Anatomical and biochemical investigation of primary brain tumours

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Abstract. Cancerous transformation entails major biochemical changes including modifications of the energy metabolism of the cell, e.g. utilisation of glucose and other substrates, protein synthesis, and expression of receptors and antigens. Tumour growth also leads to heterogeneity in blood flow owing to focal necrosis, angiogenesis and metabolic demands, as well as disruption of transport mechanisms of substrates across cell membranes and other physiological boundaries such as the blood-brain barrier. All these biochemical, histological and anatomical changes can be assessed with emission tomography, X-ray computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS). Whereas anatomical imaging is aimed at the diagnosis of brain tumours, biochemical imaging is better suited for tissue characterisation. The identification of a tumoural mass and the assessment of its size and vascularisation are best achieved with X-ray CT and MRI, while biochemical imaging can provide additional information that is crucial for tumour classification, differential diagnosis and follow-up. As the assessment of variables such as water content, appearance of cystic lesions and location of the tumour are largely irrelevant for tissue characterisation, a number of probes have been employed for the assessment of the biochemical features of tumours. Since biochemical changes may be related to the growth rate of cancer cells, they can be thought of as markers of tumour cell proliferation. Biochemical imaging with radionuclides of processes that occur at a cellular level provides information that complements findings obtained by anatomical imaging aimed at depicting structural, vascular and histological changes. This review focusses on the clinical application of anatomical brain imaging and biochemical assessment with positron emission tomography, single-photon emission tomography and MRS in the diagnosis of primary brain tumours, as well as in follow-up.

Keywords: Brain tumours – Radionuclides – Anatomical imaging – Biochemical imaging

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Introduction

The incidence of primary brain tumours in European countries and United States depends on age and is approximately 1–10 cases/100,000 persons per year (age standardised), with slight variations among different regions of the world [1, 2, 3]. There is an early peak (3.1 per 100,000) between 0 and 4 years, then a decrease (1.8 per 100,000) from 15 to 24 years, and subsequently a steady rise that reaches a plateau (17.9–18.7 per 100,000) between 65 and 79 years. A recent study on the incidence rates for CNS tumours in children aged 0–14 years has been carried out in Italy [4]. The data from this evaluation fit with the epidemiological records observed in other international population-based studies (Swedish Cancer Registry, U.S. SEER, Scottish Cancer Registry, British Childhood Registry). The overall age-standardised rates of CNS tumours are 40 per million child years for both genders together (45.3 for boys and 34.4 for girls). Although one-quarter of the cost of care for can-

cer patients is allocated for CNS tumours, survival rates are still very poor in all countries [5].

Classification of brain tumours

Intracranial brain neoplasms can be classified into primary brain neoplasms and metastatic tumours. Brain metastases are more common than primary brain tumours since lung neoplasms, as well as breast, gastrointestinal and genitourinary tumours and melanomas, frequently give rise to a secondary tumour in the CNS.

The basic classification of primary brain tumours by the World Health Organisation (WHO) [6, 7] relies on their cellular origin, and describes five different groups: tumours originating from neuro-epithelial cells, from cranial and spinal nerves, from meninges, from lymphatic and haematopoietic tissue, and from germ cells. This classification was recently revised in the year 2000 by the WHO, and some new entities or variants have been included (Table 1). This new classification considers not only the clinical course and histological appearance of neoplasms but also their immunophenotypic features and molecular/cytogenetic profile [8].

Primary brain neoplasms which derive from neuro-ectoderm (PNETs) are the most common tumours, followed by tumours of meningeal, haematopoietic and nerve sheath origin. In adults, the most frequent PNETs derive from glial cells (astrocytes, oligodendrocytes, ependymocytes and subependymocytes) [9].

Gliomas

All the tumours originating from glial cells are named gliomas, and these tumours account for more than 90% of primary brain tumours in patients older than 20 years and for more than 60% of all intracranial brain tumours in all patients.

Astrocytomas

Diffuse fibrillary astrocytomas are the commonest type of primary brain neoplasm in adults. The World Health Organisation has classified astrocytomas into four grades of malignancy according to their histopathological characteristics: low-grade astrocytomas (grade I), high-grade astrocytomas (grade II), anaplastic astrocytomas (grade III) and glioblastoma multiforme (grade IV). Some of these tumours arise in patients with longstanding seizure disorders, personality disorders resulting from temporal lobe dysfunction, or scars due to head trauma, suggesting that the malignant cells sometimes emerge from a benign glial proliferation. Even low-grade tumours are infiltrative, with a marked potential for malignant progression. Astrocytic tumours are a model for study of the progression of gliomas from low malignancy to high malignancy grade [10, 11]. There are no genetic aberrations that characterise the most benign variant of astrocytoma, the pilocytic astrocytoma (grade I), which occurs mainly in children; this tumour is mainly located in cerebellum and brain stem and has a very good prognosis. Grade II astrocytomas show loss of alleles at 13q, 17p and 22q and occur mainly in middle age. Loss of one TP53 allele (17p) is associated with mutation of the remaining allele. Half of anaplastic astrocytomas carry several alterations in genes coding for proteins that control the cell cycle, and also other genetic defects affecting unknown genes. About 80% of glioblastomas (malignancy grade IV) can be observed to have genetic alterations resulting in the aberrant control of progression from G1 to the S phase of the cell cycle. Other genetic abnormalities associated with glioblastomas are the amplification of genes coding for growth factor receptors, c-myc protein and other oncogene expression [12, 13]. The peak incidence of these tumours is in late middle age.

Anaplastic astrocytoma is the most common type of astrocytoma; it accounts for approximately 50% of astrocytomas at any age, and peaks in the fourth decade. The most malignant astrocytoma is the glioblastoma multiforme, and its frequency increases with age (1.3% in the

Table 1. Revised classification of primary intracranial tumours according to WHO

Tumours of neuro-epithelial tissue	Astrocytic tumours, oligodendroglial tumours, mixed gliomas, ependymal tumours, choroid plexus tumours, glial tumours of uncertain origin, neuronal and mixed neuronal-glial tumours, neuroblastic tumours, pineal parenchyma, embryonal tumours
Tumours of peripheral nerves	Schwannoma, neurofibroma, perineuroma, malignant peripheral nerve sheath tumours
Tumours of the meninges	Tumours of meningothelial cells, mesenchymal non-meningothelial tumours, primary melanocytic lesions, tumours of uncertain histogenesis
Lymphomas and haematopoietic neoplasms	Malignant lymphoma, plasmacytoma, granulocytic sarcoma
Germ cell tumours	Germinoma, embryonal carcinoma, yolk sac tumours, choriocarcinoma, teratoma, mixed germ cell tumours
Tumours of the sellar region	Craniopharyngioma (adamantinomatous, papillary), granular cell tumour

first decade, 7% in the second decade, 14% in the third decade, 18% in the fourth decade, 33% in the fifth decade and 44% in the sixth decade). It accounts for more than half of all astrocytomas after age 60, with survival of less than 2 years for most patients. Average life expectancy in glioblastoma patients is approximately 17 weeks without therapy, and 62 weeks with radiation and chemotherapy. Average life expectancy in low-grade astrocytomas depends upon tumour location; it is up to 89 months in cerebellar tumours, and up to 67 months in supratentorial tumours. Five-year survival in low-grade astrocytomas is only 30% due to malignant degeneration.

Oligodendroglioma

Oligodendroglioma may develop in isolation from an oligodendroglial origin or it may be mixed with other glial cells. It is mostly low-grade; the malignant form represents only 20% of cases. The incidence of oligodendrogliomas slowly increases from birth up to 40 years of age and then decreases. Approximately one-third of patients survive for 5 years after diagnosis.

Ependymomas

Ependymomal tumours arise from cells of ependymal lineage and mostly occur in the obliterated central canal of the spinal cord, the filum terminale and white matter adjacent to a ventricular surface. Forty percent of ependymomal tumours are supratentorial; all the others are infratentorial, mostly in the fourth ventricle. Ependymoma (both differentiated and anaplastic) accounts for almost 9% of brain tumours in children under 10 years old; however, it subsequently represents less than 3% in all decades except the third, where it accounts for 4.3%. Embryonal tumours (i.e. germinoma, mixed embryonal pinealomas and malignant teratomas) usually occur in the first two decades, with a low frequency of approximately 1% of brain tumours.

Survival rates for ependymomas depend on pathological grading. They are high for supratentorial low-grade tumours (87% at 5 years), while high-grade tumours are associated with a much poorer outcome [14].

Medulloblastoma

Medulloblastoma belongs to the group of primitive neuro-ectodermal tumours that share local invasiveness, subarachnoid dissemination and extraneural metastases. It is one of the most common malignancies of childhood and accounts for 20%–30% of brain tumours in children. Medulloblastoma has the highest risk of poor prognosis compared with astrocytoma [15]. Medulloblastoma has a frequency which decreases from 21% of all brain tumours in the first decade to 10% in the second and then keeps approximately halving every decade. The 5-year disease-free survival for medulloblastoma is approximately 50% [16].

Other primary brain tumours

Choroid plexus papilloma and carcinoma

Choroid plexus papilloma and choroid plexus carcinoma are rare tumours of which almost half occur under 12 years of age. In children, they are commonly located in the lateral ventricles as opposed to the fourth ventricle, which is a more frequent location in adults. Because papillomas tend to grow slowly within ventricles, they expand to fill the ventricle and block CSF flow. When a complete surgical resection can be achieved, the prognosis of choroid plexus papilloma is good; however, choroid plexus carcinoma still has an extremely poor prognosis [17].

Pituitary adenoma

Pituitary adenoma can cause anterior pituitary hormonal imbalance, structural problems related to invasion of surrounding structures or syndromes of hormone excess. These tumours can be classified according to size and invasive characteristics or according to hormonal secretion based upon hormone measurements in serum. Life expectancy following successful surgery is not significantly different from that in normal subjects.

Acoustic schwannoma

Also called acoustic neuroma, acoustic schwannoma is composed of myelin-forming Schwann cells that cover the acoustic nerve fibres. Schwann cells normally replace oligodendroglia as the nerve leaves the brain stem to enter the internal auditory meatus. These tumours are slow-growing masses that compress rather than invade normal tissue.

Meningioma

Meningiomas arise from arachnoidal cells in the meninges, especially in areas of arachnoid villi, mostly along the sagittal sinus and over the cerebral convexity. Histologically, most of these tumours are differentiated, with low proliferative capacity and limited invasiveness. Therefore overall 90% of meningiomas are benign, 6% atypical and 2%–4% malignant. The malignant cases are represented by those meningiomas which are more anaplastic with a higher proliferative capacity and therefore

are invasive. The incidence of meningiomas presents a peak at the age of 40 and a second increase after the sixth decade. They occur more frequently in women with breast cancer, and some meningiomas contain oestrogen and progesterone receptors. The symptoms and signs are related to compression of adjacent brain tissue and cranial nerves. Meningiomas may coexist with schwannomas in patients with the central form of neurofibromatosis. Complete surgical resection is usually curative. For incompletely resected or recurrent tumours not previously irradiated, radiotherapy is administered. When all other treatments have failed, immuno-chemotherapy may be considered as an option [18, 19].

CNS lymphoma

Primary lymphoma of CNS is often related to an immunologically compromised situation such as mixed humoral and cellular immune deficits. The tumour may be focal or multicentric in the subcortical white matter, ventricle walls or subarachnoid space. The incidence of CNS lymphoma was very low before the AIDS epidemic, and it occurred mainly in late middle age. Now, however, the frequency of AIDS-associated CNS lymphoma is increasing more and more and the age of occurrence has lowered. Approximately 2% of AIDS patients develop primary intracranial lymphoma. Epstein-Barr virus infection is correlated with a CNS localisation of AIDS-related non-Hodgkin lymphoma [20, 21, 22]. CNS lymphoma has a poor prognosis, with a median survival time not greater than 7 months.

Craniopharyngioma

Craniopharyngiomas arise from remnants of Rathke's pouch, derived from the primitive stomatodeum. Most tumours are suprasellar; only 15% are intrasellar. They cause symptoms related to neuro-endocrine dysfunction or visual compromise. They are not only a condition of childhood, as 45% are diagnosed in patients over 20 years old.

Risk factors and genetic alterations

A higher than expected increase in the incidence of brain tumours has been observed as a result of exposure to environmental chemicals, pesticides, herbicides and fertilisers, occupational involvement in the petrochemical industry and other professional risks [23, 24, 25, 26, 27, 28]. The risk of developing a brain tumour is elevated following use of ionising radiation for treatment of cancer in children. In children treated for a first cancer, a significant association was found between brain tumour risk and alkylating agent dose in relation to the compounds used (bleomycin and chlorampimophen) [29]. Recently, the possible association between brain tumours and exposure to magnetic field or non-ionising radiation has elicited public concern, but studies on this topics have not been able to confirm a clear connection [30, 31].

Moreover, some tumours seem to be related to the presence of viruses, gene mutations or familial diseases that accelerate the progression of molecular alterations. A possible relationship with prior exposure to polio vaccine contaminated with simian virus 40 (SV40) has been hypothesised for medulloblastoma. The occurrence of retinoblastoma appears to be related to a somatic recessive disorder associated with mutation in chromosome 13 (RB1 locus). Familial diseases including von Hippel-Lindau syndrome, tuberous sclerosis and von Recklinghausen's neurofibromatosis are apparently associated with the occurrence of haemangioblastoma, astrocytomas and acoustic neuromas, respectively. Recent studies have reported the presence of genetic abnormalities that implicate oncogenes and tumour suppressor genes (growth factor receptor gene, *p53*, *Ras*, c-*myc*, c-*erB*-1 *Nm23*, c-*myc*, c-*fos*) in the development of neurological tumours [32, 33, 34, 35]. It has been reported that the progression of gliomas to more malignant phenotypes involves numerous molecular genetic alterations. These genes control different cellular functions such as differentiation, signal transduction, cell cycle progression and angiogenesis, and these processes can be involved in the neoplastic transformation [11].

Clinical manifestations and evolution of brain tumours

Brain cancer is lethal when the tumour and its associated oedema reach the total mass of approximately 100 g. However, brain tumours already produce neurological symptoms at a size of 30–60 g. Most clinical manifestations of tumours located in the brain parenchyma are due to the "mass effect" of the growing tumour and the consequence of non-specific events such as increased intracranial pressure, oedema, shift and destruction of surrounding brain tissue. These events in turn cause further non-specific effects such as herniation syndromes, progressive alterations of mentation and personality, headache and seizures. Some focal symptoms that depend on the tumour location and result from the destruction of brain tissue may help in the diagnosis; these include focal seizures, mental changes, visual disturbances, speech abnormalities, motor weakness, sensory disturbances, cranial nerve signs and gait abnormalities. Intraventricular tumours often cause increased intracranial pressure and eventually headache, nausea, vomiting, papilloedema, ataxia and hydrocephalus. As regards intratumoural haemorrhage, the primary tumours that most commonly bleed de novo are glioblastomas and oligodendroglio-

mas; of the metastatic tumours, those from the lung and melanoma are most likely to be associated with intratumoural haemorrhage.

Methods and principles of anatomical imaging of brain tumours

Over the past two decades X-ray CT has represented the gold standard among the investigative tools available to neuroradiologists. CT has made it possible to ascertain the presence of brain lesions and to define their dimensions, their morphology (including a solid or cystic appearance), whether they are single or multiple, the presence of perilesional oedema, the precise mass location and the relationships with surrounding anatomical structures. Further information can be derived from the use of CT contrast agents. Most tumours show contrast enhancement. This abnormal accumulation of contrast results primarily from leakage of contrast into the tumour interstitium because of the absence of a blood-brain barrier within the tumour neovascularity. The region of contrast enhancement corresponds well with the main tumour mass. However, malignant tumour cells are commonly found beyond the enhanced portion of the tumour, particularly in gliomas. The type of enhancement can help in differentiating among lesions.

Contrast-enhanced CT is still routinely used for the screening and follow-up of neoplasms. Cerebral multiple metastases, meningeal carcinomatosis, typical meningiomas and epidermoids can be diagnosed without further examinations. The ability to of CT to depict bone structures is valuable in defining bone destruction or sclerosis associated with metastatic tumours, pituitary adenomas, meningiomas or adjacent carcinomas from the sinuses or pharynx, and in studying lesions with calcific components or localised close to bone structures.

Angiography has largely lost its diagnostic role in the work-up of brain tumours, the exception being lesions characterised by an abnormal vascular structure, such as haemangioblastomas or meningiomas. This technique actually has a complementary role in the presurgical assessment of neoplasms, providing information on the relationships between tumour and vessels. Angiography is still relevant in the therapeutic phase of embolisation of meningiomas or base of the skull tumours or when administering intra-arterial chemotherapy for gliomas.

Continuous developments in magnetic resonance (MR) provide new insights into the diagnosis, classification and understanding of the biology of brain tumours. MRI offers several advantages as compared to CT. First, it offers higher contrast resolution associated with multiplanarity and the lower occurrence of artefacts. This in turn permits excellent resolution of brain regions that are poorly assessed by CT, such as the infratentorial, sellar, temporal and meningeal regions. Such studies are characterised by high sensitivity for structural alterations caused by tumoural growth, and visualisation of such alterations can be further enhanced by the use of paramagnetic contrast agents. Thanks to its high spatial definition, more accurate anatomical depiction and easy three-dimensional (3-D) imaging, MRI is the best choice for the diagnosis of endocranial tumours. MRI is particularly accurate in establishing the intra- or extra-axial origin of tumours; with better definition it is possible to detect indirect signs (cortical dislocation, compression of sulci and cisterns, presence of cleavage plane for extrinsic lesions) and to evaluate direct signs of neoplasms.

MRI is more suitable than CT in the identification of gliomas, low-grade astrocytomas, brain stem gliomas, pineal region tumours, third ventricle and hypothalamic neoplasms, lymphomas, craniopharyngiomas, epidermoids and teratomas. Even though CT can better identify bone modifications, MRI is superior in defining skull base tumours. The advantages of MRI include its ability to visualise pituitary, clival and pontocerebellar lesions that are not readily detectable with CT because bone artefacts diminish its resolution.

The use of 3-D acquisition and reconstruction is not limited to diagnosis: it is also useful for presurgical planning, stereotactic procedures and radiotherapy.

The routine use of angio-MR offers the possibility of completing a standard brain MR study by adding information on the relationships between tumour and vessels (encasement, venous compressions, etc.). The demonstration of small-diameter vessels is still poor, with consequent poor definition of tumoural angiogenesis, but technical improvements will soon widen the scope of angio-MR.

All these tools have led to significant improvements in the clinical management of brain neoplasms by usually enabling the neuroradiologist to provide answers to the most common questions regarding brain tumour diagnosis: Is there a tumour? Where is it located and which complications result from its presence? Which type of tumour is it, and what is its grade?

Clinical application of anatomical imaging

Detection is the first diagnostic step in patients with symptoms and signs suggesting the presence of a brain tumour. Imaging is primarily done to prove or rule out the presence of such a lesion. To this end, both direct and indirect signs are sought.

Direct signs of brain tumours

A direct sign of a brain tumour is an area with a density (CT) or signal (MRI) different from that of normal cerebral tissue, including changes secondary to contrast media infusion. Such changes in density or signal occur secondary to the structural features of neoplasms. Three main variables differentiate tumours from normal tissue:

water content, regressive events and vascular architecture. Most types of brain tumour typically exhibit an increased water content due to the increased cellularity. Cellularity also influences the degree of water content. Changes are more pronounced in those lesions having a low nucleus/cytoplasm ratio (e.g. astrocytoma) than in lesions with a high nucleus/cytoplasm ratio (e.g. medulloblastoma). Another factor responsible for the increased water content in neoplasms is the high quantity of interstitial fluids, that is, the cytotoxic intratumoural oedema. Differences in water content determine CT hypodensity and the increase in T1 and T2 relaxation times on MRI (T1 hypointensity and T2 hyperintensity).

Regressive events include the presence of cysts, necrotic and haemorrhagic areas, calcifications and fatty degenerative areas. The cystic appearance of some neoplasms has long been utilised as an aid to differential diagnosis. Preoperative delineation of cysts is also helpful to the neurosurgeon when planning the surgical approach. Intratumoural cysts are secondary to focal mucoid degeneration, and further enlargement of the cavity occurs due to fluid transudation from cyst walls. Large cysts are commonly found in low-grade lesions (pilocytic astrocytoma, haemangioblastoma, ganglioglioma, pleomorphic xantho-astrocytoma, ependymomas, craniopharyngiomas, pituitary adenoma, acoustic neurinoma, meningioma). Cysts can be filled by pure water, or contain considerable amounts of protein or other debris deriving from prior haemorrhage. A homogeneous content is a common finding in large cysts; in some cases, cysts and solid tumours display similar imaging characteristics and cannot be differentiated. The characteristics of the fluid contained in the cysts influence the MR signal characteristics. If the water is pure and does not contain proteins, the fluid in the cyst will have the same signal as cerebrospinal fluid (CSF). When the protein content increases, protons become bound in a hydration layer adjacent to the protein, significantly decreasing the T1 relaxation time of the water solution, with a final increase in the signal intensity on both T1 and T2 images. The most benign tumours commonly show cystic fluid with an intensity near to that of CSF. On CT scans, cysts are characterised by a low density, similar to that of CSF. Higher protein density is reflected in greater CT density and may lead to simulation of a solid tumour.

Necrotic areas are due to ischaemic cell damage or intralesional haemorrhagic events that result in the formation of pseudocystic areas. Both the discrepancy between tumoural growth and blood supply and microvessel thrombosis due to wall infiltration or hyalinosis can cause intralesional ischaemia. On CT and MRI, the density and signal characteristics can be similar to those of true cysts. Morphological criteria, including an irregular shape of cavities, with indented borders and heterogeneous content, may suggest the necrotic origin of the cyst. In general, lesions containing areas of necrosis are more likely to be malignant.

A large haemorrhage originating from a tumour is a relatively uncommon event (1% in neuro-epithelial lesions), and when it occurs, it is usually very difficult to immediately identify a tumour as the cause. However, small haemorrhages are frequently seen within tumours. Certain primary intracranial neoplasms (e.g. glioblastoma, ependymoma and oligodendroglioma) and metastases from various tumours (e.g. melanoma, lung carcinoma, renal cell carcinoma, choriocarcinoma) demonstrate a characteristic tendency to bleed, and this behaviour can be useful for the diagnosis. This implies that it is necessary to use methods that are sensitive and specific for the detection of haemorrhage. Both CT and MRI are useful to depict the presence of haemorrhage, but the ability of CT to define its aetiology is very poor. On MR images it is possible to distinguish between the signal intensity pattern of intratumoural haemorrhage and that of benign intracranial haematomas [36]. The signal intensity is heterogeneous in the former, with concurrent areas of oedema and haemorrhage [36]. Furthermore, the evolution of blood within tumour tissue may be slow, as compared to the evolution of benign haematomas. These delayed changes are probably related to the hypoxic state typical of human neoplasms [37], or to repeated episodes of bleeding [38]. Another finding that helps to differentiate intratumoural bleeding from benign haematomas is the reduction or irregularity of the hemosiderin halo that can usually be found at the periphery of chronic benign intracranial haematomas [36]. The presence of non-haemorrhagic tumour tissue inside the lesion represents a clear sign of neoplasm. Lastly, the presence on long TR images of high-intensity signal in the parenchyma surrounding tumoural haemorrhage [36] requires follow-up by MRI or a biopsy [39]. In the presence of any of these signs the haemorrhagic event can be due to a benign cause, such as an occult cerebrovascular malformation; however, a work-up must be performed to exclude a tumour [39].

The presence of calcifications in brain tumours is common and is of diagnostic relevance. Tumours that commonly undergo some calcification include meningioma, craniopharyngioma, oligodendroglioma, astrocytoma, ependymoma, choroid plexus papilloma, ganglioneuroma, dysgerminoma, chordoma and all tumours after irradiation. Calcification patterns vary from punctate to diffuse, and calcifications are best seen on CT as high-density areas. Calcium produces a void signal on MRI, and calcifications are thus difficult to identify by this technique.

Areas of fatty degeneration occur secondary to macrophagic phagocytosis in necrotic areas (most common in glioblastomas). They are seen as hypodense lipidic areas on CT and with a marked reduction in relaxation time, especially T1, on MRI.

An abnormal vascular architecture is a feature of most tumours. Tumours stimulate the formation of capillaries within the tumoural tissue and sometimes in the adjacent

areas. Tumour capillaries in gliomas may have near-normal features with a functioning blood-brain barrier, so these areas of tumour tissue will not enhance with contrast [39]. On the other hand, in other, often more malignant gliomas, formation of capillaries with fenestrated endothelia is stimulated, and therefore the blood-brain barrier is absent: theoretically, these tumours should enhance [39, 40]. Metastases are characterised by non-CNS capillaries similar to their tissue of origin; this is why intense enhancement is the rule in metastatic lesions. Extra-axial tumours, like meningiomas, arise from tissue whose capillaries lack tight junctions, and, consequently, these tumours present with contrast enhancement [39].

Tumour vascularisation can be seen without contrast infusion as an increase in tumour density on CT and directly as void images on MRI. After injection of contrast medium, the modification of density and signal are due to: (a) neovascularisation of the tumour itself, which results in the presence of contrast medium inside the tumour, and (b) the presence at the blood-brain barrier interface of tumour capillaries lacking some of the features of normal vessels.

Contrast enhancement is seen as a hyperdense area on CT scans and as a hyperintense area on T1-weighted MRI. The region of contrast enhancement corresponds well with the main tumour mass. However, malignant tumour cells are commonly found beyond the enhanced portion of the tumour, particularly with gliomas. It is usually said that in the case of glial tumours, enhancement correlates with tumour grade (degree of malignancy). In general this is true, but it is important to remember that some benign astroglial lesions demonstrate strong enhancement (e.g. pilocytic astrocytoma, haemangioblastoma, pleomorphic xantho-astrocytoma and subependymal giant cell astrocytoma).

Indirect signs of brain tumours

Mass effect, oedema and bone modifications are all indirect signs that can help in brain tumour detection. In the brain, the mass effect due to the growth of a structure normally absent is particularly relevant. This is because in the adult the cranial cavity has a fixed volume, and the three elements contained therein – the brain (1,400 ml), CSF (150 ml) and blood (150 ml) – are relatively incompressible. The total bulk of the three elements is constant, and any increase in the volume of one of them must occur concurrently with a decrease in one or both of the others. As a tumour grows in one part of the brain, it compresses and destroys brain tissue and displaces CSF and blood. Intracranial pressure rises when the limits of this accommodation are reached. The rate of tumoural growth is fundamental in determining the evolution. When a lesion expands slowly, it causes displacement of the brain without an early increase in intracranial pressure. The age-related compensatory capacity is greater in aged individuals with atrophy and increased CSF spaces. In infants the skull may expand. Tumoural growth leads to a compression of the venules in the cerebral tissue adjacent to the tumour, with a secondary increase in capillary pressure that is more relevant in cerebral white matter. Proteases released by tumoural cells increase the permeability of the blood-brain barrier to proteins and contribute to the vasogenic oedema. Protease activity generates small protein fragments that exert osmotic effects, diffusing through the white matter. The result is localised cerebral oedema in the region surrounding the tumour.

The fluid in the extracellular space has a high content of plasma protein and tends to distribute in the white matter, extending from adjacent grey matter. The particular vulnerability of white matter to vasogenic oedema is not well understood. Probably it is related to its loose structural organisation, which offer less resistance to fluid under pressure than does the grey matter. It has also been hypothesised that it may be related to the morphological characteristics of the white matter capillaries.

Regional oedema causes displacement and herniation, allowing other vascular and pressure factors to come into play; respiratory impairment and hypotension contribute to the occurrence of cytotoxic oedema.

Brain oedema may occur with both intracerebral and extracerebral tumours, although extracerebral tumours (e.g. meningioma) tend to produce less oedema. Oedema is particularly frequent and severe with metastases.

From the densitometric point of view, oedema appears as an hypodense area (due to increased water content) located in the white matter, with finger-like borders following the white-grey matter junctions. On MRI, oedema causes lengthening of T1 and T2 relaxation times, with resultant hypointensity on T1-weighted images and hyperintensity on T2-weighted images. These signal features are very similar to those shown by most tumours, and distinction between lesional borders and oedematous normal tissue is difficult.

Mass effect and oedema cause brain displacement and herniations. The cranial cavity is subdivided into several compartments by sheets of relatively rigid dura (the falx cerebri, which divides the supratentorial space into right and left halves, and the tentorium, which separates the cerebellum from the occipital lobes). The pressure from a mass within any compartment, therefore, is not evenly distributed but causes shifts or herniations of brain tissue from one compartment where the pressure is high to another where it is lower. The most common types of brain herniation include subfalcial herniation (shifting of the brain across the midline underneath the rigid falx due to unilateral hemispheric or extracerebral lesions), temporal lobe descending transtentorial herniation due to unilateral or bilateral supratentorial mass lesions, transtentorial ascending herniations resulting from infratentorial lesions (very rare), and tonsillar trans-foraminal herniation secondary to posterior fossa tumours (common).

Bony modification due to the growth of lesions that are in close relationship with cranial walls, cavities, foramina and channels of the skull base are less common, and less relevant from the diagnostic point of view.

By combining direct and indirect signs obtained from CT and MRI it is possible to detect a brain tumour in 95%–100% of cases. In particular, if standard imaging sequences are used along with intravenous contrast enhancement, brain tumour detection is achieved with almost 100% accuracy by MRI. In recent years, new magnetisation transfer techniques have improved the contrast and increased the diagnostic yield by suppressing the background signal of brain tissue, thus highlighting enhancing lesions [41]. The advantage of the T1 effect in achieving a particularly high contrast between tumour and background tissue has been successfully used in contrast-enhanced fast FLAIR MRI [42].

Differentiation of intra-axial and extra-axial lesions

Differentiation between intra-axial and extra-axial lesions is crucial as the distinction permits separation of large tumour categories [43]. In some cases this distinction may appear extremely difficult. This is particularly true with superficially located lesions deriving from meningeal sheets or from brain tissue (malignant meningiomas, calvarial or dural metastases, primary brain tumours growing exophytically). Nonetheless, imaging features can help to make this distinction in most cases. Key features that help to identify an intra-axial lesion include gyral expansion, thinning or effacement of the adjacent extra-axial subarachnoid space and peripheral displacement of blood vessels along the pial surface of the brain (best seen on enhanced images) [43]. Imaging features more characteristic of extra-axial, intradural lesions include central displacement of both the grey-white junction and the blood vessels along the pial surface, peripheral displacement of the hypointense dura mater, expansion of the ipsilateral subarachnoid space at the edge of the lesion and a thin rim of CSF between the mass and the underlying brain parenchyma [43]. Extradural lesions show a similar behaviour but they usually displace the dural sheet centrally. The presence of oedema is not sufficient to exclude extra-axial lesions as in some cases meningiomas can give rise to extensive vasogenic oedema in the brain parenchyma.

Supratentorial versus infratentorial location

It is very important to determine the infra- or supratentorial location of a lesion as this is indicative of different tumoural types. In the adult population, malignant gliomas and metastases are the most common intra-axial supratentorial tumours. Metastases and haemangioblastomas are frequent intra-axial lesions located in the posterior fossa. An extra-axial supratentorial lesion is more likely to be a meningioma, whereas an extra-axial lesion in the posterior fossa is most probably a schwannoma. Recognition of the tentorium (easily seen on sagittal or coronal planes on MRI) allows the distinction between the two intracranial compartments.

Due to its direct multiplanar capability, MRI permits more reliable distinction between intra-axial and extra-axial lesions, better localisation of a lesion in the three-dimensional space of the brain and better identification of structures involved by a tumour. Determining a functional anatomical location of a tumour is of paramount importance in the presurgical planning. Functional MRI, which is based on the blood oxygen level-dependent contrast, is becoming important in the non-invasive localisation of “eloquent” areas of the cortex before tumour excision. Surgical planning is optimised in this way, making surgery safer and more effective [44, 45]. The safety of tumour surgery is also increased by neuronavigation, in which preoperatively acquired 3D MR data are used interactively to precisely localise the tumour during surgery and even to steer the instruments and the operating microscope [45]. The complex three-dimensional anatomical features of the brain and its vulnerability to surgical intervention can be monitored using intraoperative MRI, which provides real-time guidance, allowing localisation of intracranial tumours and their margins and facilitating continuous assessment of the surgical process [46].

Assessment of tumour type and grade

The last step in the neuroradiological work-up of brain tumours is the assessment of tumour type and grade. Although it is often impossible to reach a final diagnosis on the basis of historical information and neuroradiological imaging, it is very important to develop a reasonable list of potential diagnoses. There are many factors that can be considered to narrow the possible diagnoses, including (a) factors dependent on the scanner, e.g. signal resolution; (b) factors dependent on the patient, e.g. age, sex and clinical history; (c) factors dependent on the lesion appearance, e.g. dimension, margins, location and whether lesions are single or multiple; (d) the presence and shape of oedema; (e) the presence of cystic, necrotic, lipidic or haemorrhagic areas; and (f) the presence and pattern of enhancement. All these factors can help to predict tumour type and tumoural grading. The most significant features of common brain tumours are reported in Table 2.

Despite the enormous development of MRI, significant issues remains unsolved. One of the major problems is the lack of specificity of the MR signal, which often does not permit differential diagnosis among different histological lesions. In fact, despite the large number of studies regarding the T1 and T2 relaxation times of neo-

Table 2. Neuroradiological findings in primary brain tumours

Tumour	CT	MR, T1/T2	Enhancement	Cysts	Calcifications	Necrosis/ vessels	Haemorrhage	Oedema	Mass effect
Pilocytic astrocytoma	Iso-hypodense	Iso-hypo/hyperintense	Yes	Yes				Minimal	Yes
Low-grade astrocytoma	Hypodense	Hypo/hyperintense	No	Rare	Common			Minimal	Minimal
Anaplastic astrocytoma	Hypo-hyperdense	Hypo/hyperintense	Yes	Rare	Rare			Yes	Yes
Glioblastoma	Hyper-hypodenss	Hypo/hyperintense	Yes, ring-like	Yes		Yes	Common	Yes	Yes
Oligodendroglioma	Hypodense	Hypo/hyperintense	Minimal	Yes	Yes		Yes	Little	Yes
Ependymoma	Hypodense	Hypo/hyperintense	Yes	Yes	Common	No/common	Common	Yes	Yes
Medulloblastoma	Iso-hyperdense	Hypo/iso-hyperintense	Moderate	Rare	Rare	Common	Common	Moderate	Yes
Haemangioblastoma	Isodense	Iso-hypo/hyperintense	Intense	Yes	Rare	Rare/yes	Common	Moderate	Moderate
Lymphoma	Hyperdense	Iso-hypo/iso-hyperintense	Yes					Minimal	
Ganglioglioma	Iso-hypodense	Iso-hypo/hyperintense	Moderate	Yes	Common				
PNETs	Hypodense	Hypo/hyperintense	Rare	Yes	Common				
Neurocytoma	Hyperdense	Iso/iso-hyperintense	Variable	Yes	Yes		Rare		
Meningioma	Iso-hyperdense	Iso-hypo/iso-hyperintense	Intense	Rare	Yes			Common	Yes
Schwannoma	Isodense	Hypo/hyperintense	Intense	Yes					Yes
Pituitary adenoma	Iso-hyperdense	Iso-hypo/iso-hyperintense	Moderate	Rare	Rare		Rare		Yes
Craniopharyngioma	Heterogeneous	Iso-hyper/hyperintense	Yes	Yes	Yes				Yes
Epidermoid	Hypodense	CSF-like; hyperintense on proton density images	No	Yes					Yes
Dermoid	Hypodense	Hyper/hypointense	No	Yes	Yes				Yes
Colloid cyst	Hyper-isodense	Hypo-hyper/hypo-hyperintense	Rare	Yes			Rare		Yes
Metastases	Hypo-hyperdense	Hypo/hyperintense	Yes			Yes	Common	Large	Yes

PNETs, Primitive neuro-ectodermal tumours

plasms and correlation of signal intensities with morphological characteristics, the problem of histological specificity is still unresolved. Thus, a lot of effort has focussed on the development of further MR-based techniques like diffusion and perfusion imaging, and spectroscopy studies potentially able to add information.

The implementation of echo planar imaging sequences on clinical MR scanners has allowed the rapid acquisition of images with new types of contrast mechanisms [47]. One possibility that is beginning to be investigated in association with brain tumours is the use of diffusion-weighted MRI. With this technique, magnetic field gradients are applied before and after the 180_i pulse in spin-echo imaging sequences. The reversal of spins by the 180_i pulse means that these gradients do not contribute any net phase shift for static spins, whereas protons that are diffusing in the medium undergo a loss of phase coherence that is detected as a loss of MR signal amplitude [47]. Spins with higher diffusion rates generally produce a greater loss of phase coherence and a lesser MR signal than those with slower diffusion rates [47]. The apparent diffusion coefficient (ADC) reflects physical factors, such as temperature and viscosity, in addition to the restricted motion of the molecules resulting from the presence of semipermeable tissues and membranes. Differences in ADC are expected to reflect changes in cellularity, cell membrane permeability, intracellular and extracellular diffusion, and tissue structure [47]. Preliminary studies in brain tumours have typically shown low anisotropy in abnormal regions, which reflects the loss of normal tissue structure, with an increased ADC in necrosis, oedema and cysts relative to normal-appearing white matter. There have been reports that the ADC of regions of tumour is correlated with cellularity, with a tendency towards lower ADC values in high-grade as compared with low-grade gliomas [48]. The minimum ADC value in patients with tumours tends to be higher in regions of low anisotropy than in regions of normal tissue anisotropy. This parameter may be important in the effort to distinguish regions of oedema from non-enhancing tumour [47]. Moreover, diffusion-weighted MRI can be successfully used to differentiate between extra-axial cysts and epidermoid tumours [49].

Another application of echo planar imaging is in the estimation of parameters that reflect tissue vascularisation [47]. This is achieved by acquiring multiple repeat images during the first pass of a bolus of MR contrast agent. Changes in signal intensity of such dynamic data may be used to calculate an image of the regional cerebral blood volume (rCBV) [47]. Although the detailed mechanisms underlying perfusion and vascular contrast MR imaging are under investigation, the potential of the technique to provide useful information in patients with brain tumours is clear [47]. Neovascularisation has been shown to be an important factor in the regulation and malignant potential of many tumours [50], and an increasing number of new therapies that specifically target angiogenesis make the application of this technique to brain tumours of particular interest [47]. With this methodology, necrosis may be differentiated from tumour by virtue of its low rCBV relative to normal-appearing white matter in the contralateral hemisphere. The differentiation between viable tumour and adjacent grey matter is more difficult because these tissues may appear isointense on rCBV images [47]. A study of glioma patients suggested a positive correlation between rCBV and tumour grade [51]. The potential for use of rCBV imaging to define the radiation target and monitor therapeutic success was demonstrated in a study of eight glioma patients investigated three to four times serially [52]. This study showed similar results for rCBV data and positron emission tomography (PET) scans obtained at the same time points. In a more recent study the authors state that dynamic susceptibility contrast MRI is more useful for grading glioma than conventional MRI and that it can also provide supplementary information that facilitates differentiation between malignant lymphoma and glioma. The absence of tumour neovascularisation in malignant lymphoma leads to a low rCBV, which is in contrast to findings in malignant gliomas. Moreover, this technique can be used to differentiate between extra-axial tumours, e.g. between meningioma and neurinoma [53].

Biochemical assessment of brain tumours

In the early 1970s, before CT had an established role in medicine, the aim of nuclear medicine studies was to image a tumour which was suspected on a clinical basis. Nowadays, such a demand is easily answered by CT and/or MRI, but great effort has been spent on the characterisation of brain lesions beyond what is possible using simple imaging. Intracellular biochemical processes can be measured and visualised with nuclear medicine techniques. More recently, MR spectroscopic procedures have been proposed to quantify cerebral metabolites with clinical relevance.

Radionuclide imaging

The tracers

2-[^{18}F]Fluoro-2-deoxy-d-glucose (FDG). Tumour glycolysis can be assessed with 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG), which differs from glucose only in the replacement of the hydroxyl group on the second carbon atom by radioactive fluorine. Glucose and FDG share the same saturable carriers between blood and tissue, and FDG competes with glucose for hexokinase. FDG-6-P is trapped in cells in proportion to the glucose metabolic rate, and its accumulation can be detected by PET. By fitting the data of FDG accumulation under a region of

interest in a dynamic study, three constants may be derived which represent the glucose transport from blood to brain, the reverse transport from brain to blood and the phosphorylation of glucose. FDG is the most important tracer for PET oncological studies: its relatively simple synthesis and long half-life along with extensive knowledge of the mechanisms determining its uptake and retention have made it quite popular in neuro-oncology. It is well established that brain neoplasms present changes in glucose utilisation in comparison with normal tissue. In vitro tumour cells have a high rate of glucose degradation into lactic acid even in the presence of oxygen [54]. With this tracer, changes in the oxidative metabolism were first demonstrated in vivo in brain neoplasms [55, 56].

Alterations of glucose transport to experimental cancer cells have been demonstrated and related both to an increased metabolism and to an increased number of existing glucose transporters [57]. Activation of the gene coding for the synthesis of glucose transporter GLUT1 is a major early marker of malignant transformation. An over-expression of GLUT1 and GLUT3 has been observed in several tumour types, including brain tumours [58], and this may explain the raised level of glucose extraction demonstrated with PET [59].

In both experimental and human gliomas it was demonstrated that even in the presence of a normal unidirectional glucose influx into tumour cells, the glucose metabolism was doubled in comparison with normal grey matter, and that there was an uncoupling between glucose transport and phosphorylation [60, 61].

The FDG uptake into malignant cells is therefore the consequence of both increased expression of glucose transporter molecules and glycolysis. Quantitative assessment of glucose metabolism with PET in human brain neoplasms is considered to be highly reproducible [62] but cumbersome. The use of semiquantitative methods such as the standardised uptake value (SUV) has become popular for analysis of tumour activity in sites other than brain. However, some doubts have been raised as to the usefulness of quantitation or even semiquantitation in a clinical setting, where simple visual assessment of tracer accumulation by an experienced reader or measurement of the radioactivity distribution ratio between tumour and contralateral normal brain has been found to be sufficient in most cases. The latter methods remain the most common means of FDG-PET analysis in brain tumours [63, 64].

Oxygen-15. Oxygen-15 is a short-lived positron-emitting isotope that can be used to measure haemodynamic parameters. Using mathematical modelling techniques, functional images of cerebral blood flow (CBF), oxygen extraction (OER), oxygen metabolic rate ($rCMRO_2$) and regional blood volume (CBV) can be derived from the combination of sequential studies with $^{15}O_2$, $C^{15}O_2$ and $C^{15}O$. Blood flow in tumours is variable while oxygen metabolism has been found to be depressed in patients with gliomas, in keeping with the relatively anaerobic energy metabolism. The low OER implies that the tumour is not ischaemic and that perfusion is sufficient to meet the metabolic need for oxygen in brain tumours before the initiation of any therapy [65, 66].

Labelled amino acids. Imaging with radiolabelled amino acids visualises protein synthesis and amino acid transport phenomena, which are accelerated in tumours [67]. Because the uptake of amino acids in macrophages and other inflammatory cells is low, these tracers might be more tumour specific than FDG. Methionine and other large neutral amino acids, e.g. phenylalanine, leucine, tyrosine, isoleucine, valine, tryptophan and histidine, are normally supplied to the brain from systemic protein breakdown and diet. A transport system in the blood-brain barrier mediates the transcapillary movement of structurally related amino acids that compete with each other for entry into the brain, which occurs at a rate of approximately 3–10 nmol/g per minute. Use of carbon-11 methionine avoids many of the problems related to the tumour/non-tumour uptake ratio that are encountered with FDG and overcomes the difficulty in differentiating tumours from other cerebral pathologies that may cause abnormal FDG uptake, i.e. infections, radiation necrosis and oedema [68]. In tumours without obvious breakdown of the blood-brain barrier, a stereospecific process with similar properties as in the normal brain tissue is responsible for the accumulation of labelled methionine [69].

Amino acid uptake, evaluated by administration of ^{11}C-labelled L-methionine, has been found to be different in tumours compared with normal brain tissue [69, 70, 71].

^{11}C-methionine allows earlier and more accurate delineation of tumour extension than does anatomical imaging [72, 73, 74] and has been proven to be better than FDG in delineating low-grade gliomas [75, 76]. ^{11}C-methionine enters several biochemical pathways; therefore modelling of its kinetics in brain tumour tissue presents even more difficulties that those deriving from the heterogeneous features of tumour masses. Non-specific uptake has been reported in non-neoplastic lesions, including haematomas and abscesses, while the administration of branched chain amino acids inhibits the accumulation of methionine in brain tumours without severe disruption of the blood-brain barrier, as in normal brain tissue [69]. The use of ^{11}C-methionine is justified by its relatively simple synthesis and its rapid uptake in tumours and clearance from blood and other tissues.

Other amino acids used for brain tumour imaging are tyrosine, thymidine, glutamate and phenylalanine and their labelled derivatives. Tyrosine uptake in brain tumours can be assessed with its labelled derivatives: *O*-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET), L-[3-^{18}F]-α-methyltyrosine (FMT) and [^{123}I]iodo-α-methyltyrosine (IMT)

[77, 78]. Also the uptake of tyrosine-labelled derivatives is higher in brain tumours than in normal brain tissue. They are not incorporated into proteins and their distribution patterns parallel that of methionine. Other labelled amino acids for the evaluation of brain tumours include [^{18}F]fluorophenylalanine, which has a marked uptake in oligodendrogliomas [79], and [^{11}C]choline, a tracer that has a higher uptake in glioblastoma cells than in normal brain tissue [80].

Cationic tracers. One important alternative to positron tracers in neuro-oncology is thallium-201 chloride (^{201}Tl), a potassium analogue [81, 82, 83, 84, 85, 86]. That ^{201}Tl accumulates in neoplastic tissue was observed in patients undergoing myocardial perfusion studies with this tracer. In those patients who had tumours, ^{201}Tl uptake was also evident in those extramyocardial areas where the tumours were localised. The mechanism of ^{201}Tl uptake is not completely understood; however, it is thought to be largely dependent upon delivery, i.e. blood flow and blood-brain barrier permeability, cellular metabolism and efficiency of the sodium-potassium ATPase activity. Factors affecting the uptake of ^{201}Tl in brain tumours include tissue viability, tumour type, co-transport system, calcium ion channel system, vascular immaturity with leakage and increased cellular permeability. ^{201}Tl has been shown to accumulate in viable tumour tissue more than in connective tissue, especially in inflammatory cells, and it is barely detectable in necrotic tissue. ^{201}Tl has a much higher affinity for brain tumour than for white and grey matter, as the latter show little or no ^{201}Tl uptake. Disruption of the blood-brain barrier allows for greater ^{201}Tl uptake in tumours; however, in radiation necrosis and resolving haematoma, blood-brain barrier disruption can occur without ^{201}Tl accumulation. The time course of ^{201}Tl uptake in brain tumours depends upon several variables. Early uptake, i.e. within 5 min of tracer injection, depends on regional blood flow, blood volume and permeability of the blood-brain barrier. By contrast, delayed uptake depends on active transport by the membrane pump of the tumour. Sodium-potassium ATPase activity has been shown to account for ten times more ^{201}Tl uptake than tumour blood flow.

Depending on the patient selection process, the sensitivity and specificity of ^{201}Tl in localising brain tumours have been estimated to be about 70% and 80%, respectively [85]. Sensitivity is lower in low-grade gliomas, while specificity is lower in cases with haemorrhagic infarction [87]. Small tumour size and a location in the posterior fossa may further reduce the sensitivity of ^{201}Tl imaging [85]. The highest sensitivity has been observed in glioblastoma multiforme and metastatic lesions. By comparing the uptake of ^{201}Tl in tumours of different histological type [88] it has been demonstrated that the mean retention index (tumour/non-tumour activity) is higher than 0.7 for each type of malignant tumour, whereas it is lower than 0.6 in all benign tumours, except pituitary adenomas. Moreover, it has been shown that the early uptake of ^{201}Tl correlates with contrast enhancement on MRI, except in the case of schwannomas and cavernous haemangiomas. Ricci et al. have reported [86] that the extent of necrosis may affect the uptake of ^{201}Tl when the volume included within the region examined encompasses both necrotic areas and highly malignant tumour tissue. Since necrosis is related to tumour proliferative activity and represents a negative prognostic factor in astrocytoma, a possible underestimation of ^{201}Tl uptake due to intratumoural necrosis must be carefully evaluated. It must be noted that the administration of steroids diminishes the uptake of ^{201}Tl by more than 20% [89].

Another tracer that can be used to image cerebral tumours with SPET is ^{99m}Tc-methoxyisobutylisonitrile (MIBI) [90, 91], which was originally developed for the evaluation of myocardial perfusion. This tracer is a cationic complex that is concentrated in cytoplasm and mitochondria as a result of passive diffusion across highly negative transmembrane potentials in relation to metabolic demand. Entry of ^{99m}Tc-MIBI into cells depends on a combination of charge and lipophilicity. The negative potential on the inner mitochondrial membrane traps the tracer within the organelle matrix [92]. Its retention in the mitochondria is not organ specific, and appears to be a mechanism common to most tissues. Studies with this tracer have shown that its sensitivity for the detection of malignant tumours and recurrences is similar to that of ^{201}Tl. For brain tumours and cerebral metastases, ^{99m}Tc-MIBI has a sensitivity and a specificity of 85%, with a PPV of 97% and an NPV of 53%. The best results are obtained in gliomas (sensitivity 88%, specificity 92%, PPV 98% and NPV 63%), without differences between low- and high-grade tumours [91]. The use of ^{99m}Tc-MIBI for assessment of tumour response to chemotherapy has also been advocated. This proposal is based on the observation that efflux of ^{99m}Tc-MIBI is related to the expression of the multidrug-resistance *MDR1* gene and amplification or increased expression of its product, P-glycoprotein (Pgp), and to the expression of the multidrug resistance-associated protein [93]. Tests in gliomas [94] and paediatric neuroblastomas and ganglioneuromas [95] have suggested that the results of ^{99m}Tc-MIBI imaging may correlate with the presence of functional Pgp in gliomas and neural crest tumours, as has been shown for other tumours. It has also been suggested that ^{99m}Tc-MIBI imaging might be used to assess recurrent gliomas after radiation therapy [90, 91].

^{99m}Tc-tetrofosmin as a lipophilic cationic tracer which shares many of the properties of ^{99m}Tc-MIBI and is extensively used in nuclear cardiology. It has been shown that this tracer has a trapping mechanism which is similar to that of ^{99m}Tc-MIBI, depending on both cell membrane and mitochondrial potentials [96]. Recently it has been suggested that it may be a suitable radiotracer for brain tumour imaging [97].

Labelled antibodies. Imaging modalities based on the use of SPET and monoclonal antibodies have attracted increasing interest, and this is particularly true of those aimed at signal amplification and dose reduction by tumour pretargeting techniques. This is best achieved by the administration of biotinylated monoclonal antibody followed by administration of the radioactive tracer (two-step technique), or by the administration of avidin after the monoclonal antibody, and then tracer administration (three-step technique). The additional steps are aimed at the enhancement of the signal-to-noise ratio by allowing a longer time for antibody localisation on the tumour (two-step technique), and for removal of free antibody by conjugation with avidin (three-step technique), prior to the administration of low doses of radioactive tracer.

These approaches overcome the limitations deriving from the low tumour/non-tumour ratio and high dosimetry when using MoAbs directly labelled with iodine-131. In practice one of the procedures used entails the following three steps: administration of biotinylated BC2 anti-tenascin immunoglobulins; administration of cold avidin at 24 h; administration of ^{99m}Tc-labelled PnAO-biotin after a further 24 h. In glioma patients, Paganelli et al. [98] have shown a correlation between in vitro immunohistochemistry for tenascin and in vivo immunodetection with this pretargeting technique (sensitivity 93%, specificity 75%, accuracy 90%).

Somastatin analogues. Somatostatin receptor imaging in intracranial tumours is usually performed with [^{111}In-DTPA-D-Phe^1]-octreotide or [^{123}I-Tyr^3]-octreotide. Uptake depends upon receptor expression and absence or disruption of the blood-brain barrier. Non-specific uptake is commonly observed in lesions other than tumours.

Somatostatin receptor imaging in intracranial tumours has already been the object of a review summarising 15 studies on a total of 535 patients carried out between 1989 and 1996. The analysis demonstrated the usefulness of somatostatin analogues in meningiomas but not in gliomas; its role in pituitary adenomas is also considered doubtful [99].

Other receptor-bound tracers. The use of tracers which specifically bind to receptors has been applied mostly to pituitary adenomas, in particular in the assessment of non-secreting tumours in the parasellar region, where radiological differential diagnosis may occasionally be difficult. The in vivo characterisation of the biochemical and functional properties of the tissue may provide useful information about the nature of the pituitary mass. PET and SPET have been used for the assessment of adenomas and other parasellar tumours with ^{11}C-deprenyl, ^{11}C- and ^{18}F-labelled spiperone analogues, ^{123}I-IBZM and ^{123}I-epidepride [100, 101, 102, 103, 104, 105]. Some brain tumours show a high density of benzodiazepine receptors compared with normal tissue. ^{11}C-PK11195 is a ligand which binds with high affinity to peripheral benzodiazepine receptors and has been used to image human gliomas [106, 107]. The major biochemical variables that can be assessed by radionuclide techniques, as well as the tracers clinically available for both PET and SPET, are listed in Table 3.

Table 3. Variables assessed with tracers

PET tracers
Glucose metabolism
[^{18}F]fluorodeoxyglucose ([^{18}F]FDG)
Amino acid transport
[^{11}C]methylmethionine ([^{11}C]MET)
[^{18}F]fluoroethyltyrosine ([^{18}F]FET)
[^{18}F]fluorophenylalanine ([^{18}F]FPA)
[^{11}C]choline ([^{11}C]Ch)
Cellular proliferation
[^{18}F]fluorodeoxyuridine
[^{18}F]timidine
SPET tracers
Amino acid transport
[^{123}I]iodo-α-methyltyrosine ([^{123}I]IMT)
Sodium-potassium pump function
Thallium-201 chloride (^{201}Tl)
Transmembrane potential
Technetium-99m methoxyisobutylisonitrile (^{99m}Tc-MIBI)
Somatostatin receptors expression
Indium-111 octreotide (^{111}In-octreotide)
Tumour antigen expression
Technetium-99m labelled monoclonal antibodies (^{99m}Tc-MoAbs)

Clinical applications of radionuclide imaging in brain tumours

Radionuclide imaging can be of value in providing useful information in different stages of the disease process. The clinical applications are summarised in Table 4.

Pre-therapy

Evaluation of the extension of the disease. Initial studies with FDG were able to identify elevated uptake of tracer in brain tumours [108], but it rapidly became apparent that the uptake of FDG is correlated with the grade of malignancy. Thus low-grade gliomas are not easily identified or appear as cold spots surrounded by normal high uptake in the cerebral cortex, which may hinder clear definition of tumour extension. Many studies have demonstrated that ^{11}C-methionine imaging is highly accurate in the detection of brain tumour boundaries both in primary lesions and in recurrences, regardless of their pathologi-

Table 4. Summary of the indications for use of radionuclide imaging of brain tumours

FDG-PET
1. 90% accurate for tumour grading and prognosis.
2. Can be used for grading and monitoring of progression to a higher degree of malignancy, and for differentiating radionecrosis and recurrence. Recurrence may be undetectable due to high glucose consumption in surrounding normal brain tissue.
L-Amino acids PET/SPET
1. Inaccurate for tumour grading and prognosis.
2. Good separation of tumour from surrounding normal brain tissue.
^{201}Tl-SPET
1. Accurate for glioma grading (low uptake in glioma WHO I–II vs high uptake in glioma III–IV, non-Hodgkin's lymphoma, metastases).
2. Poor separation of gliomas I–II from non-tumoural lesions and of gliomas III–IV from meningiomas.
3. Good prediction of malignancy, accurate estimation of therapeutic efficacy, early detection of recurrence and of malignant transformation.
^{99m}Tc-sestamibi
1. Accurate for glioma grading (low uptake in glioma WHO I–II vs high uptake in glioma III–IV, non-Hodgkin's lymphoma, metastases).
2. High positive predictive value but low negative predictive value in tumour relapse after radiotherapy

cal grading [75, 109, 110]. In a large series of gliomas, 35 out of 37 lesions were clearly depicted as hot spots on the ^{11}C-methionine images; by contrast, FDG (45 patients) visualised 23 lesions as hot spots (these were mostly high-grade gliomas) and 18 as hypometabolic lesions, while four were difficult to distinguish from surrounding brain tissue [76]. The reported advantage of ^{11}C-methionine over FDG in delineating gliomas is probably not relevant in CNS lymphoma, where FDG uptake in tumour is much higher than in normal cortex [111].

The limited spatial resolution of the SPET technique may restrict its value in the assessment of the extension of the disease. Nevertheless, attempts have been made to delineate tumour tissue with ^{201}Tl and with ^{123}I-α-methyl-tyrosine, and it has been concluded that ^{123}I-IMT shows greater tumour extension especially in grade III gliomas, while the size of glioblastomas is shown in a comparable manner [112].

Nuclear medicine images usually lack the anatomical information needed to define treatment margins with the accuracy requisite for surgery and radiotherapy planning. Nevertheless, functional brain mapping with $H_2{}^{15}O$-PET associated with ^{11}C-methionine or FDG has been proposed as an effective tool to define higher cortical functions near a brain tumour, with the aim of achieving aggressive resections with a reduced risk of neurological impairment [113]. Similar results have recently been obtained with SPET and ^{99m}Tc-ethyl-cysteinate dimer (ECD), a tracer approved for the assessment of CBF. When this tracer is injected during a motor activation test, it clearly depicts sensorimotor and supplementary motor areas in patients with brain lesions near the central sulcus [114], and this information is relevant in planning as extensive a resection as possible.

Differential diagnosis. A different clinical presentation and CT or MRI usually establish the differential diagnosis between brain tumours and non-malignant lesions. However, this is not the case in AIDS patients as they may present with neurological manifestations characteristic of intracerebral space-occupying lesions, such as hemiparesis, aphasia, apraxia and hemisensory impairment. MRI can demonstrate single or multiple mass lesions with diffuse or ring enhancement in opportunistic infections, but these signs, and the clinical presentation or laboratory studies, are not helpful in differentiating toxoplasmosis or other non-malignant lesions from a primary intracerebral non-Hodgkin's B-cell lymphoma, which occurs in the absence of extracranial disease in approximately 2% of AIDS patients. Thus it is common practice to perform a therapy trial with anti-toxoplasmosis medication [115], which is able to ameliorate symptoms in 70% of patients with toxoplasmosis within a week of treatment and to induce a radiological response within 6 weeks in most of them. Nevertheless, cerebral biopsy is often required for a definitive diagnosis. PET with FDG has been used to differentiate between toxoplasmosis and lymphoma in AIDS patients, as high uptake of FDG is strongly suggestive of a malignant lymphoma, which is an extremely metabolically active tumour, while a relatively hypometabolic lesion is seen in toxoplasmosis [116]. The problem of specificity, however, may limit the usefulness of FDG as a routine method, as inflammatory lesions can accumulate FDG. Other tracers such as ^{201}Tl are better suited for differential diagnosis: focal accumulation of ^{201}Tl at the site of a CT/MRI abnormality strongly suggests lymphoma, while absence of uptake allows exclusion of lymphoma with a high degree of confidence [117, 118, 119].

Presurgical grading. A PET scan with FDG is considered useful in the diagnostic work-up of suspected brain tumours and metastases as it may identify focal hypermetabolic abnormalities. Different studies have related the grade of malignancy of gliomas to the rate of FDG uptake, and shown that while low-grade astrocytomas display low FDG uptake, anaplastic astrocytomas and glioblastomas have markedly elevated uptake [120, 121, 122, 123]. FDG-PET has also been proposed as a useful tool to assess the tumour grade in oligodendrogliomas [124] and gangliogliomas [125].

In some other rare intracranial tumours such as haemangiopericytomas, low uptake of FDG was not correlated with high malignancy [126]. On the other hand, the high uptake of FDG that has been observed in juvenile pilocytic astrocytomas is not an expression of malignancy as these tumours are associated with a relatively good prognosis [127].

Highly significant differences in amino acid uptake were demonstrated between low-grade and high-grade oligodendrogliomas, and in one recent study it was found that ^{11}C-methionine was even better than FDG in grading this type of tumour [128].

Thallium-201 has also been found to be useful for evaluating the histological grade of astrocytomas. In a study comparing these tracers in 23 patients, ^{201}Tl uptake was statistically different both between grades II and III and between grades III and IV, while FDG was negative in all grade II patients, positive in six out of seven grade IV patients, but highly variable in grade III patients [120].

The uptake of ^{99m}Tc-MIBI in brain tumours was first compared with that of ^{201}Tl in 1993 by O'Tuama et al. [129], and it was concluded that the spectrum of avidity is similar for both tracers. Later, the uptake of MIBI was studied in a greater number of patients and it was demonstrated that this tracer is of value in distinguishing low- from high-grade gliomas, and at the same time enables differentiation from other non-malignant lesions such as radiation necrosis, cerebral abscess or ischaemic stroke [130, 131].

Preliminary results with ^{99m}Tc-tetrofosmin indicate that this tracer does not accumulate in low-grade gliomas (grade II), but is taken up avidly by high-grade gliomas and other malignant brain tumours. Uptake in the tumour region correlates well with that of ^{99m}Tc-MIBI, so it has been concluded that ^{99m}Tc-tetrofosmin may also be useful for the non-invasive grading of brain tumours [132].

Guide for biopsy. Frequently, CT and MRI of brain tumours show single or multiple lesions that are heterogeneous in cellular composition, reflecting the combination of active disease, non-specific inflammation, necrosis and oedema. Anaplasia is considered the factor that determines the elevated uptake of glucose, and PET has therefore been proposed as a tool to guide biopsy in the high metabolic area, where it is most likely to provide diagnostic results [133, 134]. More recently, ^{11}C-methionine PET has been applied to guide, in a stereotactic environment, the biopsy of a brain tumour. In comparison with FDG, this tracer has the advantage of offering better detection of non-anaplastic tumour zones and brain regions with infiltrating neoplastic cells [135].

Follow-up

Early assessment of therapy. In the early postoperative period, FDG-PET can be used to differentiate residual tumour from the effect of surgery [136, 137]. It seems clear that a decline in tumoural uptake of FDG weeks or months after therapy is suggestive of a good response to treatment, indicating either a reduced number of viable cells or reduced metabolism of damaged cells [138].

Long-term follow-up. After intensive irradiation or chemotherapy for malignant brain tumours, MRI and CT cannot distinguish tumour progression from radiation injury or necrosis. FDG uptake suggests the presence of viable tumours (at least when high tumour uptake of FDG was noted before therapy), while absence of FDG uptake suggests that necrosis is present [139, 140].

In low-grade gliomas, the natural history of the disease is variable and malignant transformation is difficult to predict. FDG-PET is useful in this context in that detection of areas of increased FDG uptake in histologically proven low-grade gliomas is predictive of malignant transformation [141, 142].

The use of ^{11}C-methionine PET has been evaluated in low-grade gliomas after radiotherapy. It was demonstrated that stable or decreasing uptake of methionine in tumours during follow-up is apparently a favourable sign [143].

Thallium-201 SPET has been utilised to characterise treatment response and to detect recurrence after initial treatment. Patients who showed recurrence presented with high uptake of ^{201}Tl, but this technique failed to diagnose the viability of tumours that were less than 1.5 cm in diameter, owing to the partial volume effect and/or the limited resolution of ^{201}Tl SPET. In order to improve the quality of SPET images, ^{99m}Tc-sestamibi has been applied in the detection of recurrent gliomas after RT; this method is able to identify recurrent gliomas with a higher accuracy than ^{201}Tl [90, 91, 144].

Prognosis. FDG-PET has been used both to predict the survival of untreated patients and to confirm suspected recurrence of a high-grade glioma. All these studies confirmed that FDG may differentiate recurrence from other therapy-related changes. Furthermore, they demonstrated that when recurrence is confirmed, no visible uptake of FDG or uptake lower than adjacent cortical activity is associated with a longer survival than is observed in patients in whom tumour FDG uptake is higher than in the adjacent cortex [139, 145, 146, 147, 148, 149].

Later a relationship between glucose metabolism as assessed by FDG uptake and risk of malignant evolution in low-grade gliomas was demonstrated. It was concluded that in most cases the presence of areas of increased FDG uptake in a histologically proven low-grade glioma predicts an adverse course [142].

Experience with other tracers is limited, but in a quantitative evaluation of ^{11}C-methionine uptake in patients with low-grade gliomas, those patients with a low tumour uptake in the baseline study had a significantly better prognosis than those with a high uptake [143].

Magnetic resonance spectroscopy

MR spectroscopy (MRS) shares with MRI the principle that makes the production of images feasible, namely the principle of nuclear magnetic resonance. MRI is based on signal coming from hydrogen excitation; in image production, spectroscopic separation is not performed. Pixel intensity represents the totality of signals deriving from all chemical forms containing hydrogen, mainly from water hydrogen (signal contributions from nuclei other than hydrogen protons in H_2O are negligible).

In MRS the signal obtained from a single element is further separated into its different chemical forms. This is possible because the effect of a magnetic field on nuclei is not direct: it is shielded by the distribution of the bonding electrons around the nuclei being detected. Therefore, nuclei in different chemical environments give rise to signals at different frequencies. This separation of nuclear resonance frequencies is termed chemical shift, depends on magnetic field strength and is expressed in dimensionless units termed parts per million (ppm). It is thus possible to define a spectrum of nuclear magnetic resonance signal, in which the several chemical forms of an element (where "element" indicates hydrogen, carbon etc.) give peaks in specific positions.

Another difference between MRI and MRS is that in the latter it is possible to utilise nuclei other than ^{1}H. Hydrogen is the most utilised element in the CNS study.

With ^{1}H MRS, a non-invasive in vivo approach for the determination of some cerebral metabolites of clinical relevance is possible. Unfortunately, the in vivo resolution of this method is poor; only molecules small and mobile enough to tumble freely in solution can be detected. There is no way to detect signals from proteins, from most membrane components or from small molecules bound to larger ones. Moreover, only compounds present in concentrations of about 1 m*M* can be measured directly. The rationale for considering that signals originating from certain metabolites are of use in defining the viability of, or the damage to, any cellular structure is based on in vitro histochemical and cellular studies. These studies demonstrated that the individual metabolites are localised in specific cells or cerebral structures; on the basis of this evidence, signal modifications of a particular metabolite could reflect death or injury to a certain cell population.

In a brain proton MRS study the main marker resonances include:

- The generally defined choline peak at 3.2 ppm, which encompasses choline-containing compounds, such as membrane phospholipids (phosphocholine and glycerophosphocholine), and their respective degradation products
- Creatine and phosphocreatine, elements of cellular energetic metabolism
- Mobile lipids and triglycerides
- *N*-Acetyl aspartate (NAA) and *N*-acetylate groups, considered to be the markers of the neuronal population
- Lactic acid peak, which can be measured when the glycolysis terminal metabolite concentration exceeds the normal value, as in hypoxic conditions.

In addition to the metabolites cited above, it is possible to detect other compounds utilising short echo time (TE) sequences (10–50 ms). Short TEs allow the recognition of substances with a short T2, or strongly spin-coupled, like glutamate, glutamine, taurine, glycine, myo-inositol and GABA, that are very informative from the clinical point of view but very difficult to quantitate with the magnetic field normally used for clinical studies (1.5 T).

The major clinical application of MRS considered for brain tumour patients has been its potential for non-invasive tumour grading [150, 151, 152]. These studies have predominantly used MR spectroscopy techniques that detect a signal spectrum from a small region of interest (single-voxel MR spectroscopy). Trends such as higher mean choline and lower mean NAA levels in higher-grade tumours have been reported. However, most of the studies have found large standard deviations in metabolite ratios and substantial overlap in individual values, which may restrict the accuracy of the technique. Studies using sophisticated data analysis techniques have shown a higher degree of accuracy for in vitro and in vivo spectroscopy studies [153]. A significant improvement in accuracy was obtained using a two-dimensional MRS imaging technique [152]. Multivoxel techniques (chemical shift imaging or spectroscopic imaging) provide spatially encoded chemical information from large tissue slices composed of several voxels. The combination of improved spatial resolution and increased number of voxels provides many more data about tumour heterogeneity and assists in exploration of the tumour margin. As a result it is possible to measure the metabolite content of different areas of neoplasms and surrounding normal tissue. This is very useful for better characterisation of glial tumours, in which areas with different grading very often coexist, and for more accurate monitoring of possible malignant degeneration of benign tumours. In a serial proton MRS imaging study it was clearly demonstrated

that increased choline signal coincides with malignant degeneration of cerebral gliomas and that serial MRS imaging effectively and accurately differentiates between stable and progressive disease [154].

Spectroscopy studies are also very useful in the assessment of response to therapy. The sensitivity of this technique in fact exceeds that of conventional MRI, with useful information being provided in lesions treated with chemotherapy or radiation therapy. There is general agreement that within high-dose regions that correspond to the radiation target, treatment response is reflected in reduction in the levels of choline, creatine and NAA 2–3 months after treatment. In regions that are not responsive to the radiation, levels of choline may increase, corresponding to residual or recurrent tumour. This different behaviour is of paramount importance in helping to differentiate between radionecrosis and recurrence, one of the most difficult topics in oncological neuroradiology. The possibility of monitoring the efficacy of new anti-tumoural compounds explains why MRS is included as the main tool in most new experimental protocols.

The high sensitivity of MRS is not paralleled by its specificity. Although several studies have reported that MRS permits the differentiation of diverse histological tumour types or of abscesses or cystic lesions from neoplasms, the experience of routine daily practice has drawn attention to the risks related to the technique and warrants caution when considering differential diagnosis. This is true not only for differentiation of neoplastic lesions, but even more so when distinction between tumoural and non-neoplastic lesions is addressed.

The absolute quantitation of metabolites and short TE spectra may provide additional data to improve specificity. However, absolute quantitation is complex and time consuming, and short TE spectra have a poor signal to noise ratio. Although the problems of absolute quantitation and reduction of TE without impairment of quality may soon be resolved, it is still debatable whether different metabolic patterns correspond to different types of tumours.

Conclusion

Anatomical imaging procedures have become essential tools for brain tumour assessment. No patient presenting with symptoms suggesting the presence of a brain tumour can be assessed properly unless an X-ray CT and/or an MRI scan is performed, with and without the administration of contrast agents and, in the case of MRI, with various acquisition sequences [155]. Additional information can be obtained from functional imaging with emission tomography and MRS: SPET and PET with different tracers are indicated during the diagnostic work-up to determine the degree of malignancy and as a substitute or guide for biopsy, as well as to assess prognosis. After surgery and radiotherapy, anatomical and functional imaging is indicated to assess persistence of tumour, to monitor progression and changes in the degree of malignancy and to differentiate recurrence from radiation necrosis. Although somewhat similar information can be obtained with either MRI or X-ray CT, and with either SPET or PET, each technique has unique features and provides information complementary to that acquired with the other techniques. The choice of which method to use, or of synergistic use of different methods, depends upon availability, the question addressed and the stage of the disease.

In most cases SPET methods may be perfectly adequate and provide results that parallel those obtained with PET. To claiming that any single method (X-ray CT, PET, SPET, MRI, etc.) is the ultimate magical one for brain tumour assessment is simply to limit one's opportunity to achieve a proper diagnosis. Best results are achieved when anatomical imaging (X-ray CT, MRI) and functional imaging (PET/SPET) are used sequentially and to complement each other. Studies are being conducted to investigate the ability of some of the methods based on the use of radionuclides to assess processes that are relevant for disease management, such as the presence and expression of multidrug resistance in cancer. New opportunities in the area of diagnostic imaging are being created by the development of methods for the assessment of gene expression. These methods can be based on the use of antisense oligodeoxynucleotides targeted towards the mRNA of a gene of choice, or on the use of a reporter gene to assess the expression of a gene. Although these methods are still in their infancy, they may soon become relevant for application in human subjects, for example by PET imaging of the delivery of a suicide gene, i.e. a gene that, when delivered to cells, renders them sensitive to a pro-drug.

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