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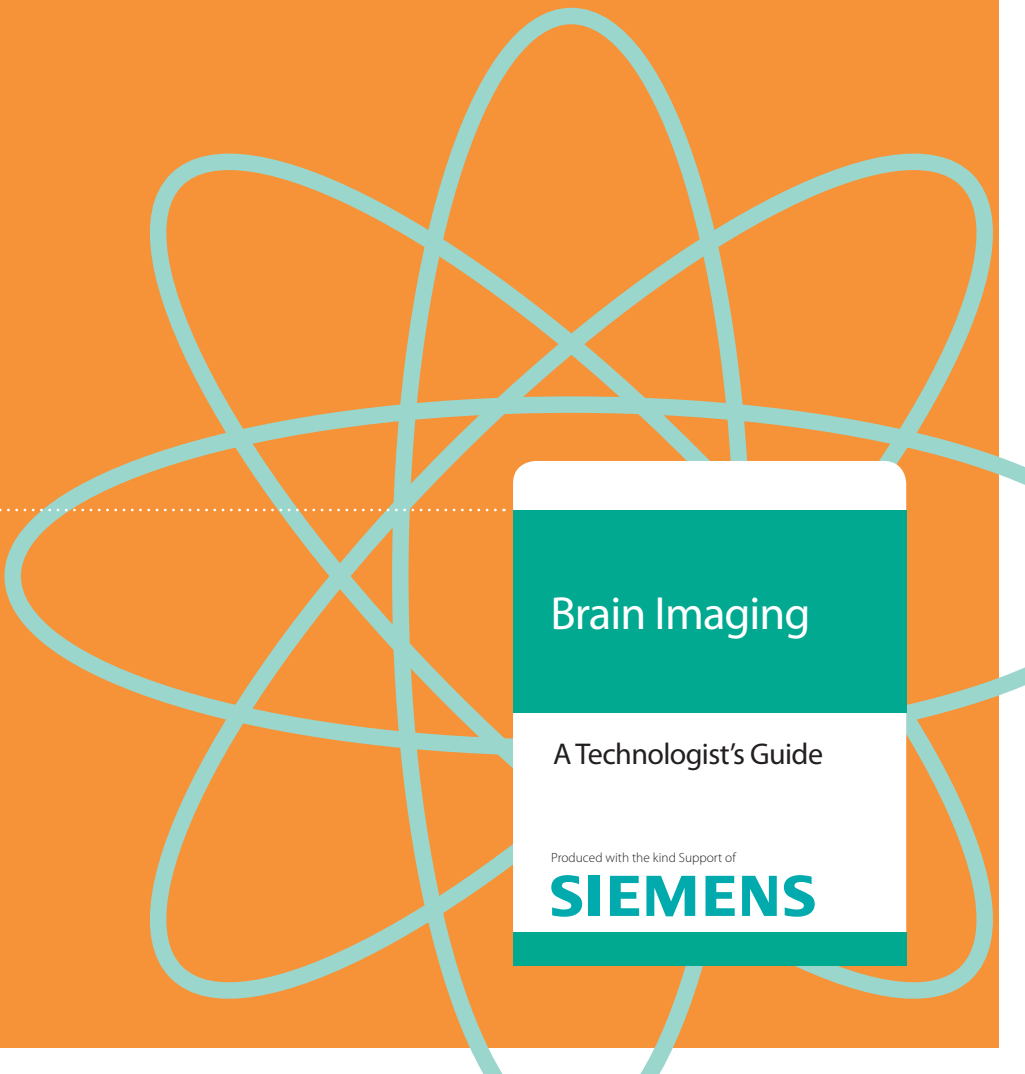

Brain Imaging

A Technologist's Guide

Produced with the kind Support of

SIEMENS

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Contents

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Foreword

During the past two decades the European Association of Nuclear Medicine (EANM) has become a leading institution for research and education in all aspects of nuclear medicine (NM), including tracer development, scanning technology and multimodality and hybrid imaging. Within the last 5 years, the EANM has followed the "Go Clinical" motto, with the intention of advancing the role of NM into clinical and research protocols. This challenge was accepted by the EANM Technologist Committee (TC), which has attempted to ensure that technologists' education, research and daily practice have a strong clinical impact. This intention is also reflected in the decision to dedicate the Technologist Guide 2015 to brain imaging.

EANM Technologist guides are developed and printed on a yearly basis for presentation at the EANM Annual Congress. They are specifically aimed at NM technologists, radiographers and all other healthcare professionals working or intending to work in a nuclear medicine department.

After dedicating three books specifically to PET/CT, we have focussed on specific clinical fields in which NM has a strong impact on clinical procedures, such as myocardial perfusion imaging and brain imaging. Brain imaging was strongly influenced by the PET/CT revolution and is now also a field of high interest for radiopharmaceutical research, thanks to the development of ^{11}C tracers, somatostatin analogues and amyloid-based tracers, which are rapidly becoming standards as diagnostic tools. Following its recent development, PET/MRI has also found many suitable clinical applications in brain imaging that have helped this new hybrid technique to find a role in clinical practice and research protocols.

I would like to thank all those who have contributed to this project as authors and reviewers, without whom the book would not have been possible. I would also like to thank SNMMITS (Society of Nuclear Medicine and Molecular Imaging Technologist Section) and the EANM Neuroimaging Committee for their help and high-quality contributions.

Special thanks are due to Pedro Fragoso Costa, Andrea Santos and Borut Vidovic for their incredible enthusiasm and competence in dealing with the editorial duties and organisational work. Finally I remain extremely grateful to the EANM Board, EANM Executive Office, Technologist Committee and all the EANM committees involved in the project.

With my warmest regards,

Giorgio Testanera
Chair, EANM Technologist Committee

Introduction

Andrea Santos, Pedro Fragoso Costa

Neurological disorders are already affecting hundreds of millions of people worldwide, of whom more than 50 million suffer from epilepsy and around 35.6 million have Alzheimer's disease or other dementias. Furthermore, greater life expectancy and the overall ageing of the general population in both developed and developing countries will contribute to continued increases in the prevalence of many chronic and progressive physical and mental conditions, including neurological disorders [1].

Diagnostic nuclear medicine investigations have evolved from being a research modality in the evaluation of function and disease of the central nervous system to an established clinical tool in neurology. During recent years, new technologies and techniques have been developed in order to improve the quality of the images acquired, thereby enhancing the clinical impact of these techniques. Moreover, radiopharmaceutical development has allowed SPECT and PET imaging to become increasingly acute and to cover more pathologies. From metabolism to perfusion, brain function has been studied in a variety of conditions, including dementia, epilepsy, movement disorders and brain tumours.

These advances represent a challenge for technologists, given that each new technique and piece of equipment requires optimisation of protocol design. In the neuroimaging context, technologists also play a key role in patient care, which can be particularly challenging owing to the inability of patients suffering from neurological disorders to cooperate and also the demanding nature of the examinations.

In this book, we begin by describing the brain's anatomy, physiology and pathology (Chapter 1). After this, tracers for brain imaging are discussed (Chapter 2). The following two chapters provide an overview on the imaging of oncological disease by means of SPECT or SPECT/CT and PET/CT techniques (Chapters 3 and 4). Imaging in neurological and vascular brain diseases is also analysed, focussing first on SPECT and SPECT/CT technology and then on PET/CT (Chapters 5 and 6). The use of PET/CT in brain tumour radiotherapy planning is discussed in Chapter 7. The application of the emerging technology of PET/MRI for brain imaging is approached in Chapter 8. Brain imaging in the case of suspicion of brain death is described in Chapter 9. The final chapter is devoted to the special health care and surveillance needs of patients affected by neurological disorders. This extended overview of neuroimaging techniques and the clinical state of art will provide a valuable tool to all clinical staff, including not only technologists but also physicians, physicists and students interested in this particular field.

The EANM Technologist Committee would like to thank all the authors who have kindly offered their time and expertise, which have been fundamental to the creation of this book.

Andrea Santos
Pedro Fragoso Costa

Reference:

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Chapter 1

Anatomy, Physiology and Pathology

Elsmarieke van de Giessen, Silvia Morbelli and Pierre Payoux

The brain serves many important functions, including movements, thoughts, learning, memory, language, integration and interpretation of our senses, and critical functions such as respiration. To understand imaging of the brain it is essential to have knowledge of the anatomy and its normal function. This chapter provides an overview and describes several common brain pathologies.

Anatomy

Brain structures

The brain consists of three major structures: the brainstem, cerebellum and cerebrum (Fig. 1). The brainstem is the lower structure of the brain, extending into the spinal cord at the point where it leaves the skull. It is an important relay station and consists of the midbrain, pons and medulla oblongata. The medulla oblongata is important for primitive functions like respiration, blood pressure and heart rate.

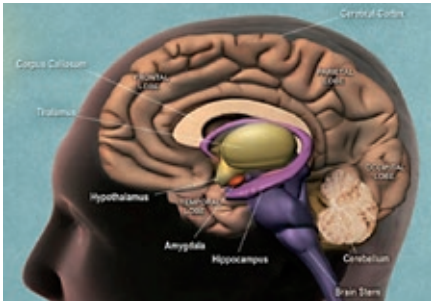

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Figure 1: The human brain

The cerebellum is located at the back of the brain and is divided into two hemispheres (left and right). It is important for coordination and timing of movement. The cerebrum is the largest structure of the brain and is also divided into left and right hemispheres, which are connected through the corpus callosum. The cerebrum is covered with the cerebral cortex that is folded into gyri and sulci to increase its surface. The cerebral cortex can be divided into four lobes: frontal, parietal, temporal and occipital. The frontal lobes are located in the front of the brain and include the primary motor cortex and prefrontal cortex, which is important for cognitive and executive functions. The temporal lobes are located on both sides of the brain and contain the auditory cortex. On the medial sides of the temporal lobes are the hippocampus, important for memory formation, and the amygdala, involved in emotions. The occipital lobes are at the back of the brain and are essential for processing visual information. The parietal lobes are located in between the frontal and occipital lobes; they include the somatosensory cortex and are involved in integrating sensory information to form a perception. The basal ganglia are located subcortically, close to the centre of the cerebrum. They play an important role in controlling and regulating activities of the motor system and in motivation and habituation. A major structure of the basal ganglia is the striatum, which is involved in the planning and modulation of movement pathways, but is also part of the cognitive processes involving executive function, such as working memory. The thalamus is located superior to the midbrain, near the centre of the brain. This is an important relay station for signals to the cerebral cortex, including motor and sensory signals, but it is also involved in sleep/wakeful-

ness and consciousness. Below the thalamus lies the hypothalamus, which is connected to the pituitary gland. The hypothalamus is considered to be the link between the nervous system and the endocrine system, regulating appetite, electrolyte balance and body temperature. The two major components of the brain structures are grey and white matter. Grey matter largely consists of neuronal cell bodies and white matter is white because of the large number of myelinated axons.

Meninges and cerebrospinal fluid

The brain and spinal cord are enveloped and protected by the meninges, which consist of three layers: dura mater, arachnoid mater and pia mater. The space in between the pia mater and the arachnoid mater is termed the subarachnoid space, which is filled with cerebrospinal fluid (CSF). CSF is produced from arterial blood by the choroid plexuses. There it is filtered through the blood-brain barrier, which protects the brain from infections and toxins. The CSF flows through the ventricular system, consisting of the lateral ventricles and third and fourth ventricles.

Cerebral vasculature

Two pairs of arteries provide the arterial blood supply of the brain: the internal carotid arteries in the neck and the vertebral arteries. They are interconnected through the circle of Willis, which ensures a back-up circulation in the event of dysfunction of one of the arteries. The three main pairs of arteries that branch off from the circle of Willis and supply the cerebrum with arterial blood are the anterior, middle and posterior cerebral arteries. The venous drainage consists of the venous sinuses in the dura mater and of veins inside the deep structures of the brain, which join behind the midbrain and then drain into the sinus system. The sinus drainage connects to the jugular veins in the neck.

Physiology

Cell types

Two main types of cell compose the brain: neurons and glial cells. Neurons transmit nerve signals to and from the brain over long distances. They consist of a cell body (or soma) with branching dendrites (signal receivers) and a projection called an axon, which conducts the nerve signal and transmits it across a synapse (Fig. 2).

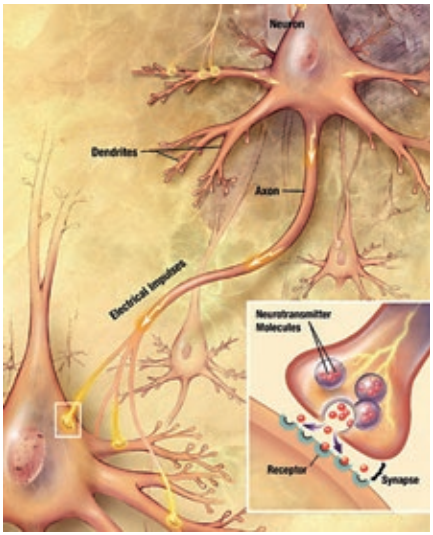

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Figure 2: Propagation of a signal down an axon to the cell body and dendrites of the next cell

Neurons can be classified according to the number of extensions deriving from the neuron's cell body (bipolar, pseudo-unipolar, multipolar) or according to the direction in which they send information (afferent/sensory, efferent/motor and interneuron).

Glial cells have supportive functions in that they help to define synaptic contacts and to maintain the signalling abilities of neurons, but they do not participate directly in electrical signalling. There are three types of glial cell in the mature central nervous system: astrocytes, oligodendrocytes and microglial cells.

Metabolism, neurotransmitters and transporters

The brain relies entirely on glucose for its energy supply and uses approximately 20% of the body's total energy requirements. Measurements of glucose consumption reflect the amount of brain activity in the various regions of the brain and allow us to learn more about how the brain works.

Neurotransmitters are the chemicals which allow the transmission of signals from one neuron to the next across the synaptic cleft. Acetylcholine is responsible for muscle stimulation and has been found in the autonomic nervous system and sensory neurons. The cholinergic system modulates cognitive performance and gait stability and has been linked with cognitive/motor dysfunction in several neurodegenerative diseases. Norepinephrine or noradrenaline is prevalent in the sympathetic nervous system. The noradrenergic system effects are alertness and arousal and influences on the reward system. Dopamine is an inhibitory neurotransmitter involved in the control of locomotion, cognition, affect and neuroendocrine secretion. Dopamine deficiency results in Parkinson's disease. GABA (γ-aminobutyric acid) is the main inhibitory neurotransmitter in the human central nervous system. The GABAergic system is the target of many drugs and substances including benzodiazepine, alcohol and barbiturates. Glutamate is the most common neurotransmitter in the CNS and is involved in most aspects of normal brain function, including cognition, memory and learning. Serotonin is an inhibitory neurotransmitter that has been found to be intimately involved in emotion, mood, appetite and sleep. Modulation of serotonin at synapses is thought to be a major action of several classes of pharmacological antidepressant.

Neurotransmitter transporters are a class of membrane transport proteins that span the cellular membranes of neurons. A variety of neurotransmitter re-uptake transporters are pharmacotherapeutic targets for modulating the synaptic neurotransmitter concentration, and therefore neurotransmission. Among neurotransmitter transporters, the dopamine transporter (DAT) has a crucial role for nuclear imaging of the dopaminergic system. DAT pumps dopamine out of the synapse back into cytosol, from which other transporters sequester dopamine and noradrenaline into

vesicles for later storage and release.

Pathology

Neurodegenerative disease

Alzheimer's disease (AD) is the most common cause of dementia among older people. Dementia is the loss of memory and other intellectual functions of sufficient severity to cause problems in patients' abilities to perform their usual personal, social or occupational activities. AD is pathologically characterised by the presence of plaques composed of amyloid-beta peptides and neurofibrillary tangles containing phosphorylated tau [1]. Enzymatic cleavage of amyloid-beta peptides is considered to play an important pathogenetic role in AD (likely occurring several years before clinical manifestations) [1]. The ongoing challenge is the distinction of slight cognitive deficit which precedes AD dementia from normal aging. Mild cognitive impairment (MCI) refers to a subtle but measurable cognitive decline in the absence of dementia and those affected include both subjects who remain stable over time and patients who become demented due to underlying neurodegenerative aetiologies, including AD [2]. Imaging and CSF biomarkers allow the identification of probable AD among MCI patients with a typical gradual and progressive (isolated or not) episodic memory impairment [3].

Dementia with Lewy bodies (DLB) is a degenerative dementia of unknown aetiology. It is the second most common form of dementia. Deficits in attention and executive function are central features. Fluctuating cognition, visual hallucination and spontaneous features of parkinsonism are typical. Finally, REM sleep behaviour disorder, severe sensitivity to neuroleptics and low dopamine transporter uptake in the basal ganglia as seen on SPECT/PET imaging scans are suggestive features [4].

Frontotemporal degeneration (FTD) refers to a group of diseases involving the temporal and/or frontal lobes. FTD is also commonly referred to as frontotemporal dementia and occurs most frequently in persons under the age of 65. FTD has a heterogeneous spectrum, with behavioural, cognitive or language changes [5].

Parkinson's disease (PD) is an idiopathic degenerative disease which results from the death of dopamine-generating cells in the substantia nigra. PD usually affects people over the age of 50. Symptoms of PD are resting tremor, rigidity, bradykinesia and postural instability. Onset of symptoms is gradual and typically asymmetrical [6].

Cerebrovascular disease

Cerebrovascular disease (CVD) refers to a group of conditions that impair the circulation of blood to the brain, causing limited or no blood flow to affected areas. Clinical symptoms depend on the location and extent of cerebral tissue affected. CVDs are subdivided into ischaemic events and cerebral haemorrhages. Ischaemic events are further classified according to the duration

of symptoms (transient ischaemic attacks last more than a few minutes and less than 24 h; ischaemic stroke lasts more than 24 h and may be progressive stable, or resolving. In some cases a number of small strokes or a large stroke may cause so-called vascular dementia (the second most common form of dementia after AD) [7].

Brain tumours

Primary brain tumours are classified according to the type of tissue in which they arise [8]. The most common brain tumours are gliomas, which begin in the glial (supportive) tissue. There are several types of glioma, including astrocytomas, oligodendrogliomas and ependymomas. Other types of brain tumour that do not begin in glial tissue are meningiomas, schwannomas, craniopharyngiomas, germ cell tumours and pineal region tumours. Cerebral secondary tumours are metastatic tumours originating in other organs and are more common than primary ones (8).

Brain inflammation and infections

Encephalitis refers to a diffuse brain parenchymal inflammation mainly due to viral infections. Meningitis is an inflammation of meninges surrounding both brain and spinal cord. It can be caused by viral, bacterial and fungal infections. Symptoms include headache, fever, confusion, drowsiness and fatigue, and in some cases seizures or convulsions, hallucinations, stroke, haemorrhaging and memory problems occur [9].

Epilepsy

Epilepsy is characterised by sudden recurrent episodes of sensory disturbance, loss of consciousness or convulsions, associated with abnormal electrical activity in the brain causing seizure (a transient occurrence of signs and symptoms due to abnormal excessive or synchronous neuronal activity) [10]. Seizures can be focal or generalised. The cause of most cases of epilepsy is unknown ("cryptogenic") although some people develop epilepsy as the result of brain injury, stroke, brain tumour or substance abuse.

References Chapter 1

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Chapter 2

Tracers for Brain Imaging

Aljaz Socan

Introduction

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging use positron- and gamma-emitting radioisotopes that can easily be incorporated into biological molecules and thus allow the measurement of functional parameters (physiological and/or pharmacological interactions) of tissue rather than just providing the anatomical definition of structures. Both techniques are exceptionally sensitive (PET more so than SPECT); they can detect picomolar or even femtomolar concentrations of radiolabelled compounds and enable the dynamic acquisition of relatively fast kinetics (of the order of seconds for PET). With these properties, PET/SPECT can facilitate the quantitative measurement of rapid physiological/pharmacological processes of biomolecules in the living brain, for example [1]. The increase in neurological applications of PET/SPECT over the past decade has been greatly aided by the significant improvements in data acquisition (hardware technology) and data quantification (model-based methodology) and by the vastly growing number of available PET/SPECT metabolic radiotracers and receptor-specific radioligands. Table 1 lists the more common PET/SPECT radiotracers/ligands and their intended targets in clinical neurology [1,2].

For the tracer (radiopharmaceutical) to be able to enter the CNS (brain), it is a prerequisite that it possesses the capacity (suitable physiochemical properties) to cross the blood-brain barrier (BBB), whether by free diffusion or by specific transport mechanisms. Depending on the brain target of the imaging and the attendant required tracer properties, tracers for brain imaging can be divided into several groups: regional cerebral blood flow (rCBF) tracers, metabolic tracers, tracers targeting neurotransmission and receptors, tracers targeting amyloid and tracers for brain tumour imaging.

rCBF tracers

In order to be used for the measurement of brain perfusion, the radiopharmaceutical must possess certain physiological properties. In addition to being able to cross the BBB, their extraction must approximate unity and must be independent of blood flow; as a consequence their initial distribution will be proportional to rCBF. They also must be retained within the brain in their initial distribution for sufficiently long to enable diagnostic images to be obtained [3]. Ideally, tracer uptake should show no redistribution, so that the initial uptake, reflecting rCBF at a fast time window after injection, will remain almost unchanged for several hours. The result is images independent of variations in rCBF after the fixation time. Two tracers are currently used for evaluation of rCBF in routine clinical practice: ^{99m}Tc-HMPAO (hexamethyl propylene amine oxime, exametazime, Ceretec®) and ^{99m}Tc-ECD (ethyl cysteine dimer, bicisate, Neurolite®); these are discussed further below. Other available tracers such as ^{123}I-IMP and $H_2{}^{15}O$ are still used mainly for research purposes.

Brain perfusion SPECT using ^{99m}Tc-labelled radiopharmaceuticals

SPECT is a technique that produces topographic images of the three-dimensional distribution of a radiopharmaceutical. Applied to the brain, it can be used to measure regional cerebral perfusion [3]. The two tracers most widely used in brain SPECT in the EU, ^{99m}Tc-HMPAO and ^{99m}Tc-ECD, differ in terms of their in vitro stability, uptake mechanism, cerebral distribution and dosimetry; nevertheless, their kinetic properties are very similar. They enter the brain cells owing to their lipophilicity and then remain there as a consequence of their metabolic conversion into hydrophilic compounds. In the case of ECD, the stable lipophilic complex crosses the BBB by passive diffusion. Its localisation in the brain depends upon both the perfusion of the region and the uptake of the tracer by the cells. Once in the brain cells, the complex is metabolised to polar, less diffusable compounds, complex de-esterification being the crucial reaction leading to hydrophilic conversion. After background clearance, brain images may be obtained from 10 min to 6 h after injection of the adult dose of 370–1110 MBq, the optimum imaging time being 30–60 min after injection. The primary route of excretion is via the kidneys, with 73% of the injected dose being cleared through the bladder during the first 24 h (up to 50% is cleared within the first 2 h). Approximately 11% of the injected dose is eliminated via the GI tract over 48 h [1].

^{99m}Tc-HMPAO primary complex is uncharged, lipophilic and of sufficiently low molecular weight to cross the BBB readily. However, it converts, at a rate of approximately 12% per hour, to a less lipophilic secondary complex which does not cross the BBB. This would limit the useful shelf-life of the product to 30 min but the addition of cobalt stabiliser, 1-5 min after preparation of radiopharmaceutical, lengthens its shelf-life to 5 h. The adult dose is 350–500 MBq. The primary complex clears rapidly from the blood after intravenous injection. Uptake in the brain reaches a maximum of 3.5–7% of the injected dose within 1 min after injection. Up to 15% of the cerebral activity washes out of the brain by 2 min post injection, after which there is slight loss of activity for the following 24 h due to the physical decay of ^{99m}Tc. Activity not associated with the brain is distributed widely throughout the body, especially in the muscle and soft tissue. Approximately 30% of the injected dose is found in the GI tract immediately after injection, with about 50% of this being excreted over 48 h. In addition, over a 48-h period, 40% of the injected dose is excreted via the kidneys and urine [1].

The different retention mechanisms of ^{99m}Tc-ECD and ^{99m}Tc-HMPAO are the reasons for the different behaviour of the tracers in specific disorders; for example, in subacute stroke the distribution of ^{99m}Tc-ECD seems to reflect metabolic activity more closely, while ^{99m}Tc-HMPAO is better correlated with cerebral perfusion (Fig. 1) [1]. The tracers are not interchangeable, and ^{99m}Tc-ECD and ^{99m}Tc-HMPAO

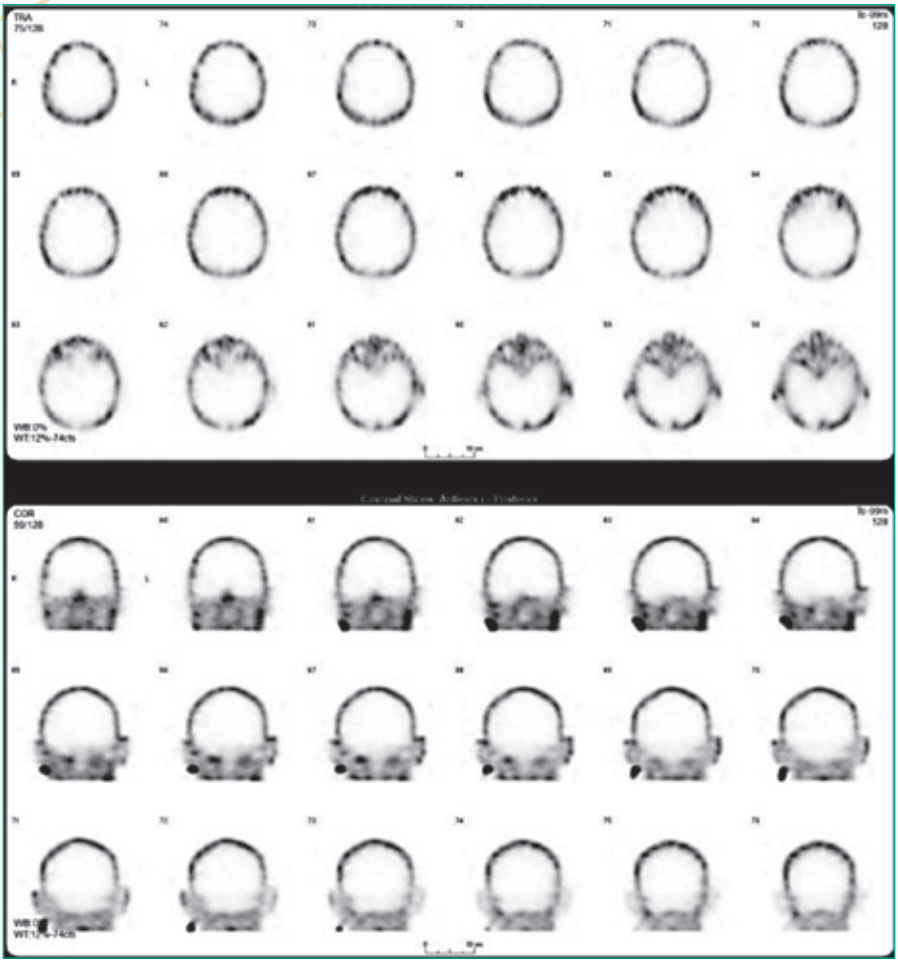


Figure 1: Brain perfusion SPECT imaging with 99mTc-HMPAO in a patient with suspected brain death after CNS trauma. There is complete absence of brain perfusion (cerebrum, cerebellum, brain stem)

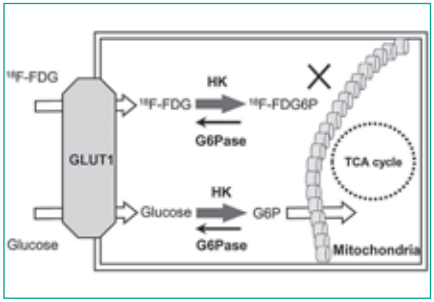
Common indications for ^{99m}Tc-ECD and ^{99m}Tc-HMPAO according to the EANM guidelines for brain perfusion SPECT are:

- Evaluation of cerebrovascular disease:
- Acute stroke
- Chronic ischaemia (chronic cerebrovascular disease)
- Preoperative evaluation for potential ischaemia following carotid artery sacrifice
- Postsurgical lateralisation and localisation of epileptogenic foci
- Evaluation of suspected dementia (early detection and differential diagnosis of various forms of dementia)
- Evaluation of traumatic brain injury
- Evaluation of suspected inflammation
- Assessment of brain death

Prior to the investigation, patients should preferably avoid excessive stimulants (caffeine, cola, energy drinks), alcohol, smoking and any other drugs known to affect the CBF. (It is necessary to discuss drug withdrawal with the clinician caring for the patient.)

Metabolic tracers

The main metabolic substrates of the brain are oxygen and glucose. Both metabolic pathways are studied with specific tracers. Oxygen-15 is the tracer used in research to study the regional cerebral metabolic rate of oxygen ($rCMRO_2$), while glucose metabolism is studied with analogues of glucose. 2-(^{18}F) Fluoro-2-deoxy-D-glucose ([^{18}F]FDG) today represents the workhorse of imaging in several fields of PET nuclear medicine. [^{18}F]FDG is a glucose analogue and is therefore taken up in cells via glucose transporters (glucose does not freely cross the BBB or cell membrane); it is then phosphorylated by hexokinase into FDG-6-phosphate, which cannot be metabolised (unlike glucose) and is consequently trapped in the cell (Fig. 2) [1].



(adopted from Oncology Reports, Spandidaos Publications)

Figure 2: Mechanism of metabolic trapping of [^{18}F]fluorodeoxyglucose in cells

Following intravenous administration of 100–400 MBq, the pharmacokinetic profile of [^{18}F]FDG in the vascular compartment is bi-exponential. It has a distribution half-life of 1 min, a large volume of distribution and an elimination half-life of approximately 12 min without being metabolised. Elimination is mainly renal. Approximately 20% of the injected dose is excreted in urine during the first 2 h. After administration, FDG is distributed mainly to the brain and heart. Approximately 7% of the injected dose is

accumulated in the brain within 80–100 min after injection. Approximately 3% of the injected activity is taken up by the myocardium within 40 min, while ca. 0.3% and 0.9%–2.4% is accumulated in the pancreas and lungs, respectively [1]. In the brain, glucose metabolism provides approximately 95% of the ATP required for brain function and is tightly connected to neuronal activity both in physiological conditions and in several diseases affecting the brain. Changes in neuronal activity induced by disease are reflected in an alteration in glucose metabolism. Since the accumulation of [^{18}F]FDG in brain tissue depends on facilitated transport of glucose and hexokinase-mediated phosphorylation, it is suitable for imaging of regional cerebral glucose consumption and is currently the most accurate in vivo method for the investigation of regional human brain metabolism. Its clinical use can be regarded as established for a number of diagnostic questions in neurology, neurosurgery and psychiatry [4].

Depending on the clinical question and the type of equipment, [^{18}F]FDG imaging may include static limited field tomographic images or dynamic tomographic images (used when absolute quantification of regional metabolic rates of glucose is needed), 2D or 3D acquisition mode and attenuation correction (mandatory for [^{18}F]FDG PET brain imaging).

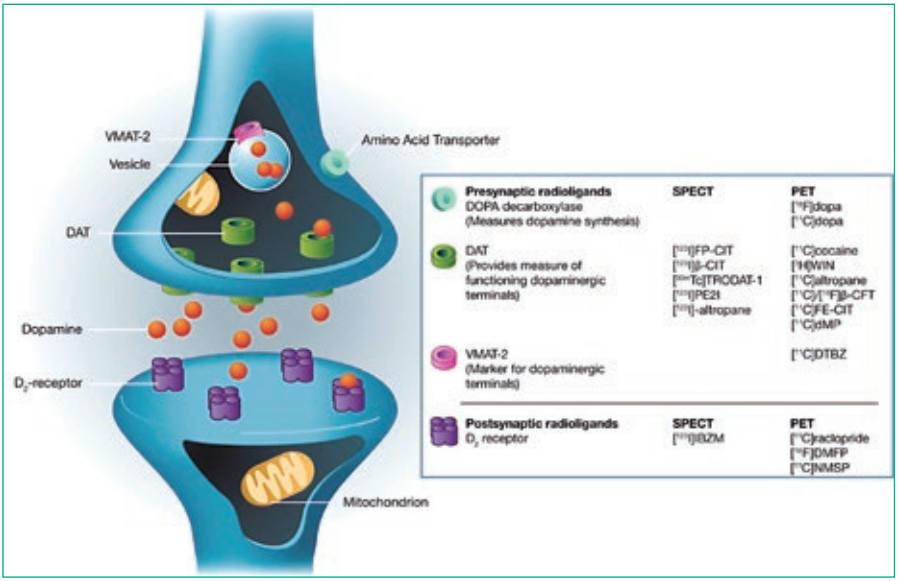
Normally, there is high tracer uptake in the grey matter of the cortex and basal ganglia; uptake in the white matter is significantly lower. Common indications for [^{18}F]FDG in PET brain imaging according to the EANM procedure guidelines for PET brain imaging using [^{18}F]FDG [4] are:

- Dementing disorders: early diagnosis and differential diagnosis of dementing disorders, such as Alzheimer's disease and frontotemporal dementia. The typical topographic patterns of hypometabolism may help to diagnose the main neurodegenerative diseases at the predementia stage.
- Neuro-oncology: differential diagnosis of cerebral space-occupying lesions, detection of viable tumour tissue (recurrence), non-invasive grading.
- Epilepsy (interictal injection): preoperative evaluation of partial epilepsy in adults and children to identify the functional deficit zone.
- Movement disorders: differentiation between Parkinson's disease and atypical parkinsonian syndromes.

Tracers targeting the dopaminergic system (neurotransmission and receptors)

The synaptic cleft is the location where interactions between cells take place. The neurotransmitter released by the presynaptic neuron reaches the postsynaptic cell

membrane, where receptors are present, and initiates the neurotransmission chain of events. The transmitter can also re-enter the presynaptic neuron via the reuptake channels, which actively participate in modulating the intracleft concentration. All the constituents of the synaptic transmission chain, i.e. transmitter, receptors and reuptake channels, can be modulated by functional requests as a consequence of local physiology or disease and under the effect of drugs. All three are possible targets of imaging with radiolabelled tracers. On account of the importance of the brain functions connected with its integrity (its dysfunction leads, for example, to movement disorders and cognitive decline), the dopaminergic system is the most extensively studied neurotransmitter system in brain nuclear medicine imaging.



(adopted from Brain, Oxford Journals)

Figure 3: Dopaminergic radioligands for SPECT and PET

Various SPECT and PET dopaminergic tracers are currently available for routine clinical practice and research (Fig. 3). [^{18}F]fluorodopa and cocaine derivatives labelled with ^{123}I and ^{99m}Tc ([^{123}I]β-CIT, [^{123}I]FP-CIT and [^{99m}Tc]TRODAT-1) are the most frequently used tracers for the study of nigrostriatal dopaminergic dysfunction in Parkinson's disease (Fig. 4).

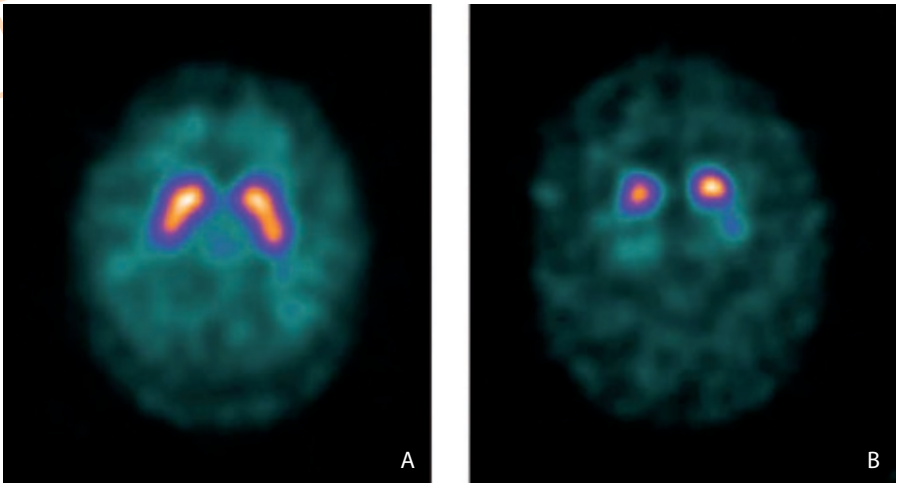


Figure 4 A, B: Dopamine reuptake transporter (DAT) SPECT imaging ([^{123}I]FP-CIT). (A) Normal uptake in the striatum (caudate nucleus, putamen). (B) Patient with Parkinson's disease: asymmetrically decreased uptake is seen in the striatum (more pronounced on the right side). There is bilaterally reduced uptake in the putamen posteriorly

PET/SPECT can also be used non-invasively to indirectly monitor changes in neurotransmitter concentration, providing that a PET radioligand specific and selective for the system of interest is available and the radioligand binds to the same site as the endogenous ligand or neurotransmitter. The D_2 receptor radioligands [^{11}C]raclopride and [^{123}I]IBZM are, for example, particularly sensitive to changes in dopamine levels. Dopamine receptor ligands have been used for the identification of postsynaptic dopaminergic deficit in parkinsonian neurodegenerative disorders (D_2 receptor ligands), for the assessment of neuroreceptor/neurochemical changes and drug occupancy in psychiatric disorders (D_1 and D_2 receptor ligands) and for pharmacological studies on endogenous dopamine changes (D_2 receptor ligands).

6-[^{18}F]Fluorolevodopa is a metabolic tracer that is taken up into dopaminergic nerve terminals and converted into [^{18}F]dopamine. The radiotracer can be used as a measure of dopamine synthesis and dopaminergic neuron density and, therefore, presynaptic dopaminergic function. In Parkinson's disease, conventional MRI is unable to identify any anatomical abnormalities. With [^{18}F]F-DOPA PET, the loss of dopaminergic neurons is clearly detected in the striata and has been shown to be useful in early differentiation of Parkinson's

disease from other movement disorders. In addition, [^{18}F]F-DOPA can be used to detect a subclinical parkinsonian-like pattern (i.e. degeneration of dopaminergic neurons) in asymptomatic adult identical twins [1].

Brain neurotransmission SPECT using ^{123}I-labelled dopamine transporter ligands

The dopaminergic neurotransmitter system plays a major role in movement disorders, particularly in parkinsonism and dementia with Lewy bodies. The nigrostriatal dopaminergic pathway is best analysed at the striatal level, where the nigrostriatal neurons end and connect to the postsynaptic nerve terminals using dopamine as a neurotransmitter which binds to the postsynaptic D_1 and D_2 receptors. Both pre- and postsynaptic levels can be targeted by PET or SPECT tracers. Presynaptic events can be summarised as follows. Dopamine is stored in vesicles before being released into the synaptic cleft. Vesicular monoamine transporter 2 (VMAT-2) transports cytosolic and newly synthesised dopamine into vesicles. The sodium-dependent *dopamine* active transporter (DAT), which is located in the membrane of the presynaptic nigrostriatal nerve terminals, is responsible for the reuptake of dopamine from the synaptic cleft. L-DOPA is taken up by the presynaptic neurons via amino acid transporter and decarboxylated to dopamine by L-aromatic acid decarboxylase (Fig. 3) [5].

Various PET tracers have been used to study these presynaptic targets, such as ^{18}F-DOPA for aromatic acid decarboxylase, ^{11}C-DTBZ for VMAT-2 and ^{11}C-PE21 for DAT. Various cocaine analogues that are labelled with ^{123}I and are suitable for SPECT have been shown to bind with high affinity to DAT. Currently β-CIT (DOPAS-CAN®) and FP-CIT (ioflupane, DaTSCAN®) are commercially available and widely used for clinical evaluation of patients in Europe [5]. The administered dose of [^{123}I] ioflupane in adults is 150–250 MBq. [^{123}I]Ioflupane is cleared rapidly from the blood, with only 5% remaining at 5 min after intravenous injection. Uptake in the brain is rapid, with 7% of the injected activity being present in the brain after 10 min, decreasing to 3% after 5 h. The primary route of excretion is via the kidneys, with 60% of the injected dose being excreted in the urine at 48 h post injection; faecal excretion is calculated at approximately 14% [1]. Normally, there is intense uptake in the striatal structures (caudate nucleus and putamen).

According to the EANM Guidelines [5], common indications for brain neurotransmission SPECT using ^{123}I-labelled dopamine transporter ligands are:

- Detection of loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain parkinsonian syndrome; differentiation of essential tremor from Parkinson's disease, multiple system atrophy and progressive supranuclear palsy (on its own, it is unable to discriminate between Parkinson's disease, multiple system atrophy and supranuclear palsy)

- Differentiation of dementia with Lewy bodies from other dementias
- Early diagnosis of neurodegenerative parkinsonism; assessment of the presynaptic deficit in early Parkinson's disease
- Assessment of disease severity (DAT binding is related to the clinical stage and severity of Parkinson's disease)
- Differentiation between presynaptic parkinsonism and other forms of parkinsonism (neuroleptic-induced parkinsonism)

Prior to the investigation, patients should avoid taking any medications or drugs of abuse which could significantly influence the visual and quantitative analysis of DAT binding ligands. A withdrawal period of at least 5 times the drug's biological half-life is suggested. Smoking may interfere with DAT availability [5].

Brain neurotransmission SPECT/PET using dopamine D_2 receptor ligands

The dopaminergic neurotransmitter system plays a major role in movement disorders, particularly in parkinsonism. Using SPECT and PET, various functional aspects of dopaminergic neurotransmission can be visualised in vivo.

Currently nuclear medicine investigations predominantly assess two aspects of the dopaminergic system: the binding of the presynaptic dopamine transporter and the status of the postsynaptic dopamine D_2 receptor, since the majority of D_2 receptors are located postsynaptically. According to their pharmacological response, dopamine receptors are divided into D_1-like receptors (D_1, D_5) and D_2-like receptors (D_2, D_3 and D_4). Assessment of D_1-like receptors has not gained any clinical significance, but a number of clinical investigations have focussed on the D_2-like receptor system [6].

The most widely applied radiotracers for imaging D_2-like receptors with SPECT are ^{123}I-labelled IBZM and epidepride, both of which are commercially available. For PET, [^{11}C]raclopride, [^{18}F]fallypride and [^{18}F]desmethoxyfallypride (DMFP) are the most commonly used radiopharmaceuticals in Europe [6]. These dopamine receptor antagonist derivatives are not selective radiopharmaceuticals for the D_2 receptor, since they also bind the D_3 receptor; however, the vast majority of D_2-like receptors in the striatum are D_2 receptors. Since the available radiotracers show considerable variation in their affinity and selectivity for the D_2 receptors and their pharmacokinetic properties, there are differences between them with respect to specific binding ratios and the optimal time point for acquisition. As with DAT tracers, there is physiological uptake of tracer in the striatum.

According to the EANM Guidelines [6], common indications for brain neurotransmission SPECT/PET using dopamine D_2 receptor ligands are:

1. Differential diagnosis of parkinsonian syndromes (differentiation of Parkinson's disease from other neurodegenerative parkinsonian syndromes characterised by loss of D_2 receptors, i.e. multiple system atrophy and progressive supranuclear palsy)
2. Assessment of the extent of D_2 receptor blockade during treatment with dopamine D_2 antagonists (neuroleptics)
3. Huntington's disease (D_2 receptor imaging can confirm degeneration of postsynaptic D_2 receptors)
4. Wilson's disease (D_2 receptor imaging findings are related to the severity of neurological symptoms and may show the degree of neuronal damage due to cytotoxic copper deposition in striatum)
5. Pituitary adenoma (D_2 receptor imaging is helpful when assessing the dopamine receptor status/availability of pituitary adenoma, which may have implications for the medical treatment strategy)

Tracers targeting other neurotransmitter systems and receptors

Use of PET as a tool for neuroreceptor mapping can be very important for elucidation of basic mechanisms of disease and for investigation of correlations with clinical parameters. The antagonist radioligand [^{11}C]WAY100635 has been used extensively to study $5HT_{1A}$ receptor (serotonin) dysfunction in human disease states (neurodegenerative disorders such as Alzheimer's disease and neuropsychiatric disorders such as depression) [1]. The neuropharmacological data obtained from receptor-specific PET/SPECT studies can additionally help to increase knowledge of potential therapeutic targets for novel pharmaceutical agents by determining their dose-occupancy profile. This can be done using the radiolabelled drug under investigation or by monitoring its effects on the binding of an established radioligand [1].

Tracers for the cholinergic system can be used for the study of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Lewy body dementia and progressive supranuclear palsy. Tracers for the central benzodiazepine (BZD) receptors ([^{11}C]flumazenil, [^{123}I]iomazenil) have been used in patients with epilepsy to identify the epileptogenic focus characterised by a focal decrease in BZD receptor density, for the study of neuronal loss in Alzheimer's disease and for the study of BZD receptor density in patients with schizophrenia or post-traumatic stress disorder (PTSD). Peripheral benzodiazepine binding sites (PBBS) are present at low levels in the normal brain. These sites are highly expressed in vivo by activated microglia, which are associated with CNS inflammation in a wide range of pathologies. In combination with MRI, to aid with anatomical definition, PET imaging using the PBBS-selective ligand [^{11}C]PK11195 provides a generic indicator of active disease in the brain and, to date, has been used in clinical studies of stroke, multiple sclerosis, dementia, Parkinson's disease, Huntington's disease, epilepsy and schizophrenia [1].

Tracers targeting amyloid

Amyloid plaques and neurofibrillary tangles are pathological markers found in the post mortem brains of patients with Alzheimer's disease. It is thought that these plaques are present as long as 10 years before any clinical symptoms of disease appear [1]. PET imaging of amyloid-β has emerged as a valuable biomarker to support the in vivo diagnosis of Alzheimer's disease. Recently, several PET tracers have been developed that bind to amyloid plaques and hence can be used as amyloid imaging agents (e.g. [^{11}C]BIP, [^{11}C] SB-13). [^{11}C]BIP PET scans show a twofold increase in retention of signal in subjects with Alzheimer's disease compared with controls. This increase in signal suggests widespread amyloid deposition in cortical areas and striata in Alzheimer's disease [1]. Further analogues of the tracer labelled with ^{18}F have been developed and are currently being introduced into clinical practice; examples include [^{18}F]florbetapir (^{18}F-AV-45), [^{18}F]flutemetamol and [^{18}F]florbetaben [1].

Brain tumour imaging using labelled amino acid analogues

Increased amino acid transport in brain tumour cells results from overexpression of the transporter systems and is related to alterations in the tumour vasculature and tumour cell proliferation. In comparison with conventional anatomical imaging methods, radiolabelled amino acids offer significant improvements in the diagnostic evaluation of cerebral tumours. The contrast they display is far superior to that obtained with [^{18}F] FDG because of the low uptake of amino acids in normal brain tissue, and they may be more tumour specific as their uptake is less influenced by inflammation [7]. The most frequently used radiolabelled amino acid is (methyl-^{11}C)-L-methionine ([^{11}C]MET). In an effort to overcome the disadvantages of the short half-life and complex metabolism of [^{11}C]MET, and despite changes in amino acid structure, several fluoro- and iodo-amino acids have been developed. These agents include 3-(^{123}I)iodo-α-methyl-L-tyrosine ([^{123}I]IMT), used for SPECT, and *O*-(2-(^{18}F)fluoroethyl)-L-tyrosine ([^{18}F]FET), used for PET. They are both transported by the same specific amino acid transport system as [^{11}C]MET but are not incorporated into proteins. They display rapid accumulation into brain tumours that is independent of BBB disruption (Fig. 5). Several ^{18}F-labelled amino acids are available; [^{18}F]FET, due to its ease of synthesis, high in vivo stability and fast brain and tumour uptake, has been selected as the representative compound of this category.

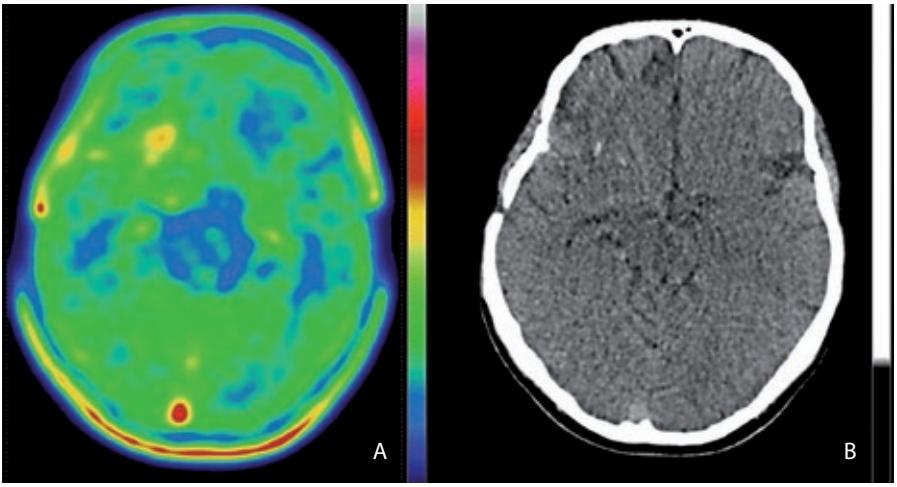


Figure 5 A, B: Brain PET/CT imaging with [^{18}F]FET in a patient with suspected recurrence of glioblastoma. (A) PET image. An area of increased tracer uptake in the frontal lobe is seen on the right side. (B) CT image.

Despite differences in blood clearance, uptake kinetics and relation to protein synthesis, [^{11}C]MET, [^{123}I]IMT and [^{18}F]FET show similar results in the diagnostic evaluation of cerebral tumours [7]. Doses in adults are 100–400 MBq (typically 185 MBq) for [^{123}I]IMT, 200–250 MBq for [^{11}C]MET and 200–250 MBq for [^{18}F]FET.

According to the EANM Guidelines [7], common indications for brain tumour imaging using labelled amino acid analogues are:

1. Detection of viable tumour tissue (radiolabelled amino acid imaging is superior to [^{18}F]FDG-PET in confirming low-grade recurrence).
2. Tumour delineation: Radiolabelled amino acid tracers are superior to CT and MRI for estimation of true tumour extension in low- as well as high-grade gliomas. Due to lower uptake in normal brain tissue, they are also superior to [^{18}F]FDG for delineation of low-grade tumours, in which [^{18}F]FDG uptake is found to be decreased compared with normal cortex or basal ganglia. With [^{18}F]FET, large brain vessels may be visualised due to high blood pool radioactivity.
3. Selection of the best biopsy site (labelled amino acid imaging is recommended to guide the stereotactic biopsy, which is the gold standard in the classification and grading of glioma).

4. Non-invasive tumour grading (grading of cerebral gliomas using labelled amino acids is controversial: [^{18}F]FDG PET appears better suited to differentiate between tumour grades).
5. Therapy planning (in conjunction with anatomical imaging, radiolabelled amino acid imaging may be used to better define the tumour volume to be resected or irradiated).
6. Tumour response (changes in uptake on labelled amino acid imaging may predict the response to locoregional chemo- and radiotherapy as early detection of residual tumour after surgery may be possible).

As the number of PET/SPECT centres grows, applications in clinical neurology will increase for early and/or presymptomatic diagnosis of diseases. As more target-specific radiotracers and ligands are developed, their use in clinical research and drug development will help determine optimal drug dosing regimens and elucidate the downstream effect of drug actions.

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Table 1

Common PET/SPECT radiotracers/ligands and their intended targets in clinical neurology (adapted from Sampson's Textbook of Radiopharmacy, 4th ed. [1]

Target	PET/SPECT radiotracer/ligand
Cerebral blood flow	[^{15}O]water, ^{99m}Tc-HMPAO, ^{99m}Tc-ECD
Cerebral glucose metabolism	[^{18}F]fluorodeoxyglucose (FDG)
Dopamine synthesis	[^{18}F]fluorodopa (F-DOPA)
Dopamine D_1 receptors	[^{11}C]SCH23390
Dopamine $D_{2/3}$ receptors	[^{11}C]raclopride, [^{11}C]FLB457, [^{123}I]iodobenzamide, [^{123}I]epidepride
Dopamine reuptake (transporter) sites	[^{11}C]RTI-32, (11C)CFT, [^{123}I]ioflupane
Serotonin (5HT) 1A receptors	[^{11}C]WAY 1000635
Serotonin (5HT) 2A receptors	[^{11}C]MDL 100907, [^{18}F]altanserin
Serotonin reuptake (transporter) sites	[^{11}C]DASB, [^{123}I]β-CIT
Peripheral benzodiazepine sites	[^{11}C]PK11195, [^{123}I]PK11195
Central benzodiazepine sites	[^{11}C]flumazenil
Amyloid	[^{11}C]PIB, [^{18}F]flutemetamol, [^{123}I]IMPY
Opioid receptors	[^{11}C]diprenorphine

Chapter 3

SPECT and SPECT/CT in Oncological Brain Imaging

Elizabeth C. Hackett

Introduction

Single-photon emission computed tomography, or SPECT as it is commonly known, has been used for many years as an imaging modality in the detection of oncological abnormalities of the brain even though it is not the modality of choice for evaluation of brain lesions. This chapter will discuss the evolution of SPECT and SPECT/CT imaging, the uses and advantages of SPECT and SPECT/CT in brain oncology, the radiopharmaceuticals that have been used for this indication, imaging technique and data processing and, finally, the future of SPECT imaging in oncology.

The evolution of SPECT and SPECT/CT

SPECT imaging was introduced in the 1970s. It enables the creation of a 3D image from multiple gamma camera images taken by cameras continuously rotating around an area of interest. The 3D images obtained using SPECT offer improved sensitivity and resolution compared with 2D images and are easier to compare with MRI and CT images. SPECT also permits better tumour localisation as the 3D imaging component allows different views (sagittal, coronal and transaxial) to be displayed, thereby offering improved visualisation of the abnormality.

SPECT/CT cameras in which both the SPECT gamma camera system and the CT camera system have been integrated into one gantry have been available since the late 1990s. The SPECT/CT systems allow for the fusion of the nuclear medicine SPECT images with the CT images. This results in a better image showing both the physiological aspects of the disease and anatomical information. It also makes it much easier to pinpoint the tumour location.

Uses and advantages of SPECT and SPECT/CT in brain oncology

SPECT and SPECT/CT have been used widely in the assessment of brain tumours and have been shown to be most useful in the imaging of recurrent gliomas and intracranial lymphomas. SPECT imaging allows assessment of tumour malignancy based on the functional imaging aspect, while SPECT/CT plays an important role in localisation of the tumour for the purpose of surgery. After surgery and/or radiotherapy, SPECT and SPECT/CT are used to help monitor the disease by evaluating differences at the tumour site that can indicate gliosis, radiation necrosis or tumour recurrence. SPECT permits the functional imaging of tumours of an indeterminate nature in order to evaluate their significance. It also helps to differentiate intracranial lymphomas from toxoplasmosis.

Radiopharmaceuticals for brain imaging with SPECT and SPECT/CT

Several radiopharmaceuticals have been used for brain imaging in SPECT and SPECT/CT (Table 1). All of these radiopharmaceuticals are discussed in detail in Chapter 2, but we shall also cover them briefly in this chapter. The most important quality that the radiopharmaceutical must have is the ability

to cross the blood-brain barrier and localise in normal brain tissue. This quality is needed to permit evaluation of abnormalities within the brain tissue. Two of the most commonly used radiopharmaceuticals are technetium-99m (^{99m}Tc) bicisate (ethyl cysteinate dimer, ECD) and ^{99m}Tc-exametazime (hexamethyl-propylene amine oxime, HMPAO).

HMPAO is used in SPECT imaging in both un-stabilised and stabilised preparations. ^{99m}Tc-HMPAO and ^{99m}Tc-ECD can appear to show normal to decreased activity in abnormal brain tissue, but ^{99m}Tc-ECD has been known to show increased activity in tumours. Thal-lium-201 chloride (^{201}Tl) is also used in SPECT oncological imaging as it has high uptake in brain tumours and can assist in biopsy guidance. Figure 1 demonstrates ^{201}Tl SPECT scans of different grades of glioma.

Technetium-99m sestamibi has also been shown to have increased activity in tumours and has been used in SPECT oncological im-aging. Figure 2 shows transaxial slices of a ^{99m}Tc-sestamibi SPECT scan.

The injected activities and uptake times for each of the above radiopharmaceuticals are displayed in Table 1.

Imaging technique and data processing

SPECT and SPECT/CT imaging should be performed bearing the following guidelines in mind:

Patient preparation:

- atients should avoid caffeine, alcohol and other drugs that can affect cerebral blood flow for 24 h prior to the study.
- Patients should not smoke cigarettes on the day of the study.
- A thorough detailed history needs to be taken, focussing on past head trauma and previous radiological studies.

Pre-injection:

- Ensure that the patient can comply with the scan procedures.
- Explain the scan procedure to the patient or to the designated healthy care proxy or caregiver.
- Have the patient relax in a dimly lit room where there are no external stimuli, including direct light, music, reading or speaking, for 20–30 min prior to the injection. Whether the eyes are kept opened or closed depends on the individual department's policy.
- Obtain intravenous access with either an angiocath or a butterfly needle at least 10 min prior to injection.
- Instruct the patient not to move, speak or read for at least 5 min after injection.

- The patient should relax in the dimly lit room for 20–60 min or according to the departmental procedure during the uptake phase of the radiopharmaceutical (see Table 1).

Acquisition:

- After the uptake phase has been completed, the patient should void before being brought into the camera room.
- Position the patient on the imaging table in a supine position so that he or she is comfortable, with the arms down. Position the head so that it is in the middle of the field of view of the camera. The entire brain should be included in the field of view and a head holder or other light head restraint should be used to help reduce patient motion.
- When imaging, use the smallest radius possible around the patient's head to ensure diagnostic images are obtained. It is ideal to be able to set up a contour radius to enable the camera head to be as close as possible to the head at all times. If the camera does not allow for a contour radius to be set up, then it is best to use the smallest circulatory radius possible to ensure maximum image resolution.
- Monitor the patient throughout the scan to ensure safety and to watch for motion.
- A camera with multiple detectors or a dedicated brain imaging camera is preferred to a single-head system for SPECT. A SPECT/CT camera is also preferred as the scans can be fused for evaluation.
- The energy peak should be set at 140 keV and the energy window to 20%.
- Low-energy high-resolution or ultra high-resolution collimators should be used and the highest resolution collimators are preferred. Fan beam, parallel-hole collimators can be used if needed.
- The matrix should be 128×128 or greater. Acquisition pixel size should be 1/3–1/2 the expected reconstructed resolution. It may be necessary to zoom in order to achieve the required pixel size.
- The orbit should be 360° and as close as possible to the patient.
- A continuous acquisition is preferred over step and shoot with 20–40 s per projection.
- Segmenting the data will help reduce patient motion in the resulting images.

Data processing:

- All studies should be filtered in three dimensions (x, y and z), using low-pass filters (Butterworth) and at the highest pixel resolution.
- Be sure to reconstruct the entire brain from vertex to cerebellum using either the filtered back projection (FBP) or the iterative reconstruction method.

- Attenuation correction should be used on all data unless a specific protocol or case states otherwise. When a SPECT/CT is performed, the CT scan should be used for the attenuation correction. In the case of a stand-alone SPECT camera, Chang attenuation correction should be used.
- Data should be reformatted for display in coronal, sagittal and transverse slices.
- When SPECT/CT is performed, not only should the CT scan be used for attenuation correction (as mentioned above) but the resulting SPECT images can also be fused with CT for detailed images.

Future of SPECT and SPECT/CT

SPECT and SPECT/CT for imaging of brain tumours both entails challenges and offers further potential rewards. PET scanners have rapidly gained popularity in the field of nuclear medicine as a means of obtaining functional images of brain tumours. In most cases, SPECT tumour studies provide a similar amount of diagnostic information to that acquired with PET. This is useful as there are areas that do not have easy access to PET radiopharmaceuticals or PET cameras. As stated earlier, the main drawback of SPECT imaging of tumours is the lack of anatomical detail. However, the advent of SPECT/CT has allowed for the co-registration or fusion of scans, resulting in images that show both anatomical and functional detail. Such images are very useful for tumour localisation and treatment planning.

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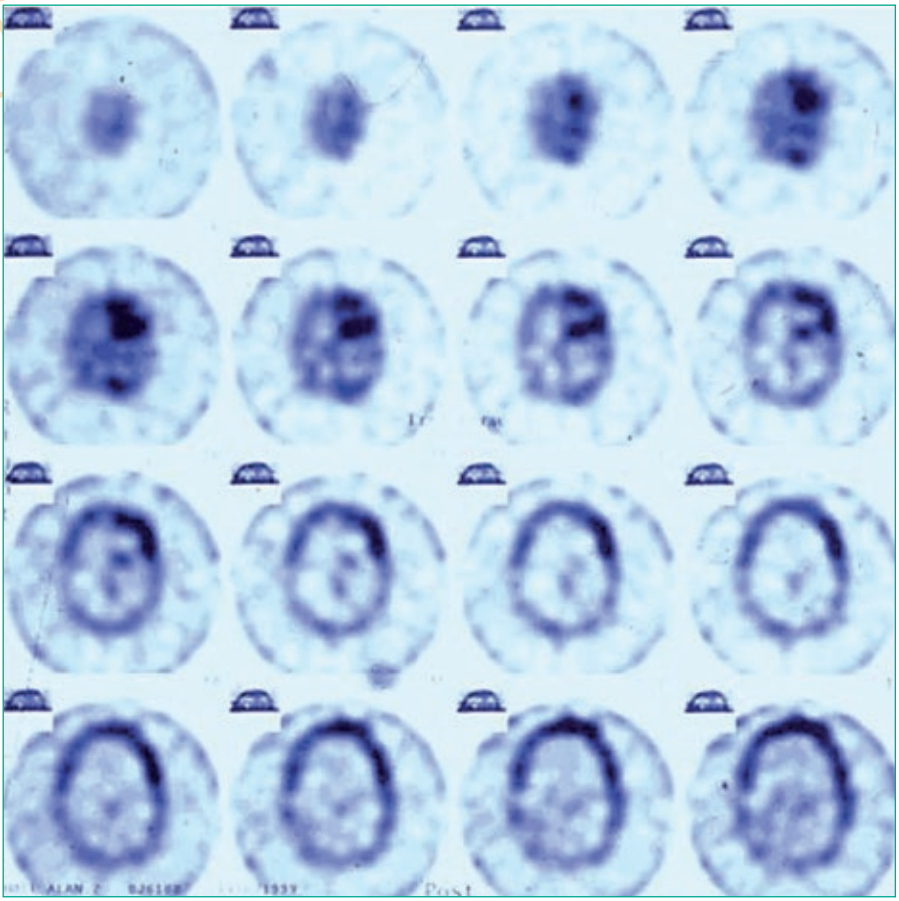
Table 1: Radiopharmaceuticals used for brain imaging in SPECT systems, with injected activities and uptake time

Radiopharmaceutical	Injected activity	Route	Uptake time
^{99m}Tc-HMPAO	555–1110 MBq (15–30 mCi)	Intravenous (through filter)	Recommended uptake time: 90 min Minimum uptake time for interpretable images: 40 min
^{99m}Tc-ECD	555–1110 MBq (15–30 mCi)	Intravenous	Recommended uptake time: 45 min Minimum uptake time for interpretable images: 20 min
^{99m}Tc-Sestamibi	740 MBq (20 mCi)	Intravenous	Recommended uptake time: 20–30 min
^{201}Tl	111–148 MBq (3–4 mCi)	Intravenous	Uptake time: 10–30 min Delayed images can be acquired 2–4 h post injection

Figure 1 A–C: ^{201}Tl SPECT scans demonstrating uptake in different grades of glioma: A grade 2 glioma; B grade 3 glioma; C grade 4 glioma.



Neurographics and Dr. Thomas Booth

Figure 2: ^{99m}Tc-Sestamibi SPECT scan of a brain glioma demonstrating uptake in the tumour.

Chapter 4

Imaging in Oncological Brain Diseases: PET/CT

Giorgio Testanera and Giovanna Pepe

Introduction

Molecular imaging techniques are used to generate maps of functional and biochemical activity in target tissues in vivo. Currently, positron emission tomography (PET) is one of the most successful techniques in the diagnostic work-up of brain tumours, its importance deriving from its ability to address various metabolic features of gliomas that are relevant to diagnosis, classification, characterisation, preoperative evaluation, radiotherapy planning and post-therapeutic monitoring. Combined PET/CT imaging of brain tumours has similarly grown in importance, especially thanks to the increasingly widespread availability of radiopharmaceuticals. PET/CT not only contributes to differential diagnosis, but also offers the possibility of tailoring imaging to different clinical indications. The two main metabolic features extensively studied so far are glucose metabolism by means of ^{18}F-FDG and amino acid transport (incorporation) using amino acid radiopharmaceuticals such as ^{11}C-methionine (^{11}C-MET), ^{18}F-fluoroethyltyrosine (^{18}F-FET), ^{18}F-labelled 3'-deoxy-3'-fluorothymidine (^{18}F-FLT) and ^{18}F-dihydroxyphenylalanine (^{18}F-DOPA; fluorodopa). In this chapter, in the spirit of continuity with EANM and international guidelines on the topic [1–5], we shall cover the major clinical applications of these techniques, together with acquisition methods and patient preparation; some notes are also provided on quantitative imaging.

PET/CT acquisition techniques

PET/CT is defined as an integrated or multimodality technique that employs a combination of a PET and a CT system with a single, conjoined patient handling system [1]. It allows sequential acquisition of corresponding PET and CT portions of the examination with the patient in the same position for both examinations and enables co-registration both data sets.

CT protocols

Attenuation correction is mandatory for PET/CT brain imaging. In older generation PET scanners, attenuation correction was achieved by transmission imaging acquired by the PET tomograph itself, using a ^{68}Ge/^{68}Ga source. Alternatively, some PET systems had transmission sources with ^{137}Cs.

PET/CT systems have the ability to use the CT scan for attenuation correction [6]. The advantage of the CT scan is that the detection of X-rays from the CT scan is not affected by the emission photons; this allows the CT scan to be performed after the injection of the radiopharmaceutical, without affecting the accuracy of the attenuation correction. A CT scan can be done for diagnostic purposes, using a regular tube current, or only for the purpose of attenuation correction, using a low tube current (typically 10–30 mAs), i.e. a low-dose CT scan, which significantly reduces the radiation exposure.

The choice of type of CT scan depends on the purpose of the imaging and the clinical indications. If anatomical information is already available, a low-dose CT scan for the purpose of attenuation correction can be considered, whereas if recent anatomical information is not available, a diagnostic CT scan (with contiguous slices) may be preferred. A diagnostic CT (high mAs, contrast media injection) requires specific skills in radiology and specific radiologist guidelines must be followed. When CT is used for attenuation correction and localisation only (i.e. is not intended to be clinically diagnostic), the suggested workflow is:

- CT topogram
- Low-dose CT
- PET acquisition

When a contrast-enhanced diagnostic CT scan is also needed, it is advisable to perform it after PET acquisition, to avoid any possible impact of IV contrast on PET images and standardised uptake value calculation.

CT acquisition parameters (Table 1) are strictly dependent on the equipment available and national regulations, the latter being particularly relevant to patient X-ray exposure. The ALARA principle always applies and must be followed to avoid unnecessary exposure.

PET protocols

High-quality PET brain images can be obtained only if strict procedures are adhered to, including respect to patient preparation, administration of adequate radiopharmaceutical activity, patient positioning and use of standardised acquisition protocols [8].

Patient preparation may vary for different radiopharmaceuticals and different indications (Table 2). It is commonly accepted that for ^{18}F-FDG PET the patient should fast for at least 4 h to allow optimal cerebral uptake that is not influenced by increased serum glucose levels. Blood glucose levels should be checked prior to ^{18}F-FDG administration. When hyperglycaemia is present (>160 mg/dl), ^{18}F-FDG uptake is reduced in the whole brain and stochastic noise is increased. However, in brain tumours, hyperglycaemia does not need to be corrected and can even enhance detectability [1].

Before the scanning procedure is started, the patient should void the bladder to ensure maximum comfort during the study. The patient should be informed about the total acquisition time and advised to void again after the scanning session to minimise radiation exposure. The patient should be positioned comfortably in a quiet, dimly lit room for several minutes before ^{18}F-FDG administration and during the uptake phase of ^{18}F-FDG (at least 20 min) and should be instructed not to speak, read or be otherwise active. It

is desirable to have the cannula for intravenous administration in place 10 min before ^{18}F-FDG administration. If a dynamic image is requested, the above procedures are to be followed with the patient positioned directly on the tomograph bed instead of in a different room.

Post-processing routines allow correction for minor obliquities of head orientation, so it is more important to reduce the probability of motion during acquisition than to achieve perfect head alignment. The patient must be informed of the necessity to avoid voluntary movements of the head and must be asked for her/his active cooperation. If cooperation is poor, sedation may be required. The patient's head should be only lightly restrained, avoiding use of a fixed container that can create claustrophobia. If movement artefacts can be expected, segmentation of data acquisition into multiple sequential acquisitions may permit the exclusion of segments of projection data affected by patient motion.

The administered dose and scan parameters are strictly dependent on national regulations and the scanner used. EANM guidelines for ^{18}F-FDG [1] suggest, for adults, 300–600 MBq (typically 370 MBq) in 2-D mode and 125–250 MBq (typically 150 MBq) in 3-D mode.

In preparation for a radiolabelled amino acid PET scan, patients are advised to take a low-protein meal 4 h before the injection, although this requirement is controversial. The patient may be requested to avoid taking specific drugs during preceding clinical evaluations [10].

Imaging may be performed as a dynamic acquisition or a static acquisition 20 min after injection of 330–400 MBq of ^{11}C-methionine or ^{18}F-FET. As with ^{18}F-FDG, radiopharmaceutical administration consists in intravenous injection of a bolus followed by flushing with physiological saline solution. After the administration, an interval of 10 min must be allowed before scanning.

Table 3 shows examples of how PET/CT scan is performed with two tomographs accredited by the EARL project [11–13]. As noted above, we suggest that protocols should be adapted according to the scanner employed, following company suggestions and guidelines, both national and international.

^{18}F-DOPA is an amino acid radiopharmaceutical that accumulates in brain tumours via a transporter-mediated mechanism similar to that responsible for uptake of methionine. Many imaging protocols have been tested, for instance with scanning starting at an

earlier time point after injection (e.g. 20 min) or at a late time point, as is recommended for striatal imaging (e.g. 60–70 min) [14]. The European Association of Nuclear Medicine guidelines on paraganglioma imaging recommend a dose of 4 MBq/kg and imaging at 30–60 min after injection. In the evaluation of brain tumours the best time interval for acquisition is between 10 and 30 min after injection because tumour uptake is near maximum and because imaging at this juncture is sufficiently early to avoid peak uptake in the striatum. All these parameters refer to adults; we recommend the EANM paediatric dosage card as a useful tool for determination of the activity to be administered in children.

Quantitative PET/CT

PET/CT scans offer the possibility of acquiring quantitative information on radiopharmaceutical biodistribution inside a living organism, but robust standardisation is required to ensure reproducibility and to allow the use of imaging biomarkers in multicentre trials in which different scanners are employed. Efforts aimed at harmonisation of acquisition, evaluation and quantification of PET/CT studies have been concluded or are ongoing worldwide.

In Europe, the research branch of EANM, EARL, set up the ^{18}F-FDG PET/CT accreditation programme, which is also endorsed by the EORTC imaging group. It was launched in July 2010 with the objective of providing a minimum standard of PET/CT scanner performance. The programme requires imaging sites to perform strict continuing quality control, making them highly eligible as participants in multicentre studies. Participation in the EARL programme is also useful as a quality self-test for departments, to ensure that routine patient examinations are of a high quality [11–13].

For tumour imaging, semiquantitative estimates of glucose metabolism such as the standardised uptake value (SUV) are typically used. SUVs may vary significantly if acquisition procedures are not standardised, and correct, reproducible standardisation requires efforts at every step of the schedule. For ^{18}F-FDG exam quantitation, a static image is sufficient, usually acquired at 30 or 60 min after injection (after ^{18}F-FDG has reached a plateau concentration in the lesion). In addition, the exact total activity of ^{18}F-FDG administered and the patient's weight and height for measurement of body surface area are required. A calibration factor is also needed. These semiquantitative estimates can be corrected for blood glucose concentration.

When using methionine, the first quantification method routinely used is the tumour-to-normal background ratio (T/N ratio), which compares uptake in the tumour to that in the contralateral frontal lobe or the corresponding contralateral hemisphere. Generally, a threshold greater than 1.5–1.9 is used for the diagnosis of brain tumour, but large prospective studies are needed to set a fixed T/N cut-off ratio. SUVs should also be used (maximum

or mean) but their true diagnostic value is still a matter of debate. MET accumulation in brain tumours reaches a plateau at 5–10 min after the radiopharmaceutical injection. As for ^{18}F-FDG scans, the SUV is influenced by many factors, some being technical, such as acquisition starting time, and others more clinical, such as the plasma concentrations of *N*-acetylaspartate, which may affect the uptake of MET in a competitive fashion.

Quality criteria and artefacts

Compliance with the above procedures may be expected to ensure an appropriate, symmetrical and readily interpretable representation of the reconstructed dataset. Internal landmarks can be used for reorientation to achieve a standardised image display. Reorientation procedures based on the intercommissural line are commonly used. The display of additional coronal and sagittal images is mandatory. Three-dimensional display of the dataset can be helpful for more accurate topographic orientation in some clinical questions and to appreciate overall patterns of disease. The images should be critically examined by technologists after the scan to ensure that quality criteria are matched. Technologists also have to discuss with reporting physicians particular cases that may require additional scanning or reconstructions. During interpretation for the presence of movement or attenuation artefacts, it is desirable to have a normal database available, preferably obtained on the same type of tomograph, using the same acquisition positioning and parameters and the same type of reconstruction and attenuation correction as are used in routine scans. Matching spatial resolution is the most important parameter for optimal database use. This allows assessment of normal variability of regional ^{18}F-FDG uptake and improves diagnostic accuracy.

Data interpretation should take into consideration global changes, such as relative cortical hypometabolism and regional decreases or increases in ^{18}F-FDG uptake. Increased uptake can be observed in active epileptogenic foci, tumours and inflammation. Known morphological changes such as atrophy should be considered in the interpretation.

The following list identifies some possible sources of misinterpretation that must be taken into consideration when deciding whether a scan matches quality criteria:

- Artefacts (Figs. 1,2)
  - Patient movement
  - Scanner related
  - Induced by inappropriate processing
  - Insufficient attenuation correction
  - Soft tissue or skull uptake following surgery in the area of the skull or brain
- Unintended cerebral activation (i.e. visual or motor activation)
- Psychotropic drugs or corticosteroid use
- Sedation
- Recent radiotherapy or chemotherapy

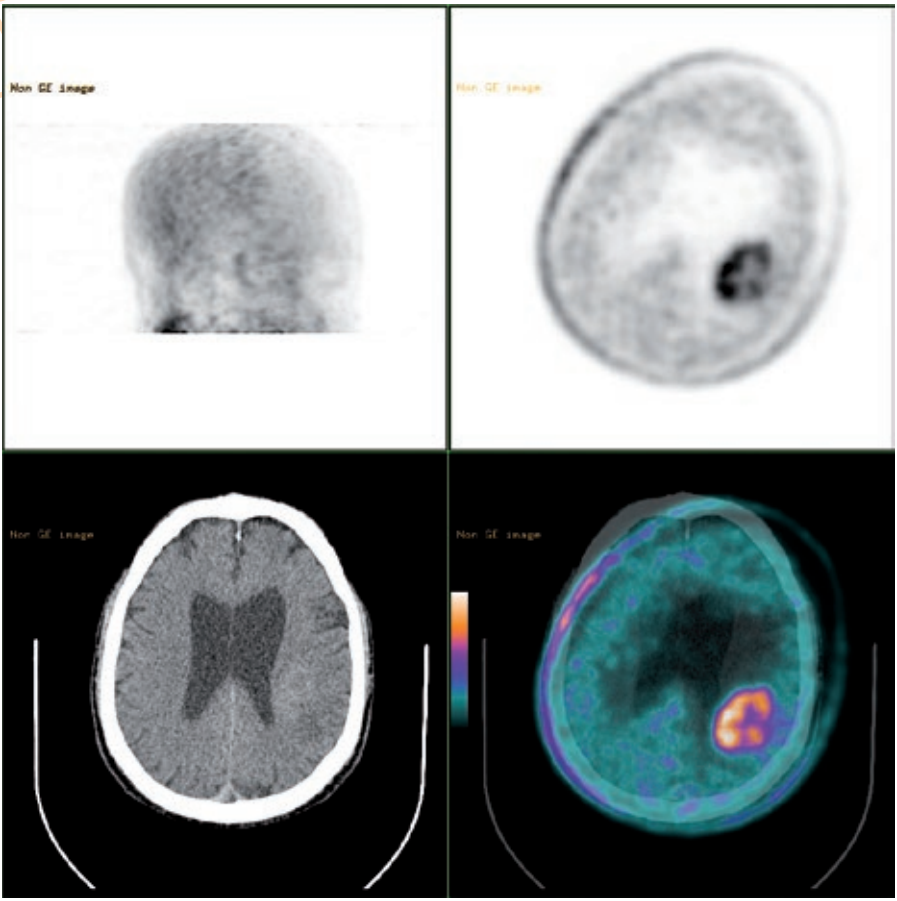


Figure 1: Movement artefact: MIP (top left), PET (top right), CT (bottom left) and fused PET/CT (bottom right) images

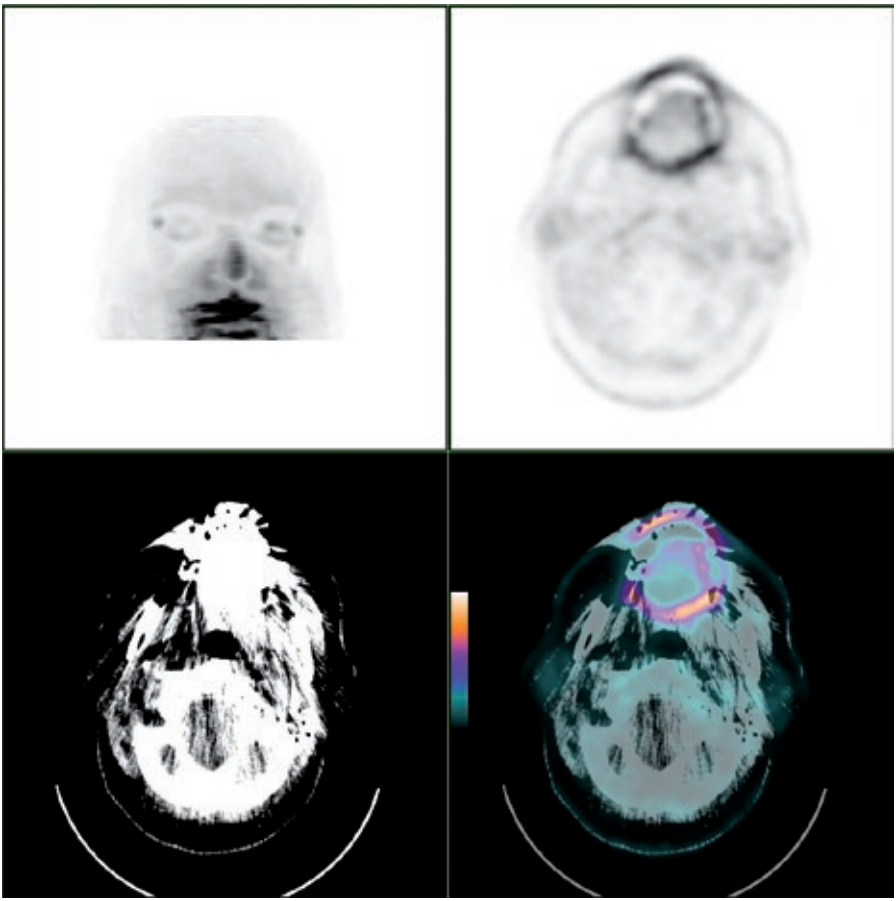


Figure 2: Metallic artefact: MIP (top left), PET (top right), CT (bottom left) and fused PET/CT (bottom right) images

Brain imaging with ^{18}F-FDG

The Warburg effect, i.e. the increase of anaerobic glycolysis even in aerobic conditions, explains the glucose avidity of tumour cells and constitutes the basis for the ^{18}F-FDG uptake (Fig. 3). Despite the high physiological background uptake of ^{18}F-FDG in normal brain, which limits the possibility of discriminating neoplastic lesions, ^{18}F-FDG PET/CT applications are reported in the literature for the purposes of tumour diagnosis, metabolic grading and prognosis, volume estimation and follow-up.

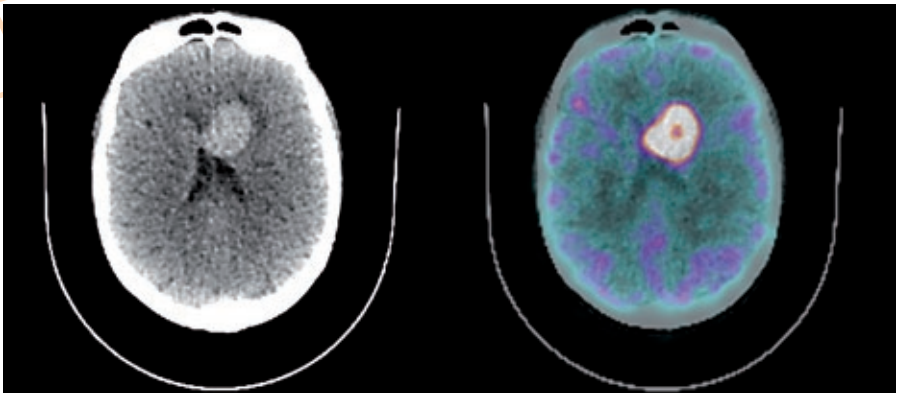


Figure 3: ^{18}F-FDG-positive brain lesion on axial CT (left) and fused PET/CT (right) images

Delbeke et al. described a sensitivity of 94% and a specificity of 77% for ^{18}F-FDG PET in the detection of high-grade gliomas [16]. Some authors suggest that delayed imaging at 3 up to 7 h post injection could help in the analysis of normal grey matter uptake and oncological uptake [17].

^{18}F-FDG uptake has been used to assess the prognosis in patients with high-grade (grade 3 or 4) astrocytomas, the uptake being higher in patients with a poorer prognosis and lower in those with a superior mean survival [18]. Similar results regarding the association of tumour ^{18}F-FDG uptake with patient survival were also reported by Alavi et al.: a positive PET scan with hypermetabolic brain lesions correlated with a poor prognosis as the rate of glycolysis increased in line with the degree of malignancy in primary cerebral tumours [19]. Another interesting potential application that has been investigated is the use of ^{18}F-FDG PET/CT to differentiate among common enhancing brain tumours such as lymphomas, high-grade gliomas and metastases [20].

^{18}F-FDG PET/CT imaging is also used to provide an early assessment of the efficacy of chemotherapy based on its value in predicting tumour metabolic response to temozolomide, which allows oncologists to adopt a more tailored approach [21]. Some authors have studied the potential of ^{18}F-FDG to improve accuracy in stereotactic biopsy. The literature available so far on the use of ^{18}F-FDG PET/CT in primary tumours remains somewhat heterogeneous; nevertheless, thanks also to its widespread diffusion and standardisation, this technique is still attractive and promising as a complementary procedure that assists in completion of tumour

characterisation as the basis for improving or changing patient management [22].

Brain imaging beyond ^{18}F-FDG

In order to overcome the limitations of the use of ^{18}F-FDG in brain imaging, which are due to its physiological uptake in the grey matter, other radiopharmaceuticals have been developed. In particular, radiolabelled amino acids (^{11}C-methionine, ^{18}F-FET, 18F-DOPA) are currently the most commonly used PET radiopharmaceuticals for imaging of brain tumours. Another radiopharmaceutical introduced for imaging of cellular proliferation is choline, a precursor in the phospholipid synthesis required for the production of the cell membrane. Choline is usually labelled with ^{11}C or ^{18}F. Somatostatin receptor expression on the tumour surface, on the other hand, may be investigated by means of somatostatin receptor PET/CT thanks to the development of somatostatin analogues.

In this chapter, however, we prefer a more technical approach to a purely clinical one, and we have therefore decided to group radiopharmaceuticals according to the radionuclide used (Table 4) instead of the tumour features analysed. Therefore the following sections will focus on ^{18}F- radiopharmaceuticals other than ^{18}F-FDG, ^{11}C-radiopharmaceuticals and ^{68}Ga-radiopharmaceuticals.

With regard to the metabolic pathways and tumour features, the main families of available radiopharmaceuticals are summarised in Table 5.

Other ^{18}F-labelled radiopharmaceuticals

L-Dihydroxyphenylalanine (L-DOPA) is not an amino acid, but it is regarded as an amino acid analogue, being the product of the essential amino acid L-tyrosine. It was first introduced as a marker of the dopaminergic system and is widely used to investigate the in vivo transport to the basal ganglia for the diagnosis and follow-up of patients affected by Parkinson's disease. Within oncology, it is known as a radiopharmaceutical for the noradrenaline system, which may be used to investigate neuroendocrine tumours such as phaeochromocytoma and neuroblastoma.

^{18}F-DOPA PET/CT has also been proposed for the study of primary brain tumours because of the high uptake in tumours (Fig. 4) as compared with the very low uptake in normal brain tissue (the basal ganglia represent the only exception). A sensitivity of 85% and a specificity of 89% have been reported for ^{18}F-DOPA PET in the detection of primary brain tumours, and the method was identified as having further prognostic potential as a predictor of tumour grade and proliferation [24].

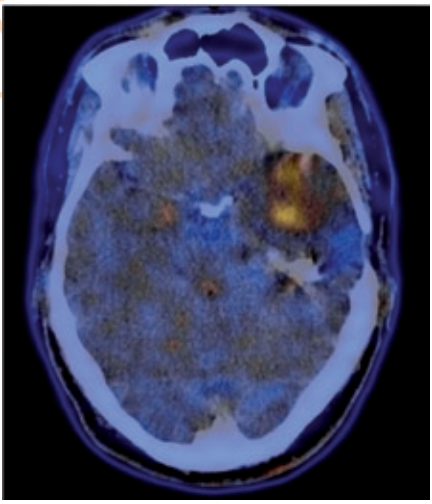


Figure 4: ^{18}F-DOPA PET/CT showing increased uptake in a left temporo-mesial astrocytoma

While a standard acquisition protocol is usually employed when imaging with ^{18}F-DOPA, in a study by Schiepers et al that focussed on the kinetics of ^{18}F-DOPA in brain tumours, dynamic PET images were acquired over a period of 75 min starting soon after injection. The results suggested that ^{18}F-DOPA was transported but not trapped in tumours and that the uptake curve could be related to tumour grade. High-grade tumours showed an early peak of activity followed by a sharp decline whereas low-grade tumours showed a more smoothed curve with a gradual decline [25].

Magnetic resonance imaging (MRI) still represents the mainstay in primary brain tumour imaging; however, in an interesting study involving comparative evaluation of ^{18}F-DOPA PET and MRI in a population of 91 patients with histologically proven gliomas, concordance between MRI and PET was observed in 90% of cases [26].

The use of ^{18}F-DOPA for detection of recurrence of primary neoplastic disease in the brain is still a largely unexplored area.

^{18}F-Fluoroethyltyrosine (FET) is an artificial amino acid taken up into upregulated tumor cells via enhanced expression of type L amino acid carriers and increased carrier-mediated transport, but not incorporated into proteins (in contrast to natural amino acids such as methionine). In a systematic review and meta-analysis by Dunet et al., ^{18}F-FET showed an excellent performance in the initial evaluation of newly diagnosed brain primary tumours, with a sensitivity of 82% and an average specificity of 76%. ^{18}F-FET yielded high-contrast images for both high- and low-grade brain tumour, with low physiological uptake in surrounding normal brain [27].

^{18}*F-Fluorothymidine (FLT)* is a marker of DNA synthesis in brain tumours; its uptake by brain tumours is possible in areas with a disrupted blood-brain barrier. Its sensitivity for low-grade gliomas has been shown to be lower than that of methionine PET.

^{11}C-radiopharmaceuticals

Methionine is an amino acid that is usually labelled with ^{11}C for brain tumour imaging. Owing to the many further evaluations beyond the early feasibility studies, it is the most commonly used radiopharmaceutical for this purpose in different countries. Analogously to ^{18}F-FET, its increased uptake appears to be a consequence of the upregulation of L-type amino acid transporter 1 (LAT1), reflecting cell proliferation.

^{11}C-methionine PET/CT is indicated both at diagnosis, when it can contribute in assessing the degree of malignancy and the prognosis, in guiding biopsy and in evaluating tumour extent during radiation therapy (RT) planning, and after treatment, for evaluation of persistence of disease, response to therapy or relapse and for differentiation of recurrence from necrosis (Figs. 5–7).

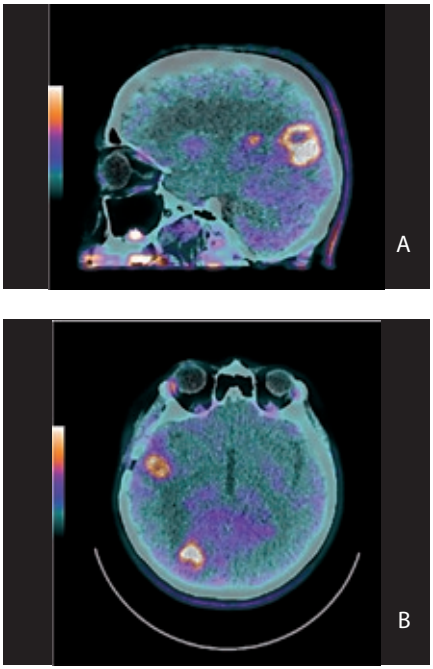


Figure 5: Methionine PET/CT [sagittal (A) and coronal (B) views] showing multiple foci of recurrent glioblastoma

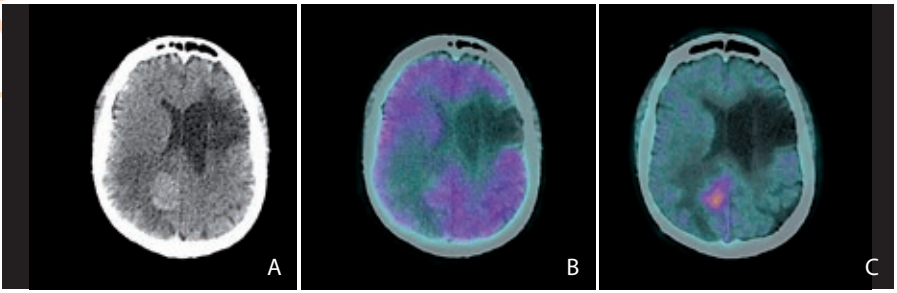


Figure 6 A–C: ^{18}F-FDG PET/CT and ^{11}C-methionine. An occipital brain lesion seen on CT images (A) shows faint ^{18}F-FDG uptake (B) and intense ^{11}C-methionine uptake

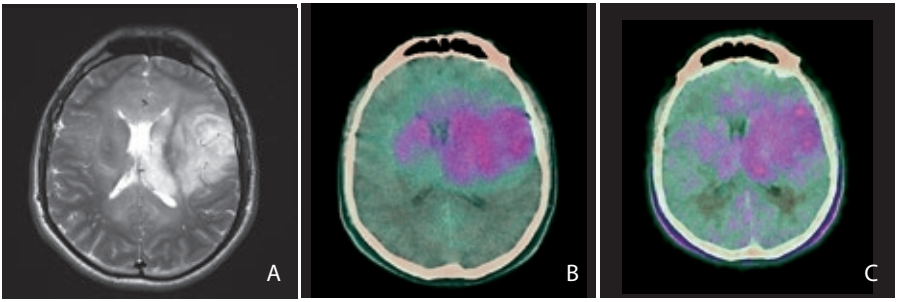


Figure 7 A–C: MRI (A), ^{18}F-DOPA (B) and ^{11}C-methionine (C) imaging of a low-grade astrocytoma

^{11}C-methionine PET offers high-contrast imaging of the brain, reportedly superior to the contrast achieved with ^{18}F-FDG PET. It allows the detection of both high- and low-grade gliomas, but it is especially useful with regard to the former, for which it has a sensitivity between 76% and 95% [28]. Other intracranial tumours such as benign and malignant meningiomas, pineal adenomas, and haemangioblastomas also show intense methionine uptake, although false-positive results may be seen in benign conditions, such as demyelination, leukoencephalitis and abscess. Imaging can be performed as a dynamic or static acquisition 10 min after injection of 370 MBq of ^{11}C-methionine.

A multimodality approach including contrast-enhanced MRI, ^{11}C-methionine PET and ^{18}F-FDG-PET is suggested for tumour grading and prognostication: a higher methionine uptake is related to a poor outcome, albeit better in low-grade and non-contrast-enhancing gliomas, whereas higher ^{18}F-FDG uptake is a better predictor of poorer outcome in high-grade and contrast-enhancing

gliomas. ^{11}C-methionine PET has also been reported to detect progression with a sensitivity of 90% and a specificity of 92%, whereas MRI alone showed a lower specificity (50%) for progression [29].

The increased phosphorylcholine synthesis in tumours constitutes the substrate for the clinical application of the choline-based radiopharmaceuticals in the imaging of brain cancer. The concentration of *choline* in normal cerebral cortex is low, whereas moderate uptake is seen in the choroid plexus and cavernous sinus. Extracerebral tissues such as extraocular eye, masticatory muscles and bone marrow show a moderately higher radiopharmaceutical activity; parotid glands demonstrate intense uptake.

Towards the end of 1990s, ^{11}C-choline was introduced as a novel radiopharmaceutical to evaluate brain and prostate cancer [30] and in 2001 brain tumour images were acquired with ^{18}F-choline in a patient with recurrent anaplastic astrocytoma [31].

Ohtani et al. compared ^{11}C-choline PET, MRI and ^{18}F-FDG PET in a series of patients with suspected brain tumours. They observed a correlation between ^{11}C-choline and the histological tumour grade, with higher choline uptake in high-grade gliomas, and suggested that the combination of ^{11}C-choline PET and MRI could improve the detection of high-grade gliomas [32] (cf. Fig. 8).

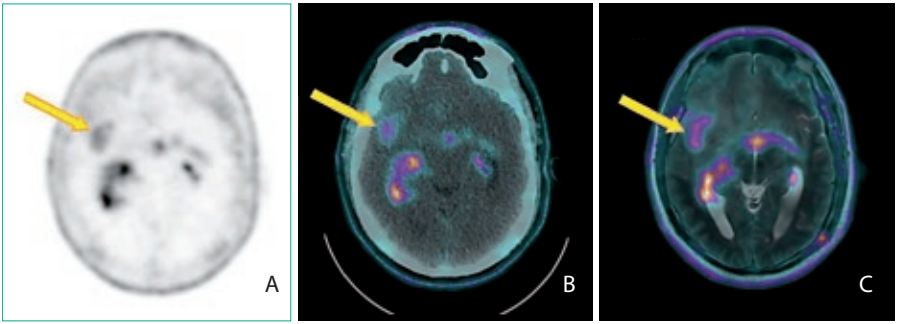


Figure 8: Oligodendroglioma. ^{11}C-Choline PET (A), PET/CT (B) and post-processing fusion with brain MRI (C). The yellow arrow highlights the temporal lesion. Normal uptake is present in the choroid plexus

In a comparative analysis of ^{11}C-choline, ^{11}C-methionine and ^{18}F-FDG PET, ^{11}C-methionine imaging was shown to be useful for the evaluation of grade, type and proliferative activity of astrocytic tumours, while choline appeared more useful in evaluating oligodendroglial tumours. Both were superior to ^{18}F-FDG PET in terms of tumour localisation in all types of glioma [33].

Glioblastomas and meningiomas are described to show moderately intense choline uptake, whereas uptake in grade II and III gliomas is generally faint.

Choline PET appears a promising imaging technique for radiation therapy planning, offering precise delineation of the biological target volume, and it is also able to discriminate between radiation necrosis and tumour recurrence with higher accuracy than MRI or ^{18}F-FDG PET.

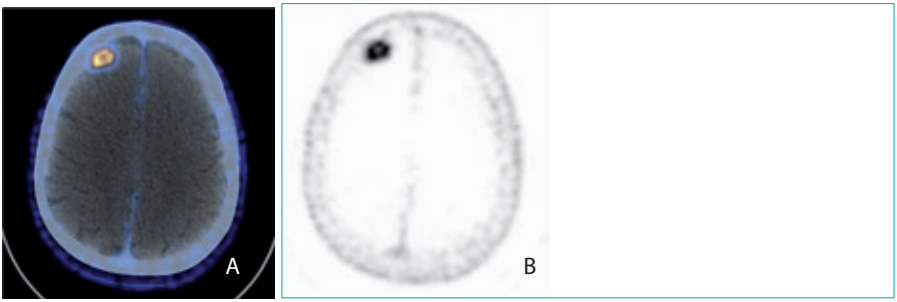


Figure 9 A, B: ^{68}Ga-DOTANOC imaging of a frontal meningioma

^{68}Ga-radiopharmaceuticals

Somatostatin is a neuropeptide produced by various neuronal, endocrine and immune cells. Imaging of somatostatin receptor (SSR) expression on tumour cells is widely applied and standardised. There are several peptides with a different range of affinity for somatostatin receptor subtypes; at present the most frequently used radiopharmaceuticals are ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC (Fig. 9) and ^{68}Ga-DOTATATE. These radiopharmaceuticals are routinely employed for the imaging of neuroendocrine tumours, in particular those arising from the gastroenteropancreatic tract; however, some intracranial tumours can show increased expression of SSR and therefore can be evaluated for this feature as well. Contradictory data have been reported on the positivity of ^{68}Ga-DOTA-peptide PET in series of glial tumours: Reubi et al. [34] concluded that SSRs are expressed predominantly by low-grade gliomas, with 82% of low-grade gliomas (WHO grades 1 and 2) showing SSR expression compared with only 2% of high-grade gliomas (WHO grades 3 and 4). Others reported SSR expression mainly in high-grade gliomas, relating this observation to the loss of differentiation [35].

Meningiomas are the most common non-glial brain tumour arising from the arachnoid membrane and overexpress SSR, particularly the SSR subtype 2; this explains the utility of ^{68}Ga-DOTA-peptide imaging for meningioma [36].

In this scenario the role of SSR PET is to better define lesions that are indeterminate at MRI or CT but also to improve the contouring in RT planning and contribute in predicting the response to radiopeptide therapy. Other possible applications of SSR PET with respect to brain tumours are represented by pituitary adenoma, haemangioblastoma, medulloblastoma and neuroendocrine metastases to the brain from other sites [37].

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Tables

Table 1: Recommended preparation, contrast medium injection and CT acquisition parameters for brain imaging (adapted from [7])

Patient preparation		Diet (3 h)
Patient position		Supine/head first
Contrast medium injection	Contrast medium	300–350 mg I/ml
	First injection	60 ml, 1 ml/s
	Delay	3 min
	Second injection	50 ml, 1.5 ml/s
	Acquisition	Starting at the end of second injection
CT acquisition parameters	Volume of investigation	Vertex to C1
	Collimation	N x 0.75 mm
	Slice thickness	3–5 mm
	Slice increments	Continuous
	Pitch	1
	Rotation time	0.75–1 s
	mAs	250
	X-ray tube voltage	120
	Resolution matrix	512 x 512
	FOV	240 mm
	Reconstruction filter	Soft tissue

Table 2: Patient preparation when using radiopharmaceuticals other than ^{18}F-FDG (adapted from [9])

^{11}C-Flumanezil	No seizure during 1 day before scan (no standard/common practice)
^{11}C-Methionine	Low-protein diet 4 h before scan (no standard/common practice)
^{18}F-Fluorothymidine	No fasting required
^{18}F-DOPA	No dopaminergic or dopaminomimetic drugs 12 h before scan
^{18}F-Fluoroethyltyrosine	Low-protein diet 4 h before scan (no standard/common practice)

Table 3: Practical examples of different parameters used for brain imaging with two different EARL-accredited PET/CT scanners: scanner A is from 2006, with no time-of-flight technology and 6-slice CT; scanner B is from 2012, with time-of-flight technology and 64-slice CT (adapted from [14])

Scanner A		Scanner B	
CT protocol		**CT protocol**	
Topogram	50 mA 110 kV 256 mm	Topogram	10 mA 120 kV 250 mm
Dose modulation parameters	80 mA 130 kV	Dose modulation parameters	280 mA, maximum value 140 kV
Slice	3 mm	Slice	3.75 mm
Collimation	6 x 2 mm	Collimation	64 x 3.75 mm
Rotation time	1 s	Rotation time	1 s
Pitch	1.0	Pitch	0.984:1
Reconstruction for attenuation correction	H10s very smooth + 3 mm, FOV 300 mm	Reconstruction for attenuation correction	AC wide view 3.75 mm, FOV 500 mm
Reconstruction for imaging	H31s medium smooth + 3 mm, FOV 250 mm	Reconstruction for imaging	Standard wide view 0.625 mm, FOV 500 mm

Scanner A		Scanner B	
PET protocol		**PET protocol**	
Scan duration bed	10	Scan duration bed	10 min
Matrix	256	Matrix	256
Zoom	2	DFov	30 cm
Reconstruction	Iterations 2, subsets 8	Reconstruction	VUE Point FX, iterations 3, cut-off 4 mm, subsets 18, sharp IRON
Filter	Gaussian	Filter	No filter axis Z
FWHM	4 mm	FWHM	/

Abbreviations: AC, attenuation correction; DFOV, display field of view; FOV, field of view; FWHM, full-width at half-maximum; IRON, General Electric proprietary name; VUE Point FX, General Electric proprietary name

Table 4: PET radionuclides in brain tumour imaging (modified from [23])

Radionuclide	Half-life (min)	Mean ß+ energy (MeV)	Maximum ß+ energy (MeV)	Example of radiopharmaceutical
^{18}F	109	0.25	0.63	^{18}F-Fluorodeoxyglucose (FDG) ^{18}F-Dihydroxyphenylalanine (F-DOPA) ^{18}F-Fluoroethyltyrosine (FET) ^{18}F-Fluorothymidine (FLT) (^{18}F-Choline)
^{11}C	20.4	0.39	0.96	^{11}C-Choline ^{11}C-Methionine
^{68}Ga	68.1	0.84	1.90	^{68}Ga-DOTA-peptide

Table 5: PET radiopharmaceutical families in brain tumour imaging

Metabolic pathways/tumour features	Radiopharmaceutical
Amino acids: protein synthesis	^{11}C-Methionine
	^{18}F-Fluoroethyltyrosine (FET)
Amino acid analogues	^{18}F-Dihydroxyphenylalanine (F-DOPA)
Nucleosides: DNA replication/cell proliferation	^{18}F-Fluorothymidine (FLT)
Phospholipids: cell membrane synthesis	^{11}C-Choline
	(^{18}F-Choline)
Somatostatin receptor expression	^{68}Ga-DOTA-peptides

Chapter 5

Imaging in neurological and vascular brain diseases (SPECT and SPECT/CT)

Filipa Lucena, Eva Sousa and Tânia F. Vaz

Introduction

Since the first in vivo studies of cerebral function with radionuclides by Ingvar and Lassen [1], nuclear medicine (NM) brain applications have evolved dramatically, with marked improvements in both methods and tracers. Consequently it is now possible to assess not only cerebral blood flow and energy metabolism but also neurotransmission [2]. Planar functional imaging was soon substituted by single-photon emission computed tomography (SPECT) and positron emission tomography (PET); it now has limited application in brain imaging, being reserved for the assessment of brain death [3, 4]

In recent years, owing to their wide availability and superior spatial resolution, structural techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have replaced NM functional imaging techniques in the assessment of patients with neurological disorders. However, SPECT and PET can make valuable contributions in an expanding number of clinical situations, complementing structural imaging [5, 6]. In fact, multimodal approaches now have an established clinical role in neuroimaging applications, whereby the structural images permit anatomical localisation of the radiopharmaceutical distribution and also allow for some corrections (e.g. attenuation correction) [6].

Commonly accepted clinical indications for SPECT brain imaging include presurgical lateralisation and localisation of epileptogenic foci and the evaluation of suspected dementia, movement disorders, traumatic brain injury, cerebrovascular diseases (acute stroke, chronic ischaemia, preoperative evaluation and assessment of brain death), brain tumours and brain infections [7–10].

The available radiopharmaceuticals include brain perfusion tracers and neurotransmission binding agents. There are currently no SPECT tracers for the specific study of brain metabolism [11] (cf. Chapter 2).

Brain perfusion scintigraphy

Brain perfusion scintigraphy allows the assessment of regional cerebral blood flow (rCBF), using radiopharmaceuticals that distribute proportionally to the regional tissue blood flow after intravenous injection and remain trapped for a sufficient length of time to allow acquisition of SPECT images. These specific perfusion compounds are small, neutral, lipophilic and able to cross the blood-brain barrier by passive diffusion [12]. The most widely used radiopharmaceuticals for brain perfusion SPECT are ^{99m}Tc-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) and ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD). Non-specific perfusion radiopharmaceuticals, such as ^{99m}Tc-diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA), can also be used for the evaluation of brain death, providing information on intracranial vascular flow.

Patient considerations

General information regarding patient preparation can be found in Table 1, including specific considerations for each step of the

procedure. From a general point of view, patient preparation includes the withdrawal of any factor known to disturb rCBF, as it will affect the normal pattern of radiopharmaceutical distribution in brain. The length of time for which restrictions are imposed varies depending on the duration of the disturbance produced in the rCBF. The restrictions may include dietary constraints, withholding of medication and control of environmental variables, such as exposure to visual, auditory and somatosensory stimuli. Special attention should be paid to potential disturbances in the minutes prior to injection of the radiopharmaceutical and during the uptake phase.

The preparation procedure requires correct evaluation of the patient's ability to cooperate and good communication skills on the part of the NM technologists so that all the information and recommendations can be effectively conveyed [7, 13]. In uncooperative patients, sedative medication (e.g. short-acting benzodiazepine) can be considered as long as administration is after the radiopharmaceutical uptake phase, thereby avoiding sedation-induced blood flow changes [7, 8].

Technical considerations regarding image acquisition and processing

When positioning the patient for image acquisition, NM technologists should observe various guidelines in order to avoid factors that may interfere with the obtained data and the clinical interpretation of results (cf. Table 1).

Correct head positioning should be achieved using a head holder provided by the gamma camera manufacturer [13]: the centre of the head of the patient should be aligned with the centre of rotation, preventing displacement of the head to the periphery of the field of view; the canthomeatal line (i.e. the line extending from the ear to the eye) should be oriented as vertically as possible; and there should be no rotation or lateral tilt of the head. Commercially available brain SPECT processing applications allow reorientation of the data after acquisition; however, these data manipulations may introduce errors, including image blurring, highlighting the fact that head positioning is an important step in the procedure [13, 14]

Immobilisation devices should be used to provide slight restraint and, when complemented by a comfortable position for the patient, reduce the probability of movement during SPECT acquisition [13].

Different acquisition protocols (cf. Table 1) can be used according to the clinical indications. Currently, planar imaging is used only for brain death studies, in early and delayed phases, either alone or in combination with SPECT, with brain-specific or non-specific agents. On the other hand, SPECT imaging is acquired in most clinical situations, after intravenous injection of 370–1110 MBq (in adults) of ^{99m}Tc-brain-specific radiopharmaceuticals and with a variable time delay between the injection and the acquisition in accordance with the radiopharmaceutical and

the clinical indication [7, 8, 15, 16]. Regardless of these variations, images should be completed within 4 h after injection owing to the radioactive decay [7].

Concerning SPECT acquisition parameters, the radius of rotation should be as short as possible, preferably less than 15 cm [7, 13, 17]. In this context, head holders deliver an additional advantage in eliminating the distance imposed by the shoulders and gamma camera bed and allowing closer positioning of the detectors around the patient's head. A typical SPECT acquisition is best acquired over a 360° rotation, along 120 projections with sufficient time per image to obtain a total number of counts exceeding 5 million (without scatter correction) [7, 13, 17]. Multidetector or dedicated brain SPECT cameras will contribute to a decrease in total scan time and yield high-quality images. Also, detector sensitivity should be taken into account so that the time per projection can be controlled in order to obtain suitable statistical data [7, 13, 17].

Occasionally, brain perfusion scintigraphy can be performed under the effect of certain interventions with the goal of performing comparisons with a baseline procedure. In these cases, acquisition and processing are identical to those for the general procedure:

• Vasodilatory challenge with acetazolamide (Diamox™) or an equivalent is indicated in the evaluation of several brain vascular disorders as it leads to an increase in rCBF in normal cerebral vessels via dilatation. The 2-day protocol is simpler and preferable. The challenge portion is performed first and if this yields normal results, omission of the baseline study may be considered. For further information regarding this intervention, the relevant guidelines should be consulted [7, 8].

• Epileptic focus localisation: It is well established that during an epileptic seizure an increase in cortical blood flow occurs in the area of the focal discharge [11]. Patients with focal epilepsy refractory to therapy may benefit from surgical ablation of the seizure focus [4] and brain perfusion scintigraphy contributes in localisation of the epileptogenic focus during the ictal state [11]. For this purpose a 2-day protocol that documents perfusion in the ictal and interictal states can be performed. The main challenge when using this procedure concerns the radiopharmaceutical injection. Individual doses must be readily available at the patient's bedside, allowing for rapid injection by a trained NM technologist at the onset of the seizure. In this way, the distribution of the radiopharmaceutical will reflect the rCBF at the time of ictus and delayed SPECT images will show the location of increased blood flow. Interictal SPECT studies add useful information to the ictal study [7, 8].

General information on technical considerations regarding imaging acquisition and processing is presented in Table 1.

Table 1: General information and procedures for brain perfusion SPECT and SPECT/CT [3, 7, 8, 18, 19]

PATIENT PREPARATION	
Before arrival	• Avoid, if possible, caffeine, alcohol, smoking, and any drugs known to affect rCBF.
At NM department	• Evaluate the patient for ability to cooperate (e.g. lie still for approximately 30–60 min). • Place an intravenous cannula 10–15 min prior to radiopharmaceutical injection. • Position the patient comfortably in a quiet room, with no interaction with other patients. • Instruct the patient to keep the eyes and the ears open and also to not speak, read or move from at least 5 min before until 5 min after injection. • If sedative medication is considered, it should be administered at least 5 min after radiopharmaceutical injection, and a few minutes before data acquisition. • If vasodilation is considered, contraindications must be evaluated and the dosage of acetazolamide, prepared. The radiopharmaceutical is injected about 15–20 min after injection of acetazolamide because it is at this time that the vasodilatory effect is most pronounced. • Patients should void prior to acquisition for maximum comfort during the study.
Continuous supervision of patients during the procedures is necessary, especially for those with epilepsy and dementing disorders. **In the case of brain death scintigraphy no preparation is needed.**	

RADIOPHARMACEUTICAL	
Administered activity	Adults: • 259–925 MBq for 99mTc-HMPAO (typical activity: 740 MBq) [7, 15] • 370–1110 MBq for ^{99m}Tc-ECD (typical activity: 1110 MBq) [8, 16]
	Children (according to the EANM paediatric dosage card table Version 1.2.2014): • ^{99m}Tc-HMPAO: "baseline activity" = 51.8 MBq • 99mTc-ECD: "baseline activity" = 32 MBq • Administered activity = "baseline activity" × multiple • Minimum recommended: 110 MBq

DATA ACQUISITION	
Time delay, injection - imaging	• ^{99m}Tc-HMPAO: best image quality at 90 min; after 30 min the image will be interpretable • ^{99m}Tc-ECD: best image quality at 30–60 min • Acquisition completed within 4 h after injection
Patient positioning	• Supine position with head on head holder and lightly restrained by immobilisation device • Maximum possible vertical orientation of canthomeatal line • No rotation or lateral tilt of the patient's head • Head of the patient centred in the gamma camera centre of rotation
Gamma camera	• Multiple detector (triple or dual head) or dedicated brain SPECT • LEHR or LEUHR parallel-hole collimators. Fan-beam collimators might be preferred
Photopeak	• 15–20% energy window centred around 140 keV
Dynamic[a]	• 1–3 s per frame for at least 60 s. Matrix 64×64 pixels. Anterior projection
Static[a]	• 500–1000 kcts. Matrix ≥128×128 pixels. Anterior, lateral and (if possible) posterior projections
SPECT	• Radius <15 cm, Matrix ≥128×128 pixels, <3° angulations in a 360° rotation; hardware zoom may be necessary; mode acquisition step and shoot (frequently) or continuous (reduce scan times); 120 projections, 20–30 s per projection, >5 million total counts (without scatter correction)
Zoom	• Selected to give an acquisition pixel size 1/3 to 1/2 of the expected resolution (e.g. 1.5 zoom)

DATA ACQUISITION	
CT scan (SPECT/CT systems) [20–23]	• CT for attenuation correction: 120–140 kV, 2.5 mA, rotational speed of 1 s, slice thicknesses of 3–5 mm, increment of 2.5 mm

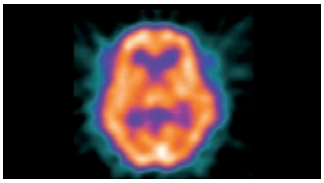
DATA PROCESSING	
Review of projection data	• Review of projection data in cine mode and sinograms is helpful for an initial determination of scan quality, patient motion and artefacts. • Motion correction algorithms, if available, may be used before reconstruction for minor movements, but rescanning is necessary if there is substantial head motion.
Colour scale/ table	• Continuous colour scales. (For example, a common colour scale used is represented here:  . The brain regions with high perfusion are orange to white, and regions with lower perfusion are blue to black.) • After use of a standard colour scale, only adjustments for background subtraction or contrast are recommended.
SPECT Reconstruction	• Reconstruct the whole brain, including cerebellum. • Filtered back-projection (FBP) or iterative reconstruction (e.g. OSEM) (may improve detection accuracy). • Highest pixel resolution (one-pixel slice thickness). • Filter and reconstruction parameters (cut-off, order, iterations and subsets) will depend on the injected activity, camera sensitivity and resolution, type of acquisition, clinical application and diagnostic reporting sensitivity.
Attenuation correction	• Chang's method (homogeneous correction matrix, μ=0.12–0.14 cm^{-1}) using the shape contouring of the head. • Non-uniform attenuation correction method (e.g. CT scan) is recommended.
Display	• Images are reformatted into slices in 3 orthogonal planes (axial, coronal and sagittal). Correct reorientation is important for visual interpretation and semiquantification.

DATA PROCESSING	
Semiquantification	• Regions of interest (ROIs) can be used to determine tracer uptake ratios in different cerebral regions, allowing estimation of the relative rCBF distribution within the brain. Corresponding structures in contralateral hemisphere or another reference region (e.g. cerebellum, hemisphere, total brain) can be compared and asymmetry indices may be used to enhance differences in rCBF. • Spatial normalisation, comparison to normal databases and voxel-based analysis can also be performed. • Image subtraction can be useful in the assessment of patients with epilepsy.

[a] Acquired only in cases of brain death scintigraphy with ^{99m}Tc-DTPA

Normal and pathological brain patterns

Although the brain presents a high vascular demand (about 15–20% of the cardiac output), its limited ability to store energy means that a tightly regulated blood flow is required in order to provide the necessary amount of glucose and oxygen [5, 17, 24, 25]. Synaptic activity at the neuronal cell bodies represents the primary utilisation of blood, explaining the increased grey matter to white matter blood flow ratio of approximately 4:1 (80 ml/min/100 g and 20 ml/min/100 g, respectively) [5, 11, 25]. This factor impacts on the distribution of the radiopharmaceutical in brain structures and the effect is visible on the acquired images. Cortical and subcortical grey matter structures are clearly distinguishable from white matter, presenting symmetrical uptake in both hemispheres [13]. Even though both ^{99m}Tc-labelled radiopharmaceuticals (^{99m}Tc-HMPAO and ^{99m}Tc-ECD) express the same specific brain pattern, slight differences may be observed (e.g. with regard to regional uptake in the thalamus and the cerebellum and non-specific scalp and facial tissue background activity) that seem to be related to the trapping mechanism [11, 13, 17] (Fig. 1).



Courtesy of Nuclear Medicine Department – CUF Descobertas, Lisbon, Portugal

Figure 1: Normal brain perfusion SPECT with ^{99m}Tc-HMPAO (transverse plane), showing cortical and subcortical grey matter uptake.

In several pathologies, this normal pattern can be altered and the characterisation of distinct pathological patterns may help in the differential diagnosis. For example, certain subtypes of dementia, such as Alzheimer's disease (AD), frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB) present different patterns of regional hypoperfusion on brain perfusion scintigraphy. Classically, hypoperfused regions involve the

parieto-occipital cortex in AD, the bilateral frontal cortex in FTD and both frontal regions and the posterior association cortex in DLB [26].

In patients with intractable partial epilepsy who are candidates for epilepsy surgery, brain perfusion scintigraphy has an important role in localising the ictal onset zone and seizure propagation pathways, both of which present as a focus or regions of hyperperfusion on ictal phase imaging. Regions of functional deficit associated with the ictal onset zone may also be identified on interictal phase imaging. In this context, image subtraction may be a valuable tool in the assessment and interpretation of the results [27].

Brain perfusion scintigraphy is also helpful in vascular brain diseases owing to its value in predicting the malignant course of brain swelling with large hemispheric infarctions and in evaluating cerebral perfusion in non-acute cerebrovascular disease [18, 28].

Flow imaging of rCBF with suitable radiopharmaceuticals has been used for early detection of stroke. Depending on the stage of stroke, i.e. early or late (cf. Fig. 2), the scintigraphic findings can be used to select those patients who may benefit from thrombolytic therapy. Although CT and MRI are more often employed, SPECT is sometimes advantageous owing to its ability to detect ischaemic events earlier and with greater sensitivity and to predict accurately the infarct size (including the penumbra area, i.e. the area that benefits from early reperfusion interventions and is at the highest risk for expansion of irreversible injury) [6, 18, 29].

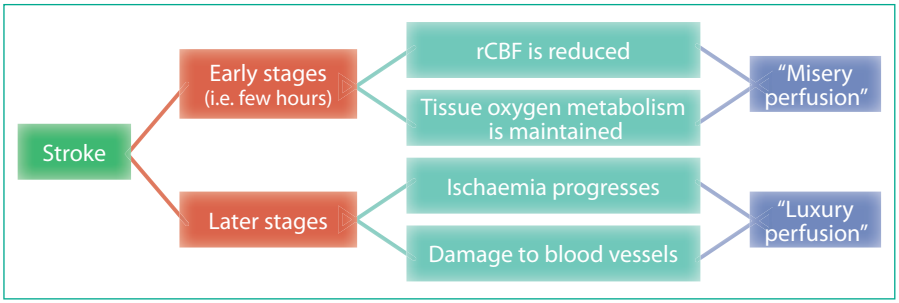


Figure 2: Early and later stages of stroke and flow/metabolism characterisation

Brain perfusion scintigraphy has also been shown to be effective in the study of transient ischaemic attacks. In these cases, imaging is performed under pharmacological stress using a cerebrovascular dilator such as acetazolamide. Since abnormal vessels do not display a dilatory response to acetazolamide, SPECT images show a significant reduction in

radiotracer uptake in the cerebral regions fed by the affected blood vessels (analogous to observations when performing myocardial perfusion imaging with dipyridamole) [6].

In cases of chronic ischaemia, brain perfusion scintigraphy can assess the functional reserve capacity before and after the administration of acetazolamide in order to demonstrate impaired vascular reserve and maximum vasodilation in a territory referable to the presenting symptoms [7, 19].

Semiquantification based on regions of interest (ROIs) provide an estimate of relative differences in rCBF based on comparison of radiopharmaceutical uptake ratios between affected and reference regions (e.g. right/left asymmetries) [7, 19].

Brain neurotransmission SPECT

There are several neural pathways that can be evaluated by brain SPECT imaging. In this chapter we focus on the assessment of dopaminergic system neurotransmission.

Parkinson's disease (PD) is a neurodegenerative disorder in which there is progressive loss of dopamine neurons in the nigrostriatal system, leading to widespread motor symptoms (e.g. bradykinesia, rigidity, tremor and impaired balance) and cognitive impairments [30, 31]including Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. The results of post-mortem studies point to dysfunction of the dopaminergic neurotransmitter system in patients with parkinsonism. Nowadays, by using single-photon emission tomography (SPET.

Studies with radiopharmaceuticals that bind to transporters or receptors of neurotransmitters are usually very accurate and offer a good approach for quantification of the dopaminergic neurons lost. These techniques of functional molecular imaging are very useful for evaluation of disease progression and response to therapeutic interventions and for assessment and monitoring of the neural mechanisms underlying parkinsonisms. Additionally, other major clinical applications are the differential diagnosis between PD and other neurodegenerative parkinsonian syndromes, between parkinsonian syndromes and essential tremors (ET) and between DLB and other dementias [9, 10, 30, 32]performing, interpreting and reporting the results of clinical dopamine D2 receptor SPECT or PET studies, and to achieve a high quality standard of dopamine D2 receptor imaging, which will increase the impact of this technique in neurological practice.The present document is an update of the first guidelines for SPECT using D2 receptor ligands labelled with (123. In Europe, the most widely used radiopharmaceuticals for SPECT in this context are iodine-123 *N*-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([^{123}I]FP-CIT) and iodine-123 2β-carboxymethoxy-3β-(4-iodophenyl)tropane ([^{123}I]β-CIT) for imaging of the DAT (presynaptic) and [^{123}I]iodobenzamide (^{123}I-IBZM) and [^{123}I]epidepride for imaging mainly of the D_2 receptor (postsynaptic).

The study of transporter and receptor binding allows assessment of (a) the presynaptic nigrostriatal neurons through evaluation of the dopamine transporter (DAT) and (b) the postsynaptic dopaminergic function through evaluation of the dopamine receptors D_2 and D_1 [9, 10, 30]including Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. The results of post-mortem studies point to dysfunction of the dopaminergic neurotransmitter system in patients with parkinsonism. Nowadays, by using single-photon emission tomography (SPET.

Patient considerations

General information regarding patient preparation can be found in Table 2, including specific considerations for each step of the procedure.

Table 2: General information and procedures for brain SPECT with DAT ligands ([^{123}I]β-CIT and [^{123}I]FP-CIT) and dopamine D_2 receptor ligands ([^{123}I]IBZM and [^{123}I]epidepride) [9, 10]

PATIENT PREPARATION		
	[^{123}I]β-CIT and [^{123}I]FP-CIT	[^{123}I]IBZM and [^{123}I]epidepride
Before arrival	Avoid smoking, and any drug that causes binding potential deficit, such as: cocaine, amphetamines, central nervous system stimulants, modafinil, antidepressants, adrenergic agonists, anticholinergic drugs, opioids, anaesthetics.	Withdrawal of drugs known to affect D_2 receptor binding, such as: dopamine agonists, neuroleptics, other drugs (e.g. metoclopramide, cinnarizine, flunarizine, amphetamine, methylphenidate).
At NM department	• Evaluate the patient for ability to cooperate (e.g. lie still for approximately 30–60 min). • For exams with ^{123}I-ligands it is necessary to block the thyroid gland with an adequate regimen (e.g. at least 200 mg of sodium perchlorate given at least 5 min prior to injection) to prevent accumulation of free radioactive iodine in the thyroid. • Patients should void prior to acquisition for maximum comfort during the study.	
RADIOPHARMACEUTICAL		
Administered activity	• **Adults**: 150–250 MBq (typical activity, 185 MBq) [9, 10]	
	• **Children**: No data available and no clinical indications established	

DATA ACQUISITION	
Time delay, injection – imaging	• [^{123}I]FP-CIT: 3–6 h after injection • [^{123}I]β-CIT: 18–24 h after injection • [^{123}I]IBZM: 1.5–3 h (best image quality at 2 h) • [^{123}I]Epidepride: 2–3 h
Positioning	• Similar to brain perfusion SPECT

The preparation procedure requires correct evaluation of the patient's ability to cooperate and good communication skills on the part of the NM technologist so that all the information and recommendations can be effectively conveyed. Sedation can be considered in uncooperative patients and should be given at the earliest 1 h prior to the SPECT acquisition [9, 10].

For exams with ^{123}I-ligands it is necessary to block the thyroid gland with an adequate regimen (cf. Table 2).

Patient preparation includes the withdrawal of any drugs that affect the binding to DAT or D_2 receptors: a withdrawal period at least five times the drug's biological half-life is recommended. Antiparkinsonian drugs do not markedly affect DAT binding and therefore do not need to be withdrawn prior to DAT SPECT, but it is possible that L-DOPA drugs down-regulate DAT expression and caution is advised in intra-individual follow-up studies. The binding of the radioligand to the D_2 receptors can be compromised by many antiparkinsonian drugs (in particular dopamine agonists), neuroleptics and other drugs [9, 10].

Technical considerations regarding imaging acquisition, processing and quality control

When positioning the patient for imaging acquisition, NM technologists should take into account various factors that may interfere with the data obtained and the clinical interpretation of the results. Correct head positioning is essential, as previously described for brain perfusion SPECT, and immobilisation devices are also recommended [9, 10].

Different acquisition protocols (cf. Table 2) are used for image acquisition with DAT ([^{123}I]β-CIT and [^{123}I]FP-CIT) and D_2 receptor ligands ([^{123}I]IBZM and [^{123}I]epidepride). All of these radiopharmaceuticals are administered by intravenous injection of 150–250 MBq (typically 185 MBq). For DAT tracers, the interval between the injection and image acquisition is 8–24 h for [^{123}I]β-CIT and 2–6 h for [^{123}I]FP-CIT. Regarding the D_2 receptor tracers, the images should be acquired 1.5–3 h (preferably 2 h) after administration of [^{123}I]IBZM and 2–3 h after administration of [^{123}I]epidepride [9, 10].

Regardless of the variations, it is recommended that a fixed interval is used between radiopharmaceutical administration and image acquisition to ensure that data are comparable between subjects and intra-individual follow-up studies [9, 10].

General information on imaging acquisition and processing is presented in Table 3.

Table 3. General data acquisition and processing information for brain SPECT and SPECT/CT with dopamine transporter ligands ([^{123}I]β-CIT and [^{123}I]FP-CIT) and the dopamine D_2 receptor ligand ([^{123}I]IBZM and [^{123}I]epidepride) [9, 10, 33, 34]

		[^{123}I]β-CIT and [^{123}I]FP-CIT	[^{123}I]IBZM and [^{123}I]epidepride
DATA ACQUISITION	Gamma camera	• Multiple detector (triple or dual head) or dedicated brain SPECT • LEHR or LEUHR parallel-hole collimators. Fan-beam collimators may be preferred	
	Rotation	• Smallest possible rotational radius (typical 11–15 cm) with appropriate patient safeguard • Angle increments of 3° (360° rotation) with circular orbit	
	Matrix	• ≥128×128 pixels	
	Photopeak	• 15–20% energy window centred around 159 keV	
	Zoom	• Selected to give an acquisition pixel size 1/3 to 1/2 of the expected resolution (e.g. 1.5 zoom)	
	Acquisition	• Step and shoot (frequently) or continuous mode (reduces scan times)	
	Total counts	• >1.5 million (FP-CIT); >1 million (β-CIT)	• >3 million
	Total scan time	• Triple-head camera: 30 min (e.g. 120 projections, 40 each head; 45 s/projection) • Dual-head camera: 30–45 min (e.g. 120 projections, 60 each head; 30–40 s/projection) • The number of s/projection depends on the sensitivity of the system	• Dual-head camera: 40–50 min (e.g. 120 projections, 60 each head; 40–50 s/projection) • Triple-head camera: for the same scan time, higher count statistics
	CT scan (SPECT/CT systems) [20–23]	• CT for attenuation correction: 120–140 kV, 2.5 mA, rotational speed of 1 s, slice thicknesses of 3–5 mm, increment of 2.5 mm • Anatomical location of radiopharmaceutical accumulation: 20–40 mA (other parameters are the same)	

		[^{123}I]β-CIT and [^{123}I]FP-CIT	[^{123}I]IBZM and [^{123}I]epidepride
DATA PROCESSING	Review of projection data	• Review of projection data in cine mode and sinograms is helpful for an initial determination of scan quality, patient motion and artefacts. • Motion correction algorithms, if available, may be used before reconstruction for minor movements, but rescanning is necessary if there is substantial head motion.	
	Colour scale/ table	• Continuous colour scales, preferably the "cold" colour scales. • After use of a standard colour scale, only adjustments for background subtraction or contrast are recommended.	
	Re-construction	• Filtered back-projection (FBP), or preferably, iterative reconstruction (e.g. OSEM). • For FBP, a low-pass Butterworth filter is recommended, with a cut-off of 0.4–0.5 and a power factor of 8–10. Filtering includes either 2D prefiltering of the projection data or 3D postfiltering of the reconstructed data. • For OSEM, the reconstruction parameters can be: 2, 4 or 6 iterations, 10 subsets. • The reconstructed pixel size should be 3.5–4.5 mm with one-pixel slice thickness.	
	Attenuation correction	• Chang's method (homogeneous correction matrix, μ=0.1 cm^{-1}) using shape contouring (if available) of the head. • CT scan (measured correction matrix).	
	Display	• Images are reformatted into slices in 3 orthogonal planes (axial, coronal and sagittal). Correct reorientation is important for visual interpretation and semiquantification.	
	Semiquanti-fication	• Select transverse slices (highest striatal binding slices, at least 3 consecutive slices, or the entire striatal volume) for ROI definition. • ROIs should be drawn in the striatum and the striatal subregions (caudate, putamen), to assess specific dopamine transporter (CIT)/receptor ([^{123}I]IBZM) binding. The reference regions (background) without (or with low) density can be the occipital cortex or cerebellum. • Semiquantification techniques: classic manual ROIs (most widely used), manual volumes of interest (VOIs), more advanced automated systems using VOIs and voxel-based mathematical systems.	

The influence of SPECT acquisition parameters, such as radius of rotation, rotation, number of projections and use of dedicated cameras, has already been described and those considerations also apply to DAT and D_2 receptor ligand scintigraphy. After the data acquisition, planar projection images and the sinogram/linogram should be immediately inspected by the NM technologist in order to identify any patient motion that might require repetition of the acquisition. Minor patient movement can be easily corrected using motion correction algorithms provided by commercial workstations. In these exams a certain degree of movement is to be tolerated given the patients' clinical conditions; nevertheless, the correction provided by algorithms may not be accurate and therefore should be used wisely.

In general, after processing and image reformatting into three orthogonal planes, visual assessment of the images is performed and segmentation procedures are used to obtain semiquantitative information. Several segmentation methods may be applied (e.g. ROI) manually, semi-automatically or full automatically. When segmentation is performed manually, the use of non-continuous colour tables may overestimate findings due to abrupt colour changes. Semiquantification is intended to allow assessment of the ratio between specific binding (in the striatum and striatal subregions) and non-specific binding regions (e.g. occipital cortex, cerebellum). The reference ROI is drawn in regions with absent (or low) binding potential (low density of DAT and D_2 ligands). The segmentation method is similar for DAT and D_2 receptor ligands. It is helpful if the ROI size (which should be at least twice the full-width at half-maximum) and shape are standardised (e.g. by use of an atlas or templates). When feasible, ROI definition may be based on individual morphology as revealed by image fusion with MRI, which is particularly important when low specific binding is expected (e.g. in the case of a severe loss or blockage of the DAT) [9, 10, 35].

It is useful to compare the patient-specific binding values (cf. Eq.1) [33] with data from normal subjects (preferably age-matched) obtained with the same technique.

$$\text{Specific binding values} = \frac{(\text{mean counts of striatal ROI} - \text{mean counts of non-specific ROI}}{(\text{mean counts of non-specific ROI})} \quad \text{(Eq.1)}$$

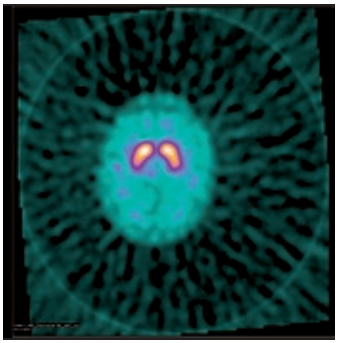
These values can be obtained from a central database or can be established for each department. It is only possible to use control values from a central database if phantom studies are performed and are demonstrated to allow comparable calculations for the different imaging set-ups used. Sometimes intra-individual comparisons are useful in patient follow-up (i.e. baseline vs follow-up for therapy control or assessment of disease progression), and standardised evaluations using approaches based on stereotactic normalisation are especially useful for more reliable verification of subtle changes [9, 10, 35].

Normal and pathological brain patterns

Functional imaging provides information on regional abnormalities in dopaminergic system function (pre- and postsynaptically). The highest density of dopamine neurons occurs in the nigrostriatal dopamine pathway, which is related to the increased radiopharmaceutical uptake by these structures in DAT and D_2 receptor imaging.

In the transverse plane of the normal brain image, the striatum is clearly visible and symmetrical (right and left striatum). It is composed of the caudate and the putamen, the head of the

caudate having the shape of a small sphere and the putamen, that of a crescent (Fig. 3). The image appearance is similar with both types of ligand in healthy controls [30, 35].



(Courtesy of Nuclear Medicine Department – CUF Descobertas, Lisbon, Portugal)

Figure 3: [^{123}I]FP-CIT scintigraphy (transverse plane) reconstructed by FBP, showing the symmetrical striatum in a healthy control.

When imaging with DAT ligands, binding decreases with the evolution of PD, parkinsonian syndromes (e.g. multiple system atrophy and progressive supranuclear palsy) and DLB. Initially, reduced uptake is observed in the putamen, while in later stages caudate uptake is also affected. In patients with PD, the uptake of DAT ligands is related to the clinical stage and disease severity and has an important role in early diagnosis and assessment [30, 35].

In dementias other than DLB and ET, the SPECT image with DAT ligands is normal [9, 10, 30, 32]performing, interpreting and reporting the results of clinical dopamine D2 receptor SPECT or PET studies, and to achieve a high quality standard of dopamine D2 receptor imaging, which will increase the impact of this technique in neurological practice.The present document is an update of the first guidelines for SPECT using D2 receptor ligands labelled with (123, allowing the differential diagnosis between parkinsonian syndromes and ET and also DLB and other dementias.

In the case of D_2 receptor imaging, there is a difference in binding between PD and other parkinsonian syndromes, which allows differential diagnosis that is not possible on the basis of DAT imaging [30]including Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. The results of post-mortem studies point to dysfunction of the dopaminergic neurotransmitter system in patients with parkinsonism. Nowadays, by using single-photon emission tomography (SPET. In the early stages of PD there is a short-lived increase in D_2 receptor binding (postsynaptic) in response to depletion of synaptic dopamine levels. Disease progression and increasing degeneration of nigrostriatal dopamine neurons leads to a slight decrease in binding in late stages; by comparison, in other parkinsonian syndromes a decrease is observed throughout the course [30]including Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. The results of post-mortem studies point to dysfunction of the dopaminergic neurotransmitter system in patients with parkinsonism. Nowadays, by using single-photon emission tomography (SPET).

As the presynaptic dopaminergic neurons are affected in PD and in atypical parkinsonism, it is useful to perform joint evaluation of pre- and postsynaptic function, by assessing, with specific radiopharmaceuticals, DAT and D_2 receptors [36].

Challenges and opportunities in SPECT and SPECT/CT imaging for neurological and vascular brain diseases

In recent years neuroimaging has evolved rapidly, with major contributions from functional and structural imaging techniques. The greatest challenges at present include the optimisation of instrumentation and computation and also the development of new, more accurate radiopharmaceuticals.

Improvements in image quality and quantification methods will enhance spatial resolution and sensitivity, optimise the integration of different modalities and support the development of new algorithms for reconstruction and processing of data [37]. In this context the use of databases of normalised values representative of normal or pathological populations also has an important role, providing anatomical information or localisation and allowing more accurate quantification procedures [38]. Attenuation correction (AC) for brain SPECT imaging is also a subject that will need further research. For brain perfusion images, AC should be performed with CT (from SPECT/CT) rather than Chang's method given that application of the latter approach often causes overestimation of frontal perfusion and underestimation of posterior perfusion, i.e. non-uniform attenuation correction is required to accurately estimate rCBF [20, 39]. On the other hand, when performing DAT and D_2 receptor imaging no significant differences in visual interpretation or semiquantification are observed depending on whether CT or Chang's method is used for AC; Chang's method is to be preferred in this context in order to avoid the additional radiation exposure from CT [21].

Crucial to the growth of NM techniques is the continued development of molecular probes that can bind to the target biological receptor with high selectivity. In the field of brain imaging, the development of new tracers with more specific and better characteristics is contributing greatly to improvements in SPECT imaging, and numerous relevant research initiatives are being conducted [40]. It is certain that new challenges and opportunities will arise from closer collaboration between those working on fundamental/applied research and on the clinical applications of brain SPECT; the outcome will be enhanced non-invasive in vivo visualisation of biological processes at the molecular and cellular levels, to the benefit of patients.

References Chapter 5

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Chapter 6

Imaging in Neurological and Vascular Brain Diseases (PET/CT)

Ian Law, Valentina Garibotto and Marco Pagani

PET/CT cameras and brain imaging

Since the introduction of the first systems in 2001, the field of clinical PET/CT has experienced impressive growth in terms of system design and functionality, supportive software solutions and the availability and range of clinically approved PET tracers. Developments were initially directed towards the creation of solutions for implementation primarily in systemic oncology, rather than in brain studies. Over the intervening years, however, clinical brain PET imaging has benefitted tremendously through the use of available equipment and organisation. The number of clinical brain PET scans at a clinical site might not initially be sufficient to justify the acquisition of a PET/CT scanner, but as a supplementary element in a production line dominated by oncology, brain PET studies can play a very significant role.

There are no technical or practical limitations, as such, to the potential uses of PET/CT scanners for clinical brain PET scanning. Unenhanced CT of the head is performed initially and may be either of a clinical quality for diagnostic reading or a low-dose CT scan for the purpose of attenuation correction. The CT scanning has a duration of <1 min, so the number of CT slices, 4–128, is of no practical consequence in clinical routine. The number of CT slices does not significantly impact the clinical CT quality. All PET/CT systems have an axial field of view of 15–21 cm and will, thus, be able to acquire a full 3D brain volume in one bed position (see "Fact Box" next page").

PET/CT clinical indications in neurological and vascular diseases

Dementias

Dementia is a syndrome characterised by deterioration in multiple cognitive functions, associated with functional impairment and with a chronic course, due to a brain dysfunction. Neurodegenerative dementias are increasingly prevalent, given their strong association with aging of the population, and are one of the most relevant causes of disability and dependency among elderly people [1]. Alzheimer's disease (AD) is the most common form, accounting for up to 70% of cases; among other types, the most frequent are vascular dementia, dementia with Lewy bodies (DLB) and frontotemporal lobar degeneration (FTLD). The neurodegenerative process of dementia presumably lasts over decades, with a long preclinical phase without symptoms and a "prodromal" phase, identified by the term "mild cognitive impairment" (MCI), during which symptoms are mild, with a cognitive performance below average but without functional impairment [2]. The differential diagnosis among the various forms is a critical and complex process, particularly in these early phases. An early diagnosis is important for disease management and proper treatment and also represents a relief for patients and caregivers [3]. The different forms of dementia affect specific brain areas and neurotransmission systems and have different neuropathological features, identified by PET imaging, such as regional neuronal dysfunction or abnormal protein depositions; PET imaging is thus considered a "biomarker" of disease in the current recommendations on diagnostic guidelines [4].

FACT BOX

Tips and tricks for the technologist:

Optimising scanner use

A 10-min ^{18}F-FDG PET brain scan can be performed 40 min p.i. Whole-body ^{18}F-FDG PET/CT is performed 60 min p.i. Thus, brain PET/CT scanning need not occupy a time slot for whole-body PET/CT if it is performed as the first scan in the morning. The two patients for brain and whole-body PET scanning are injected at the same time point with ^{18}F-FDG when it becomes available, and the brain scanning will be finished before the whole-body PET scanning needs to commence.

Head movements

The most important duty of the technologist in order to accomplish a successful and diagnostic PET brain scan is to ensure secure head fixation during the scanning period, and to identify any head movements that nevertheless occur. Patients with neurological diseases may have difficulties in understanding and retaining instructions, have seizures during scanning, be agitated or suffer age-related degeneration in the spine. All of these factors may contribute to head movements during scanning. It is important (a) to identify these "at risk" patients prior to scanning through direct contact with patients, caregivers and referring clinicians and inspection of patient history and (b) to take appropriate measures. Such measures might be:

- Secure head fixation in a sturdy head holder, and placement of a leg rest under the knees to prevent downward patient movement.
- Placement of marks on the skin using a marking pen.
- Performance of a list mode acquisition or a range of short dynamic scans, e.g. 5 × 2 min. If head movements occur during the scan, a reconstruction of the first 5 min may be of sufficient clinical quality.
- Control for significant movement (>5–10 mm) at the end of scanning. If such movement has occurred, repeat CT for attenuation correction alone or in combination with a new brain ^{18}F-FDG scanning sequence depending on circumstances.

If head movements occur, the CT attenuation and PET emission scans will no longer be aligned and significant artefacts may be present. If these artefacts were to pass unnoticed, an erroneous diagnosis would be made (e.g. Fig. 1). For more details, see the EANM guidelines [7].

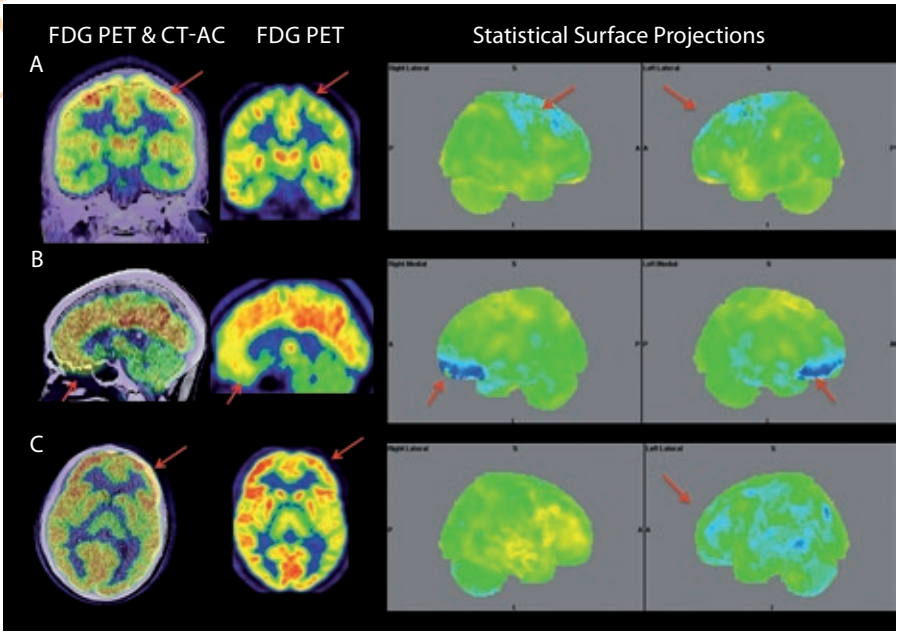

Figure 1 A–C: Examples of typical ^{18}F-FDG PET images in healthy young subjects who moved their heads after low-dose CT (CT-AC), causing misalignment and quantitative reduction in regional activity. To the right are statistical surface projections (Scenium, Siemens) comparing the subjects with a database of age-matched controls. The observed changes could have led to misdiagnosis in a clinical setting if their cause had gone unnoticed, underlining the importance of head fixation. (A) Coronal images showing the consequence of movement (1.0 cm) in the scanner in the axial direction, with false reductions in uptake in the frontal areas bilaterally (red arrows). (B) Sagittal images showing the consequence of rotation of the head anteriorly (1.2 cm), with false reductions in uptake in the mesial frontal areas bilaterally (red arrows). (C) Transverse images showing the consequence of rotation of the head to the left (1.0 cm), with false reductions in uptake in the left cortical hemisphere and false increases in uptake in the right cortical hemisphere (red arrows)

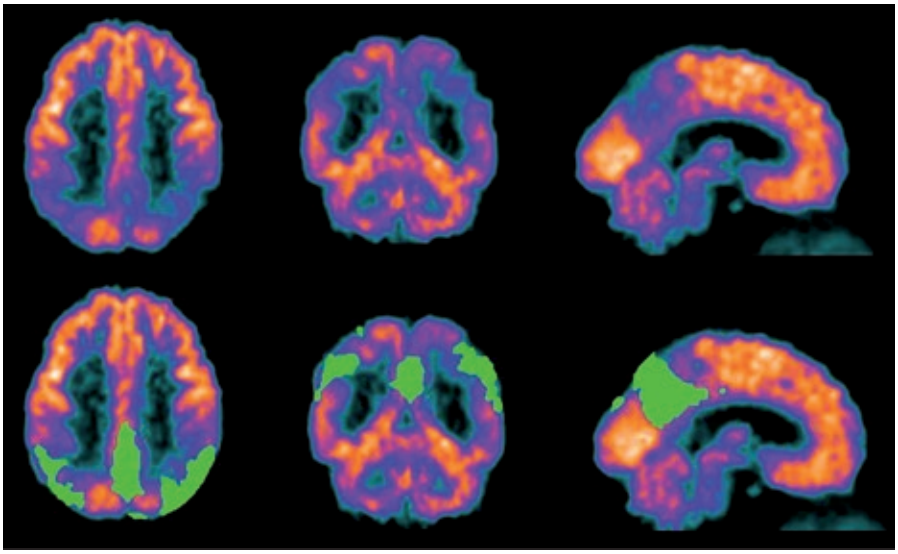

Figure 2: Example of a typical ^{18}F-FDG PET image in Alzheimer's disease (AD): the posterior cingulate cortex, precuneus and lateral parietal cortex have a significantly reduced metabolism (upper row) compared with a normal reference population (lower row: the green overlay indicates areas with significant hypometabolism, as analysed by BRASS™, Hermes Medical Solutions)

PET imaging of brain glucose metabolism, using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) as the tracer, is a validated and routinely used method to show regional abnormalities, some of which are typical for the different dementia syndromes [5–7]. AD is characterised by hypometabolism involving the temporoparietal association cortices, in particular the precuneus and posterior cingulate cortex (an example is provided in Fig. 2). Patients with DLB have a pattern similar to AD patients, the hypometabolism often extending to the occipital cortex and possibly sparing the posterior cingulate region. FTLD includes various syndromes, such as the behavioural variant of frontotemporal dementia (bvFTD), characterised by hypometabolism in frontal regions, and corticobasal degeneration (CBD), which typically shows asymmetrical cortical (frontoparietal) and subcortical hypometabolism contralateral to the affected hemibody (Fig. 3). The visual identification of these specific patterns can be supported by various automated methods, usually based on the normalisation of individual images to a reference space and then on the semi-quantification of abnormalities relative to the distribution observed in a group of healthy subjects [8, 9]. An example is provided in Fig. 2.

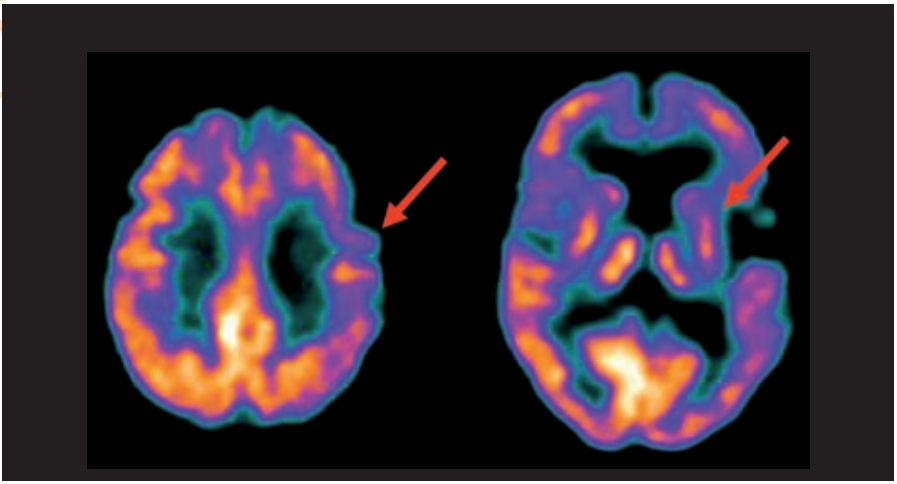

Figure 3: Example of the hypometabolism observed in cases of corticobasal degeneration (CBD) involving the frontoparietal cortex and the basal ganglia of the left hemisphere (arrows)

During the last decade, specific tracers able to visualise amyloid plaques in vivo have been tested and validated in humans. The first was the ^{11}C-Pittsburgh compound B (^{11}C-PIB), which was able to bind fibrillary amyloid with a good correlation with post-mortem measures [10–12]. More recently, ^{18}F-labelled compounds, patented by industrial companies, have been approved by regulatory agencies both in Europe and in the United States for use in patients with prodromal or atypical dementia. These tracers have been validated in phase II and phase III trials for their ability to discriminate healthy controls and patients with AD and to identify amyloid deposits in vivo, as compared with results at autopsy [13, 14]. Different strategies for visual reading of the images have been proposed for the different tracers, based on the use of quantitative indices such as the ratio of the mean standardised uptake value (SUV) across cortical regions to the SUV measured in a reference region, typically the cerebellum. In general, a positive image shows significant cortical uptake of the tracer, while a negative image shows variable uptake in white matter and no relevant cortical signal (examples are provided in Fig. 4).

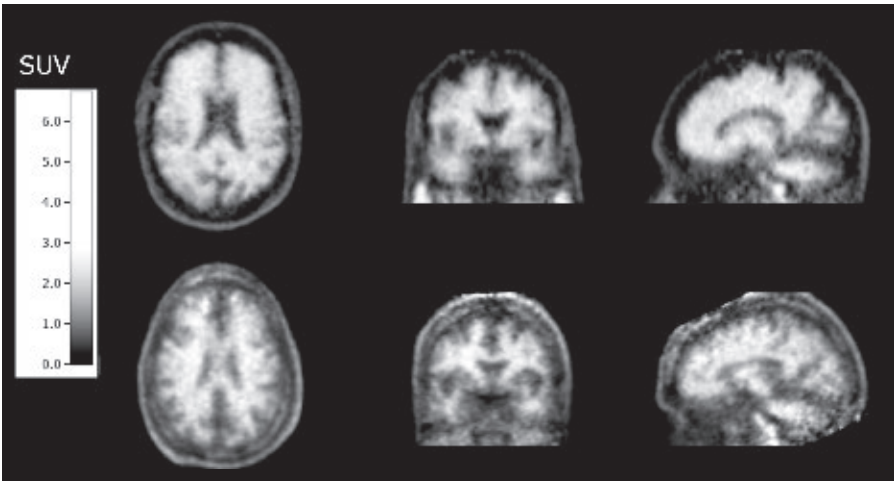

Figure 4: Examples of typical positive (upper row) and negative (lower row) amyloid PET images, obtained using an ^{18}F-labelled tracer [in this case florbetapir (AV-45)]

Amyloid imaging is considered an early marker of the AD pathological process, reaching the threshold of positivity about 17 years before the clinical onset of overt dementia [15]. Appropriate criteria for the clinical use of amyloid PET imaging have been published recently [16]. In particular, this examination is advised for patients with persistent or progressive cognitive impairment that has an atypical or unclear clinical presentation or early onset (before 65 years of age). In subjects with MCI, amyloid imaging has a high positive predictive value for progression to AD [12]. A consistent finding across different amyloid PET imaging studies is that around 30% of cognitively normal elderly subjects have a positive scan, in agreement with the proportion of cognitively normal elderly subjects with an autopsy diagnosis of AD [17, 18]. These individuals might be at higher risk for subsequent development of dementia, but this is still a debated topic, currently under investigation. First, the expression of clinical disease is due to not only the amount of "pathology" in the brain but also the capacity of the brain to cope with damage, called the "reserve capacity". The concept of cognitive reserve is based on the observation that individuals with a high educational level and intelligence preserve a normal functional level for longer than less educated people, despite neurodegeneration [19]. Various PET studies have shown that cognitive reserve modulates the interaction between some measures of pathology and clinical severity [20–22]. Second, amyloid deposits are possibly the first event in the pathological cascade of AD, but by themselves do not account for cognitive decline: other factors, such as the

aggregation of hyperphosphorylated tau protein, play a central role in the onset and progression of neurodegeneration [2]. New PET tracers aimed at imaging tau aggregates are currently under development and preliminary results suggest that they may provide crucial information about the interplay of amyloid deposits and the earliest clinical signs [23].

Finally, a large panel of other PET tracers relevant to the investigation of dementias exists, e.g. tracers able to visualise different neurotransmission systems, such as the cholinergic or dopaminergic system, or to measure the occurrence of neuroinflammation, which is presumably a factor contributing to the progression of the neurodegenerative process [24]. These tracers, which are of utmost interest for a better understanding of the pathological processes of dementia, are still limited to dedicated research centres and are being evaluated in clinical trials.

Epilepsy

Epilepsy is one of the most common chronic neurological conditions, affecting 0.7% (0.5–1%) of the population. It has very significant social and professional consequences and is associated with increased mortality. Around 30–40% of patients with epilepsy suffer from focal seizures that are refractory to anti-epileptic drug treatment [25]. In these patients, surgical resection of the epileptic focus is the only treatment that can possibly cure the condition, and its success depends strongly on accurate presurgical localisation of the focal abnormality. ^{18}F-FDG PET is one of the imaging modalities of choice for this purpose. The intravenous administration of the tracer has to be performed during EEG monitoring of the epileptic activity, which is a major determinant of the imaging findings. Indeed, while an "ictal" injection, during a seizure, will show the increased perfusion and metabolism in the epileptic focus, an "interictal" injection will depict the dysfunctional cortex (often including the epileptic focus and some regions of seizure propagation) as a hypometabolic area compared with the surrounding cortex [26]. Interictal imaging is preferable, given that truly ictal images require coordination of radiotracer availability and seizure onset and duration, which is difficult to assure. Interictal ^{18}F-FDG PET has a sensitivity above 80% for identification of the epileptic focus in temporal lobe epilepsy [27–30]. The contribution of ^{18}F-FDG PET imaging is particularly relevant when no lesion is identified on magnetic resonance imaging (MRI) or in the case of multiple abnormalities as it limits the need for invasive recording [26, 31]. Indeed, it has been reported that MRI-negative temporal lobe epilepsy patients with clear unilateral anterior temporal hypometabolism show the same positive outcome as patients with a morphologically visible lesion [32]. An example of a "non-lesional" patient with a positive PET is shown in Fig. 5. PET can also be decisive in situations of multifocal lesions or multifocal epileptic activity. In tuberous sclerosis, an autosomal dominant disorder characterised by multiple cortical malformations (tubers), the most hypometabolic tuber is concordant with invasive localisation of the epileptic focus in a majority of patients [33].

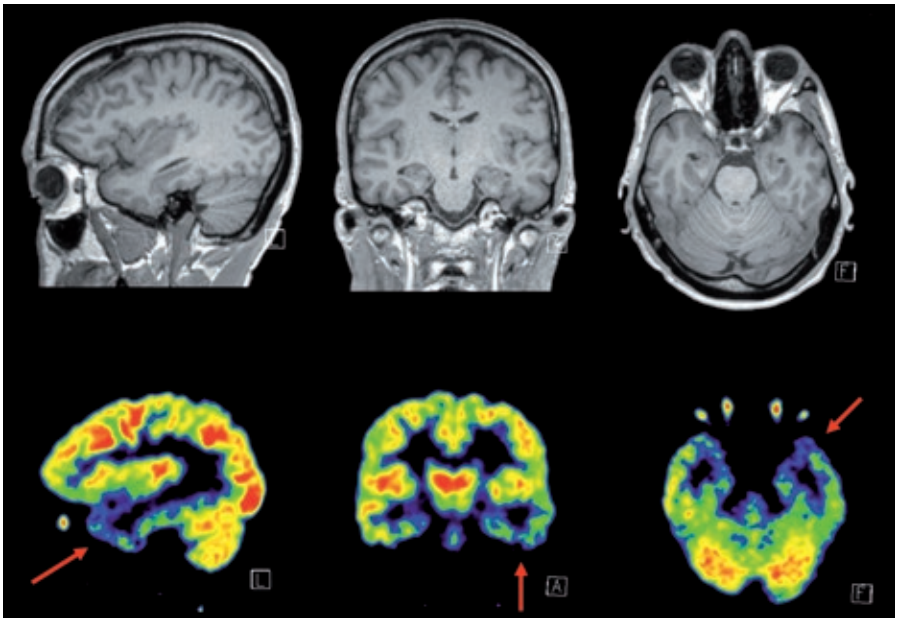

Figure 5: Example of a patient with no visible lesion on MRI (upper row) but with clear hypometabolism in the left temporal pole on ^{18}F-FDG PET (indicated by arrows, lower row), concordant with the clinical and EEG findings

Other PET tracers have shown promising results in specific applications: for example, ^{11}C-flumazenil, a GABA antagonist, could be useful to localise pathological brain tissue in temporal lobe epilepsy, with increased uptake on the pathological side [34]. ^{11}C-AMT (α-[^{11}C]-methyl-L-tryptophan) displays positive uptake in the most epileptogenic tuber in tuberous sclerosis in about 70% of cases [33]. These tracers are used in specific research settings and are not currently applied in clinical practice.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that has an incidence of 2–3/100,000 new cases per year [35] and is characterised by progressive muscle paralysis associated with degeneration of motor neurons in primary motor cortex, brainstem and spinal cord [36]. ALS-mimicking conditions include pure upper motor neuron disease (primary lateral sclerosis, PLS), pure lower motor neuron disease (progressive muscular atrophy) and FTLD, the latter sharing with ALS similar cognitive symptomatology.

PET represents a valuable tool in the diagnostic work-up and for the differentiation of ALS from mimicking diseases. Various radiotracers (^{11}C-flumazenil [37], ^{11}C- (R)PK11195 [38], ^{18}F-DPA-714 [39], ^{11}C-(L)-deprenyl-D2 [40]) have been used to assess changes in regions affected by ALS, including those for the evaluation of activity in the white matter [38–40], which plays a significant role in the progression of the disease. However, most of the PET studies in ALS have been performed using ^{18}F-FDG, focussing on patients and normal controls as a comparison group and looking for ALS-related metabolic patterns. Patients with ALS usually demonstrate diffusely decreased ^{18}F-FDG uptake in primary and supplementary motor and premotor cortices as well as clusters of relative hypermetabolism in the mesiotemporal regions, occipital cortex, cerebellum, corticospinal tracts and upper brain stem (Fig. 6), reflecting a complex neuropathophysiology involving degeneration of grey matter and areas of reactive microglial activation. The presence of astrocytosis and activated microglia in corticospinal tract, midbrain and pons has also been supported by findings from ^{1}H-magnetic resonance spectroscopy (increased myo-inositol [41]) and other PET investigations (increased uptake in peripheral benzodiazepine receptors [38, 39] and astrocytes [40]).

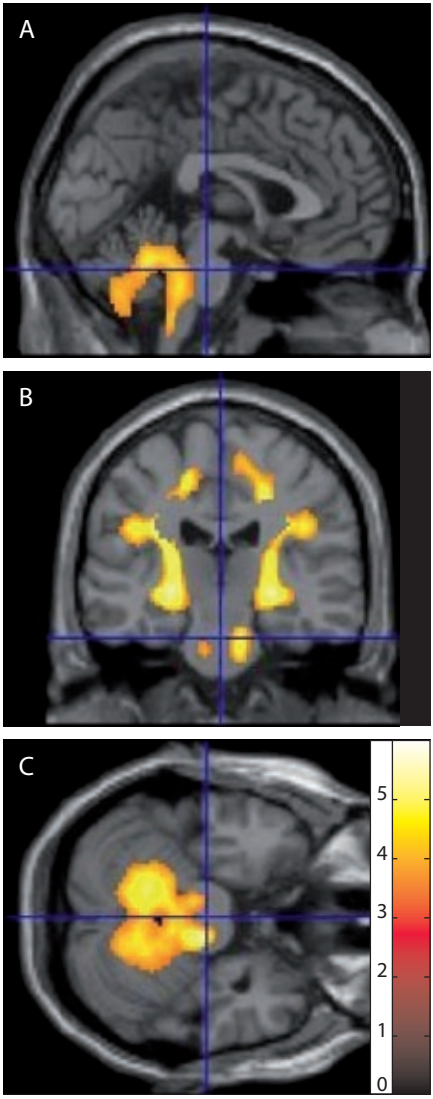

Figure 6: Comparison of ^{18}F-FDG PET findings in ALS patients and controls using statistical

parametric mapping. Statistically significant differences ($p<0.05$ false discovery rate corrected) are highlighted on an MRI T1 template. (A) sagittal view; (B) coronal view; (C) transverse view. Clusters of significant hypermetabolism are seen in the midbrain, cerebellum, medial temporal lobes and corticospinal tracts

Recently the potential of ^{18}F-FDG as an important biomarker for the diagnosis of ALS has been confirmed by two investigations in which extremely large patient cohorts were recruited [42, 43]. Both studies analysed the diagnostic ability of PET in ALS and found that it showed a sensitivity of about 95% in separating patients from controls [42, 43] and of 71% in separating ALS from PLS [43]. Pagani et al. [42] reported in 195 ALS patients a mixed ^{18}F-FDG hypermetabolic–hypometabolic pattern, with marked hypometabolism in the frontal, premotor and occipital cortices and relative hypermetabolism in white matter, midbrain and the medial temporal cortex.

PET findings have also been compared in patients with sporadic ALS without mutations of ALS-related genes, patients with ALS and comorbid FTD and patients with ALS carrying the *C9orf72* mutation [44]. More widespread cortical and subcortical involvement, especially in the frontotemporal cortex, was associated with a more severe clinical course in those with the *C9orf72* mutation.

In addition, PET has a promising role in discriminating ALS from ALS-mimicking pathologies, thereby contributing to recruitment of suitable subjects for clinical trials and allowing early interventions when appropriate [45]. Longitudinal examinations, identifying significant changes over time, and novel PET/MRI technology, providing a simultaneous assessment of structural and functional lesions, will in the future play a pivotal role in better understanding the pathophysiology of this complex and fatal disease.

Stroke

Background

Stroke is the third leading cause of death globally and the second most frequent cause of death in the developed world after coronary artery disease [46]. It is also a major cause of chronic disability, particularly among the elderly population. The annual stroke rate is in the range of 1.4–4 per 1000. Approximately 30% of cases are attributed to cerebral haemorrhage and 70% to cerebral ischaemia. Stroke may arise as a result of a combination of different factors. Ischaemic strokes can be produced through thrombotic, embolic and haemodynamic mechanisms. Clinically infarcts are commonly considered as *atherothrombotic* (local thrombosis in relation to atheroma of the vascular wall), *cardioembolic* (embolism of cardiac origin, e.g. atrial fibrillation, recent myocardial infarction, aortic valve

disease) or *lacunar* (occlusion of one of the small penetrating end-arteries at the base of the brain, often resulting from microatheroma formation). A lesion between 3 and 15 mm in diameter is commonly regarded as a lacune. Occasionally, an ischaemic infarction may turn into a haemorrhage. The clinical symptoms are of sudden onset and depend on the location and size of the lesion. Infarcts, particularly the lacunar ones, may be clinically silent or transient. If the symptoms last <24 h, the term transient ischaemic attack (TIA) is used. While TIAs generally do not cause permanent brain damage, they are a serious warning sign and should not be ignored. There are many risk factors for stroke: age, gender, ethnicity, heredity, hypertension, cigarette smoking, hyperlipidaemia, diabetes mellitus, obesity, fibrinogen and clotting factors, oral contraceptives, erythrocytosis and haematocrit level, prior cerebrovascular and other diseases, physical inactivity, diet and alcohol consumption, illicit drug use and genetic predisposition [47].

Nuclear imaging has been used extensively in the study of neurovascular diseases over the past five decades and has yielded important knowledge on the pathophysiology of acute stroke. In clinical practice, however, the primary methods of choice in the diagnostic work-up of acute stroke and neurovascular diseases are CT and MRI scanning. At the moment non-enhanced CT of the brain remains the mainstay of imaging in the setting of an acute stroke (Fig. 7) since it is fast, inexpensive and readily available. Its main limitation is the low sensitivity in the acute setting, where MRI has an advantage. PET/CT is not indicated in acute stroke. However, diagnostic CT of the brain is easily available in all PET/CT systems and can provide important additional information relevant to the interpretation of any functional defects found, e.g. in dementia. Knowledge of the various presentations of neurovascular disease becomes important in the differential diagnosis of vascular dementia (VaD), AD and mixed dementia (AD with concomitant stroke or small vessel disease).

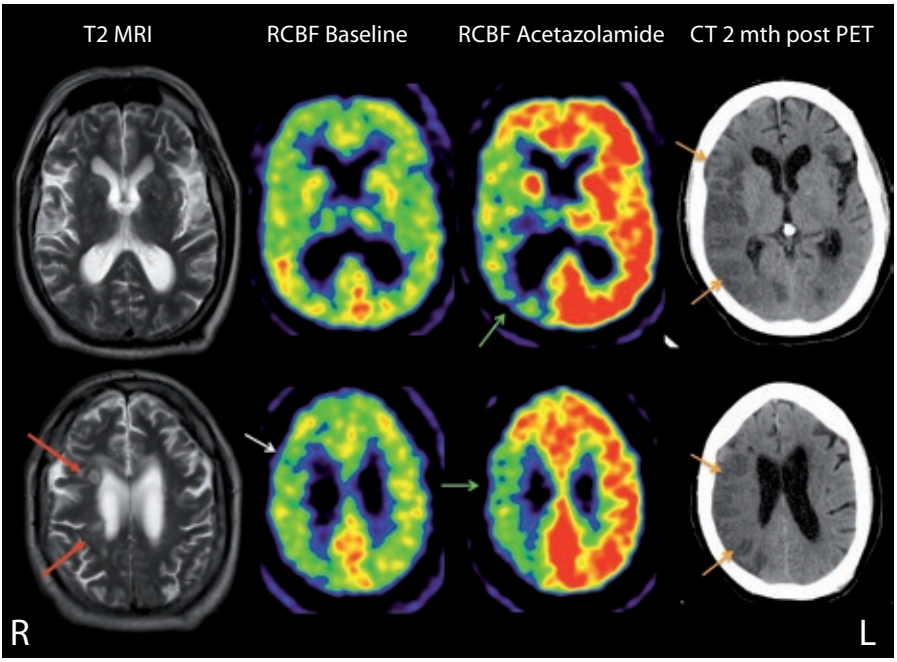

Figure 7: Patient with diabetes mellitus, hypertension and multiple previous TIAs. CT angiography showed occlusions of the right internal carotid and right vertebral arteries. There are typical watershed infarctions in the centrum semiovale on T2-weighted MRI (red arrows). PET measurements of rCBF at baseline using ^{15}O-water show discrete hypoperfusion in the right hemisphere, which is particularly pronounced above the infarcts (white arrow). During acetazolamide stimulation, the perfusion was increased by 60% in the left hemisphere, but decreased by 9% in the right middle cerebral artery territory, consistent with cerebrovascular steal (green arrow, same scale as baseline). The patient refused reconstructive vascular surgery and sustained an ischaemic stroke during an infection-induced hypotensive episode in the same risk areas as had been defined on PET 2 months earlier (hypointense lesions, orange arrows), demonstrating the clinical validity of the method

Furthermore, quantitative measurements of the regional cerebral blood flow (rCBF) using positron emission tomography (PET) still occupy a specialised clinical niche within nuclear imaging for evaluation of the haemodynamic response in patients with cerebrovascular occlusive disease prior to revascularising surgery.

Dementia and stroke

Many of the risk factors mentioned in the preceding section are shared between dementia and stroke. About 30% of dementia patients will show signs of cerebrovascular disease that may be synergistic with AD in producing the clinical syndrome of dementia. Mixed dementia is the second most common form of dementia after AD (10–20%), while VaD alone accounts for 10% of cases. VaD increases in prevalence with age [48]. It may arise from multiple cortical infarctions, strategic strokes and subcortical white matter lesions [49]. The neuropsychological characteristics of VaD may be different from those seen in AD. Disturbances in frontal-executive functions (Fig. 8), rather than memory, are often the more dominant feature and memory impairment may be absent in some patients with significant cognitive deficits.

Vascular disease will often give rise to a regional decrease in activity encompassing the infarcted area and neighbouring areas to varying degrees (Fig. 8). Cases of vascular disease may also be metabolically silent. It is important to be familiar with the concept of diaschisis, the idea that damage to one part of the nervous system can have effects at a distance due to loss of input [50]. Thus, it was demonstrated as long ago as 1964, using the Lassen-Ingvar krypton-85 method [51], that stroke patients had a strikingly low rCBF measurement also in the structurally intact healthy hemisphere [52]. The most common forms are *crossed cerebro-cerebellar diaschisis* [53], where damage to one hemisphere leads to depression of the contralateral cerebellar hemisphere; *thalamo-cortical diaschisis,* where damage/stroke in the thalamus leads to depression of the ipsilateral hemisphere [54]; and *cross cerebello-cerebral diaschisis*, where damage to one cerebellar hemisphere leads to depression of the contralateral cerebral hemisphere [55]. Furthermore, decreased activity in cortical areas may be evident if the infarct is located subcortically, involving and undercutting white matter tracts (Fig. 8). Thus, for each individual area of decreased metabolic activity in patients evaluated for dementia using ^{18}F-FDG PET/CT, it is necessary to determine whether the reduction in activity can be explained by local or distant neuronal damage/vascular lesion.

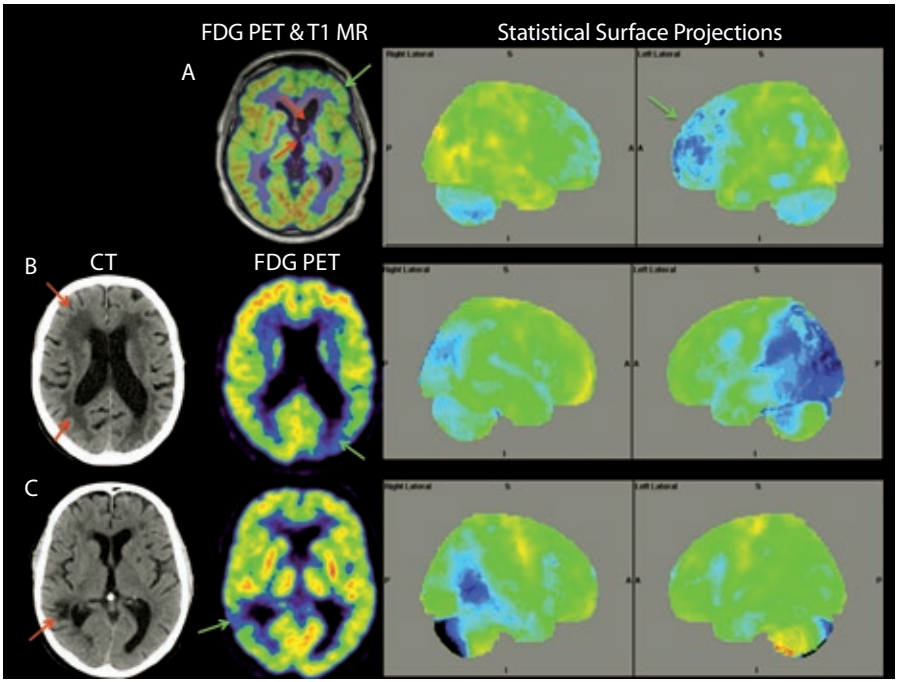

Figure 8 A–C: Examples of typical ^{18}F-FDG PET images in patients referred for PET/CT or PET/MRI for evaluation of dementia. To the right are statistical surface projections (Scenium, Siemens) comparing the subjects with a database of age-matched controls. (A) PET fusion with simultaneously acquired T1-weighted MRI: transverse images. The red arrows indicate circumscribed lacunar infarcts with decreased activity uptake involving the left head of the caudate and the anterior thalamus; these lesions are undercutting projections to the structurally intact left frontal lobe, giving rise to a moderate reduction in activity (green arrows). FTD could have been considered, but this is vascular dementia. There is also an infarct in the pons (not shown). (B) CT and PET transverse images. CT shows extensive subcortical hypointense signals (leukoaraiosis) indicative of subcortical ischaemia (red arrows) that cannot alone explain the pattern of cortical metabolic reduction (green arrow), suggesting a mixed vascular and neurodegenerative origin. (C) CT and PET/CT transverse images show a subcortical infarct in the right temporal region (red arrow), leading to a larger metabolic defect in the temporoparietal cortex (green arrow) through disruption of subcortical–cortical circuits. The PET image alone could be misread as demonstrating signs of neurodegeneration in the absence of supportive correlation with CT

Chronic cerebrovascular disease

Atherosclerotic internal carotid artery occlusion causes approximately 10% of TIAs and 15–25% of ischaemic strokes in the carotid territory. The 2-year risk of ipsilateral ischaemic stroke while a patient is receiving medical therapy is 10–15% [56]. This risk, however, depends on the capacity of the brain tissue to compensate, e.g. by increasing the regional oxygen extraction fraction (rOEF). Increased rOEF indicates that the last defence before stroke has been mobilised. In symptomatic patients with increased rOEF, the 2-year risk of ipsilateral ischaemic stroke is 30–40%, while it is only 5% in symptomatic patients with normal rOEF [57]. In the event of symptomatic occlusions of the carotid arteries to the brain, a revascularising surgical procedure may be considered: the so-called extracranial–intracranial bypass operation (EC-IC). In the most common version of the EC-IC bypass operation, a branch of the external carotid artery, usually the superficial temporal artery, is anastomosed to a branch of the internal carotid artery on the occluded side, usually the meningeal artery. The procedure is not without risk, and there is a 10–15% likelihood of perioperative stroke [58, 59]. Thus, the overall risk is the same as in medically treated symptomatic patients over 2 years. Consequently, only the subgroup of high-risk patients should be considered for the operation. Supportive symptoms and findings that may predict haemodynamic failure and high risk of stroke and death are usually manifested as repeated TIAs or stroke, with typical subcortical "watershed" infarcts on T2-weighted MRI (Fig. 7), orthostatic limb shaking, impaired vasoreactivity to acetazolamide challenge and increased rOEF on PET scanning [60].

In the event of carotid occlusion, the affected hemisphere receives its blood supply from communicating arteries of the circle of Willis and collaterals between the extracranial and intracranial arteries. If these are not sufficiently developed, there will be a pressure drop in the most distant arterioles of the arterial tree at the border zones between vascular territories (watershed areas). This will initially be compensated haemodynamically by vasodilation, which will stabilise rCBF and can be measured as an increase in regional cerebral blood volume (Fig. 9). Metabolic compensation will follow via an increase in oxygen extraction from the capillary blood, the rOEF rising from 30–40% to 70–80%. In patients with exhausted perfusion reserve, rCBF will behave in a pressure-passive manner. The arterioles are maximally dilated, and rCBF will change with the perfusion pressure. If the patient experiences a longer lasting pressure drop (e.g. due to systemic infection, cardiovascular disease, dehydration or blood pressure-lowering drugs) and the compensatory mechanisms are insufficient, an ischaemic infarction will develop (Fig. 7) [61, 62]. Acetazolamide (Diamox) is a carboanhydrase inhibitor and a potent vasodilator of the cerebral vessels that increases rCBF by 20–60%. Only arterioles that are not already dilated will respond to acetazolamide, while the haemodynamic response in affected regions will be either reduced, unaffected or negative. The last-mentioned phenomenon

is called "cerebrovascular steal" or the "reverse Robin Hood effect". The increased rCBF in the unaffected hemisphere decreases perfusion pressure and rCBF in the affected hemisphere (Fig. 9). EC-IC bypass surgery can reverse these changes [63] and may increase the cognitive performance [64], but the clinical benefit in terms of stroke risk and survival is still controversial. In a recent randomised clinical trial, 195 patients were randomised to either optimal medical treatment or surgery based on PET measurements of increased rOEF in the symptomatic hemisphere (the COSS study). The study endpoint was 2-year stroke recurrence, the rate of which was found to be 21% in the surgical group and 23% in the medically treated group. The latter was far below the expected rate of 40% from prospective observational investigations, and the study failed to demonstrate a significant difference in the two treatments [58].

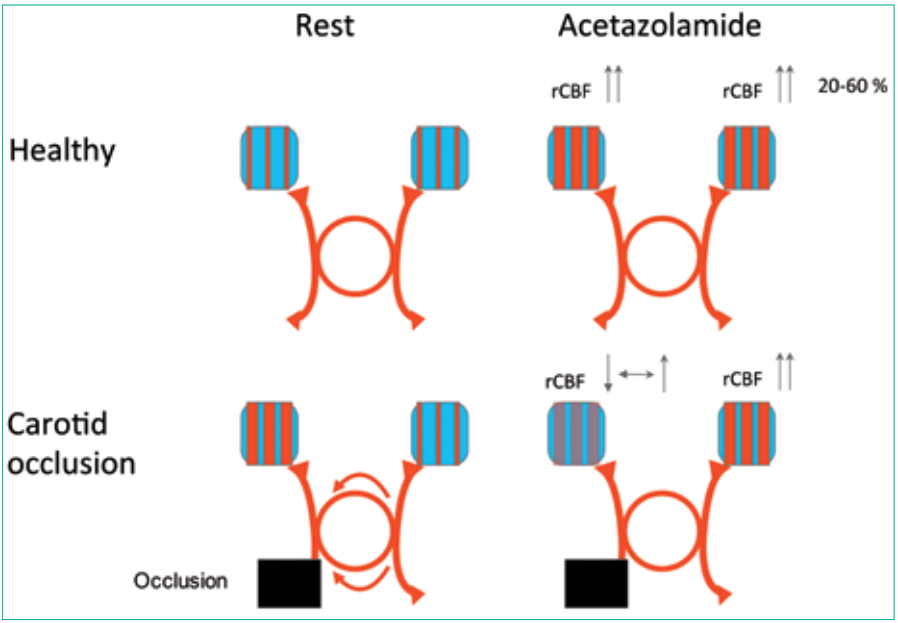

Figure 9: A schematic representation of the vascular response to carotid occlusion and vasodilation using acetazolamide. The two internal carotid arteries are represented as two arrows connected by the circle of Willis, which subsequently supplies feeding arteries to the two hemispheres. The bars in the hemispheres represent the vasodilatory state of the arterioles in brain tissue. In the healthy brain (top row), acetazolamide dilates the arterioles and increases rCBF symmetrically in

the two hemispheres by 20–60%. In carotid artery occlusion (lower row) – represented by the black box in the left carotid – the ipsilateral hemisphere is fed through a more or less patent collateral blood supply in the circle of Willis; these arterioles are dilated because of the ensuing decrease in perfusion pressure, which stabilises rCBF. When the arterioles in the unaffected contralateral hemisphere are dilated, the perfusion pressure will decrease even further ipsilaterally. Depending on the residual vasodilatory capacity, the rCBF will be increased, unaffected or decreased. The last-mentioned phenomenon is known as the cerebrovascular steal phenomenon

The measurement of vasoreactivity in response to acetazolamide requires quantitative assessment of the rCBF using either ^{15}O-water PET or the stable xenon-CT SPECT method [65]. Both methods are available only in specialised units. ^{15}O-water has a half-life of only 2 min and an on-site cyclotron is required for on-line continuous production of the tracer. Furthermore, quantification of rCBF measured in mL blood flow per 100 g tissue per minute necessitates arterial cannulation and continuous blood sampling with radioactivity measurements for kinetic modelling with calculation of parametric images.

In the acetazolamide challenge, rCBF is measured at rest and approximately 20 min after injection of 500–1500 mg acetazolamide i.v. The baseline rCBF image is subtracted from the acetazolamide-stimulated rCBF image, and all images are fused to T2-weighted/FLAIR MRI. The baseline rCBF image allows estimation of the extent of infarction and hypoperfusion around the areas of signal change on MRI. Regions of interest are drawn on the three major intracerebral artery territories in both hemispheres for quantification of rCBF and reactivity. However, as compromised haemodynamic reactivity is often in the watershed areas, the subtraction image is the most efficient way of directly revealing the location of increased and decreased rCBF.

Acetazolamide challenge is also used in combination with transcranial Doppler flow measurements. To date there have been virtually no reports of adverse effects of acetazolamide challenge [66]. One case report did, however, cite a stroke episode 24 h after injection, which could have been related to the mildly diuretic effect of acetazolamide [67].

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Chapter 7

PET/CT in Radiotherapy Planning of Brain Tumours

Roberto Delgado-Bolton, Adriana K. Calapaquí-Terán and Javier Arbizu

Introduction

Brain tumours can be classified, according to their origin, into primary (those originating from the central nervous system) or secondary (those originating from other tissues and metastasising to the central nervous system). Primary brain tumours include low-grade and high-grade malignant lesions according to the World Health Organisation, the most frequent being meningioma (30%) and glioblastoma multiforme (20%).

For patients with high-grade brain tumours, the ideal treatment is surgery (complete resection of the tumour, if possible preserving neurological function) followed by adjuvant chemotherapy and radiotherapy. The utility of radiation therapy has been demonstrated. Technological advances are increasingly improving the efficacy of the treatment (measured by survival) based on increased treatment precision (reducing the radiation dose to healthy tissue and the associated toxicity) without any reduction in the radiation dose to the treatment volume.

Radiotherapy planning requires multidisciplinary collaboration and a sequential process that begins with a tumour board deciding to irradiate a tumour and ends with the application of a treatment plan signed by a board-certified radiation oncologist [1, 2]. A key aspect is the appropriate selection and delineation of the target volumes and organs at risk, which is typically done by a radiation oncologist on contrast-enhanced CT and/or MRI. The images used need to be the best available in terms of diagnostic efficacy (sensitivity, specificity, positive and negative predictive values) and must have high spatial resolution. CT and MRI comply with these requirements [2]. However, a high contrast resolution (i.e. the ability to differentiate pathological from normal tissues) is also essential. This is where PET enters the picture.

Why add PET/CT to radiotherapy planning of brain tumours?

PET/CT in radiotherapy planning

CT and MRI have a high spatial resolution and display the anatomy and morphological changes in great detail. Their main drawback is their low contrast resolution, as a consequence of which it is not possible to differentiate between viable tumour tissue and surgery-, radiotherapy- or chemotherapy-related changes (pseudo-progression, pseudo-regression) [3]. In contrast, PET has a high contrast resolution, and by supplying functional information on the biological and molecular characteristics of the tumour it helps in differentiating viable tumour from treatment-related changes, thereby improving treatment planning for high-precision radiotherapy. Many studies have analysed the role of different PET tracers for gross tumour volume (GTV) delineation.

PET tracers

^{18}F-Fluorodeoxyglucose (^{18}F-FDG) is the main PET tracer used in oncology as it provides useful information in many tumours. However, it has been shown to be of limited value in the radiotherapy planning of brain

tumours [3, 4]. The main issue with ^{18}F-FDG is the low contrast between viable tumour and normal brain tissue. ^{18}F-FDG uptake is increased in anaplastic areas [3].

Radiolabelled amino acids (AA) such as ^{11}C-methionine (MET), ^{18}F-fluoroethyl-tyrosine (FET) and ^{18}F-fluoro-L-dopa (FDOPA) are the main PET tracers used for the characterisation, therapy planning and follow-up of brain tumours, and all three of the aforementioned tracers share similar characteristics regarding uptake intensity and distribution in brain tumours. Normal cerebral tissue has a relatively low uptake of AA PET tracers as compared to tumour cells, which incorporate them at a high rate; furthermore, uptake of AA PET tracers is not dependent on disturbances of the blood-brain barrier.

Tumour target volumes defined using AA PET differ from those outlined with MRI using standard sequences such as T1-weighted after gadolinium contrast enhancement (T1-Gd), both in size and in geometrical extension [5]. In fact, the tumour target volume as defined on T1-Gd MRI seems insufficient to include the real biological tumour extension of high-grade brain tumours.

PET/CT technical requisites

In order to maximise the potential benefits of incorporating the metabolic information provided by PET, it is crucial to be aware of all the factors that must be taken into account to guarantee that the images acquired comply with the requirements for treatment planning and treatment delivery [6, 7]. These factors are:

1. *Initial patient positioning*. Accurate positioning that ensures consistency and daily reproducibility of treatment is essential when delivering high doses to a tumour, as an important limitation is the tolerance level of the surrounding normal tissue [7]. To ensure the comfort of the patient during all treatment sessions, the initial evaluation must include the physical status and limitations as well as the psychological impact (claustrophobia). In order to achieve accurate alignment, an immobilisation device is used in conjunction with reference ink or tattoo marks [7]. Positioning includes: (a) removing all clothing from the upper body to promote comfort and ensure daily reproducibility; (b) removing dentures or implants and instructing the patient not to chew anything during the treatment; (c) supporting the head to prevent or limit involuntary movements.

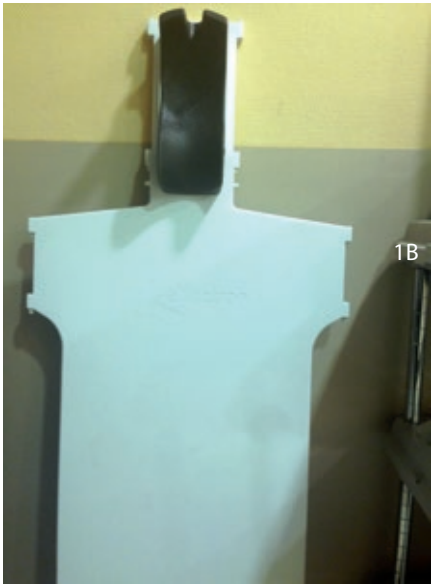
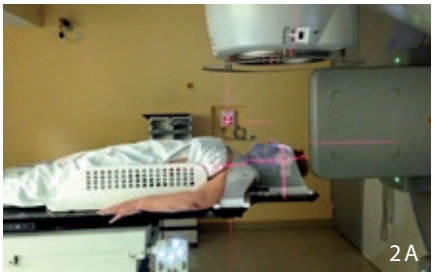


Figure 1 A, B: Table top with a nek support

2. *Table top*. The table top must be flat, narrow and rigid and should allow registration or indexing of immobilisation devices [7]. Figure 1 presents a table top with a neck support.



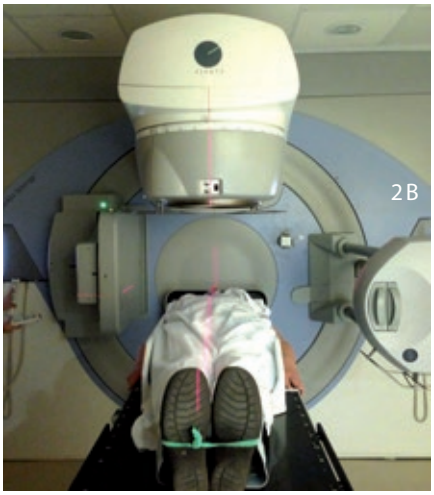
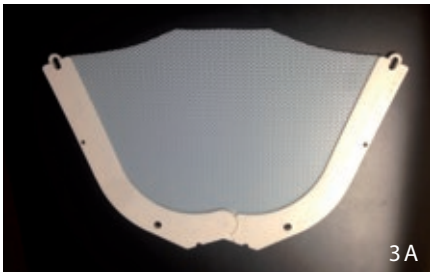
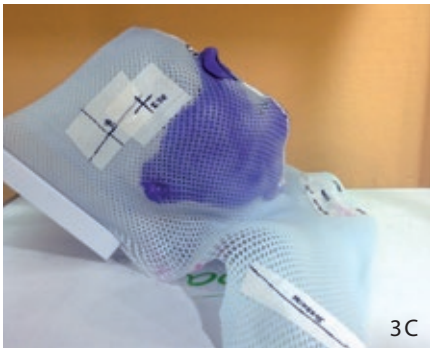


Figure 2 A, B: Positioning of a patient with the laser light system

3. *Laser lights*. Lateral and sagittal lasers must be used to ensure accurate alignment and positioning. The laser light system installed in the PET/CT unit must be in accordance with the one installed in the radiotherapy unit. Quality controls of the laser lights of the PET/CT system must be done routinely to maintain consistency with the treatment unit [7]. Figure 2 shows positioning of a patient with the laser light system.





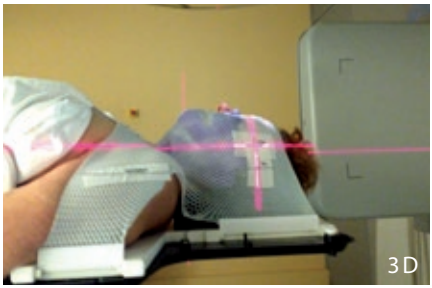


Figure 3A–D: Immobilisation systems that must be individualised include thermoplastic masks. The mask is initially rigid (A) but can become pliable when placed in warm water (B). This permits the mask to be moulded to the head and shoulders of the patient (C). It can be attached to the treatment table once the material has cooled (D)

4. *Immobilisation.* The use of immobilisation devices is essential to deliver high doses of radiation to the treatment volume while ensuring the protection of critical organs (e.g. crystalline lens, optic chiasm, pituitary gland). Immobilisation systems must be individualised for each patient and should be anchored to fastening systems which in turn must be fixed to the treatment table. For brain tumours, immobilisation systems include: (a) neck supports (standard, frames or vacuum bags) (Fig. 1) and (b) thermoplastic masks which are initially rigid (Fig. 3 A) but become pliable when placed in warm water (Fig. 3 B), allowing moulding of the mask to the head and shoulders of the patient (Fig. 3 C) and attachment to the treatment table once the material has cooled (Fig. 3 D).

When does radiotherapy planning with PET/CT have an added value?

AA PET/CT is of specific value for delineation of the GTV in high-grade gliomas, especially those that are non-contrast enhancing on T1-Gd MRI, and low-grade tumours that are ill defined on MRI. Additionally, as already mentioned, it is of great value in differentiating between treatment-related changes (pseudo-progression and pseudo-remission or pseudo-response) and residual/recurrent tumour [3, 8]. PET/CT with radiolabelled AA or DOTATOC can be used for GTV delineation in meningiomas and glomus tumours. Further research is needed regarding the role of PET with other tracers, such as ^{18}F-fluorothymidine (FLT) to evaluate proliferation, ^{18}F-fluoromisonidazole (FMISO) to assess hypoxia and ^{18}F-galacto-arginine-glycine-aspartic acid (RGD) to analyse angiogenesis and peptide expression [3,8].

How should it be done? Procedure, technical aspects and quality control

PET/CT procedure

^{18}F-FDG PET/CT must be performed in accordance with the EANM guidelines [9, 10]. When radiolabelled AA analogues are used instead of ^{18}F-FDG, the guidelines dedicated to these must be followed [11]. If the PET/CT data are used for radiation planning, the examination should be performed in the position which will be used for radiotherapy, employing the same dedicated positioning devices as are used in the radiotherapy department [9]. The CT part of PET/CT must have special characteristics as it will be used for radiotherapy planning, and an additional CT will not be performed.

Technical approach to patient positioning for PET/CT for radiotherapy planning

Multidisciplinary collaboration between the nuclear medicine and radiation oncology units is essential. The patient must be positioned using the technical instruments mentioned above in the section "PET/CT technical requisites".

Quality control of image fusion of PET/CT and planning CT for tumour delineation

Quality control of image fusion must be done routinely, ensuring the patient has been positioned adequately in accordance with the protocols.

PACS/RIS and software issues

DICOM must be transferred from the PET/CT to the radiotherapy unit.

Who should participate? Multidisciplinary collaboration

The nuclear medicine and radiation oncology units must collaborate closely when planning the radiotherapy and delineating the volumes to treat. The relevant protocols must be strictly followed to achieve the maximum accuracy, consistency and reproducibility. The PET/CT study should be reported in accordance with established guidelines [9–11]. Volume delineation is done taking into account both MRI and PET. The GTV based on PET is added to the GTV based on MRI and they are fused with the CT (Fig. 4).

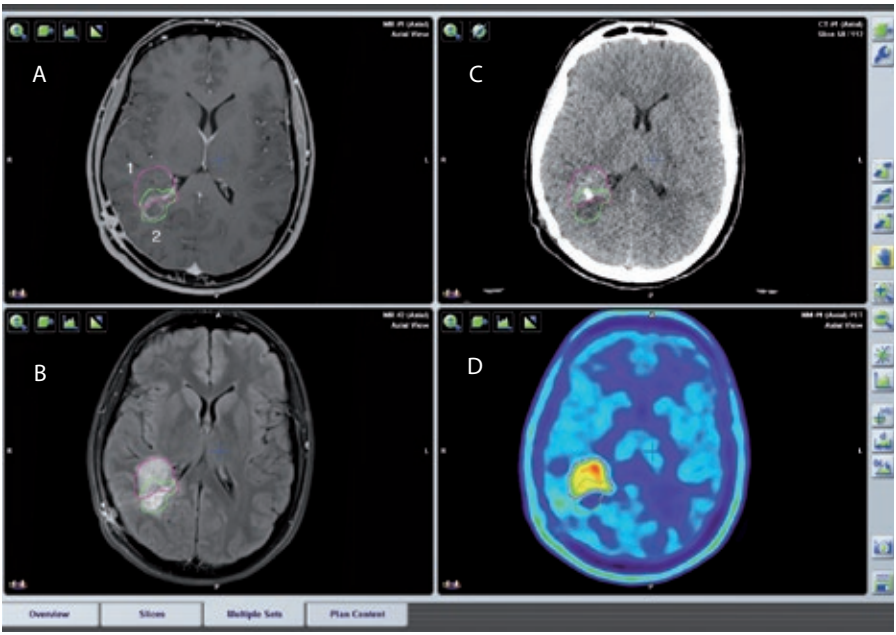


Figure 4 A–D: Radiotherapy planning of a high-grade glioma using MRI and ^{11}C-MET PET/CT: T1-weighted MRI (A), non-contrast-enhanced CT (B), T2-weighted MRI (C) and ^{11}C-MET PET (D). T2-weighted MRI shows an extensive area of enhancement (volumes 1 and 2) that could be due to active tumour and/or oedema. T1-weighted MRI shows a small area of enhancement (volume 2) and an area that does not enhance (volume 1). CT shows an area of changes (volumes 1 and 2). If only MRI or CT were available, the treatment volume would have included both areas (volumes 1 and 2). However, ^{11}C-MET PET evidenced high uptake (tumour) in volume 1 but no uptake at all (non-tumour) in volume 2. Because of this information, the treatment volume included only volume 1, sparing unnecessary toxicity in volume 2

What must be taken into account?

Radiation protection issues: focus on radiotherapy workers

When radiotherapy planning is done on PET/CT, radiation protection for radiotherapy workers must take into account their close contact with patients who have been injected with PET tracers.

Patient scheduling

Patients referred for radiation treatment planning must be scheduled at the end of the morning or afternoon, after the standard PET/CT studies, in order to cause the least possible delay to the daily routine. These studies entail further complexity and time and therefore must be scheduled last.

Conclusion

Accurate position reproducibility to ensure daily reproducibility of treatment is essential when delivering high doses to a tumour. Multidisciplinary collaboration also plays a key role in patient positioning.

References Chapter 7

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Chapter 8

PET/MRI for Brain Imaging

Peter Werner*, Torsten Boehm*, Solveig Tiepolt, Henryk Barthel, Karl T. Hoffmann, Osama Sabri

Current clinical applications of PET/MRI in neurology

Magnetic resonance imaging (MRI) is pivotal in the work-up of the majority of neurological and psychiatric diseases since it provides morphological and functional information about the brain. Positron emission tomography (PET), on the other hand, is able to detect and quantify a variety of pathophysiological processes with very high sensitivity. In patients with symptoms of cognitive impairment or movement disorders, for example, high-resolution and multi-contrast brain MRI is essential to rule out non-neurodegenerative causes such as tumours, haemorrhages, ischaemic lesions or inflammatory diseases. Further, it is used to detect specific atrophy patterns, white and grey matter degeneration and the implications of some metabolic changes [1]. However, structural changes that are specific to neurodegenerative diseases are usually preceded by months to years of characteristic molecular and functional alterations that can be detected with multi-tracer PET exclusively [2]:

1. Characteristic impairments of brain glucose metabolism can be detected by [^{18}F] fluorodeoxyglucose (FDG) PET and allow the early diagnosis of dementia disorders while MR findings are still absent or unspecific (Fig. 1A).

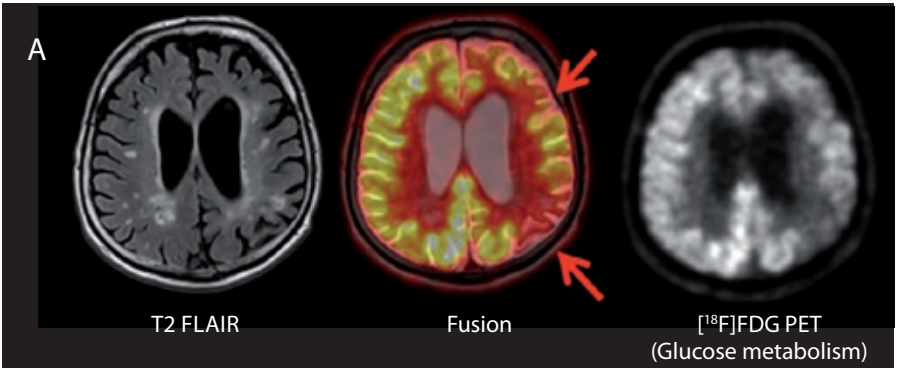

Figure 1 A–C: Multi-tracer brain PET/MRI in neurodegenerative diseases.
(A) A 61-year-old man with progressive aphasia and cognitive impairment; T2-weighted fluid attenuation recovery (FLAIR) MRI (left) shows enlarged ventricles, mainly left cortical atrophy and white matter lesions. Simultaneous [^{18}F]FDG PET revealed severe left cortical hypometabolism (arrows, middle), indicating a form of frontotemporal dementia as underlying disease.

2. Amyloid PET can accurately detect brain amyloid load in Alzheimer's dementia (AD), in which the presence of amyloid deposits ultimately leads to cognitive decline (Fig. 1B).

* Contributed equally

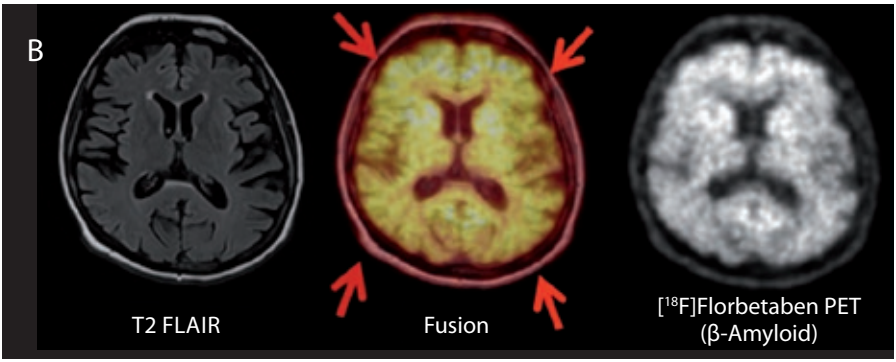

Figure 1 A–C: Multi-tracer brain PET/MRI in neurodegenerative diseases.
(B) A 44-year-old woman with cognitive impairment and a family history of Alzheimer's dementia (father). Brain MRI (left) was unremarkable but the presence of intense β-amyloid depositions in the whole brain grey matter on [18F]florbetaben PET (arrows) confirmed the clinical suspicion of AD.

3. [18F]DOPA PET can specifically visualise dopaminergic neurotransmission in the basal ganglia and is used in clinical routine in specialised centres to diagnose parkinsonian syndromes [3] (Fig. 1C).

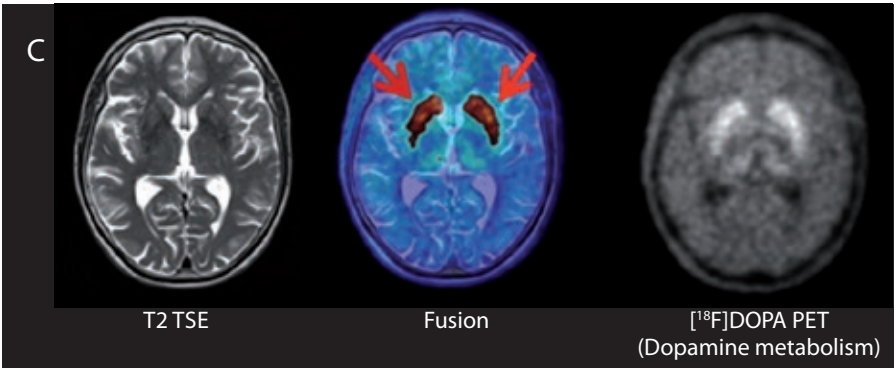

Figure 1 A–C: Multi-tracer brain PET/MRI in neurodegenerative diseases.
(C) A 76-year-old woman with unspecific movement disturbance of the legs. T2-weighted turbo spin echo (TSE) MRI was unremarkable; moreover [18F]DOPA PET revealed age-appropriate dopamine synthesis in the basal ganglia (arrows). Thus, PET/MRI allowed the exclusion of neurodegenerative Parkinson's disease as the underlying disorder

Recently, an integrated amyloid PET/MRI examination algorithm has been proposed to deliver a maximum of imaging parameters, necessary for the diagnosis of a wide range of dementia disorders [1]. Conventional MRI is also essential in the clinical management of brain tumours. With a variety of contrasts it provides information about the type of tumour and its size, extension and grading. Moreover, (a) enhancement of areas after application of a contrast agent (e.g. Gadovist) allows an estimation of blood-brain barrier breakdown, which is typical of high-grade malignant brain tumours, (b) dynamic susceptibility contrast perfusion measurements improve differentiation between recurrent tumour and radiation-induced necrosis and (c) MR spectroscopy provides information about malignant proliferation and promising targets for eventual tumour biopsy.

In various clinical situations, however, MRI is insufficiently specific and does not deliver the desired information. Here, simultaneous amino acid PET is helpful, since it reflects the vastly increased amino acid transport into brain tumour tissue. PET is able to distinguish between unspecific changes after tumour (radiation) therapy and tumour relapse. Amino acid PET is also helpful in the primary evaluation of unspecific MR findings to decide whether surgery or biopsy of cranial masses is necessary (Fig. 2A). In addition, amino acid PET delivers reliable tumour volumes for radiation or surgery planning in situations in which the tumour itself cannot be distinguished from unspecific surrounding MRI signal abnormalities (e.g. due to oedema) (Fig. 2B). Lastly, somatostatin receptor PET can highly selectively visualise tumour tissue arising from the meninges (Fig. 2C). Simultaneous PET/MRI also plays a role in basic research into brain function and pathological mechanisms in neurological diseases such as stroke, dementia and addiction. The combination of functional MRI, contrast-enhanced MRI and multi-tracer PET allows the simultaneous assessment of rapidly fluctuating brain signals like brain perfusion, transmitter release or the occupancy of specific receptors in the brain. Related examination protocols exhibit a high degree of complexity and are usually restricted to special research facilities (for more information, see Werner et al. [2]).

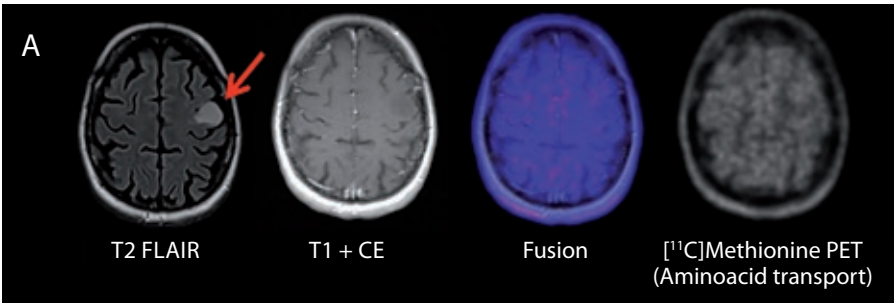

Figure 2 A–C: Multi-tracer brain PET/MRI in neuro-oncology.
(A) A 60-year-old woman with unspecific T2 fluid attenuation recovery (FLAIR) signal alteration, without contrast enhancement (CE) on the T1 contrast image (arrow). Moreover, amino acid transport assessed by [^{11}C]methionine PET was unremarkable (right). A highly malignant glioma could be excluded and, due to the lack of symptoms, follow-up imaging was chosen over biopsy.

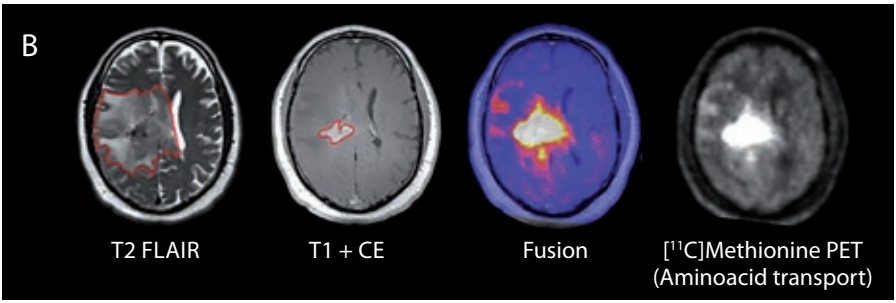

Figure 2 A–C: Multi-tracer brain PET/MRI in neuro-oncology.
(B) In this glioma patient the extension of signal alterations on the T2 FLAIR and T1 CE images (red lines) differed substantially. [^{11}C]Methionine PET identified highly active tumour areas with increased amino acid transport (right).

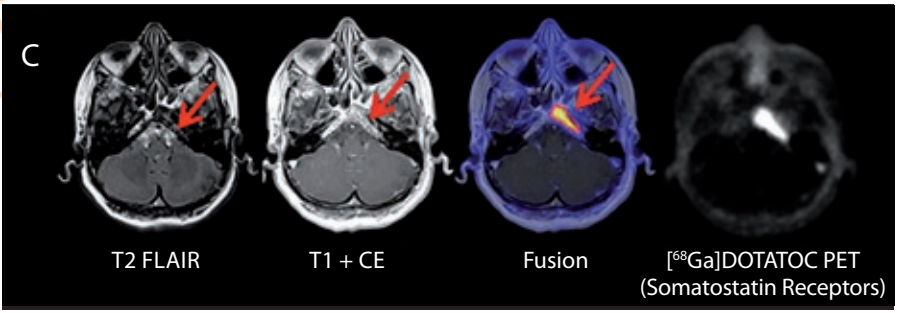

Figure 2 A–C: Multi-tracer brain PET/MRI in neuro-oncology.
(C) Somatostatin receptor imaging with the highly selective PET radioligand [^{68}Ga]DOTATOC traced tumour tissue in this 74-year-old woman with a meningeal brain tumour (arrows). On MRI the contrast between tumour and healthy tissue was lower

Advantages and limitations

Even before the introduction of hybrid PET/MRI, the combination of sequentially acquired brain MRI and PET information often proved superior to the single-modality approach in the diagnosis and work-up of neurological diseases. Although favourable, this imaging approach has not been applied consistently in clinical routine, mainly due to organisational issues and reimbursement questions. It may be hypothesised that hybrid brain PET/MRI, simply by ensuring consistent availability of both modalities and their joint interpretation by trained physicians, may improve diagnostics in this field [2]. Compared with sequential MRI and PET(/CT) a hybrid examination has other obvious advantages, such as improved patient comfort (through the scheduling of fewer examinations), reduced overall examination time and reduced radiation exposure. It has to be mentioned, however, that in order to obtain quantitative PET data the correction of the photon attenuation by head tissue is necessary and that, unlike in PET and PET/CT, this attenuation information is not gathered by CT or dedicated transmission scans but indirectly by MRI. An associated drawback is the fact that the attenuation correction (AC) algorithms currently implemented in PET/MRI systems do not consider cortical bone, which leads to significant underestimation of the AC-PET signal. New AC approaches addressing this important issue have been developed but have not yet been implemented in the commercially available systems (May 2015). Moreover, running a hybrid PET/MRI requires technologists who are specifically trained in both modalities. Nuclear medicine technologists are trained in handling ionising radiation and are acquainted with time-critical scheduling of examinations

with short-lived radiotracers. In contrast, MRI technologists are trained in MR safety and skilfully operate the MR scanner to provide high-quality diagnostic images and minimise artefacts in a large variety of different sequences and protocols. For combined PET/MRI, a basic understanding of the underlying physics of both modalities is required in the first instance in order to be able to adapt acquisition parameters during a patient scan. To run a hybrid PET/MRI with a small staff, dual-trained technologists are desirable but such technologists are extremely rare. A joint statement of the Society of Nuclear Medicine and Molecular Imaging Technologist Section and the Section for Magnetic Resonance Technologists has underlined the need for advanced-level educational programmes for PET/MRI technologists [4].

Technical background and workflow aspects

Positioning and preparation

All patients receive intravenous access and are repeatedly asked about contraindications (e.g. ferromagnetic metal implants, pacemakers). Due to the strong magnetic field, patients need to remove all metal objects and dentures before entering the examination room. The patient is then placed on the patient bed as comfortably as possible. This is achieved by use of positioning aids such as knee rolls and foam wedges to stabilise the head. The patient's shoulder should be in contact with the head and neck coil. If the head is too big for the coil, the support pad can be removed to create some space. For hearing protection, earplugs or earphones should be chosen over headphones since they cause less attenuation of the PET signal. The upper part of the head and neck coil is closed and the patient is instructed regarding the emergency bell. It is possible to attach a mirror to the coil which shows the window to the control room in order to avoid the otherwise oppressive feeling when looking at the ceiling of the gantry. Due to the relatively low room temperature at a PET/MRI facility, use of a blanket to cover the patient is recommended. Finally, the head centring is done via laser positioning, which should only be activated once the patient's eyes are closed. With a strongly reclined head the patient is moved into the gantry until the laser cross is a little below the nose and the centre position is then confirmed by pressing a button. Thereafter, the single MR sequences need to be defined and the PET scan is planned; care has to be taken that the entire brain is within the field of view. While the PET acquisition times differ depending on the specific tracer, the following reconstruction parameters have generally been found to be optimal for brain imaging on a Siemens mMR PET/MRI system: 8 iterations, 21 subsets, Y offset = -41, zoom = 2.8, 3.0-mm Gaussian filter (University Hospital Leipzig, Germany).

Once set-up has been completed, the PET/MRI workflow itself is straightforward. The start of the PET acquisition is accompanied by automatic acquisition of the MR sequences for AC. During the PET acquisition, MRI can be handled flexibly; all subsequent

MR sequences are adapted and planned by means of a three-axis localiser prior to the actual MR scan. Additional individual MR sequences can be planned and acquired as desired during the remaining PET scan time or beyond. Usually, the overall duration of a simultaneous PET/MRI study is determined by the MR examination time. Due to the distribution dynamics and the relatively long half-lives of the radiotracers, they are generally injected prior to the PET/MRI session. The injection of MR contrast medium, on the other hand, is tightly coupled to individual MR sequences within the hybrid imaging protocol and is performed while the patient is lying in the scanner; however, even with simultaneous injection (e.g. [^{15}O]H_2O and gadobutrol in research applications in the scanner), no interactions have been reported [2].

Dual time-point amyloid PET/MRI

By collecting early dynamic (e.g. 1–8 min p.i.) data in an amyloid PET scan, information on perfusion as a surrogate of glucose metabolism and on brain amyloid load can be derived with only one radiotracer. When this approach is combined with simultaneous MRI, the most important brain imaging information for the assessment of neurodegenerative disorders can be gathered during one imaging session [1]. Despite use of a non-magnetic tungsten syringe shield, the space in the gantry is limited and intravenous access via a vein on the back of the hand is helpful in facilitating the mandatory tracer application within the system. Two MR localisers are acquired first, then a workflow break needs to be implemented in the protocol immediately before the actual diagnostic MRI and PET scan begins. Upon tracer injection within the scanner room by the technologist, the actual scan is started by a second person sitting at the console; it is necessary to write down the application time for post hoc calibration of the injected activity. If the tracer is applied during the actual scan, the tracer activity can only be entered into the system afterwards, which makes a retrospective reconstruction mandatory. At the end of the 10-min PET scan, during which MR sequences can be acquired, the patient is allowed a break and leaves the examination room so that another patient can be examined. After about 60–70 min the second part of the examination starts, again with two localisers. Now the application type and time can be entered and during the subsequent 20-min PET scan, acquired from 90 to 110 min, the remaining MR sequences can be acquired (see Fig. 3 for details).

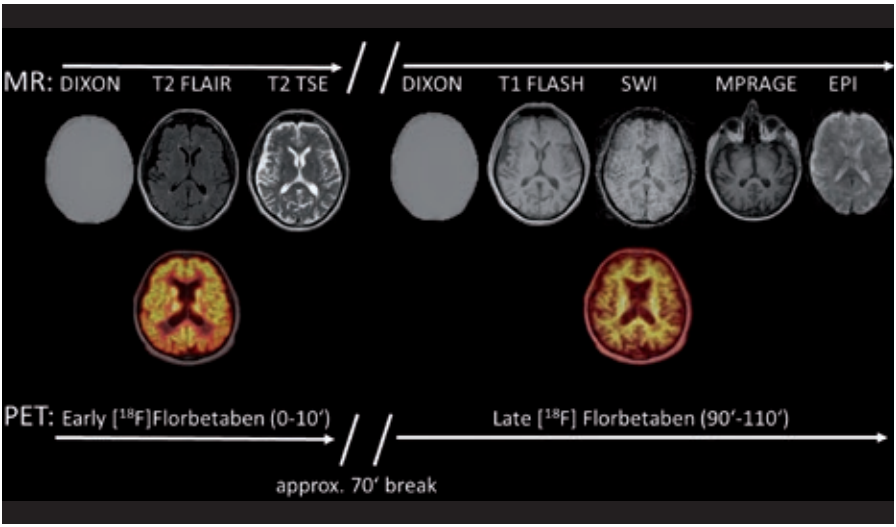

Figure 3: [^{18}F]Florbetaben (amyloid) PET/MRI workflow. Upon injection of the radiotracer, the early 10-min PET scan is started, which is accompanied by the acquisition of the DIXON sequence for attenuation correction (AC) and two more diagnostic MR sequences. After a break of ~70 min, the patient re-enters the scanner and during the late 20-min PET scan more diagnostic MR sequences can be acquired. Note: the DIXON VIBE sequence needs to be acquired again for AC of the second PET scan. Sequence: image plane/slice thickness (mm)/no. of slices/TR and TE (ms)/FOV (mm)/matrix; 3D Dixon Vibe (DIXON): coronal/3.12/128/3.6 and 1.23/500×300/256; T2 fluid attenuation inversion recovery (FLAIR): axial/3/46/9000 and 93/230/320; T2 turbo spin echo (TSE): axial and coronal/3/50/6000 and 100/230/384; T1 FLASH: axial/3/50/395 and 2.97/230/320; susceptibility weighted imaging (SWI): axial/1/112/25 and 20/230/256; T1 magnetisation prepared rapid gradient echo (MPRAGE): sagittal/1/176/1900 and 2.53/250/256; echoplaner imaging (EPI): sagittal/1/176/1900 and 2.53/250/256. Note: PET reconstruction parameters are provided in the main text

Possible artefacts

As stated above, the PET signal needs to be corrected for the attenuation of photons on their passage through the tissue of the head. Current PET/MRI AC sequences classify three tissue classes: fat, water and air. As already noted, bone tissue is currently not considered, which leads to a ~10–15% underestimation of the PET signal in the vicinity of cortical bone [5]. Since the attenuation values in PET/MRI cannot be measured but rather must be predicted from the MR signal by advanced computer algorithms, problems may arise if there are any deviations

with irregular facial bone or skull lesions (e.g. due to prior neurosurgery). Hence, a ventricle shunt system may lead to misclassification of the surrounding brain tissue classes (Fig. 4A), but even without any visible cause the underlying algorithms sometimes fail to assign the orrect attenuation values to the head tissue classes (Fig. 4B).

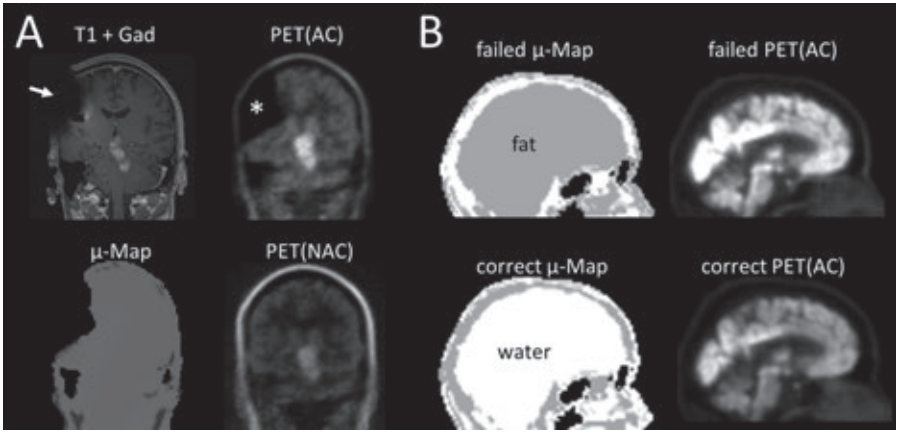

Figure 4 A, B: Attenuation correction (AC)-related artefacts. (A) In this patient the MR signal is heavily distorted in the vicinity of the ventricular brain shunt [arrow in T1 with gadolinium (Gad)]. As a consequence, the system fails to derive a correct μ-map from the Dixon VIBE sequence for AC (μ-map) and this area is misclassified as air but not as part of the head. Hence, there is no corrected PET information in the affected voxels available [asterisk in PET(AC)] and the non-corrected PET data need to be evaluated instead [PET(NAC)]. (B) The system wrongly assigned the attenuation values of fat and water (failed μ-map) whereas the correct assignment can be seen below (correct μ-map). Incorrect assignment of photon attenuation values results in an overall overestimation of the PET signal after reconstruction [failed PET(AC)]. The PET reconstructed from the correct Dixon-based μ-map delivers a substantially lower PET signal [correct PET(AC)]

References Chapter 8

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Chapter 9
Brain Death
Marko Grmek

Introduction
Brain death (BD) may be defined as the complete and irreversible loss of all brain and brain stem functions [1, 2]. A person with BD is considered legally dead [3]. In certain cases, for example when treatment with mechanical ventilation is performed, some somatic functions such as circulation can be active despite BD.

In most European countries, when and how a person can be pronounced brain dead is precisely defined [4]. One would expect the procedures for determination of BD to be similar across Europe; in fact, however, they differ considerably. In approximately 50% of European countries, the diagnostic procedure requires two or three clinical tests, with a specified minimum time interval between them, usually 6–24 h [4]. In other countries, an ancillary or confirmatory test is also required. The apnoea test is usually the final step in the determination of BD. Within the United States, the procedures for determining BD also differ considerably [5].

Ancillary tests
Legislation and/or the guidelines usually define precisely when a certain ancillary test may be used in the diagnostic process for determining BD. The following are the most frequently used ancillary tests [6, 7]: cerebral angiography, electroencephalography (EEG), transcranial Doppler ultrasonography and cerebral scintigraphy. Selection of the test depends on the state or condition that has resulted or could result in BD and on the availability of the test. Ancillary tests can shorten the procedure for determining BD in some cases because these tests can immediately follow the clinical examination; this is especially relevant in persons who are potential organ donors. An ancillary test can also be used in persons who are suspected of being brain dead but cannot be completely clinically examined, for example those with severe head injuries [7]. When the results of both the clinical examination and the ancillary test match the BD diagnostic criteria, an apnoea test can be performed. Ancillary studies for determination of BD can also be performed in children [8].

Ancillary test results alone without a clinical examination do not suffice for a diagnosis of BD.

Brain death scintigraphy
Two types of scintigraphic examination can be used in the procedure for determining BD [2, 9, 10]. In the past, scintigraphy of the head (the brain) with hydrophilic agents was employed. Such radiopharmaceuticals [^{99m}Tc-pertechnetate, ^{99m}Tc-glucoheptonate and ^{99m}Tc-diethylene triamine penta-acetic acid (DTPA)] do not cross the blood–brain barrier (BBB). When using hydrophilic radiopharmaceuticals, only blood flow images of the head should be acquired. Since such images are sometimes difficult to interpret, this type of examination is now used only rarely when determining BD. Instead, the main diagnostic procedure for this purpose is brain perfusion scintigraphy with lipophilic

radiopharmaceuticals that do cross the BBB, e.g. ^{99m}Tc-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) and ^{99m}Tc-bicisate (^{99m}Tc-ECD).

Brain perfusion scintigraphy

Brain perfusion scintigraphy enables both presentation of the blood flow and perfusion of the brain [2], making interpretation of examination results considerably easier. In line with the SNM Practice Guideline for Brain Death Scintigraphy, brain perfusion scintigraphy is primarily used as an ancillary test in determining BD when the presence of certain clinical conditions is likely to render clinical assessment less reliable [11]. Such conditions include severe hypothermia, coma caused by barbiturates, electrolyte or acid–base imbalance, endocrine disturbances, drug intoxication, poisoning and neuromuscular blockade. BD scintigraphy may also be helpful in persons who are being considered as possible organ donors.

The performance of brain perfusion scintigraphy to diagnose BD differs somewhat from its use in patients with neurological conditions [12]:

1. The examination must not further compromise the medical condition of the patient. For this reason, brain perfusion scintigraphy for determination of BD is usually not performed in persons with circulatory instability or when transport or movement could further compromise the person's medical condition.

2. It must be ensured that the radiopharmaceutical, ^{99m}Tc-HMPAO or ^{99m}Tc-ECD, is of the appropriate quality. Radiochemical purity should be determined on each vial prior to injection using the methods outlined in the package inserts. Radiochemical purity should be >90% for ECD and >80% for HMPAO. The recommended radiopharmaceutical activity is 370–1110 MBq. It is necessary to make sure that the correct radiopharmaceutical is applied.

3. The radiopharmaceutical is administered intravenously with the bolus technique. Such a technique allows acquisition of good blood flow images.

4. The acquisition takes place in two stages. First, a blood flow study of the head and neck is performed. Data acquisition begins simultaneously with the administration of the radiopharmaceutical. Usually, a one-minute series of 1- or 2-s images is acquired. Perfusion images are obtained during the second stage, acquisition commencing 20 min after administration of the radiopharmaceutical. SPECT acquisition is most frequently used; only occasionally is planar scintigraphy in multiple projections performed. In both cases, the entire brain and the brain stem must be visualised.

5. Interpretation of the results of blood flow studies requires an experienced specialist who can recognise the presence or lack of activity in the brain. Interpretation of perfusion images is less complicated. If activity in the brain and the brain stem does not appear

on the perfusion images, the examination result is compatible with BD.

Brain perfusion scintigraphy for determination of brain death – our experience

New legislation regarding the use of brain perfusion scintigraphy as an ancillary test in the process of determining BD was adopted in Slovenia in 2001. Prior to that, BD scintigraphy was used only rarely for this purpose. Since 2001, brain perfusion scintigraphy has been performed on 30–40 persons a year in whom the findings of clinical examination were compatible with BD. Between 2001 and 2008, a total of 259 examinations in 253 persons (174 men and 79 women) were performed [13]. Patients were on average 41±19 years old; 38 (15%) were younger than 20. Complete discontinuation of brain perfusion was established in 233 (90%) persons; in the remaining 26 (10%), BD was not confirmed because activity was present in a small or large part of the brain. Brain perfusion scintigraphy was repeated after 1–8 days in six of these patients. Upon re-examination, no activity was visible in the brain in any of the patients.

In the Ljubljana University Medical Centre, Department for Nuclear Medicine, brain perfusion scintigraphy in the diagnostic process for determining BD is performed as follows:

A request for BD scintigraphy: The nuclear medicine physician who receives a request for BD scintigraphy asks the radiopharmacy unit to prepare a radiopharmaceutical. The patient's ward is asked to prepare the patient for transport to the Department for Nuclear Medicine within one hour. The schedule of work on the gamma camera is rearranged if necessary.

Preparation of the radiopharmaceutical: The radiopharmacist needs about one hour to synthesise stabilised ^{99m}Tc-HMPAO and perform quality control. A radiochemical purity of at least 80% is required.

Transportation and positioning of the patient to the gamma camera: When the radiopharmaceutical has been prepared, the physician asks the patient's ward to bring over the patient. The transportation usually takes around 10 min. The patient is carefully moved from the bed to the gamma camera table and his or her head is fastened.

Radiopharmaceutical administration: Most patients already have an intravenous line inserted. We check whether the intravenous line is unobstructed, apply the stabilised ^{99m}Tc-HMPAO, activity 600 MBq (proportionately less in children), and flush the system with saline solution.

Image acquisition: A blood flow study is usually not performed. SPECT acquisition is initiated 15 min after the radiopharmaceutical administration and must encompass the entire brain, including the brain stem. The acquisition is usually performed on a double-head gamma camera with the following

acquisition parameters: time per view, 20 s; no. of views, 2×32; matrix size, 128×128; zoom, 1.23; orbit, non-circular.

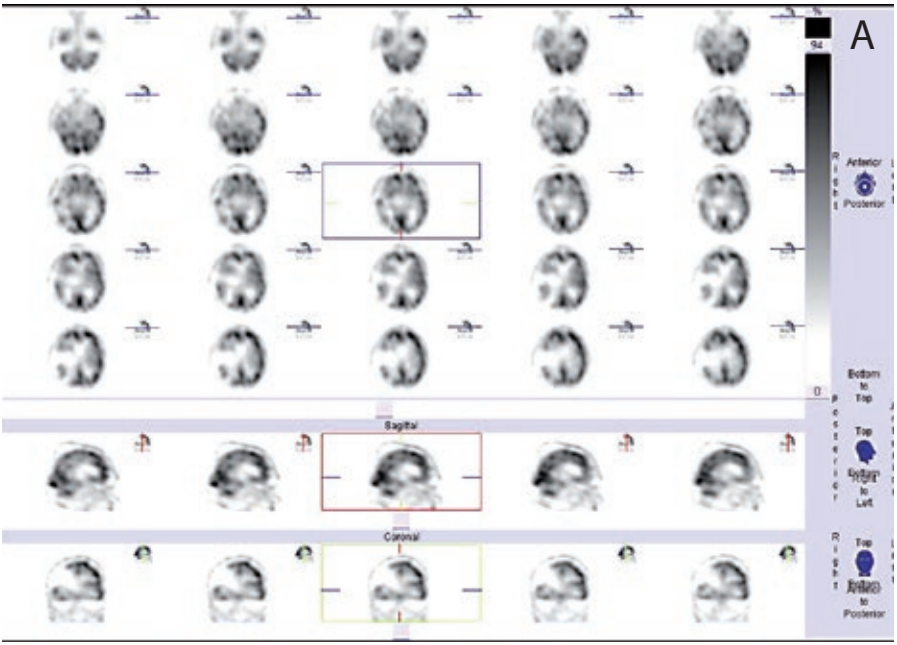
Reconstruction: The quality of the raw images is examined. If the images meet quality standards, a reconstruction is made. Iterative reconstruction is performed, with 12 iterations and 4 subsets. At the same time, the examinee is moved from the gamma camera to his or her bed.

Interpretation and reporting: Assessment of the scintigrams that have been obtained is straightforward (Fig. 1). Absence of activity in the brain and the brain stem is concordant with a diagnosis of BD.

The duration of the procedure is approximately 2 h.

Summary

Brain death scintigraphy is one of the ancillary tests that can be used in the process of determining BD. The most frequently used scintigraphic method is brain perfusion scintigraphy with ^{99m}Tc-HMPAO. The procedure for and the interpretation of this examination are relatively uncomplicated.



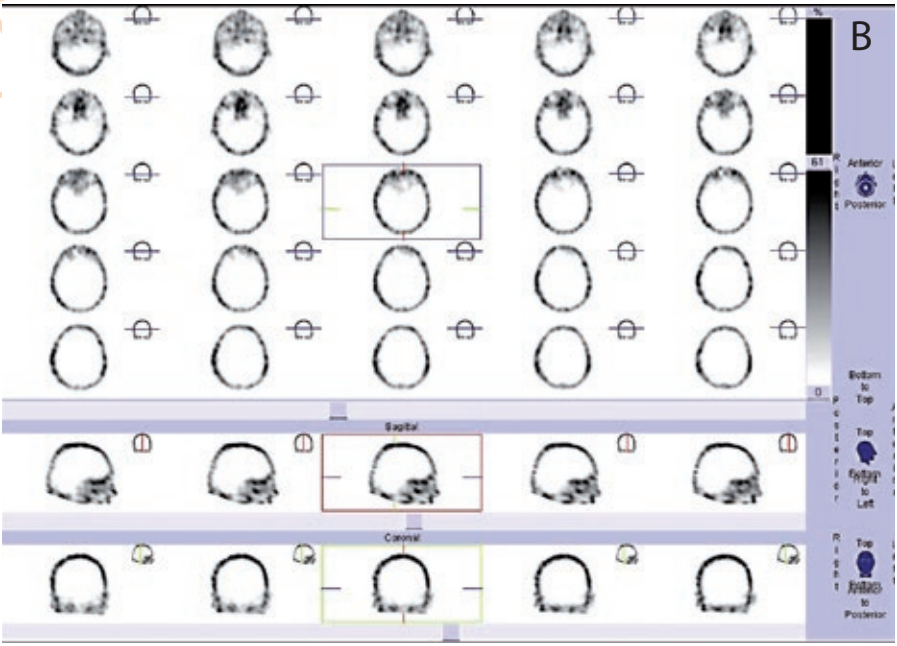


Figure 1A, B: Brain perfusion scintigraphy in determining BD. In the first investigation (A), activity is present in the brain and the criterion for BD is not fulfilled. The investigation was repeated on the same patient after 7 days (B). Absence of activity in the brain and brain stem confirms the cessation of brain circulation – the result is compatible with BD

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Chapter 10

Health Care in Patients with Neurological Disorders

Claudiu Peștean

Introduction

All medical activities are focussed on patients. Even in the contexts of medical research, the medical industry and medical care, every effort made by those involved is ultimately intended to benefit patients. Nursing aims to meet patients' needs but also to promote their state of health, to prevent illness, to restore health and to help the patient to deal with illness or even death.

From a nursing point of view, health promotion consists in all those actions that influence the lifestyle of the patient in order to enhance quality of life. It entails not only measures that help in avoiding illness, but also steps to encourage the patient to be aware of his or her health status and to teach behaviours that can contribute in maintaining or improving health. The provision of pertinent information and appropriate use of referrals are important elements in this process [1].

Prevention of illness means to reduce risks and to maintain optimal functioning of the individual. In addition, early detection of illness is essential. For these purposes, educational programmes are needed, as well as health assessments at different levels and in different areas of interest [1].

By definition, in the ill patient these aims have not been accomplished, so the first priority is to assist in restoration of health. The specific activities employed to achieve this end represent the core of nursing practice; they start with those actions designed to assist in early detection of disease and end with patient education during the recovery process, which is very important in helping the patient to maintain his or her recovered health [1].

Nursing care

Nursing care consists in the nursing process. The nursing process should be constructed on the basis of a very strong relation with the patient and with the family or caregivers, and patients should be partners in the design and implementation of the process [1]. Nursing care involves a holistic approach to patients and their problems, as is underlined by most papers on nursing theory [2]. It is considered simultaneously to be both an art and a science [1]. In order to provide effective nursing care, it is necessary to have special skills such as determination, empathy, critical thinking abilities, and comprehensive medical knowledge.

At the same time, the nursing process is a systematic and accurate method for provision of suitable medical care. Theoretical knowledge and practical skills are deployed with the aim of developing a strategy that will be most effective in helping the patient to recover health and also in teaching the patient how to maintain this state in collaboration with those close to him or her and taking into account all the environmental factors that influence the patient's life. The nursing process starts as all systematic methods start, with accurate documentation and a research

step, the so-called nursing assessment. Once the assessment has been completed, the practitioner will establish the nursing diagnosis, identifying the actual but also the potential health problems. With these problems as input data, the nursing plan is established and applied, with inclusion of all nursing interventions to be imposed. Based on this, one can conclude that nursing care is an individualised process adjusted according to each patient's needs. In the final part of the process – evaluation – the effectiveness of the implemented plan is assessed in order to determine the achievement of goals. Bearing in mind these steps, the nursing process can be characterised as a systematic process, comprising an ordered sequence of activities. It is also a dynamic process because of the extensive interaction and the overlap between the nursing steps.

The nursing process is interpersonal in nature, being based, as already mentioned, on the complex relation between the practitioner and the patient and being patient focussed and not task centered [1]. While the process is focussed on the patient, it is outcome oriented because its aim is to achieve the goals identified as benefitting the patient; this is very important because knowing the outcomes that may be expected, nursing actions can be prioritised and nursing care successfully provided.

The nursing process should be universally applicable and able to respond to a wide variety of individuals/patients and situations. The typical standardisation of the nursing process involves four main steps: assessing, diagnosing, outcome identification and planning, and evaluating (Fig. 1).

Assessing

During the assessment, data are collected relating to the patient's health status, ability to manage his or her healthcare and the need for nursing care. In this phase a pertinent and comprehensive database is created which provides the starting point for the nursing plan (Fig. 1). Assessment is not limited to the initial part of the nursing care process; rather it should be ongoing because the health status of the patient may change quickly, new information may be obtained and some information may no longer be relevant owing to changes that occur during the attainment of cure. The person who assesses the health status of patients will collect the data during a comprehensive interview designed to gather information on the patient, the family, and the environment, thereby providing a holistic perspective. The information is then prioritised according to the patient's immediate needs or how the interviewer anticipates the situation developing. Furthermore, the assessment is not restricted only to the interview. It is also based on data collected using an observational method, i.e. the person who assesses the patient will analyse the patient's condition, and on the results of evidence-based techniques such as the nursing examination and measurements of specific medical parameters.

The recorded data are critically evaluated to detect all possible forms of bias, possible abnormal findings, possible inconsistencies, and missing information. The data will be structured upon significance-based criteria. Usually during the initial assessment the focus is on a specific problem. It is also possible to encounter physiological or psychological emergencies (as often occurs in neurology) and in these circumstances the assessment will concentrate on life-threatening problems. When the nursing process continues over a longer period, the initial assessment may be followed by further assessment activities designed to evaluate the patient's status and compare it with the initial one. This is not so relevant in diagnostic nuclear medicine for neurological disorders, but it could be applied as a phase in the nursing process implemented by the nursing team who assess the patient in the neurology department and send the patient for specific nuclear medicine procedures. The collected data may be subjective, taken from the patient's perspective, or objective, i.e. measurable and observable. Both types of data should be collected because they complement one another [1].

Diagnosing

Upon completion of data collection, all the information is analysed and synthesised. A list of suspected problems, potential problems and risk factors is created and resources and strengths are identified as the basis for health promotion and health recovery actions [1] (Fig. 1). This second step of the nursing process is termed nursing diagnosis. It is good to use a body systems approach to organise assessment data in order to better detect nursing problems [1]. The nursing diagnosis comprises all the identified problems that the nurse can treat independently. These problems may change from day to day in accordance with the patient's response to illness and the provided health care. Usually the written nursing diagnosis has two elements: the patient's problem and its cause, i.e. the etiology; in addition, a third element can be included, namely the characteristics of the problem [1]. The nursing diagnosis should be critically evaluated and validated. When appropriate, the nursing diagnosis may also be validated by the patient. This is one more example of how the patient is a partner in the nursing process, not merely a client.

Outcome identification and planning

After the health problems have been identified and prioritised, the nursing actions can be planned (Fig. 1). In this stage the outcomes will be established and the appropriate nursing interventions will be planned according to nursing theory and evidence-based nursing guidelines. The nursing plan will be communicated to the patient and to the health care team. The nursing plan aims to prevent, solve or reduce a patient's health problem and to achieve the patient's expectations relating to health [1].

During this step of the nursing process the first intention is to identify the expected outcomes, which are individualised on the basis of the patient's characteristics and condition.

When identifying the anticipated outcomes, the first partner is the patient and then the family, who can subjectively formulate their expectations. Starting from the diagnosis, outcomes may be derived in order to respond to the patient's needs. The outcomes will be identified on the basis of clinical expertise, scientific and medical evidence, associated risks, costs and benefits, the patient's values and ethical considerations. The time points by which these outcomes should be met are then established. The identified outcomes may be modified if this is necessitated by changes in the status of the patient. All the above will be documented [1].

In order to meet the expected outcomes, the patient will need professional help. Nursing interventions must be established that are appropriate in the context of the nursing diagnosis. These interventions must take account of nursing abilities, available time and resources and must be safe, efficient, realistic, in accordance with research findings and standards of care, compatible with all the patient's values and beliefs, acceptable to the patient and compatible with other therapeutic activities. Nursing interventions may be nurse initiated, when no physician's order is needed and the intervention is based only on the nursing diagnosis, or physician initiated, when the nursing personnel implement interventions ordered by the physician in response to the medical diagnosis.

The nursing plan should be documented in written form, which will help the nursing team to deliver goal-oriented, pertinent nursing care and will assist in standardisation of the activities requested to help the patient.

Implementing

In this step of the nursing plan, all the activities planned on the basis of the information gathered in the previous steps should be implemented by the nursing team (Fig. 1).

The nurse will have the role of health care coordinator. Patients are seen by various specialists during the provision of medical care and each of them focusses on different aspects. The nurse needs to summarise all the findings and recommendations from all the healthcare professionals and to prepare patients and their families to participate maximally in the plan of care. The nurse may also have an important role in liaising between the members of the medical team. When implementing the nursing plan, critical thinking is necessary: nursing personnel should identify the best means of implementation and assess whether the interventions are indeed supported by research findings in the field of interest. If, during monitoring, new evidence arises relating to the patient's response, the plan should be modified accordingly [1].

Evaluating

Evaluation of the achieved outcomes established within the nursing plan is very important since this step assesses the success of nursing care and the need to correct, change, improve or continue the nursing care activities (Fig. 1). It is important that evaluation is

performed as early as possible; postponing it until just before patient discharge can lead to failure to implement modifications in a timely manner. The evaluation is based on various criteria and standards designed to assess the accomplishment of desired outcomes. Final data are collected by nursing personnel in order to evaluate the success of the nursing plan. If all the outcomes have been achieved and no additional nursing diagnostics are identified, the nursing process may be closed. Very often, however, the process must be continued owing to failure to achieve the established outcomes. The nursing plan then needs to be reviewed and revised as necessary; this revision may include the deletion or modification of nursing diagnoses, alteration of the expected outcomes so that they are more realistic, adjustment of the time points for achievement of specified outcomes and alteration of nursing interventions [1].

Neurological care

In this section we shall review those neurological disorders more often addressed in diagnostic nuclear medicine departments using specific radiotracers described earlier in the guide. The main clinical characteristics of each disorder and the appropriate nursing interventions will be summarised.

Alzheimer's disease

Alzheimer's disease is a common neurological disorder that affects a high percentage of elderly persons and accounts for more than half of cases of dementia. The prognosis is very poor. Initial signs and symptoms are insidious and include memory loss. There may also be difficulty in learning and memorising new information, difficulty in concentrating and impaired hygiene. Gradually, progression to severe signs and symptoms occurs, with impairments of linguistic and spatial abilities and appearance of complex symptoms. These include difficulty in abstract thinking, difficulty in performing activities that require judgment, deterioration in motor function and coordination, impaired ability to read and write, disorientation and performance of repetitive actions [3, 4].

The nursing personnel will focus on supporting the patient to maintain present abilities and to compensate for those abilities that have been lost. The patient and his or her family will be assisted in establishing an effective communication system according to the altered cognitive abilities. Emotional support will be offered. The patient will be protected from injuries by providing a safe environment. The patient will be encouraged and taught to perform physical exercises to maintain physical abilities. Appropriate information about the disease will be provided to the patient and to the family [4].

Parkinson's disease

The early symptoms of Parkinson's disease are non-specific and include slower walking and dressing and non-motor symptoms such as disturbed sleep, anxiety and depression. The most obvious symptoms are bradykinesia (lack of spontaneous movements,

lack of facial expression, reduced arm swing), rigidity and rest tremor; although the last-mentioned symptom is the most frequent, still 20% of patients do not display it [3]. Parkinson's disease is often accompanied by dementia.

The nursing personnel should initiate appropriate interventions to help the patient to cope with these symptoms. An efficient communication system should be established that will enable patients to adjust communication in accordance with their altered cognitive abilities. Emotional support should be provided. The patient should be protected from potential injuries by creation of a safe environment and should be encouraged to perform physical activities so as to maintain mobility and physical performance. Physiological support will be provided: the patient and the family will be taught about the disease and any concerns should be listened to and addressed through appropriate advice [4].

Epilepsy

The symptoms of epilepsy differ mainly due to variations in the origin of pathological electrical discharges in the brain. There are two main forms of epilepsy: generalised epilepsy, in which the abnormal electric discharge arises in the deep structures of the brain and spreads throughout the entire cortex, and focal epilepsy, in which a localised area of the brain is involved. The typical major symptom of an epileptic patient is the tonic-clonic seizure, formerly known as grand mal seizure [3, 4]. Depending on the localisation and duration of the abnormal electrical discharge, the symptoms may be: severe stress, nausea, a sinking sensation in the stomach, a dreamy feeling, visual sensations, unusual taste, unintelligible speech, confusion, a loud cry (before generalised tonic-clonic seizure), tongue-biting, loss of consciousness, incontinence and apnoea. After the seizure the patient may complain of fatigue, headache and weakness and may fall into a sleep [4].

Given this variety of symptoms, the nursing personnel should have good knowledge of this complex disease so that they can support the patient in dealing with, and teach the family how to react during, the epileptic attack. First, the patient should be encouraged to express his or her feelings about the condition; support will be offered to enable the patient to understand the disease. The importance of compliance with the prescribed medication must be underlined and the safety and efficacy of the medication should be stressed. The drug blood levels should be checked regularly [4].

The family will be instructed to avoid restraining the patient during an epileptic seizure, to lie the patient down, to place something soft under the head, to remove hard objects from the vicinity of the patient, to ensure an open airway by turning the patient's head appropriately, and, if the mouth is open, to place a soft object between the teeth so as to protect the tongue [4].

Cerebral ischaemia and stroke

Cerebral stroke is the irreversible interruption of blood supply to the brain tissue caused by two main pathological events: occlusion of arteries, termed cerebral ischaemia, and cerebral haemorrhage, the latter being much more destructive than the former [3]. When the blood flow to the brain is reduced, ischaemia occurs, which is a reversible condition; if the condition is severe or prolonged, cell death ensues, which is termed infarction. If complete recovery from ischaemia occurs within minutes or hours, the episode is referred to as a transient ischaemic attack. If the ischaemic condition lasts more than 24 hours, neurologically one speaks of stroke [3].

The associated symptomatology varies greatly depending on the involved arterial branch (and the location and size of the affected brain territory) and the length of time for which the ischaemia persists. The main neurological symptoms and signs in brain ischaemia are as follows: In middle cerebral artery ischaemia there may be loss of use of and feeling in the contralateral face and arm, dyslexia, dysphasia, dysgraphia and dyscalculia. Anterior cerebral artery ischaemia produces loss of use of and feeling in the contralateral lower limb. Contralateral homonymous hemianopia is suggestive of posterior cerebral artery ischaemia. Internal carotid artery ischaemia involves the face, arms or legs with or without homonymous hemianopia. Monocular loss of vision indicates ophthalmic artery occlusion. Vertebrobasilar artery ischaemia produces double vision, facial numbness or weakness, vertigo, ataxia, bilateral loss of use or feeling of arms and legs, dysphagia or dysarthria, depending on the affected cranial nerve. Finally, small vessel ischaemia may produce pure loss of use of or feeling in the contralateral arm and leg [3].

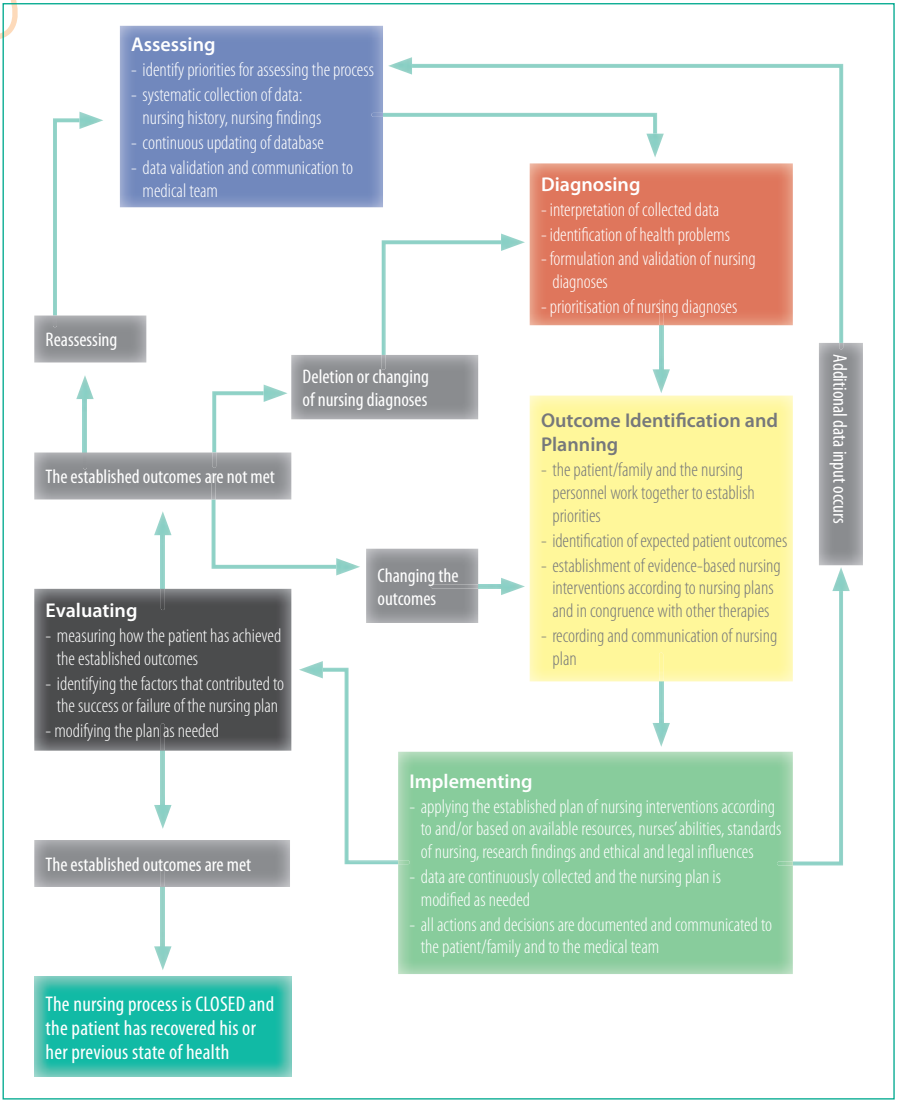
Nursing interventions are complex and differ according to the type and localisation of ischaemia. The airway and oxygenation should be maintained and constricting clothes should be removed. In unconscious patients the lateral position should be adopted, and mechanical ventilation or oxygen should be provided if necessary. The vital signs and neurological status should be monitored, including blood pressure, heart rate, respiratory movements, pain, pupillary changes, sensory function and speech. The nursing personnel must pay attention to the electrolyte and fluid balance and ensure adequate nutrition (in terms of quantity and quality). Gastrointestinal activity should also be monitored, with attention to the diet in order to ensure efficient digestion and elimination. Adequate hygiene is to be ensured through specific care actions to ensure that the body, eyes and mouth remain clean. The nurse must pay special attention to the patient's position, and this is especially important in unconscious patients. The body is to be aligned in the correct position, and special attention is required to avoid pressure sores and to prevent pneumonia by changing the patient's position regularly. Patients will be taught and encouraged to perform exercises. Communication with the patient

is to be established and maintained according to the patient's abilities; the family will be instructed how to communicate with the patient and psychological support will be offered [4].

Multiprofessional aspects of nuclear medicine practice related to neurological diseases

Healthcare systems are becoming more complex owing primarily to scientific and technical progress, but also because of social and economic factors related to health insurance systems, societal factors such as patients' expectations and society's demands on the medical system. It is impossible for one individual to cover all necessary aspects of healthcare, especially in the age of ultra-specialisation. Collaborative multidisciplinary work is essential and will provide benefits to patients on the basis of the expertise of different professions, including physicians, nurses, therapists, technologists, social workers, etc. [5]. Effective nuclear medicine practice in relation to neurological diseases presupposes efficient interdisciplinary work between the referral team, the neurologist, the nursing personnel specialised in neurology, the nuclear medicine team (in which the nuclear medicine physician will have an in-depth knowledge of neurology) and other specialist personnel, among whom the technologists have an essential role. Neurological patients are patients with special needs and the technologist, as the person in the medical team who has the most interaction with the patients, should therefore have a strong knowledge of the field and possess the skills to deal with this category of patient. In recent decades a change towards overlapping of competencies or responsibilities has been noted in medical professions, and this trend may be regarded as normal in such a dynamic and challenging profession as nuclear medicine [6].

Figure 1: Schematic r



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