Position of nuclear medicine techniques in the diagnostic work-up of brain tumors

Although any patient with a suspected brain tumor, either primary or metastatic, should be studied with anatomic imaging modalities such as angiography, computerized tomography (CT) or magnetic resonance imaging (MRI), nuclear medicine techniques are available to further characterize some biological features of brain lesions and help in diagnosis and therapy planning. Blood-brain-barrier disruption can be easily assessed with single-photon emission tomography (SPET), whereas focal metabolic changes can be better demonstrated by positron emission tomography (PET) as specific radiopharmaceuticals are available to detect changes in glucose utilization and aminoacid uptake with this technique. Expression of specific tumoral antigens is the basis of imaging with radioimmunoscintigraphy, a promising technique that can be applied to brain tumor therapy. The major clinical applications of nuclear medicine in the study of brain tumors — evaluation of the extension of a tumoral mass, differential diagnosis and evaluation of therapy and prognosis — are discussed.

KEY WORDS: Brain neoplasms - Nuclear medicine - Tomography, emission computed - Tomography, emission computed, single photon.

Intracranial brain neoplasms can be classified into primary brain tumors and metastatic tumors. Metastatic brain tumors are more common than primary brain tumors and are associated with lung neoplasms as well as breast, gastrointestinal, genitourinary tumors and melanomas.

The basic classification of primary brain tumors by the World Health Organization (WHO) relies on their cellular origin, the clinical course and histological appearance of the neoplasms, immunophenotypic features and molecular/cytogenetic profile (Table I).

Primary brain neoplasms which derive from neuroectoderm (primitive neuroectodermal tumor, PNET) are the most common, followed by tumors of meningeal, hematopoietic and nerve sheath origin. In adults the most frequent PNETs derive from glial cells (astrocyte, oligodendrocyte, ependymocytes and subependymocytes).

In the Western world, the incidence of primary brain tumors depends on age and ranges between 1-10 cases/100 000 persons per year (age standardised). The distribution of tumor types for children and adults differs. In adults it is more frequent to find pituitary tumors, meningiomas, and glioblastomas. In children primitive neuroectodermal tumors, astrocytomas and pilocytic astrocytomas can be found.

Non-nuclear medicine diagnostic procedures

Most clinical manifestations of brain tumors are due to the “mass effect” of the growing tumor and can be detected when the tumor reaches the size of about 40 g. They consist of herniation syndromes, progressive
alterations of mentation and personality, headache and seizures. Other focal symptoms depend on the tumor location and include focal seizures, mental changes, visual disturbances, speech abnormalities, motor weakness, sensory disturbances, cranial nerve signs and gait abnormalities. Computerized tomography (CT) has been the first imaging modality that could directly visualize the presence of a brain tumor and is still widely used. Other radiological techniques have been applied to ascertain the presence of brain lesions more recently.

**Computerized tomography**

For many years, CT has been considered the gold standard in the diagnosis of brain tumors because it is able to demonstrate the presence of a brain lesion and define its dimensions and morphology and its relation with surrounding brain structure. It is also able to identify perilesional edema and define the number of brain lesions.

This imaging technique is widely available and is useful when magnetic resonance imaging (MRI) cannot be used; CT is less degraded by artefacts due to motion of the patient for the short time of duration of the exam, but is less sensitive than MRI in brain regions that are near some bony areas of irregular shape, such as the posterior fossa and the floor of the middle fossa, due to the presence of beam-hardening artefacts and can miss non-enhancing tumors such as low-grade gliomas.

**Contrast enhanced computerized tomography**

The administration of a contrast agent increases X-rays attenuation due to the high electron density of the iodinated compounds. Contrast enhanced CT can detect blood-brain-barrier (BBB) disruption that occurs in many neurological disorders that include acute stroke, inflammatory and infectious cerebral diseases and multiple sclerosis. Moreover most brain tumors directly disrupt the blood-brain-barrier. Themselves, while in angiogenesis the BBB is absent.

The region of contrast enhancement corresponds well with the main tumor mass. However, malignant tumor cells are commonly found beyond the enhanced portion of the tumor, 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 or epidermoids can be diagnosed without further examinations. CT ability to represent bone structures makes this technique relevant in defining bone destruction or sclerosis associated with metastatic tumors, pituitary adenomas, meningiomas, adjacent carcinomas from the sinuses or pharynx, and in studying lesions with calcific components or localized close to bone structures.

**Magnetic resonance imaging**

MRI has several advantages as compared to CT. The technique has a higher contrast resolution and a lower occurrence of artefacts than CT, associated with the possibility of 3D-acquisition and reconstruction and a high spatial definition. These qualities permit an excellent resolution of brain regions that are poorly assessed by CT, such as infratentorial, sellar, temporal and meningeal regions. MRI studies are characterised by high sensitivity for structural alterations.

### Table I. Revised classification of primary intracranial tumors according to WHO.

| Tumors of neuroepithelial tissue | Astrocytic tumors, oligodendrogial tumors, mixed gliomas, ependymal tumors, choroid plexus tumors, glial tumors of uncertain origin, neuronal and mixed neuronal-glial tumors, neuroblastic tumors, pineal parenchyma, embryonal tumors |
| Tumors of peripheral nerves | Schwannoma, neurofibroma, perineuroma, malignant peripheral nerve sheath tumors |
| Tumors of the meninges | Tumors of meningotheelial cells, mesenchymal non-meningothelial tumors, primary melanocytic lesions, tumors of uncertain histogenesis |
| Lymphomas and hematopoietic neoplasms | Malignant lymphoma, plasmacytoma, granulocytic sarcoma |
| Germ cell tumors | Germinoma, embryonal carcinoma, Yolk sac tumors, chorioncarcinoma, teratoma, mixed germ cell tumors |
| Tumors of the sellar region | Craniopharyngioma (adamantinomatous, papillary), granular cell tumor |
caused by tumoral growth, that can further be enhanced by the use of paramagnetic contrast agents. For these reasons, MRI is the procedure of choice for imaging all types of brain tumors. MRI is particularly accurate in establishing the intra- or extra-axial origin of tumors; with a better definition it is possible to detect indirect signs (cortex dislocation, compression of sulci and cisterns, presence of cleavage plane for extrinsic lesions) and evaluate direct signs of neoplasia. A normal contrast-enhanced MRI scan essentially rules out the possibility of a brain tumor.

**Angiography**

The assessment of vascular structure as depicted by angiography has largely lost its diagnostic role in the work-up of brain tumors; a relevant exception is represented by those lesions that are characterized by an abnormal angiogenesis, such as hemangioblastomas and meningiomas. At the moment angiography has a complementary role in the pre-surgical assessment of neoplasms, providing information on the relationships between tumor and vessels. Angiography is still relevant in the therapeutic phase of embolization of meningiomas or base of the skull tumors or intra-arterial chemotherapy for gliomas. The routine use of angio-MR offers the possibility to complete a standard brain MR study adding information on the relationships existing between tumor and vessels. The demonstration of small diameter vessels is still poor, with a consequent poor definition of tumoral angiogenesis, but incoming technical amelioration will soon widen angio-MR capabilities.

**Magnetic resonance spectroscopy**

The separation of nuclear resonance frequencies of hydrogen, termed chemical shift, can define a spectrum of signals that are a representation of the several chemical forms of hydrogen that are present in the volume studied. It is a non-invasive approach for the determination of some cerebral metabolites with clinical relevance, such as membrane phospholipids (choline containing compounds) and respective degradation products, creatine and phosphocreatine (elements of cellular energetic metabolism), N-acetyl aspartate and N-acetylated groups (marker of neuronal population) and lactic acid (marker of hypoxic condition). The technique is relatively insensitive because it can only detect compounds that are present in concentrations of about 1 mM.

### Table II.—Radioisotope uptake and histological grade of gliomas.

<table>
<thead>
<tr>
<th></th>
<th>Grade IV gliomas</th>
<th>Grade III gliomas</th>
<th>Low-grade tumors</th>
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</thead>
<tbody>
<tr>
<td>Thallium index</td>
<td>1.9±3.2</td>
<td>1.4±1.5</td>
<td>1.0±2</td>
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<tr>
<td>BUdR</td>
<td>7.6±3.4</td>
<td></td>
<td>0.61±0.83</td>
</tr>
</tbody>
</table>

**Nuclear medicine diagnostic procedures**

Nuclear medicine techniques were once used to confirm the presence of a brain mass that was suspected on a clinical basis. Nowadays, morphological imaging techniques, namely CT and MRI, are usually able to adequately demonstrate the presence of a brain lesion, to define its size and its relation with surrounding brain structures and to identify direct or indirect signs that can assist in the diagnosis of brain tumor with a high degree of confidence. Nuclear medicine methods can assess and quantify biochemical parameters in vivo, that are useful to further characterise brain neoplasms.

**Studies of the blood-brain-barrier and Na/K pump**

Scintigraphic studies aimed at the detection of a leaky blood-brain-barrier can be useful in a variety of clinical situations including fever, toxins, and tumors. Without the disruption of the BBB tracer uptake will not occur. Due to tumor growth, the BBB will be disturbed allowing tracer uptake. Under these conditions some tracers, like 99mTc-DTPA and 301Tl-chloride will show a significant. But the disruption of BBB is not the only explanation of Thallium uptake, as it accumulates in neoplastic tissues depending upon blood-flow, cellular metabolism and efficiency of sodium-potassium ATPase.

Initial studies on comparative tracer uptake in brain tumors were carried out by Kaplan et al. including 29 patients with gliomas grade III and IV, of which 7 could be studied post mortem. They found that 201Tl gave the most accurate localization, 67Ga was good if steroids were not being used, while 99mTc-GH could not differentiate fibrosis, non-fibrosis, necrosis and neoplasma. Similar data were presented by Mountz et al. An improvement in the technique was the use of SPET. In a methodological paper Kim et al. described semi-quantitative analysis of the results. The best analysis method was mean counts in attenuation-corrected slices. They were able to show that low-grade tumors had a lower uptake index as compared to high-grade tumors: 1.20±0.40 vs. 2.40±0.61, respectively.
A close relationship between Thallium uptake and proliferative activity was shown by Oriuchi et al. They could demonstrate a positive correlation between bromodeoxyuridine (BUDR) and the $^{201}$Tl uptake index. Besides the tumor related index values, patients who died after surgery presented much higher values than survivors (Table II).

**Metabolic studies**

Metabolic studies aim at the detection of either tumor metabolism or of cell proliferation. For tumor metabolism both glucose utilization ($^{18}$F-FDG) and amino acids uptake ($^{123}$I-IMT, $^{124}$I-IMT and other thyrosine derivatives, or $^{11}$C-methionine) can be used. Tracers for cell proliferation include $^{124}$I-deoxy uridine and $^{11}$C-2-thymidine. In a similar fashion as shown for $^{201}$Tl and BUDR, $^{123}$I-IMT uptake in gliomas appears to correlate with cellular density (light microscopy) and proliferative activity (Ki-67 nuclear antigen). Uptake indices for $^{123}$I-IMT are higher in cases of tumor recurrence as compared to patients without recurrence. Also $^{99m}$Tc-SestaMIBI and $^{99m}$Tc-Tetrofosmin concentrate in hypermetabolic processes such as tumors.

**Studies of glucose metabolism**

Glucose utilization in tumors can be assessed using $^{2-}$[18F]fluoro-2-deoxy-D-glucose ($^{18}$F-FDG), which differs from glucose only for the replacement of an hydroxyl group with radioactive fluorine. Both $^{18}$F-FDG and glucose share the same carriers between the blood-brain-barrier. The accumulation of $^{18}$F-FDG, as detected by PET, is in proportion to glucose metabolic rate of the studied organ. It is well established that brain neoplasms present an increased glucose utilization respect to normal tissue, due to a high rate of glucose degradation into lactic acid even in presence of oxygen. Moreover, an over-expression of GLUT1 and GLUT3, members of the hexose transporter family, has been observed in several brain tumor types.

$^{18}$F-FDG is able to identify the elevated glucose consumption in brain tumors, and it is now accepted that the uptake of the tracer correlates with the grade of malignancy of astrocytic tumors and also in oligodendroglomas and gangliogliomas. On the other hand, low-grade gliomas are not easily identified or may appear as cold spots surrounded by normal high uptaking cerebral cortex, hampering a clear definition of tumor extension.

**Studies of amino acids uptake**

Imaging with radiolabeled amino acids visualizes protein synthesis and amino acid transport, which are accelerated in tumors. Methionine and other large neutral amino acids, are normally supplied to the brain from protein breakdown and diet through a transport system in the BBB; because the amino acids uptake in macrophages and other inflammatory cells is low, these tracers might be more tumor specific than $^{18}$F-FDG and difficult differential diagnoses with other cerebral pathologies, i.e., infections, radiation necrosis, edema, that may cause abnormal $^{18}$F-FDG uptake, can be avoided by using $^{11}$C-methionine (MET). $^{11}$C-methionine allows a earlier and more accurate delineation of the extension of the tumor boundaries than contrast-enhanced CT or MRI and is superior than $^{18}$F-FDG in delineating low-grade gliomas. The use of $^{11}$C-methionine is justified by its relatively simple synthesis, rapid uptake in tumors and clearance from blood and other tissues. Other amino acids used for brain tumor imaging are tyrosine, thymidine, glutamate, phenylalanine and their labeled derivatives. Tyrosine uptake in brain tumors can be assessed with its labeled derivatives: O-$(2^{18}$F-fluoroethyl)-L-tyrosine ($^{18}$F-FET), L-$(3^{18}$F)-a-methyltyrosine ($^{18}$F-FMT), $^{123}$I-iodo-α-methyltyrosine ($^{124}$I-IMT). Also the uptake of tyrosine labeled derivatives is higher in brain tumors than in normal brain tissue. Other labeled amino acids for the evaluation of brain tumors include $^{18}$F-fluorophenylalanine that has a marked uptake in oligodendroglomas.

**Radioimmunoscintigraphy**

Some researchers have tested the feasibility of using monoclonal antibodies directed against neuroblastoma antigens, epidermal growth factor receptor, placental alkaline phosphatase, di-sialoganglioside GD2 and tenascin. A more elaborated construction has been reported using $^{99m}$Tc-PnAO-Biotin together with an anti-tenascin antibody. More complex techniques have been proposed to enhance the signal-to-noise ratio, to overcome the limitations deriving from low tumor/non-tumor ratio and high dosimetry from the use of MoAbs directly labeled with Iodine-131. This technique has a good accuracy for the in vivo immunodetection of gliomas.
Clinical indications

Table III summarizes the role of various imaging modalities in different clinical settings in the work-up of primary brain tumors.

<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Diagnosis of primary tumor</th>
<th>Differential diagnosis</th>
<th>Biological characterization</th>
<th>Pathology</th>
<th>Treatment</th>
<th>Follow-up of the treated patients (clinically free from disease)</th>
<th>Restaging</th>
<th>Monitoring of treatment response</th>
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</thead>
<tbody>
<tr>
<td>Imaging modality of choice</td>
<td>CT and MRI with contrast agent</td>
<td>CT and MRI with contrast agent</td>
<td>Refer to table in the text</td>
<td>Neurosurgery radiation chemotherapy</td>
<td>In asymptomatic patients: CT and MRI with contrast agent every 3 months, alternating</td>
<td>CT or MRI with contrast agent</td>
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<td>Nuclear medicine</td>
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<td>In AIDS patients: FDG-PET or 201Tl-SPET</td>
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Evaluation of the extension of the disease

An accurate definition of the tumor boundaries is requested to plan an aggressive surgical treatment that should spare critical brain structures, such as the language areas. $^{11}$C-methionine is able to detect brain tumors boundaries, both in primary lesion and recurrence, with a high accuracy, regardless of their pathological grading. Also $^{201}$TI and $^{123}$I-$\alpha$-metyl-tyrosine can be used in this situation, but the limited spatial resolution of the PET technique may restrict their value in the assessment of the extension of the disease.

Differential diagnosis

Differential diagnosis between brain tumors and benign lesions is usually based on clinical presentation, laboratory tests and different presentation in CT and MRI images. In AIDS patients, toxoplasmosis and primary intracerebral non-Hodgkin's B cell lymphoma are both common and clinical presentation and laboratory tests are not useful to establish a correct diagnosis. In this setting, $^{201}$TI can be helpful to demonstrate the presence of a malignant lesion as a focal accumulation of this tracer at the site of CT/MRI abnormality strongly suggests lymphoma, while the absence of uptake of $^{201}$TI allows to exclude the diagnosis of lymphoma with a high degree of confidence.

Guide for biopsy

High grade brain tumors are characterised by the presence of an heterogeneous cellular composition for...
the combination of active disease, non-specific inflammation, necrosis and edema. Both $^{18}$F-FDG and $^{11}$C-MET can be used in the stereotactic environment to identify the areas of anaplasia or infiltration when a definitive biopsy is to be performed, in an effort to include the most malignant tissue in the pathologic specimen. 14, 15

**Follow-up**

**EARLY ASSESSMENT OF THERAPY**

The assessment of presence of residual tumoral mass by means of CT or MRI is difficult in the early phase after surgical or radiant therapy, due to inflammatory reaction. $^{18}$F-FDG can differentiate residual tumor from the effect of therapy and a decline in $^{18}$F-FDG uptake in a tumor weeks or months after therapy suggests a good response, indicating a reduced number of viable cells or reduced metabolism of damaged cells. 16

**LONG-TERM FOLLOW-UP**

Even several months after irradiation or chemotherapy for brain tumors, MRI and CT cannot easily distinguish tumor progression from radiation injury or necrosis. In high-grade tumors with elevated $^{18}$F-FDG uptake before treatment, focal uptake of $^{18}$F-FDG in areas of BBB breakdown detected by CT or MRI suggests the presence viable tumor cells, while absent FDG uptake suggests that necrosis is present. 17

In low-grade gliomas, malignant transformation to high-grade tumors after treatment is not infrequent. The detection of areas of increased $^{18}$F-FDG uptake in histologically proven low-grade glioma predicts malignant transformation in such cases.

**PROGNOSIS**

In high-grade gliomas, the most powerful predictor of survival is pathological grading. In low-grade gliomas, the presence of areas of increased $^{18}$F-FDG uptake predicts, in most cases, a worse prognosis. Experience with other tracers is still limited, but a low uptake of $^{11}$C-methionine in the baseline study is associated with a longer survival.

**References**