chance.

Eight of the 18 studies included in the systematic review performed by Shie et al. (2009) compared the SUVmax for the benign and the malignant lesions. Mean SUVmax for 73 benign lesions was 4.6±2.1 (SD) and for 52 malignant lesions was 6.8±4.6 (SD). There was an obvious overlap however, by applying the Students *t*-test they found a statistically significant difference between the two groups ($P<0.001$). The respective SUV did not seem to follow a normal distribution. It is not known whether the use of a nonparametric test would have changed the *P*-value. A number of later publications support our finding of no statistically significant difference in SUV between benign and malignant lesions (Kwak et al. 2008, Are et al. 2007, Nam et al. 2007, Eloy et al. 2009, Chen et al. 2009, Lin et al. 2010). Two exceptions are the studies by Bae et al. (2009) and Zhai et al. (2010). Both papers claim that high FDG uptake raises the probability of malignancy. Our own experience is that the lesions with the highest FDG uptake are most likely oncogenic (Hürthle) cell adenomas. The relationship between lesion size and SUVmax is discussed in details in chapter 8.1.3.

All of our patients with focally increased FDG uptake had a corresponding lesion found on ultrasound. Only a few authors have reported focally increased FDG uptake without a corresponding lesion on US (Eloy et al. 2009). It is probably wise to follow those patients with US.

A limitation of most of the published studies, including our own, is the lack of cytologic or histologic verification of the etiology of numerous nodules. The group of patients with the highest likelihood of having metastases to the thyroid gland from a non-thyroid cancer was not biopsied. This group consisted of patients with advanced metastatic non-thyroid cancers with a poor prognosis in whom a confirmed additional primary or secondary cancer in the thyroid gland would not change the patient management.

FNA biopsies of thyroid nodules are discussed in European and American guidelines (Cooper et al. 2009, Gharib et al. 2010). About 20% of FNA biopsies of thyroid nodules have an indeterminate diagnosis. Of these about 80% are found to be benign and 20% are malignant after diagnostic thyroidectomy. Having considered the high prevalence of malignancy in thyroid nodules with increased FDG uptake found incidentally on PET, some groups have studied the possibility of using FDG PET in preoperative evaluation of thyroid nodules of indeterminate cytology to reduce the high number of futile hemithyroidectomies (Bloom et al. 1993, Mitchell et al. 2005, de Geus-Oei et al. 2006, Sebastianes et al. 2007, Kim et al. 2007, Hales et al. 2008, D'Souza et al. 2010, Traugott et al. 2010). Even if malignant and benign groups cannot be completely separated based on SUV, there may exist a SUV cut-off

below which malignancy is unlikely and diagnostic thyroidectomy futile (de Greus-Oei et al. 2006, Sebastianes et al. 2007, Traugott et al. 2010). Such a value would be valid only for solid tumors with homogeneous FDG uptake larger than about 1.5 cm because of false low visual impression and measured SUVmax caused by intensity diffusion (partial volume effect) for smaller lesions. However, so far data are conflicting and more prospective studies on larger patient groups are needed.

9.3 FDG PET in patients with DTC and increased level of TgAb

As discussed in chapter 4, Tg is a very sensitive and specific tumor marker for residual or recurrent DTC. In patients with circulating autoantibodies to Tg (TgAb), however, Tg measurements are unreliable. Tg is commonly undetectable in TgAb-positive patients (false-negative Tg) despite leakage of Tg from residual thyroid tissue,

As dicussed in chapter 5.3.1, the only well established indication for the use of FDG PET in thyroid cancer is in radioiodine negative DTC patients with persistently elevated or with increasing blood levels of Tg (Fletcher et al. 2008, Robbins and Larson 2008, Cooper et al. 2009, Dong et al. 2009, Chao 2010, Heston and Wahl 2010, Miller et al. 2010). In addition to locating residual or recurrent disease not detected by conventional imaging, there is strong evidence that increased FDG uptake on PET is an independent prognostic indicator for increased risk of thyroid cancer-specific death in patients with DTC (Wang et al. 2000, Robbins et al. 2006). Furthermore, Wang et al. (2000) found a statistically significant correlation between SUVmax and of the FDG avid lesions and survival indicating that the tumors with the highest metabolic activity were those with the most rapid growth.

We found that persistently increased TgAb in patients with DTC after primary treatment (surgery and radioiodine) was associated with FDG avid residual lesions and progressive disease (paper III). A limitation of our study was that we did not make a record of the SUVmax of the individual FDG avid lesions. A negative PET predicted the disappearance of TgAb over time, suggesting the absence of active disease.

Our results were consistent with a recent article by Seo et al. (2010). Their results are discussed in our paper. Seo et al. (2010) reported the prevalence of residual or recurrent disease to be 28% in patients with stable TgAb ≥140 U/mL and 38% in patients with increasing TgAb levels. Malignancy was confirmed in 76 residual or recurrent lesions in 37

patients. Sixteen out of 57 metastatic neck lymph nodes (28%) were missed by US but detected on FDG PET/CT. All 17 distant metastatic lesions were detected on FDG PET/CT. The authors concluded that a thorough evaluation including FDG PET/CT should be conducted to detect possible residual or recurrent disease in patients with DTC with persistently elevated TgAb after total thyroidectomy and radioiodine ablation.

There seems to be no further studies reporting the value of FDG PET in DTC patients with increased level of TgAb. However, a few other research groups have used FDG PET in the evaluation and follow-up in the subgroup of patients with DTC. Chung et al. (2002) studied the clinical importance of elevated TgAb and undetectable Tg in 51 patients with DTC. All of the patients had had a total or subtotal thyroidectomy followed by radioiodine ablation. The proportion of patients with residual or recurrent disease was high: 29 of the 51 patients (59%) had confirmed residual or recurrent disease. The number corresponds to the findings in our study: 12 out of 17 patients (71%) had residual or recurrent disease. In the study by Chung et al. (2002), FDG PET was performed in 13 of the 25 patients and was positive in 11 and false negative in 2. In our study FDG PET was positive in 10 and false negative in 2 of the 12 patients with confirmed residual or recurrent disease. Chung et al. (2002) found that TgAb was higher in patients with persistent disease compared to patients without other evidence of possible residual disease. In our study, both the agglutination test and the sandwich assay used were designed primarily for identification of potentially unreliable serum Tg measurements in the follow-up of patients with DTC. Quantified measures and serial measurements of TgAb were available for 8 patients only. All patients with TgAb>332 U/mL had progressive metastatic disease except 1 patient who had stable metastatic disease (Table 2 paper III). Furthermore, Chung et al. reported that TgAb levels tended to be higher in patients with more extensive disease compared to patients with less widespread disease. These findings correspond to the suggestion that TgAb measured serially using the same laboratory method, may be used as a surrogate tumor marker in TgAb-positive patients (Spencer et al. 1998, Spencer 2004, Spencer et al. 2005, Spencer and Lopresti 2008). In the study by Chung et al. (2002) TgAb spontaneously decreased in 19 out of 26 patients without evidence of residual or metastatic disease during follow-up for an average period of 25 months. In our study, 5 of the 17 included patients had no evidence of residual or recurrent disease. In 4 of these 5 patients, TgAb level went from positive to negative spontaneously within a median of 18 months (range, 4-36 months); Tg level in all of these patients was less than 0.1 ng/mL. In one patient, increased TgAb level persisted without any evidence of

residual or recurrent disease on follow-up for 68 months, when the patient died of primary lung cancer. FDG-PET was true-negative in all 5 patients.

Kim at al. (2008b) studied the clinical value of any change in TgAb levels as a predictor for recurret disease in DTC patients with increased TgAb after total thyreoidectomy followed by radioiodine ablation. Kim et al. (2008b) did not evaluate the value of FDG PET in DTC patients with an increased level of TgAb but used FDG PET/CT as one of more imaging modalities to localize recurrent disease. FDG PET/CT was true positive in 5 out of 6 patients with TgAb>100 U/mL (defined as positive TgAb) and false negative in 1 patient (Table 2 their article). Out of 56 patients with persistent increased level of TgAb 10 patients (18%) had persistent or recurrent disease on follow-up for an average period of 74 months compared to 10 out of 741 patients (1%) in whom TgAb changed from positive to negative during 6-12 months after primary treatment with surgery followed by radioiodine ablation. Kim et al. found that patients with TgAb decrease to a level of 50% or less compared to the initial post-treatment level were disease free on follow-up.

The increased TgAb level may, however, last for years before TgAb declines to normal, and years may be too long to wait (Chiovato et al. 2003). Neck US and chest CT will be the primary imaging procedures in follow-up of these patients. When conventional diagnostic imaging is negative or indeterminate, FDG PET/CT may be indicated since the proportion of FDG PET positive patients seems to be high in this subset of patients with DTC.

Blood level of thyrotropin receptor mRNA (TSHR mRNA) have in a limited number of studies shown to demonstrate high concordance rates with present methods of detecting thyroid cancer recurrence and may appear to be more accurate, especially in patients with increased levels of TgAb (Milas et al. 2009, Milas et al. 2010). The TSHR mRNA test is still under development but may be used in the future to select patients for a FDG PET-scan. A potential advantage is that monitoring patients with TSHR mRNA may be performed on TSH suppression. Circulating Tg mRNA was found to be of no use in detecting recurrent or residual DTC by one research group (Lombardi et al 2008).

Stunning is known as the phenomenon of reduced radioiodine uptake of a therapeutic radioiodine dose by radiation effect of an immediate preceding diagnostic radioiodine scan (Park et al. 1994). The phenomenon is reviewed and discussed by a number of authors (Brenner 2004, Kalinyak et al. 2004). Down-regulation of the sodium/iodide symporters responsible for transmembrane iodine transport is a possible explanation of ^{131}I-induced thyroid stunning (Nordén et al. 2007). The degree of stunning effect is reported to be

proportional to the ^{131}I dosage (actually the absorbed radiation dose). A per oral ^{131}I activity as low 74 MBq has been reported to result in a subsequent temporary decreased uptake of radioiodine (Lassmann et al. 2004). The phenomenon is important to consider as stunning may cause a failure of radioiodine therapy. Stunning following a diagnostic ^{131}I whole body scan or following treatment with radioiodine may also lead to temporarily reduced FDG uptake on subsequent PET scans (Hung et al. 2008). None of our patients were studied within the possible critical period of 3 months after radioiodine treatment.

In the vast majority of the studies on the use PET in patients with DTC the radiopharmaceutical used has been FDG. Other radiopharmaceuticals may be relevabnt as well. Phan et al. (2008c) compared the performance of ^{11}C-methionine (MET) with FDG in 20 patients with differentiated thyroid cancer with suspected recurrent or metastatic disease. There were consistent findings between the two radiopharmaceuticals in 13 patients. The uptake intensity appeared to be somewhat higher on FDG PET compared to MET PET. In 3 patients lesions were seen only on FDG PET, and in 3 other patients lesions were seen only on MET PET. The authors concluded that PET with radiolabeled amino acids was feasible in patients with DTC. MET PET was not superior to FDG PET in the detection of recurrent disease in patients with DTC. MET PET and FDG PET seemed to give complementary information.

9.4 PET in patients with anaplastic thyroid cancer

In our patients with ATC, all primary tumors, all residual and recurrent lesions, all lymph node metastases, and all extranodal metastases showed consistently high to very intense FDG uptake. This was in agreement with a number of prior case reports (Jadvar and Fischman 1999, Kresnik et al. 2003, Poppe et al. 2004, Iaguaru and McDougall 2007, Nguyen and Ram 2007, Strobel et al. 2007). The high FDG uptake in ATC is consistent with the findings of an overexpression of glucose transporter GLUT-1 in the cell membranes of ATC cells (Schönberger et al. 2002).

Our results are also in agreement with a recently published paper by Poisson et al. (2010). Twenty consecutive patients with ATC were examined with FDG PET/CT for initial staging. FDG PET/CT were further repeated in 7 of the patients after two cycles of chemotherapy, and / or after finished radiation therapy in 6 of the patients, and / or after finished chemoradiation therapy in 5 of the patients, and during follow-up in 4 of the patients.

The results on FDG PET/CT were compared to total-body contrast enhanced CT. As in our study, they found high FDG uptake in all primary tumors, in all cervical and mediastinal lymph node metastases, and in all distant metastases. FDG PET/CT detected more cervical and medistinal metastatic lymph nodes compared to CT.

The failure of FDG PET to detect numerous, tiny lung metastases in three of our patients was probably not attributed to low FDG uptake in these lesions, but rather attributed to the small size, resulting in an underestimation of the FDG uptake by SUVmax measurements as well as on visual interpretation. This physical phenomenon of intensity diffusion is discussed in chapter 8.1.3. In our paper we suggest that lesions too small to be characterized by PET may easily be detected on low-dose CT in PET/CT. Poisson et al. (2010) found that PET/CT had the same sensitivity as contrast enhanced CT for detection of lung metastases as tiny metastases too small to be characterized by PET, were easily visualized on low-dose CT.

Poisson et al. (2010) found that contrast enhanced CT did not provide any clinically important information for disease staging. The authors concluded that FDG PET/CT provided a better staging than contrast enhanced CT and should be routinely performed for staging of patients with ATC. Contrast enhanced CT should be indicated in addition to PET only for preoperative evaluation of the neck in selected patients for whom surgery would be considered. Furthermore, FDG avid lesion volume (≥300 mL) and the intensity of FDG uptake (SUVmax ≥18) were found to be significant prognostic factors for survival. We did not evaluate the tumor volume in our patients. Poisson et al. (2010) also found FDG PET/CT to assess tumor response to treatment earlier than CT in 4 out of 7 patients in whom interim PET was performed after 2 cycles of chemotherapy.

Three of their patients with a negative FDG PET/CT after treatment were still alive 14, 20 and 38 months after primary diagnosis. The patient in our study with the longest survival, 30 months from diagnosis to recurrence, had the lowest FDG-uptake in the primary tumor of the included patients. Two patients in our study had no evidence of residual or recurrent disease by the end of the study period. Follow-up information was available for 15 and 23 months after the diagnosis. Both of these patients had 2 and 6 negative follow-up PET scans, respectively.

After chemoradiation significant residual mass and scarring are common, FDG PET may be useful to discriminate between post-treatment inflammation and residual viable cancer. Poisson et al. (2010) concluded that FDG PET/CT appeared to be the reference imaging modality for ATC not only at initial staging but also in the early evaluation of

treatment response and follow-up. Patients with a negative FDG PET/CT after chemoradiation and a well-defined demarcated residual intra-thyroidal mass may be eligible for surgery.

Poisson et al. (2010) found that PET/CT had an important impact on patient management in 25% of the patients, compared to 50% in our study. The difference may not be statistically significant because of the low number of patients in both studies.

Because of the consistently very high FDG uptake in ATC, it is likely that FDG PET/CT may improve the initial staging in patients with indeterminate or negative conventional radiologic imaging. Accurate initial staging is crucial for prognostication and for choosing the optimal treatment. Metastases are common in ATC, and FDG PET/CT whole body scanning is well suited to detect unknown distant metastases. If conventional imaging does not show regional or distant metastases a FDG PET/CT will be indicated. Primary surgery is not an option in most patients with ATC because of advanced disease at the time of diagnosis (Are and Shaha 2006). Hyperfractionated radiation therapy combined with radiosensitizing doses of doxorubicin is normally the treatment of choice to achieve local disease control. In the few patients with intrathyroidal ATC without metastases curative treatment will be the goal.

There seems to be no studies so far on FDG PET/CT in radiation therapy planning in patients with ATC. There is substantial experience on PET/CT in radiation therapy planning in patients with other cancer types. Troost et al. (2010) have recently reviewed the experience with FDG PET/CT in radiation therapy planning in head and neck squamous cell carcinomas (SCC). Haie-Meder et al. (2010) have recently reviewed the use in SCC of the uterine cervix (2010). De Ruysscher and Kirsch (2010) have recently reviewed the use of FDG PET/CT in radiation therapy planning in patients with lung cancer. Like SCC (head and neck, cervix, and lung) and most lung adenocarcinomas, ATC shows consistently intense FDG uptake in primary tumors as well as in metastases. Because of the intense FDG uptake in these tumors including ATC, PET can be used in precise edge delineation of the gross tumor volume (GTV). Based on the increasing experience with SCC and lung cancer adenocarcinomas, it may be reasonable to assume that FDG PET/CT may be useful in image-guided radiation therapy planning in patients with ATC as well.

Furthermore, FDG PET may identify metastatic lymph nodes missed by US and CT which should be included in the target volume for therapeutic radiation dose. Sanguineti et al. (2008) studied 50 patients with oropharyngeal SCC and found that 50% of locoregional

treatment failures occurred as a result of metastatic lymph nodes that were not detected on CT and were treated with a prophylactic dose only.

A novel technology used in radiation therapy is intensity-modulated radiotherapy (IMRT) (Ford et al. 2009). This new technology can deliver a very precise radiation dose to the tumor and spare adjacent radiosensitive organs. In the neck region the spinal cord can be spared despite delivery of a high radiation dose to a neck tumor, and in the chest a high dose can be delivered to a tumor while heart and lungs can be spared. The more precise the dose delivery is, the more important becomes precise tumor delineation. Tumor delineation based on CT has a high interobserver variability, caused by difficulty in determining the precise boundary of the tumor. FDG PET/CT may contribute to improved tumor delineation and to reduce the interobserver variability, which will probably be just as valuable in ATC as in head and neck SCC. The use of PET imaging of hypoxia in various cancer types is reviewed by a number of authors (Krohn et al. 2008, Lucignani 2008, Dunphy and Lewis 2009, Lapi et al. 2009, Piert 2009, Laking and Price 2010). ^{18}F labeled fluoromisonidazole (FMISO), ^{18}F-labeled Fluoro-5-deoxy-α-D-arinofuranosyl-2-nitroimidazol (FAZA), and Cu-64-labeled diacetyl-*bis*(N4-methylthiosemicarbazone) (CuATSM), or other radiopharmaceuticals targeting hypoxia may be useful in radiation therapy planning of patients with ATC and in poorly differentiated carcinoma.

Important limitations of our study are the retrospective design and the low patient number. ATC is a rare cancer with very poor prognosis and most patients will have advanced disease at the time of the primary diagnosis. FDG PET/CT will not add useful information to conventional imaging in many of these patients. Our results should encourage the initiation of prospective studies to elucidate the most effective use of FDG PET in patients with ATC.

Because of the dismal prognosis of ATC, research is ongoing in the pursuit of novel and more effective oncologic treatments for that cancer. As with other aggressive thyroid cancers, FDG PET may be useful in early prediction of treatment response in patients with ATC. FDG PET may have an important role as a surrogate endpoint for assessing the efficacy of new cancer treatments in ATC (Shankar et al. 2006, Larson and Schwartz 2006).

9.5 PET in patients with medullary thyroid carcinoma

In most studies performed on the use of FDG PET in patients with residual or recurrent MTC, PET has been compared to other nuclear medicine or radiologic imaging

procedures (Gasparoni et al. 1997, Conti et al. 1999, Diehl et al. 2001, Szakáll et al. 2002, de Groot et al. 2004, Iagaru et al. 2007). In our study we did not compare the PET findings with other imaging modalities. Rather, the results of US, CT, or MRI were used to confirm the PET findings when cytology or histology was not available. Our focus was primarily on the evaluation of results on FDG PET as a prognostic indicator in patients with MTC. Our results clearly indicated that the presence of FDG avid residual or recurrent lesions were associated with an unfavorable prognosis, while a negative FDG PET was associated with indolent disease even in patients with high calcitonin levels.

Some authors have concluded that FDG PET is a promising tool in the management of patients with MTC with a good performance compared to other imaging modalities while others have found a limited usefulness of FDG PET restricted to patients with aggressive disease. Giraudet et al. (2007) studied prospectively the performance of FDG PET/CT in 55 MTC patients with persistently elevated calcitonin after primary surgery. They concluded that FDG PET has no place in routine imaging of MTC. Furthermore, they concluded that FDG PET had a low value as a prognostic indicator in patients with MTC. Oudoux et al. (2007), however, found that FDG PET/CT was useful in staging patients with progressive MTC. They suggested that the intensity of the FDG uptake measured as SUVmax may be a prognostic indicator. Ong et al. (2007) found FDG PET/CT to be potentially useful in patients with MTC, particularly in patients with calcitonin levels above 290 pmol/L (1000 pg/mL). Both of these studies support our results, indicating that the more aggressive the MTC, the better FDG performs compared to other imaging modalities.

However, FDG PET may detect disease even in patients with low calcitonin levels, particularly when calcitonin doubling time is short (Barbet et al. 2005). Thus, not only the level of calcitonin is important for lesion detection on FDG PET, but also the calcitonin doubling time (Barbet et al. 2005, Oudoux et al. 2007, Giraudet et al. 2008). A limitation of a number of previous studies is that only the level, not the calcitonin doubling time has been considered. This is probably a partial explanation as to why different authors indicate a wide variation for the level below which diagnostic imaging is unlikely to localize residual or recurrent disease (Yen et al. 2003, Giraudet et al. 2007, Ong et al. 2007).

The lowest calcitonin level for a PET positive patient in our study was 113 pmol/L (390 pg/mL), however, the calcitonin doubling time was only 11 months. Neck and mediastinal metastatic lymph nodes were confirmed. All other patients with localizable disease had calcitonin levels higher than 287 pmol/L (977 pg/mL). According to the most

recent Medullary Thyroid Cancer Managament Guidelines of the American Thyroid Association, postoperative MTC patients with calcitonin <44 pmol/L (150 pg/mL) should be evaluated primarily with neck US (Kloos et al. 2009). Distant metastases may still occur, but they will usually be small and difficult to detect on any imaging modality (Yen et al. 2003, Koopmans et al. 2008). Tisell et al. (1986) were not able to localize residual or recurrent disease by any radiologic procedure in MTC patients with postoperative calcitonin levels <29 pmol/L (100 pg/mL). However, since 1986 there has been a substantial improvement in image resolution of all imaging modalities.

In our study we did not find any statistically significant difference in CEA between the group of patients with indolent disease and the group of patients with progressive disease. Our findings were consistent with Oudoux et al., who did not find any significant correlation between SUVmax and CEA doubling time (Oudoux et al. 2007). Barbet et al. (2005) concluded that calcitonin doubling time is a better prognostic indicator than CEA doubling time. However, it is important to know that poorly differentiated MTC may be associated with moderate or low calcitonin levels despite large tumor masses and progressive disease (Figure 11). In such patients CEA may be high with a short doubling time (Kloos et al. 2009).

FDG PET seems to be most useful in MTC patients postoperatively when the calcitonin level is >290 pmol/L, when calcitonin doubling time is <10 months, or when there is a disproportion between high CEA and calcitonin. When the use of such limits for calcitonin and CEA is considered, it is important to realize that imaging technology is continuously improving and the ability to detect smaller lesions gets constantly better. Thus, the degree of precision attained for tumor marker limits should change in parallel with improved image technology.

Limitations of our study are the retrospective design, the lack of quantification of the FDG uptake, and the lack of cytologic or histologic verification of numerous lesions detected on imaging. Only a few studies on the performance of FDG PET in patients with MTC have included quantification of the intensity of the FDG uptake (Giraudet et al. 2007, Giraudet et al. 2008, Oudoux et al. 2007). The leading criterion for FDG-PET interpretation in our study was the presence of localized, pathologically increased uptake clearly seen on MIP images as well as on PET/CT fused transaxial, sagittal, and coronal slices. Thus, we cannot tell whether the FDG image intensity was higher in the group of patients who died during the follow-up period compared to those in the group of patients with slowly progressive or stable metastatic

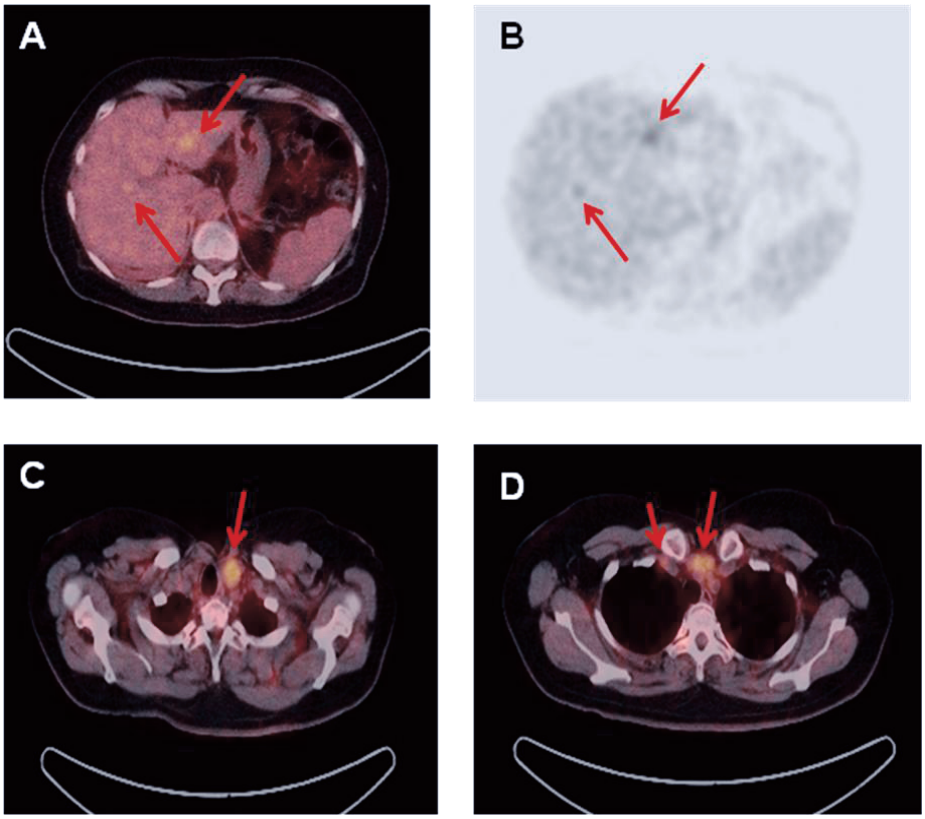


Figure 11. Sixty-three year old female with recurrent aggressive medullary thyroid cancer. FDG PET/CT was performed for restaging. **A:** Transaxial FDG PET/CT upper abdomen. **B:** PET, same transaxial slice as in A. **C.** Transaxial FDG PET/CT lower neck. **D:** Transaxial FDG PET/CT upper chest. PET shows increased FDG-uptake in metastatic lesions in the neck (**C and D**), subpleural / parasternal right side (**D**), in two lesions in the liver (**A and B**), and in the lungs (not displayed). Calcitonin is low, 34 pmol/L, however CEA=38µg/L. As demonstrated in this figure, poorly differentiated MTC may be associated with moderate or low calcitonin levels despite large tumor mass and progressive disease.

disease. One of the reasons why we did not quantify the FDG uptake was that metastases from MTC frequently involve multiple sites with multiple lesions in each site. The lesions are often small and the FDG uptake is frequently heterogeneously distributed not only among but also within individul lesions. Thus, the intensity diffusion effect (partial volume effect) would have introduced substantial error in the SUV measurements. Nevertheless, in future studies we intend to report the SUV. It will then be easier for other research groups to make comparisons with their own studies and for readers to compare different studies. In our study both PET-only (13 patients) and combined PET/CT (16 patients) were used. As discussed in a separate paragraph, PET/CT has a clear advantage compared to stand-alone PET because of higher specificity and improved interpreter confidence (Beyer et al. 2000 , Kluetz et al. 2000,

Palmedo et al. 2006, Nahas et al. 2006, Shammas et al. 2007, Zoller et al. 2007, Miles 2008). Thus, another limitation of our study was that PET without integrated CT was used in almost half of the patients.

Even if our study was not primarily designed to compare PET findings with findings on other imaging modalities, some comparisons were made. In all PET positive patients, one or more of the conventional imaging modalities also gave positive results. PET was false positive in only one patient. In that patient a hypermetabolic lymph node seen on PET corresponded to a slender, enlarged, neck lymph node also seen on US. Repeated US-guided FNA were negative for malignancy. One limitation of FDG PET/CT used in oncology is that FDG is increased not only in malignant lesions, but in acute and chronic inflammatory tissue and in a number of benign tumors as well (reviewed in Zhuang and Alavi 2002, reviewed in Lin and Alavi 2009). Increased FDG uptake in inflammatory lymph nodes is a common problem in PET interpretation. An ideal PET-radiopharmaceutical in oncology should have high uptake in malignant lesions and no uptake in inflammatory or benign lesions.

MTC is a neuroendocrine tumor and PET with ^{18}F-labeled dihydroxyphenylalanine (FDOPA) has been shown to successfully localize residual and recurrent disease (Hoegerle et al. 2002). In a recently published study of 26 patients with MTC, Luster et al. (2010) found that FDOPA PET/CT with contrast enhanced CT was superior to CT in detecting residual or recurrent MTC. FDOPA is the precursor of dopamine, and Gourgiotis et al. (2003) have reported a case in which a metastatic lesion was detected on PET-scanning with 6-[^{18}F]-fluorodopamine. Jager et al. (2008) have reviewed basic aspects and emerging clinical applications of FDOPA PET in neuroendocrine tumors in general, including MTC. The mechanism of dopa and dopamine uptake and retension in neuroendocrine tumors is not fully understood (Kauhanen et al. 2009).

Some studies have evaluated the performance of FDOPA PET compared to FDG PET in patients with residual or recurrent MTC (Hoegerle et al. 2001, Beuthien-Baumann et al. 2007, Koopmans et al. 2008, Beheshti et al. 2009, Marzola et al. 2010). Based on these studies of small patient series, FDOPA may seem to be superior to FDG PET for lesion detection in patients with residual or recurrent MTC.

In a recent study, Beheshti et al. (2009) found that FDOPA detected more lesions than FDG PET/CT. For lesions with uptake of both radiopharmaceuticals, SUVmax was significantly higher for FDOPA compared to FDG (mean 20±10 *vs.* 7±3; $P<0.001$). Also, the specificity was higher for FDOPA, mainly because FDOPA did not concentrate in

inflammatory lesions as much as FDG did. Among the 26 patients studied, only one patient had calcitonin doubling time <6 months and in that patient FDG uptake was more intense than FDOPA uptake.

Koopmans et al. (2008) compared the performance of FDG and FDOPA PET/CT in 21 patients with biochemical residual or recurrent MTC. They found that patients with indolent MTC were prone to have positive FDOPA PET and negative FDG PET, while patients with more aggressive cancer were prone to have negative FDOPA and positive FDG PET. To explain the conflicting uptake of FDOPA and FDG, the authors suggested that shorter calcitonin and CEA doubling times are associated with dedifferentiation with decreased tumor FDOPA metabolism and increased tumor glucose metabolism.

In a review article on FDOPA PET in neuroendocrine tumors (NET), Jager et al. (2008) reported that their own unpublished data indicate that FDOPA is superior to FDG PET in patients with MTC, particularly when tumor marker doubling time is long.

Marzola et al. (2010) performed PET with both FDG and FDOPA in 18 patients with MTC and rapidly increasing calcitonin. They found FDOPA PET/CT to be highly sensitive and to have a potential complementary role to FDG PET/CT in detecting metastatic lesions. Combined FDOPA and FDG PET/CT performed better than conventional imaging. The higher the SUVmax on FDG PET, the more aggressive was the tumor.

These studies support our findings: In patients with aggressive MTC, FDG PET is prone to be positive. In slowly growing residual or metastatic MTC, however, FDOPA may be superior to FDG. Thus, FDG PET and FDOPA PET seem to contribute with complementary information in patients with MTC (Marzola et al. 2010). In the 2009 American Thyroid Association guidelines on the management of MTC, FDG and FDOPA PET are both suggested as optional imaging procedures in patients with a detectable but modestly elevated postoperative serum calcitonin (Kloos et al. 2009).

In a recent study, Ong et al. (2007) reported a per-patient sensitivity of 62% for detection of residual or recurrent MTC with FDG PET in patients with elevated calcitonin levels. In this study PET was classified as true positive if the findings were positive on histopathology, if a detectable lesion was present at the corresponding site on any conventional imaging studies, or if an increase in lesion size was seen on follow-up imaging. Thus, patients with elevated calcitonin without other evidence of disease were called negative.

In our study on MTC, FDG PET was true positive in 13 out of 29 patients, which resulted in sensitivity of 44%. We defined the sensitivity (%) as the number of patients with a true positive PET divided by the total number of patients with increased level of calcitonin multiplied by 100. Thus, we considered all patients with elevated calcitonin independent of the findings on any imaging modality to have residual or recurrent disease. This explains our much lower sensitivity of 44% compared to Ong et al. (2007) and Koopmans et al. (2008). We did not include any control patients, and thus it does not make sense to calculate specificity.

Koopmans et al. (2008) found a per-patient sensitivity of 62% for FDOPA and 24% for FDG. Like Ong et al. (2007) they called any patients with elevated calcitonin without other evidence of disease negative. There is no obvious reason why their sensitivity for FDG PET was that low. The important message is not the sensitivities per se but the difference between FDOPA and FDG PET.

In the work by Luster et al. (2010), the per-patient sensitivity of FDOPA PET/CT in patients with MTC was calculated to 74%. They too defined sensitivity as the ratio between the sum of true-positive and false negative patients to the number of patients with confirmed malignancy on histology or clinically on follow-up. Based on information on patient characteristics, history and findings presented in Table 1 in the article, recalculated sensitivity is 57% if all patients with increased level of calcitonin are used in the denominator of the equation.

Thus, when comparing the sensitivity of PET for detecting residual or recurrent MTC between different studies, an understanding of how the diseased patients are defined is crucial. Furthermore, it is crucial to discriminate between per-patient sensitivity and per-lesion sensitivity. Unless a control group without MTC is included, calculation of specificity does not make sense.

In addition to FDOPA, other amine precursors may also be useful PET radiopharmaceuticals in patients with MTC. The thyroid C-cells and MTC produce serotonin and 5-Hydroxytryptophan (5-HTP), a serotonin amino precursor. PET/CT with ^{11}C-labeled 5-HTP (^{11}C-5-HTP) may be a useful complement to conventional imaging in patients with neuroendocrine tumors including MTC (Orlefors et al. 2005, Nikolaou et al. 2010). Using ^{11}C-5-HTP PET/CT, Nikolaou et al. detected more liver metastases in one patient with metastatic MTC compared to CT, MRI and ^{111}In pentetreotide SPECT. Orlefors et al. studied 18 patients with histologically confirmed neuroendocrine tumors with ^{11}C-5-HTP, and

compared the findings with CT. However, no patients with MTC were included. All lesions showed high 5-HTP uptake. One advantage of 5-HTP seemed to be high tumor-to-background uptake for liver metastases. An important disadvantage of ^{11}C-5-HTP is the short 20 min half-life of ^{11}C. No studies have so far compared the performance of ^{11}C-5-HTP with FDG or FDOPA in any neuroendocrine tumors.

A characteristic feature of neuroendocrine tumors is the high density expression of somatostatin receptors (SSTR) on their cell membranes (de Herder et al. 2005, Conry et al. 2010). Somatostatin receptors 2 (SSTR2) and 5 (SSTR5) are the most common subtypes in MTC, however, the density is low compared to most other neuroendocrine tumors. The indium-111 (^{111}In) labeled somatostatin receptor analogue ^{111}In-pentetreotide (OctreoScan, Mallinckrodt Medical, Inc, St. Louis, MO, USA) has been used in functional imaging with planar and SPECT gamma cameras in neuroendocrine tumors including MTC for almost 20 years (de Herder 2005). During the last 10 years, ^{99m}Tc-labeled somatostatin analogues have been introduced as well. In one study ^{99m}Tc-EDDA-HYNIC-TOC was shown to be superior to ^{111}In-pentetreotide in the detection of SSTR-positive tumors (Gabriel et al. 2003). PET with gallium-68 (^{68}Ga) labeled somatostatin receptor analogues have been shown to be superior to ^{111}In-pentetreotide in a variety of neuroendocrine tumors (Buchmann et al. 2007, Srirajaskanthan et al. 2010). PET has a much higher spatial resolution compared to gamma cameras, and a further advantage of PET is the possibility of precise tracer uptake quantification.

In a recent study, Conry et al. (2010) compared the performance of the somatostatin receptor analogue ^{68}Ga-DOTA-TATE with FDG PET/CT for detection of residual or recurrent MTC in 18 patients. FDG identified more lesions than ^{68}Ga-DOTA-TATE, however, neither FDG nor ^{68}Ga-DOTA-TATE could fully map the extent of the disease. The authors suggested that ^{68}Ga-DOTA-TATE or other labeled somatostatin receptor analogues might potentially be useful primarily in identifying patients eligible for targeted radionuclide therapy with somatostatin analogues.

Kayani et al. (2008) compared FDG and ^{68}Ga-DOTA-TATE PET/CT in 38 patients with primary or recurrent neuroendocrine tumors and compared the findings on PET with tumor grade based on Ki-67 and mitotic rate. They found that well-differentiated NET showed greater avidity for ^{68}Ga-DOTA-TATE while poorly differentiated NET showed greater avidity for FDG. The lower the histologic grade, the higher was the FDG uptake. They concluded that ^{68}Ga-DOTA-TATE PET/CT was a useful novel imaging procedure for NET

and superior to FDG PET/CT for imaging well-differentiated NET. PET/CT imaging with both ^{68}Ga-DOTA-TATE and FDG might have a potential for a more comprehensive tumor assessment in intermediate- and high-grade tumors. No patients with MTC were included in their study, but it is reasonable to suppose that their conclusion may be valid for patients with MTC as well. In our study on patients with MTC, we did not register the histologic grade. We used disease progression as a measure for a standard of reference.

10. SUMMARY OF FINDINGS, CONCLUSIONS AND FUTURE PERSPECTIVES

"Writing papers is not for the purpose of showing how much we know and what we are doing, but is an opportunity to learn." William J Mayo, 1935.

10.1 Summary of findings and conclusions

Imaging with positron emission tomography (PET) using the fluorine-18 labeled deoxyglucose analogue 2-deoxy-2 [^{18}F]fluoro-D-glucose (FDG) is not indicated for any benign thyroid disease. However, a thorough knowledge of the characteristics of uptake in the normal thyroid gland and in benign thyroid diseases is important not only to the nuclear medicine physician or radiologist interpreting whole body PET, but also to the referring physician. The FDG uptake in a normal thyroid gland is low, consistent with the assumption that free fatty acids are the main source of energy in thyroid cells.

We found diffusely increased FDG uptake on whole-body PET with integrated CT (PET/CT) as an incidental finding in 138 out of 4732 patients (3%) with non-thyroidal malignancy (paper I). The finding was associated with chronic autoimmune thyroiditis with or without the presence of hypothyroidism. The intensity of the FDG uptake was neither suggestive of the degree of the hypothyroidism nor correlative with the level of thyroid peroxidase autoantibody (TPOAb). If thyroid functional status is not known, the finding of diffusely increased FDG uptake in the thyroid gland should result in laboratory assessment of FT4, TSH and TPOAb in order to disclose a possible hypothyroidism.

As opposed to diffusely increased FDG uptake, focally increased uptake in the thyroid gland is associated with a high rate of malignancy. We found focally increased FDG uptake in the thyroid gland as an incidental finding on whole-body PET/CT in 79 out of 7347 (1.1%) of patients with non-thyroidal malignancy, and malignancy was most highly likely or histologically confirmed in 17 out of 48 patients (35%) with adequate follow-up (paper II). The most common malignancy was papillary thyroid cancer accounting for 12 out of the 17 malignancies. In our group of patients the intensity of the FDG uptake in the lesions measured as standardized uptake value SUV, did not discriminate between benign and malignant lesions. Regardless of the SUVmax value, an incidental finding of a focal high uptake in the thyroid gland should be reported as a possible primary or secondary thyroid cancer and an

ultrasound evaluation with possible ultrasound guided FNA should be recommended for further follow-up.

The only well established indication for the use of FDG PET in thyroid cancer is in patients with differentiated thyroid carcinoma (DTC) with a negative post-therapy radioiodine scan and persistently elevated or increasing blood levels of thyroglobulin (Fletcher et al. 2008, Robbins and Larson 2008, Dong et al. 2009, Chao 2010, Cooper et al. 2009, Heston and Wahl 2010, Miller et al. 2010). In addition to localizing residual or metastatic disease not detected by other imaging modalities in these radioiodine negative, Tg-positive patients, there is good evidence that the presence of FDG-avid metastatic lesions indicates increased risk of recurrence and of cancer-associated mortality, while negative FDG-PET results indicate good prognosis. FDG PET performs best at higher Tg-levels (Tg>10 μg/l) (Wang et al. 2000, Wang et al. 2001, Robbins et al. 2006).

The follow-up of patients with DTC having increased level of thyroglobulin autoantibody (TgAb) constitute a particular challenge as thyroglobulin (Tg) measurements are unreliable because of laboratory analytic interference of TgAb in the Tg-assays (Spencer et al. 1998, Chung et al. 2002, Spencer 2004, Spencer et al. 2005). Based on our study of 17 TgAb positive, radioiodine negative patients with DTC, we found that FDG-avid residual lesions were associated with aggressive disease, persistently increased TgAb and poor outcome (paper III). A negative FDG PET was associated with the absence of active disease and disappearance of TgAb over time. Thus, we found that FDG PET seems to have the same prognostic value as reported for TgAb negative, radioiodine negative DTC-patients with increased Tg. Furthermore, our results indicated that persistently elevated blood level of TgAb may be associated not only with residual disease per se, but may also be indicative of an unfavorable prognosis.

Routine use of FDG PET has not been established in patients with anaplastic thyroid carcinoma (ATC). Our results based on the study of 16 patients with ATC (paper IV), indicate that FDG PET/CT should be considered for routine use in inital staging, in defining target volume in radiation therapy planning, in evaluation of treatment response, in re-staging, and in follow-up of patients with ATC. We found that all primary tumors, all residual and recurrent disease, all lymph node metastases and all distant metastases showed consistently high to intense FDG uptake. According to the medical records, in 8 out of the 16 patients with ATC (50%), the PET findings had an impact on the management of the patients.

As for patients with ATC, routine use of FDG PET has not yet been established in patients with medullary thyroid carcinoma (MTC). FDG PET has, however, been compared to conventional imaging and to other nuclear medicine procedures in a number of studies (Brandt-Mainz et al. 2000, Diehl et al. 2001, Szakáll et al. 2002, de Groot et al. 2004). These studies indicate that FDG PET may be complementary to conventional imaging in patients with suspected residual or recurrent disease based on the presence of persistently elevated calcitonin levels after primary surgery. Based on our study of 29 patients with residual or recurrent MTC, including long time follow-up, we found that the result of FDG PET might have prognostic value (paper V). Patients with elevated calcitonin but negative FDG PET seemed to have indolent disease, while patients with positive FDG-PET seemed to have more aggressive disease with a less favorable prognosis. However, not only the calcitonin level, but also the calcitonin doubling time might be important as a prognostic indicator. FDG PET might be useful primarily in patients with more aggressive residual or recurrent MTC; that is in patients with a calcitonin level above 260 pmol/L (>900 pg/mL) or a doubling time shorter than 10 months.

10.2 Future perspectives

10.2.1 *New radiopharmaceuticals and new applications*

One limitation of PET/CT in oncology in general, including thyroid cancer, is that FDG uptake is increased not only in malignant lesions, but in acute and chronic inflammations and in a number of benign conditions and benign tumors as well. These important limitations have been reviewed by a number of authors (Bogsrud et al. 2006, Bogsrud and Lowe 2006, Shreve and Bui 2009, Lin and Alavi 2010, Liu et al. 2010). In the future new radiopharmaceuticals that better differentiate between cancer and inflammatory tissue will probably become available.

The use of ^{18}F labeled 3-[^{18}F]-3-deoxythymidine (FLT) as an alternative to FDG has been reviewed by a number of authors (Dunphy and Lewis 2009, Hicks 2009, Vallabhajosula 2009c, Weber 2010). FLT is used to image cell proliferation. FLT is not incorporated into DNA, but is rather a substrate for the enzyme thymidine kinase (TK). This enzyme is particularly active during cell division, but the activity is very low in resting cells. FLT undergoes phosphorylation and is trapped in the cells and the uptake is closely correlated with tumor proliferation. FLT seems to better differentiate between cancer and inflammation compared to FDG PET and may be useful in therapy evaluation and assessing prognosis. A

disadvantage of FLT is physiological high uptake in bone marrow and liver, therefore, FLT may be less useful in detection of metastases to these organs. Another limitation of FLT is lower tumor uptake compared to FDG. Fluorine-18 labeled 1-(2′-deoxy-2′-[^{18}F]fluoro-β-D-arabinofuranosyl) thymin (FMAU) is another marker of DNA synthesis (Dunphy and Lewis 2009). Lower bone marrow uptake compared to FLT favours detection of skeleton metastases.

Not only glucose metabolism and DNA-synthesis are increased in malignant cells. Amino acid uptake and protein synthesis are increased as well. Carbon-11 labeled ([^{11}C]methyl)-L-methionine (MET) is the most commonly used amino acid tracer for PET imaging (Dunphy and Lewis 2009). Most publications on MET PET have concerned brain tumors. A limitation of FDG PET for detection and characterization of brain metastasis is the normal high uptake of FDG in the brain cortex. Amino acid tracers may have an advantage in the detection of brain metastases as these tracers show normal low brain uptake but high tumor uptake. Their possible usefulness in patients with brain metastases from thyroid cancer has not yet been published. Phan et al. (2008c) compared FDG PET/CT with MET PET/CT in 20 patients with differentiated thyroid cancer with suspected recurrent or metastatic disease. MET PET was not superior to FDG PET in the detection of recurrent disease, but MET PET and FDG PET seemed to give complementary information.

Other amino acid PET tracers are the ^{18}F-labeled L-tyrosine analogue *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) and recently *O*-([^{18}F]fluoro-methyl)-D-tyrosine (FMT). PET with amino acid tracers have all been used in research in humans for tumor detection and for monitoring cancer therapy including early phase prediction of the effect of radiation therapy (Dunphy and Lewis 2009, Murayama 2009, Vallabhajosula 2009c). A number of other tracers targeting amino acid metabolism and protein synthesis have been developed and investigated in numerous animal and human research projects.

In addition to FDOPA, ^{11}C-labeled hydroxytryptophan (HTP) may be useful in the detection and characterization of metastatic MTC (Hoegerle et al. 2002, Orlefors et al. 2005, Beuthien-Baumann et al. 2007, Koopmans et al. 2008, Beheshti et al. 2009, Marzola et al. 2010, Nikolaou et al. 2010). Both of these new radiopharmaceuticals show less intense uptake in inflammatory tissue compared to FDG and both are more specific for neuroendocrine cancers including MTC than FDG. ^{68}Ga-labeled somatostatin receptor analogues (e.g. DOTATOC, DOTATATE, and DOTANOC) may be useful in selection of patients with MTC eligible for radionuclide treatment with somatostatin receptor analogues (e.g. ^{177}Lu or ^{90}Y octreotate) (Conry et al. 2010). For pretreatment dosimetry calculations, however, labeling

with ^{64}Cu may be more suitable compared to ^{68}Ga because of a more favorable half-life (12.8 h for ^{64}Cu *vs.* 1.14 h for ^{68}Ga).

The tremendously expanding use of of FDG PET in assessment of cancer therapy has been reviewed by a number of authors (Juweid and Cheson 2006, Shankar et al. 2006, Weber 2009, Weber 2010). A number of authors have reviewed the use of new targeting drugs like tyrosine kinase inhibitors in patients with advanced thyroid cancer (Pinchot et al. 2008, Pinchot et al. 2009, Chougnet et al. 2010, Sherman et al. 2010a). Clinical trials evaluating these new targeting drugs in patients with advanced thyroid cancer of follicular cell origin as well as of C-cell origin are showing promising results (Frank-Raue et al. 2007, Dawson et al. 2008, Sherman et al. 2008, Schlumberger and Sherman 2009, Carr et al. 2010, Frank-Raue et al. 2010, Lam et al. 2010, Sherman 2010a). FDG PET is being used in the evaluation of treatment effect of these new cytostatic drugs in different cancer types like renal cell carcinomas and gastrointestinal stromal tumors (GIST). A recent paper reported the use of FDG PET/CT in assessment of early treatment response of the multitargeted tyrosin kinase inhibitor sunitinib in patients with DTC and MTC (Carr et al. 2010). It is expected that PET/CT may be used extensively in future development and evaluation of new drugs for treatment of different cancer types including aggressive thyroid cancer (Juweid and Cheson 2006, Shankar et al. 2006).

Radiation therapy and concomitant chemotherapy is the primary treatment of ATC, and adjuvant radiation therapy may be used in aggressive DTC and MTC after incomplete surgery according to international guidelines (Cooper et al. 2009, Kloos et al. 2009). FDG PET may be useful in radiation therapy planning by aiding the definition of the radiation target volume (Ford et al. 2009).

Molecular imaging of hypoxia is comprehensively reviewed by a number of authors (Krohn et al. 2008, Lucignani 2008, Dunphy and Lewis 2009, Lapi et al. 2009, Piert 2009, Laking and Price 2010). Hypoxic tumor regions are less sensitive to both cytotoxic drugs and to radiation therapy. Severely hypoxic cells require two to three times higher radiation dose compared to normal oxygenated cells for good treatment response. Thus, tumor hypoxia in aggressive cancers is an indicator of poor prognosis. Water labeled with ^{15}O has been used for years to measure tumor perfusion (Laking and Price 2010). The half-life of ^{15}O is 122 seconds and is therefor not suitable for clinical use. New PET radiopharmaceuticals for imaging hypoxia like ^{18}F labeled fluoromisonidazole (FMISO), ^{18}F-labeled [^{18}F]fluoro-5-deoxy-α-D-arinofuranosyl-2-nitroimidazol (FAZA) and ^{64}Cu-labeled [^{64}Cu]Copper(II)-diacetyl-bis-(N4-

methylthiosemicarbazone) (CuATSM) may be used to predict treatment response and survival. Information on hypoxic regions within a tumor may be used to redistribute the radiation dose within the tumor volume with higher doses to hypoxic areas (Krohn et al. 2008, Dunphy and Lewis 2009, Lapi et al. 2009). Such optimization of dose distribution within tumors that tend to be hypoxic, like ATC, may improve the treatment effect. More clinical research is needed before hypoxia imaging and hypoxia-guided IMRT can be routinely used. Anaplastic thyroid carcinoma could be a good model for such trials.

Apoptosis, or programmed cell death, is one of the mechanisms by which tumor cells are affected by radiation therapy and antineoplastic agents. Molecular imaging of apoptosis has been reviewed by a number of authors (Blankenberg 2008, Tait 2008, Reshef et al. 2010). The first nuclear medicine biomarker used for apoptosis imaging was ^{99m}Tc-labeled annexin V. Later, derivatives of annexin V labeled with ^{18}F, ^{64}Cu, and ^{124}I have been developed for PET. Recently ^{11}C or ^{18}F labeled small-molecule PET probes targeting various steps in the apoptotic cascade like caspatase activity, collapse of mitochondrial membrane potential and detection of apoptotic membrane imprints have been developed. PET-imaging of apoptosis may be used clinically in the future to monitor treatment effect in ATC and other aggressive thyroid cancers.

Angiogenesis is the formation of new blood vessels and is a fundamental process in the growth of malignant tumors. Multimoadlity molecular imaging of tumor angiogenesis has been comprehensively reviewed by Cai and Chen (2008). Angiogenesis inhibitors and other new targeted molecular therapies for dedifferentiated thyroid cancer have recently been reviewed by Antonelli et al. (2010). A number of angiogenic growth factors, receptors and steps in the angiogenetic cascade can be targeted by PET radiopharmaceuricals (Cai and Chen 2008). Clinical PET imaging of angiogenesis may be used in the future in order to monitor tumor growth and treatment response. Cancer therapy monitoring with PET imaging of angiogenesis for assessment of antiangiogenic therapy in patients with aggressive thyroid cancer may be used in the future.

10.2.2 *^{124}I PET/CT*

It is expected that the ^{124}I PET/CT will become a useful tool in patients with DTC in the future. The advantages of PET/CT using ^{124}I over SPECT/CT using ^{123}I, ^{131}I or ^{99m}Tc-pertechnetate, are primarily related to the higher spatial resolution and corresponding higher signal, and superior physical sensitivity (counts/MBq) of a PET scanner compared to a

gamma camera (Freudenberg et al. 2008, Phan et al. 2008, Capoccetti et al. 2009). ^{124}I PET/CT has been shown to localize more radioiodine avid lesions in patients with DTC compared to ^{131}I or ^{123}I on a SPECT system, and dosimetric calculations based on ^{124}I-PET/CT have an advantage over ^{131}I and even over ^{123}I SPECT/CT (Jentzen et al. 2008).

10.2.3 *Improved technology*

PET technology is constantly improving (Pichler et al. 2008, Mawlawi and Townsend 2009). The introduction of new reconstruction algoritms, time-of-flight detection and more detector rings make the new generation of scanners more effective with improved spatial resolution resulting in better signal (higher SUV). The new scanners are faster and the patient turnover can be increased. Modern PET-scanners have integrated multislice CT and are capable of performing state of the art diagnostic CT with intraveneous contrast. Despite the evidence that the use of contrast enhancement for CT imaging when doing PET/CT is less important, radiologists and nuclear medicine phycicians in Europe are expecting that the proportion of CT with contrast enhancement as an integrated part of PET/CT will increase in the future (Cuocolo et al. 2009).

Modern PET//CT scanners are capable of performing dynamic acquisitions potential useful in the development of new drugs, new radiopharmaceuticals and in the evaluation of early treatment response.

There are high expectations for the emergance of PET/MRI. In PET/MR the integration of PET and MRI is possible with simultaneous acquisition of PET and MRI datasets (Hicks and Lau 2009, Wehrl et al. 2009, Pichler et al. 2010). Shao et al. (1997) have published their developement of a prototype PET/MRI scanner. PET/MRI systems dedicated for brain imaging have been designed. However, combined PET/MRI are more complicated and challenging to develop compared to PET/CT systems, and there is probably still a way to go before such systems will be used in clinical routine for whole-body imaging (Hicks and Lau 2009, Wehrl et al. 2009, Pichler et al. 2010). Attenuation correction is possible with MRI but is more complicated compared to CT. Motion correction of PET images based on special simultaneously acquired MRI sequences seems to be possible and this will improve the PET images. An additional advantage of PET/MR compared to PET/CT is the absence of additional ionizating radiation from the MRI.

Patient and organ motions that cause blurred PET images and misregistration between PET and CT in combined PET/CT-scanners represent limitations in PET imaging (Daouk et

al. 2008). Respiratory gated PET acquisition (4-dimensional or 4D PET) is feasible and will reduce the motion artefacts and the problem with misregistration. As a result, this technology will probably be used extensively in the future (Farrar et al. 2008, Mawlawi and Townsend 2009).

Clinical PET has expanded tremendously the last few years and it will continue to expand. The use of FDG PET/CT in patients with thyroid cancer today is far from reaching its full potential and new applications will be put into use during the next few years. Furthermore, the number of radiopharmaceuticals available for clinical PET-imaging will increase, not only in order to better differentiate between malignancy and inflammation, but also to target different molecular characteristics caused by malignant transformation and response to therapy. New PET applications are expected to influence the management of patients with thyroid cancer to a great extent. Faster and more effective scanners will result in a more rapid patient turnover, which will contribute to making PET scanning more available for a higher number of patients.

10.3 Final remarks

It has been very encouraging for the writing of this thesis to recognize that our articles have been used as references in a number of international text books and articles in international medical journals. It has been particularly encouraging to recognize that the articles have been used as references in Drs. Heston and Wahl´s (2010) recent review article on molecular imaging of the thyroid gland, in the 2009 American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer (Cooper et al. 2009), in the 2009 National Comprehensive Cancer Network Task Force Report: Clinical Utility of PET in a Variety of Tumor Types (Podoloff et al. 2009), in the 2009 edition of Dr. Richard L. Wahl´s highly regarded textbook Principles and Practice of PET and PET/CT (Wahl 2009c), and in the 2009 edition of Lin and Alavi´s reputable textbook: PET and PET/CT: a Clinical Guide (Lin and Alavi 2009a).

According to data collected from 1131 patients by the National Ongologic PET Registry (NOPR) in the USA, physicians changed their intended patient management in 36% of the patients with thyroid cancer as a result of the PET-findings (Hillner et al. 2008b, Barry Siegel personal email communication October 6 and 7, 2009). This number is in accordance with the 37% change in intended patient management across all cancer types (Hillner et al. 2008a). FDG PET used in radioiodine negative Tg positive patients was already covered by

reimbursement from Centers for Medicare and Medicaid Services (CMS), and the 1131 patients included in the NOPR study were examined with FDG PET on indications not previously covered by CMS. Based on the articles included in this thesis, the data collected by NOPR, and data presented in numerous past and recent articles on PET and thyroid cancer referred to in this thesis, it is expected that the general utilization of and the indications for the use of PET in patients with different types of thyroid cancers will continue to expand.

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12. ERRATA LIST

Page	Location / paragraph	Original	Corrected
5	1	advice	advices
5	2	Jimmy Jones´s	Jimmy John´s
5	3	from him	from whom
5	3	One year sent	One year spent
5	3	skilful	skillful
5	3	in Oslo in 1989 was	in Oslo in 1989 has
6	2	acquanted	acquainted
6	3	white beared	white bearded
6	4	has on occation	has on occasion
6	4	surgey	surgery
7	1	From the Eva	From Eva
7	1	I have have acquired	I have acquired
7	2	boss	supervisor
10	2	artefacts	artifacts
13	3	kinetic energy and the higher	kinetic energy. The higher
16	2	biologic	biological
17	1	deoxyphenylalanine	3,4-dihydroxy-6[^{18}F]-phenylalanine
18	1	3-[18F]-3-deoxythymidine	3-[^{18}F]-3-deoxythymidine
18	2	*O*-(2-[^{18}F]fluoroethyl)-L-Tyrosine	*O*-(2-[^{18}F]fluoroethyl)-L-tyrosine
18	2	*O*-([18F]fluoro-methyl)-D-Tyrosine	*O*-([^{18}F]fluoromethyl)-D-tyrosine
18	3	fluoro-5-deoxy-α-D-arinofuranosyl-2-nitroimidazol	[^{18}F]fluoro-5-deoxy-α-D-arinofuranosyl-2-nitroimidazol
20	3	thyroid cancer the intensity	thyroid cancer, the intensity
20	4	modelling	modeling
22	4	St. Louise, MO	St. Louis, MO
22	4	mid seventies	mid-seventies
22	4	for clinical use	in clinical use
22	4	mid eighties	mid-eighties
22	5	speeded up	sped up
23	Figure text	Figur 5.	Figure 5.
23	Figure text	The University Clinic the	University Clinic the
26	1	cells, but is seen in	cells, but it is also seen in
26	2	incidental findings	incidental finding
28	1	FDG uptake, but also	FDG uptake but also
29	3	lesions on FNA appears	lesions on FNA appear
30	2	is descends	is descended
31	4	lymphoma the typical	lymphoma, the typical
34	3	DTC and MTC, but may be	DTC and MTC but may be
35	2	used used	used
36	2	tumors, but in some	tumors but in some
39	4	thyroid cancer: when DTC	thyroid cancer, when DTC
40	Figure text	respons	response
42	1	immunometric Tg-assay Tg	immunometric Tg-assay, Tg
43	2	As discussed already	As already discussed
45	3	if practical achievable.	if achievable.
48	1	*P*=0,089	*P*=0.089
48	1	*P*=0,675	*P*=0.675
49	2	confirmed in 36 out of 48	confirmed in 31 out of 48
51	3	was performed, by histology	was performed by histology
57	3	12 min	12 minutes
59	4	In paper I, II and III	In papers I, II and III
61	2	fat uptake is low the scan	fat uptake is low, the scan
64	3	to tumor size, but to tumor	to tumor size but to tumor
66	3	corrections the corrected	corrections, the corrected
66	3	true intensity while	true intensity, while
66	4	are high the finding is a true	are high, the finding is a true
67	1	affects	affect

Page	Location / paragraph	Original	Corrected
67	3	increased uptake and it seems	increased uptake, and it seems
67	4	studies however, the	studies, however, the
68	2	138 patients US-guided	138 patients, US-guided
68	2	eccho	echo
69	1	in ablating	in ablation of
69	2	thyroiditis however, only	thyroiditis, however, only
69	3	(2009) 31 patients	(2009), 31 patients
70	4	thyroid function and some	thyroid function, and some
72	1	*P*<0,001	*P*<0.001
75	3	may however, last	may, however, last
77	5	are common and FDG PET	are common, and FDG PET
77	5	at initial staging, but also	at initial staging but also
78	3	uptake in ATC it is	uptake in ATC, it is
80	1	unfavourable prognosis while	unfavorable prognosis, while
80	3	partly	partial
81	1	resoloution	resolution
87	1	with MTC we did	with MTC, we did
89	3	DTC we found	DTC, we found
89	4	Our results, based on	Our results based on
90	3	3-[18F]-3-deoxythymidine	3-[^{18}F]-3-deoxythymidine
91	3	*O*-([18F]fluoromethyl)-D-tyrosine	*O*-([^{18}F]fluoromethyl)-D-tyrosine
91	4	Hydroxytryptophan	hydroxytryptophan
92	2	respons	response
92	4	Fluoro-5-deoxy-α-D-arinofuranosyl-2-nitroimidazol	[^{18}F]fluoro-5-deoxy-α-D-arinofuranosyl-2-nitroimidazol
92/93	4/1	Cu(II)-diacetyl-bis-(N4-methylthiosemicarbazone)	[^{64}Cu]Copper(II)-diacetyl-bis-(N4-methylthiosemicarbazone)
96	1	NORP	NOPR
99	Ref list	Brenner DJ, Hall EJ.	Line adjusted
99	Ref list	Capoccetti F, Criscuoli B,	Corrected order in list
119	Ref list	Van den Bruel A,… AND van Heerden JA	References seperated by line-shift

IV

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^{18}F-FDG PET in the Management of Patients with Anaplastic Thyroid Carcinoma

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Background: Anaplastic thyroid carcinoma (ATC) is one of the most aggressive solid tumors in humans. The use of positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in ATC has not been studied, and only a few case reports have been published. The objective of this study was to investigate the potential contribution of ^{18}F-FDG PET to the clinical management of patients with ATC.
Methods: All patients with ATC studied with ^{18}F-FDG PET from August 2001 through March 2007 were included. The PET results were correlated with computed tomography, ultrasound, magnetic resonance imaging, bone scan, histology, and clinical follow-up. The FDG uptake was semiquantified as maximum standard uptake value. Any change in the treatment plan as a direct result of the PET findings as documented in the clinical notes was recorded.
Results: Sixteen patients were included. True-positive PET findings were seen for all primary tumors, in all nine patients with lymph node metastases, in five out of eight patients with lung metastases, and in two patients with distant metastases other than lung metastases. In 8 of the 16 patients, the medical records reported a direct impact of the PET findings on the clinical management.
Conclusions: ATC demonstrates intense uptake on ^{18}F-FDG PET images. In 8 of the 16 patients (50%), the medical records reported a direct impact of the PET findings on the management of the patient. PET may improve disease detection and have an impact on the management of patients with ATC relative to other imaging modalities.

Introduction

Anaplastic thyroid carcinomas (ATC) are undifferentiated carcinomas arising from the thyroid follicular cells and comprise 1.6% of all thyroid cancers in the United States (1). ATC are one of the most aggressive solid tumors in humans with a very poor prognosis (1,2). It is not unusual for the tumor volume to double in a span of 1 week (1). Although ATC account for only a small fraction of all thyroid cancers, they are responsible for more than half of the deaths from thyroid cancer. The median survival for patients with localized disease is 8 months and only 3 months for patients with metastatic disease. Most patients die from uncontrolled local tumor growth, regardless of the extent of the disease. Treatment is mainly a combination of radiotherapy, chemotherapies, and surgery (1,2). Patients with small tumors, disease restricted to the thyroid gland or with only local spread, survive longer than patients with more extensive disease. The disease is somewhat more common in females than in males. The mean age at diagnosis is 55–65 years. The most common clinical manifestation is a rapidly growing thyroid tumor, and about 70% of the patients will have local invasion and metastases at the time of presentation. The most common sites for metastases are the regional lymph nodes and the lungs, and less common are metastases to bone marrow and brain. Metastases may also be found in liver, pancreas, adrenal glands, kidneys, skin, and heart. The diagnosis is normally established by fine-needle aspiration biopsy (FNAB). About 20% of the patients with ATC have a history of well-differentiated thyroid carcinoma, and about 20% have a synchronous papillary or follicular thyroid carcinoma. About 50% of the patients have a history of multinodular

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goiter (1,2). Diagnostic imaging with neck ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are used routinely to define the extent of the primary tumor as well as regional and distant spread (1,2).

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is a well-established imaging modality for staging and restaging of thyroglobulin positive, radioiodine negative patients with well-differentiated thyroid carcinoma (3), and a number of studies have shown that ^{18}F-FDG PET may provide important prognostic information about overall survival (4–6). To our knowledge, the use of ^{18}F-FDG PET in ATC has not been studied and only a few pertinent case reports have been published (7–11). The objective of this study was to investigate the potential contribution of ^{18}F-FDG PET to the clinical management of patients with ATC.

Materials and Methods

This study was approved by the Mayo Clinic Institutional Review Board. All patients included had consented to have their clinical data used for research purposes. The study population consisted of all patients with ATC referred for ^{18}F-FDG PET in our institution from August 2001 through March 2007. A further follow-up period through October 2007 was added. The PET studies and written reports were retrospectively reviewed by two experienced PET readers with knowledge of the diagnosis. In cases of discrepancy, a consensus was reached. The results from the PET readings were compared to the status of the disease. The status of the disease was established after evaluation of imaging workup by US, CT, MRI, plain films, bone scans, as well as cytology, histology, clinical notes, and follow-up results within less than 3 months. The PET findings were compared to the findings on other imaging modalities lesion by lesion. Primary tumors, recurrent disease, and lymph node metastases were all confirmed by cytology and when surgery was performed, by histology as well (Table 1). According to this comparison, the PET findings were characterized as true positive (TP), false positive (FP), true negative (TN), and false negative (FN). Further, any change in the treatment plan as a direct result of the PET findings as documented in the clinical notes was recorded.

The FDG uptake in the abnormal lesions was semiquantified as a maximum standard uptake value (SUV_{max}) (Table 2). The SUV_{max} is the decay-corrected ratio of the highest voxel activity within a region of interest to the injected dose corrected for the body weight. A circular region of interest with a fixed diameter of 1.5 cm was placed over the visual hottest part of the hypermetabolic lesions and the uptake was automatically semiquantified as SUV_{max}. The SUV_{max} was measured for all primary tumors and recurrent disease, for the most intense regional and distant lymph node metastases and lung metastases, as well as for other lesions suspected to be metastatic disease.

PET and PET/CT

The ^{18}F-fluoride was produced by an on-site GE Trace Cyclotron (GE Medical Systems, Milwaukee, WI). ^{18}F-FDG (FDG) synthesized by the standard automated Hamacher method.

PET imaging was performed on a GE DLS combined PET/CT scanner (General Electric Medical Systems, Milwaukee, WI) in all patients but one, for which a GE Advance

Table 1. Patient Data

Patient no.	*Sex*	*Age*	*PET*	*Indication for the PET study*	*Histology*
1	M	78	PET/CT	IS	Grade 4 (of 4) ATC
2	M	40	PET/CT	IS	Postradiation (^{131}I and XRT) grade 4 (of 4) ATC transformation of PTC (diagnosed 7 years earlier)
3	F	62	PET/CT	IS	Grade 2 PTC with foci of ATC with SC differentiation. 10 years earlier minimal invasive FTC
4	F	83	PET/CT	IS+R	ATC
5	F	73	PET/CT	IS+R	ATC (SC differentiation)
6	M	76	PET/CT	IS+R	ATC (SC differentiation), metastatic LN = PTC
7	M	58	PET/CT	IS+R+R	Grade 4 (of 4) ATC
8	F	45	PET/CT	IS+R+FU×2	ATC arising from PTC
9	M	71	PET/CT	R+FU	ATC
10	M	68	PET/CT	R	Recurrent grade 4 (of 4) PTC with anaplastic features (1 year after diagnosed grade 2 (of 4) PTC
11	M	40	PET only	R	ATC (pleomorphic type) arising in association with PTC in preexisting goiter (Hashimoto)
12	M	74	PET/CT	R	ATC (sarcomatoid features). 0.9 cm foci of grade 1 PTC also identified
13	F	53	PET/CT	R	ATC (sarcomatoid type) associated with multifocal PTC (Cowden's syndrome)
14	M	55	PET/CT	R+FU×2	Small, localized ATC in dedifferentiated FTC with Hürthle cell changes
15	M	60	PET/CT	R+FU×3	ATC
16	F	54	PET/CT	R+R+FU×4	Grade 3 FTC with foci of dedifferentiation to ATC

PET, positron emission tomography; CT, computed tomography; IS, initial staging; ATC, anaplastic thyroid carcinoma; XRT, external radiation therapy; LN, lymph node; PTC, papillary thyroid carcinoma; SC, squamous cell; FTC, follicular thyroid carcinoma; R, evaluation of treatment/restaging; FU, follow-up PET scan; FU×2, FU×3, and FU×4, follow-up PET scans 2, 3, and 4 times, respectively.

Table 2. SUV_{max} and Correlative Imaging Modalities

Patient no.	*SUV_{max} primary tumor*	*SUV_{max} recurrent disease*	*SUV_{max} lymph nodes metastases*	*SUV_{max} lung metastases*	*SUV_{max} other metastases*	*Correlative imaging modalities*
1	72		36			US, CT
2	15		8.4		6 (bone)	CT, MRI, bone scan
3	12		3.4			US, CT
4	33		17.6	11		US, CT
5	28		10.2	3.8		US, CT, MRI
6	30		4.1			CT, MRI
7	8.5	13.5				US, CT, MRI
8	19		13.2		9.4 (bone)	US, CT, MRI
9			3.5			CT, MRI
10			4.5	4.9		US, CT
11		11	14.9			US, CT, MRI
12		*FP*				CT, MRI, bone scan
13		8.2		38	5.3 (adrenal gland)	US, CT, MRI
14						US, CT
15		7.9		3.4		US, CT
16			*FP*			US, CT
Mean ± SD	27.2 ± 18.9	10.2	11.6 ± 9.5	11		

SUV_{max}, maximum standard uptake value; US, ultrasound; MRI, magnetic resonance imaging; *FP*, false-positive PET finding; SD, standard deviation; CT, contrast enhanced diagnostic computed tomography.

PET Tomograph was used. All of the patients had been fasting for at least 6 hours before injection of FDG. PET emission images from the base of the skull to the proximal thighs were obtained 60 minutes after an intravenous injection of 740 MBq of FDG. Projection data were acquired in 2D mode. Emission images were reconstructed using iterative reconstruction. Attenuation correction was used on all data. The CT data used for attenuation correction in the PET/CT fusion scans and the uncorrected data were available for review. Emission data were corrected for scatter, random events, and dead time losses using the manufacturer's software. Image pixel size was 4.25 mm, displayed in a 128-by-128 array. Standard orthogonal views, as well as maximum intensity projections, were reviewed during scan interpretation.

Diagnostic CT

CT imaging was performed using a General Electric Lightspeed QXI multidetector CT scanner (GE Medical Systems). Five-millimeter (or less) axial slice thickness images were obtained. Intravenous iodinated contrast was used routinely in the absence of contraindications.

Ultrasound/fine-needle aspiration biopsy

All US examinations were performed using a commercially available US machine (Siemens Acuson Sequoia; Siemens, Mountain View, California). Imaging was performed using multifrequency transducers (15L8 and 15L8W) operating at 10 MHz. In patients with a very large mass, 6–8 MHz transducers were also necessary for adequate depth of penetration to evaluate the deeper portion of the mass. Gray scale images of all thyroid nodules were obtained, and color Doppler images were obtained in selected cases.

US-guided FNAB procedures were performed by a radiologist experienced with thyroid FNAB techniques. A "free-hand" method was used to allow for optimum needle adjustment during the procedure. A 10 MHz US transducer was used for continuous real-time needle visualization during needle insertion. Six passes were made into each thyroid nodule using a standard 25-gauge injection needle. The cytological material that was obtained was expelled and smeared onto glass slides. The material was wet-fixed in a 95% alcohol solution, and the smears were stained using a modified Papanicolaou technique. Interpretation was performed by a cytopathologist experienced with thyroid cytological interpretation.

Magnetic resonance imaging

MRI was performed using a GE Signa Twin Speed Excite 1.5T MRI (General Electric Medical Systems, Milwaukee, WI). The routine neck MRI protocol extended from the orbits through the thoracic inlet with the following standard imaging sequences: unenhanced axial and sagittal FSE T1, axial FSE T2 with fat-saturation, and axial SPGR T1 with fat-saturation. Postgadolinium contrast enhanced images were often also obtained with an axial (and optional coronal) FSE T1 with fat-saturation.

Statistical analysis

Because of the small number of observations ($n = 8$) and the lack of normal distribution of the data, we used a nonparametric test (Spearman) to assess a potential relationship between SUV_{max} and the time of survival after diagnosis for the subgroups of patients who were studied for initial staging.

Results

Patients

A total of 35 ^{18}F-FDG PET or PET/CT studies were performed on 16 patients with ATC during the study period. The 16 patients were 10 males and 6 females, mean age

62 ± 13 (SD) years, range 40–83 years. Further patient data are given in Table 1.

True-positive PET findings

PET was true positive for all eight primary tumors, for all four recurrent tumors, and in all 10 patients with lymph node metastases. PET was true positive in five out of eight patients with lung metastases. In three of the patients with lung metastases, the lesions were too small (less than 3 mm) to be characterized by PET. Further, PET was true positive in two patients with bone metastases and in one patient with a metastasis to the left adrenal gland. In one of the patients (patient 8) with abnormal focal FDG uptake in the fourth lumbar vertebra ($SUV_{max} = 9.4$), MRI was reported negative for metastatic disease to the spine. However, on the CT portion of the PET/CT, the lesion was suspicious for metastasis as well. Based on the positive PET/CT finding, the MRI was thoroughly re-reviewed and a small lesion in L4 suspicious for metastatic disease was seen. A follow-up PET/CT scan showed interval development of extensive new and worsening hypermetabolic abnormalities throughout the body consistent with metastatic disease.

False-positive PET findings

False-positive PET findings were confirmed in two patients. One of these two patients (patient 16) had two enlarged jugular chain lymph nodes (AJCC level II) with increased FDG uptake ($SUV_{max} = 3$ and 5, respectively) that on US looked benign (long, slender with fatty hilum). On a follow-up PET, the uptake had significantly decreased in intensity and repeat US again indicated benign enlargement, most likely inflammatory. The PET study was elsewhere negative. There was no evidence of residual or recurrent disease during 18 months of follow-up.

In another patient (patient 12), PET was positive in multiple pretracheal foci in the lower neck ($SUV_{max} = 20$). US and CT showed posttherapy changes only. A biopsy was negative for malignancy and showed growth of *Streptococcus* viridans. The patient was treated with antibiotics and did well until recurrent disease was confirmed in the PET positive neck area 7 months later. Even though the disease recurred in the neck area after 7 months, we are obligated to call the study false positive because of the negative biopsy at the time of the PET study. The patient died from the disease 6 months later, 25 months from the initial diagnosis.

Negative-PET findings

PET was negative in nine studies on four patients after treatment of primary or residual disease. In two of the patients, the disease recurred during the study period. One of these two patients (patient 6) died from the disease 7 months after the diagnosis and 5 months after the negative PET/CT scan. In the other patient (patient 7), the disease recurred 20 months after the negative PET/CT scan. In the two other patients (patients 14 and 16), there was no evidence of recurrent disease 12 and 18 months after the first negative PET scans, respectively.

SUV_{max} values

The SUV_{max} values are given in Table 2. For lung lesions, the SUV_{max} value is the measured uptake in the hottest lung lesions >1 cm. The false-positive uptake in the neck of patient 12 possibly caused by an infection was very intense with $SUV_{max} = 20$. The SUV_{max} of the two enlarged jugular chain lymph nodes likely involved by inflammation in patient 16 was 5.0 and 3.0, respectively.

PET findings and patient outcome

Outcome and follow-up information are listed in Table 3. All the patients who died during the follow-up period had PET positive metastatic disease after finishing primary treatment. We did not find any statistically significant correlation between SUV_{max} for the primary tumors and the time of survival after diagnosis for the subgroup of patients studied with PET for initial staging ($p < 0.34$).

Table 3. Outcome and Follow-Up Data

Patient no.	*Treatment*	*Time from diagnosis to death (months)*	*Follow-up time (months)*	*Status of disease in survivors on follow-up*
1	Chemoradiation	3.5		
2	Chemoradiation	5.5		
3	Chemoradiation	5		
4	Chemoradiation		5	Disease progression
5	Chemoradiation	5.5		
6	Surgery, chemoradiation	7		
7	Chemoradiation		30	Disease progression
8	Surgery + chemoradiation	4		
9	Chemoradiation		12	No evidence of disease
10	Surgery + chemoradiation	9		
11	Surgery, chemoradiation	10.5		
12	Chemoradiation + surgery	25		
13	Surgery + chemotherapy	21		
14	Surgery + chemoradiation		15	No evidence of disease
15	Chemoradiation		21	Disease progression
16	Surgery + chemoradiation		23	No evidence of disease
	Mean ± SD (months)	9.6 ± 7.1	17.7 ± 8.1	

SD: standard deviation.

Impact of the PET findings on the patient management

In four patients, the results of the PET findings changed the planned treatment. In two of these patients (patients 2 and 5), unsuspected distant metastases, subsequently confirmed by MRI (bone) and CT (lung), resulted in cancellation of planned surgery. In one patient (patient 7), planned extensive surgery for suspected residual disease in the neck was changed to close observation based on a negative PET scan. In the fourth patient (patient 15), further observation was planned based on unchanged interval US and CT, but it was changed to chemotherapy after PET results indicated recurrent disease confirmed by biopsy.

In four other patients (patients 6, 8, 9, and 11), the clinical records indicated a direct supportive impact of the PET findings on the patient management. Three of these patients (patients 6, 8, and 9) had surgical resection after US, CT, MRI, and PET were all negative for distant metastases. In the fourth of these patients (patient 11), the PET results were used in radiation planning.

Discussion

High FDG uptake is a prerequisite if PET can be considered useful in patients with ATC. As might be expected from a poorly differentiated cancer, this study indicates that primary ATC, residual tumors, recurrent disease, lymph node metastases, and extranodal metastases consistently show high to very intense FDG uptake. PET scanners have limited spatial resolution, and small lung metastases <5 mm may be missed on PET (12,13). In three of the patients with confirmed lung metastases, the lesions were too small to be characterized by PET, but they were seen on the low-dose CT as part of the PET/CT study. Hence, combined PET/CT was actually true positive in all patients with lung metastases. Zoller *et al*. have shown the advantage of PET/CT as compared to PET in patients with differentiated thyroid cancer (14). It is likely that PET/CT should be preferred to PET in patients with ATC as well. In two patients with negative PET, MRI, CT, and US after primary treatment, the disease recurred during the study period. The residual disease may have been too small to be detected by PET or temporarily stunned by the treatment. Because the disease recurred in these two patients, the PET/CT exams may be more correctly regarded as false negative for predication of recurrence. However, in this study they were classified as true negative based on the information available at the time of the PET scan.

Lazar *et al*. have shown a 3- to 10-fold increase in the glucose transporters 1 (*GLUT1*) gene in thyroid carcinomas compared to normal thyroid tissue (15). Schönberger *et al*. have studied the expression of glucose transporters in paraffin-embedded tissue obtained from 45 patients with thyroid carcinomas; 5 ATC, 20 papillary, and 20 follicular carcinomas (16). They found that an overexpression of *GLUT1* on the cell membrane of these thyroid carcinomas was closely related to tumors demonstrating aggressive behavior. There was a significant correlation between prognosis and membranous *GLUT1* expression. All ATC were found to be highly *GLUT1* positive. They suggest that determination of *GLUT1* expression may be used as a prognostic *in vitro* marker and that FDG PET may identify patients at high risk requiring more aggressive treatment as cellular FDG uptake is facilitated by this transporter. In the current study including ATC only, all primary tumors imaged had high FDG uptake, but we did not find any correlation between survival and intensity of FDG uptake in the primary tumors ($p = 0.34$). These results, however, should be considered with caution due to the small number of observations ($n = 8$).

The patient with the longest survival, 30 months from diagnosis to recurrent disease, had the lowest FDG uptake in his primary tumor. This patient did not show any metastases on an initial staging PET scan, and a PET scan for restaging after the completion of chemoradiation was negative as well. The only two patients without evidence of residual or recurrent disease by the end of the study period after follow-up for 15 and 23 months after the diagnosis were both negative on two and six repeat PET scans, respectively. Even if the number of patients were too small to make any conclusion about FDG uptake and prognosis, we may anticipate that a negative FDG PET after completed therapy may indicate a better chance of extended survival.

Accurate assessment of the extent of the disease is important to predict prognosis and for therapy planning (1,2). The diagnosis and staging of ATC is usually easy as most patients will have local invasion and metastases seen clearly on US and CT at the time of diagnosis. Therefore, in the majority of patients with ATC, a PET study will not influence the clinical decision and will consequently not be indicated. In 8 out of our 16 patients (50%), the medical records reported a direct impact of the PET findings on the management of the patients. In all of these eight patients, other imaging modalities were negative or indeterminate and this was the reason why the PET scan was ordered. Indeed, PET is probably most useful when US, CT, and MRI are negative or indeterminate.

Many patients with ATC will at the time of presentation already have postoperative changes in the neck region from prior surgeries for well-differentiated thyroid carcinoma or multinodular goiter. Additionally, patients with resectable disease may undergo major surgery resulting in extensive postoperative changes, and a residual posttreatment mass after successful chemoradiation is common. Such intervention-induced changes may challenge the interpretation of US, CT, and MRI at the time of diagnosis and on follow-up. ^{18}F-FDG PET is used to assess the nature of residual masses after therapy, including radiation therapy, chemotherapy, and surgery for a number of cancers (17–20). Therefore, it is expected that the use of ^{18}F-FDG PET may be useful to differentiate between posttherapy changes and malignancy in ATC as well. Indeed, in one of our patients (patient 7, Fig. 1), CT, US, and MRI showed a large residual mass in the neck without increased FDG uptake. Because the PET scan did not show increased uptake within the residual tumor, further observation was favored instead of extensive, debulking surgery. However, the disease recurred within the residual tumor after 30 months.

The study was not primarily designed to compare the PET findings with other imaging modalities. The results of US, CT, and MRI were rather used to confirm the PET findings, but some comparisons can be made. Two patients had false-positive PET findings. The findings were confirmed to be inflammatory lymph nodes and localized infection with *Streptococcus* viridans. It is well known that FDG uptake is increased not only in malignant tumors but in inflammation

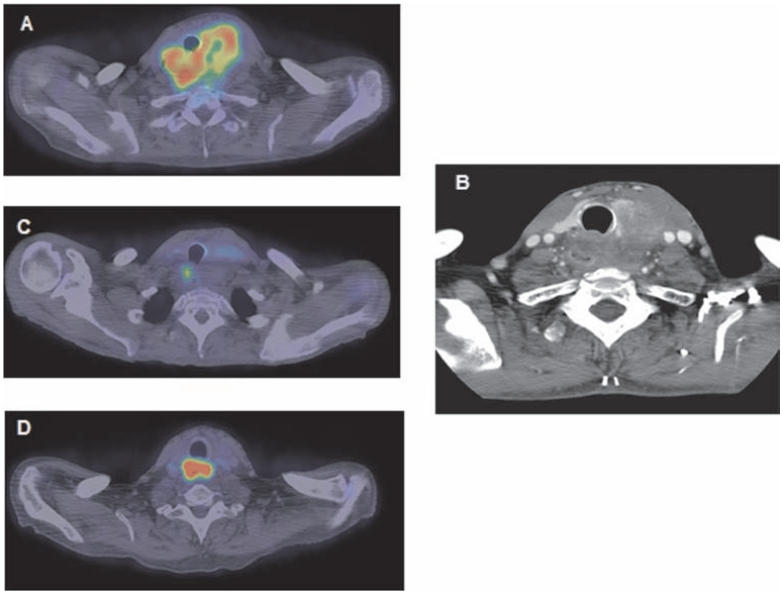

FIG. 1. (**A**) Initial staging positron emission tomography (PET)/ computed tomography (CT) in patient number 7 (transaxial fused PET/CT images). (**B**) Contrast enhanced diagnostic CT 10 weeks after completed chemoradiation shows a large residual mass left thyroid lobe with encasement of esophagus and displacement of trachea. (**C**) The residual mass is negative on PET/CT except for postirradiation inflammatory uptake in esophagus. (**D**) Recurrent disease with intense FDG uptake 30 months later.

and infection as well (17). The possibility of false-positive findings should always be questioned and a biopsy performed if needed (17). ATC have such a dismal prognosis that even a negative PET scan should not exclude a frequent follow-up.

In conclusion, the current study showed that ATC demonstrate intense uptake on ^{18}F-FDG PET images. In 8 of the 16 patients (50%), the medical records reported an impact of the PET findings on the clinical management of the patients. A negative PET scan after completed therapy may be indicative of extended survival. PET may improve disease detection and have an impact on patient management in patients with ATC relative to other imaging modalities.

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