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Nuclear Medicine in Neuro-Oncology

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The usefulness of radionuclides in medicine has been well established through in vitro studies, diagnostic imaging, and the treatment of malignant and nonmalignant disease. The myriad permutations and developments in the use of radionuclides in medicine are directly reflected in the extensive medical literature on this subject. The specialty of nuclear medicine has involved translating this large body of data in a meaningful and efficacious way into clinical practice and research. This chapter examines the clinical application of nuclear medicine in neuro-oncology, particularly incorporating the results of in vitro and in vivo studies and diagnostic imaging into therapeutic schemes to improve patient care.

TRANSLATION BETWEEN IN VITRO AND IN VIVO STUDIES

Because of the high specific activities (i.e., radioactivities or disintegration per second per mass) of available radionuclides, their sensitivity of detection is also very high. For instance, ^{99m}Technetium (^{99m}Tc) is available at 1000 Ci/g, a level of radioactivity that translates into 3.7×10^{13} disintegrations per second per gram, or 3.7×10^{14} counts per second per mole. With a 10% counting efficiency, only approximately 0.3 pm of material is thus required to achieve a statistically significant count of 10,000 for 100 seconds of counting and detection. Radiopharmaceuticals commonly used in medical practice are in the subnanomolar concentration range. In general, the biologic effects from chemicals used at this low

concentration are physiologically negligible. Because of this, only radioactivity units (e.g., Curie [Ci], mCi, or μCi), are used in nuclear medicine. These units represent the only measurable quantities that remain after initial quality control procedures are performed. This superior ability to detect subnanomolar ranges of molecular change confers advantages for nuclear medicine that surpass conventional radiology, including computed tomography (CT) and magnetic resonance imaging (MRI). CT and MRI can only deal with water and proton alterations at molar and millimolar levels. In contrast, radionuclide labels cause little perturbation in the chemical structure of host molecules. As a result, they provide true measures of in vivo physiology and pathology in terms of minute changes of biochemicals. This is especially true for ^{11}Carbon (^{11}C)- and ^{15}Oxygen (^{15}O)-labeled biochemicals that have nearly identical behavior compared with similar, unlabeled biochemicals.

The high sensitivity and low level of chemical perturbation from radionuclides enables accurate translation of results between in vitro, in vivo, and in situ studies. For instance, ^{64}Copper (^{64}Cu)-labeled Cu-pyruvaldehyde-bis(N4-methylthiosemicarbazone) (Cu-PTSM) was used to label C6 glioma cells in rats and to trace their biologic routes following intravenous injection. A micro positron emission tomography (PET) instrument capable of 2 mm resolution was used to monitor in vivo distribution of glioma cells for as long as 24 hours (Adonai et al., 2000). Although concordance between findings from in vitro and in vivo studies is often the rule, discordance was illustrated by a comparative study of peripheral ben-

zodiazepine receptors in human brain tumors. 1-(2-Chlorophenyl)-*N*-methyl-*N*-(1-methylpropyl)-3-iso-quinoline carboxamide (PK11195) in vitro binding to gliomas demonstrated more than a 20-fold elevated receptor density on the tumor cells (Price et al., 1990). Ex vivo autoradiography confirmed only an approximately sixfold elevated receptor density when the tissue was sectioned in thin layers and exposed to the ligand (Pappata et al., 1991). Human ^{11}C PK11195 PET images revealed a mere twofold increase in signal detected in tumor compared with that in surrounding brain tissue (Starosta-Rubinstein et al., 1990). The explanation for this loss of signal/noise ratio may be the multiple factors involved in biodistribution of any drug: transport, diffusion, endogenous competition, ligand binding, internalization of receptor, and imperfect detection of the signal in the living organism. Loss of signal between in vitro and in vivo studies is not unique to the brain or brain tumors and has been observed in other tumors and structures in the body.

Exaggeration of signals from in vitro experiments is occasionally encountered during in vivo studies. In the case of human meningioma detection by [111]Indium (^{111}In)-labeled octreotide (a somatostatin receptor ligand), very intense signal is usually the rule. However, in vitro receptor binding studies did not detect somatostatin receptors in about one-half of the meningioma surgical specimens assayed (Krenning et al., 1995). However, florid expression of somatostatin receptors occurred in the endothelium of the blood vessels surrounding the tumors. Such discordance between in vitro and in vivo studies is encountered in all medical disciplines. The use of radionuclides is often the first and only feasible approach that can be taken to verify concordance or to discover discordance. These observations, in turn, help direct rational planning of appropriate diagnostic and therapeutic strategies.

CONVENTIONAL SCINTIGRAPHY

Single-Photon Emission Computed Tomography, Brain Perfusion, and Cerebrospinal Fluid Circulation

The application of conventional scintigraphy to study cerebral structural integrity has largely been replaced by CT and MRI, which provide superior spatial reso-

lution at the submillimeter level. The current resolution for PET and single-photon emission computed tomography (SPECT) is in the 5 to 10 mm range. PET and SPECT are important tools for evaluating physiologic functions and pathologies in neuro-oncology because of their ability to detect molecular changes near the submicromolar range. The practical lower limit of CT, MRI, or functional MRI is, however, at a millimolar level. Furthermore, the diagnostic imaging industry has provided clinicians with only a handful of CT and MRI contrast agents, and gram quantities are required for their use in humans. In contrast, hundreds of radionuclides have been synthesized that can be applied to study tumors, making the technology even more attractive.

Traditional SPECT techniques involve producing multiple planar images in quick succession followed with their reprojection according to algorithms similar to those used in CT and MRI. This approach has helped to delineate small structures deep within the body and head. It is limited clinically because no algorithm is available that allows absolute quantification of results. Nevertheless, this approach has provided invaluable qualitative and semiquantitative clinical information for tracer distribution in different parts of the body, including the brain. For patients without brain tumors, SPECT using ^{99m}Tc hetamethylpropyl-eneamine oxide (HMPAO) has been extensively applied to study the integrity of cerebral perfusion under pathologic conditions. One study has even correlated reversible perfusion defects with neuropsychological deficits in oncology patients receiving interferon (Meyers et al., 1994).

Figure 2–1 illustrates the use of [67]Gallium (^{67}Ga) to detect CNS lymphoma. [67]Ga empirically accumulates in many tumors with a high signal-to-background ratio. Although its uptake may be related to the transferin receptors that exist on lymphoma cells, the exact mechanism of localization remains unclear.

Early reports provide data for the use of [201]Thallium (^{201}Tl) SPECT, with its high uptake by tumor, to confirm recurrent glioma. In contrast, uptake in normal brain tissue or in necrotic tissue is quite low (Black et al., 1989). In this technique, typically, as much as 4 mCi of ^{201}Tl chloride is injected intravenously, followed shortly by acquisition of SPECT images. The advantage of ^{201}Tl-SPECT is that because normal brain tissue has little tracer uptake, malignant tissue with its high uptake appears with a high contrast ratio and can thus be defined. Uptake is usually
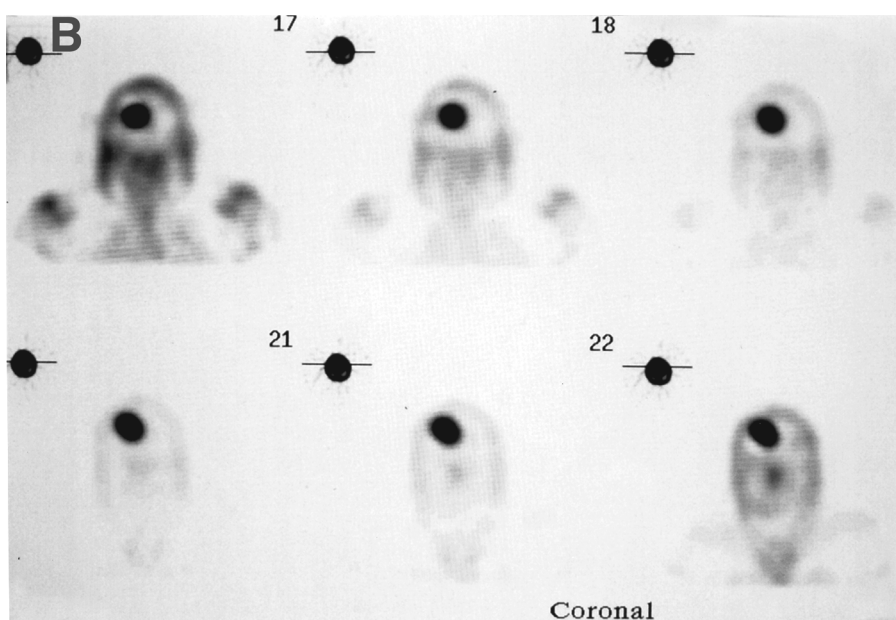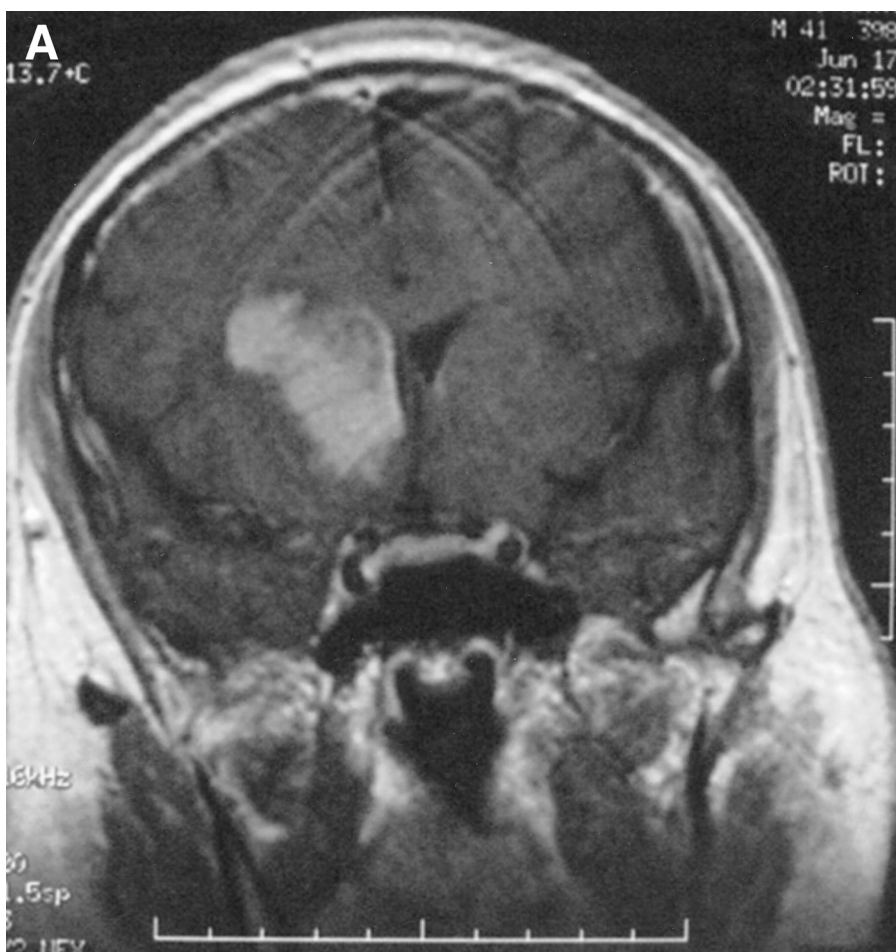
measured against either contralateral normal brain structures or the contralateral scalp, which has a relatively stable uptake (Holman et al., 1991). Earlier studies established lesion-to-scalp ratios above 3.5 for malignant tissue and ratios of 1.5 or below as being in the nonmalignant tumor range. This classification has defined ratios between 1.5 and 3.5 as undecided or nonspecific. Earlier investigators have attempted to use the perfusion index of tumor-to-cerebellum ratios to further distinguish lesions in this nonspecific range (Carvalho et al., 1992). The combined ^{201}Tl-SPECT and ^{99m}Tc-HMPAO SPECT approach is, however, technically demanding and time-consuming. Subsequent studies and our experience in patient care have failed to find this combined SPECT approach to be clinically feasible. Instead, our approach has been to adopt a maximum tumor-to-scalp ratio greater than 2.5 as a conclusive cut-off point for the diagnosis of recurrent tumor. For the range between 1.5 and 2.5, collaborative evidence, including conformation of lesion and temporal changes from measurements of varied intensities, are required to accurately interpret ^{201}Tl-SPECT data. Figure 2–2 shows a patient with recurrent anaplastic astrocytoma who had a high lesion-to-scalp ratio of 3.0.

^{99m}Tc-labeled sestamibi (MIBI) is an FDA-approved agent used to detect breast cancer. Although the exact mechanism of tumor uptake has not been established, it is energy dependent and requires mitochondrial integrity. The use of MIBI in detecting brain tumors in adults and children has been reported (O'Tuama et al., 1993). Its advantages include a higher allowable injected radiation dosage (to 40 mCi). However, because MIBI accumulates in the choroid plexus in a manner that cannot be suppressed by other drugs, false-positive or false-negative findings might ensue, particularly if the clinician chooses to ignore uptake in ventricular or periventricular areas where the choroid plexus resides. Nevertheless, recent reports in nuclear medicine have indicated that MIBI may provide better clinical confirmation of tumor recurrence than ^{201}Tl (Yamamoto et al., 2000). In a manner analogous to the study of the myocardium, temporal changes of

^{201}Tl uptake in tumors have been delineated with early results (15 to 30 minutes) compared with results from later (3 hour) phases. In other types of tumors, such analysis has yielded interesting correlations with the presence of recurrent tumor, although brain tumors have not been specifically addressed.

Other SPECT agents have been developed to measure altered metabolic pathways in brain tumors. For instance, ^{123}I-iodomethyltyrosine (IMT) has been extensively studied in Europe and Asia. The critical step in tumor IMT uptake is via a neutral amino acid transporter. Indeed, the level of IMT uptake in human brain tumor has been found to directly correlate with patient survival (Weber et al., 2000). Radioiodine analogues (^{123}I, ^{131}I, and ^{124}I) of iododeoxyuridine (IrdU) have also been applied to tomographic studies of brain tumor to nondestructively assay their elevated nucleotide production (Tjuvajev et al., 1994). Their correlations with tumor presence and grade were found to be independent of glucose metabolism.

In addition to tomographic imaging, dynamic or sequential images measured over different durations provide invaluable physiologic and pathologic information for neuro-oncologists. Determination of brain death is a task occasionally encountered in neuro-oncology. Although brain death as the sole determinant of death is somewhat controversial in the United States, realization of brain death per se can be difficult because administration of multiple medications and electroencephalographic variances can sometimes confound its determination. Scintigraphic dynamic and static imaging using either ^{99m}Tc-DTPA, ^{99m}Tc-neurolite (ECD), or ^{99m}Tc-ceretec (HMPAO) remain the most reliable methods to assess cerebral perfusion as an ancillary test for the determination of brain death. Typically, the imaging study itself is performed under stringent quality control. The absence of blood flow (radioactivity) in the parenchyma of the entire brain can be used as one of the ancillary criteria for brain death.

Dynamic and static scintigraphic images are helpful for evaluating cerebrospinal fluid (CSF) flow in neuro-oncologic patients, especially those with leptomeningeal metastasis who require intrathecal ther-

Figure 2–1. A patient with a history of central nervous system lymphoma presented with an enhancing lesion in the right basal ganglia extending to the periventricular area on MRI **(A).** The 48 hour delayed ^{67}Ga-SPECT (7 mCi, IV) showed intense uptake corresponding to the same location while the rest of the brain did not demonstrate significant uptake **(B).** Only small amounts of tracer are seen in the scalp, nasopharnx, and shoulders.
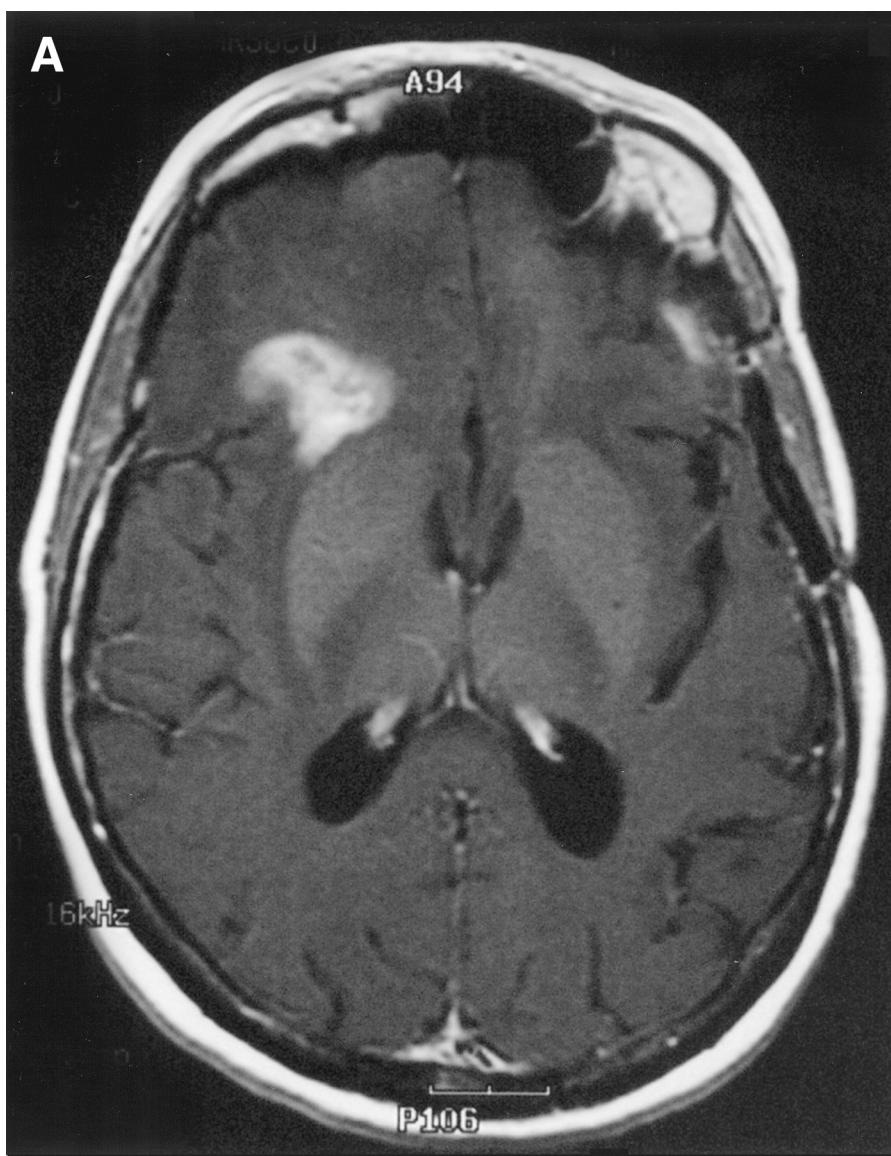
Figure 2–2. A patient with a history of treated anaplastic astrocytoma presented with a new enhancing MRI lesion **(A)** in the right posterior frontal lobe. The 30 minute delayed ^{201}Tl-SPECT (4 mCi, IV) in coronal, sagittal, and transverse projections **(B)** revealed an intense uptake in the lesion with a lesion-to-scalp ratio of 3.0, which is consistent with recurrent tumor. There is minimal tracer activity in the rest of the brain and physiologic tracer activity in the nasopharynx and scalp. The anterior planar image (lower right, B) of the head did not show enough signal-to-background activity to reveal the tumor. (*continued*)

apy. Our group has developed an algorithm to semi-quantitatively measure CSF flow from four serial whole-body images over 24 hours. Considering the entire CSF space as a single compartment, the effective half-life (Te) of ^{111}In-DTPA has been determined to be 12 to 20 hours (Wong et al., 1998a) with a monoexponential decline. Cerebrospinal fluid flow rates can be altered by a CSF leak or by turning on the valve of a ventriculoperitoneal (VP) shunt (Wong et al., 1999); both result in a significantly shortened Te (3
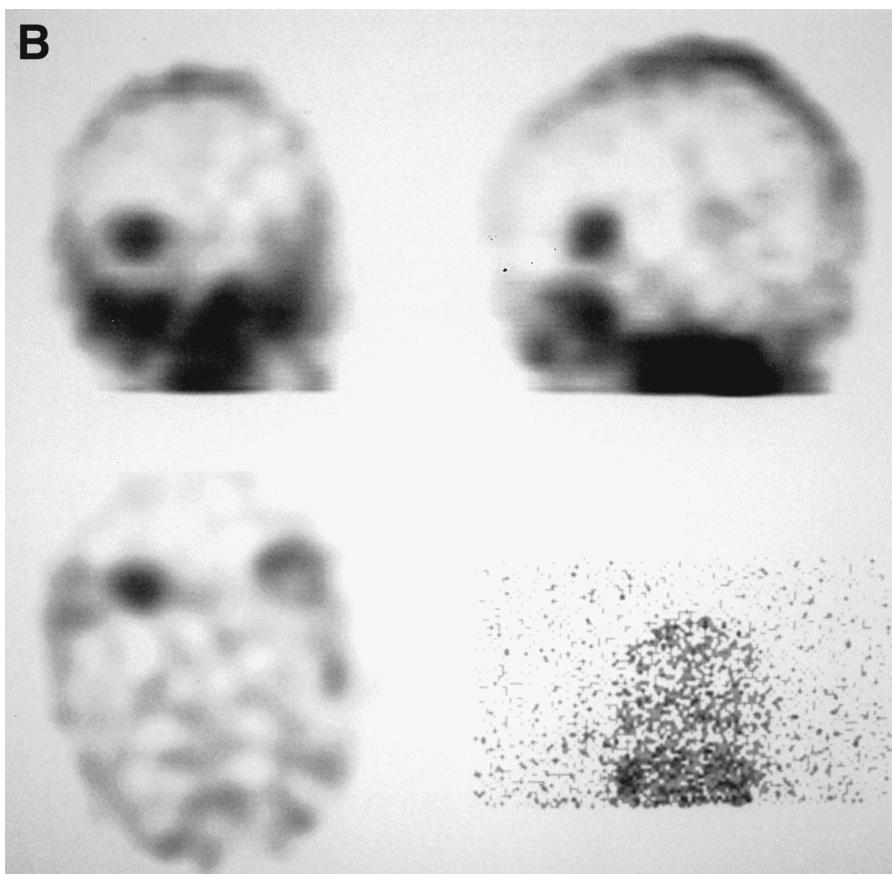
Figure 2–2. (*Continued*)

to 10 hours; Wong et al., 2000a). On the other hand, obstructive symptoms lengthen Te to over 20 hours (Wong et al., 1998b). Figure 2–3 illustrates that opening a closed VP shunt valve decreased Te from 40 hours to 7 hours in a patient with obstructive symptoms. The therapeutic implication of Te is that, owing to its monoexponential decline, total intrathecal tracer exposure (measured by the area under the curve [AUC]) is directly proportional to the tracer Te (Loevinger et al., 1988). For instance, methotrexate is a small, ionized molecule whose intrathecal pharmacokinetics are similar to those of ^{111}In-DTPA by simultaneous CSF sampling (Mason et al., 1998). Therefore, determining the Te of ^{111}In-DTPA will also provide an estimation of the effects of exposure to methotrexate or to similar drugs that are predominantly cleared from the CSF by bulk flow. This parallelism is not limited by whether the patient has a VP

shunt or whether the VP valve is in the on or off position as long as the predominant route of clearance of the drug is via bulk CSF flow. In fact, Te measurement may be applied to guide the adjustment of intrathecal dosages of methotrexate or similar drugs in pathologic situations where the Te of ^{111}In-DTPA markedly deviates from the normal range.

The different techniques available in conventional scintigraphy continue to provide invaluable temporal and spatial information about brain tumor physiology and pathology.

APPLICATION OF POSITRON EMISSION TOMOGRAPHY IN NEURO-ONCOLOGY

The development of PET preceded that of MRI but was limited by medical practice policy, including the
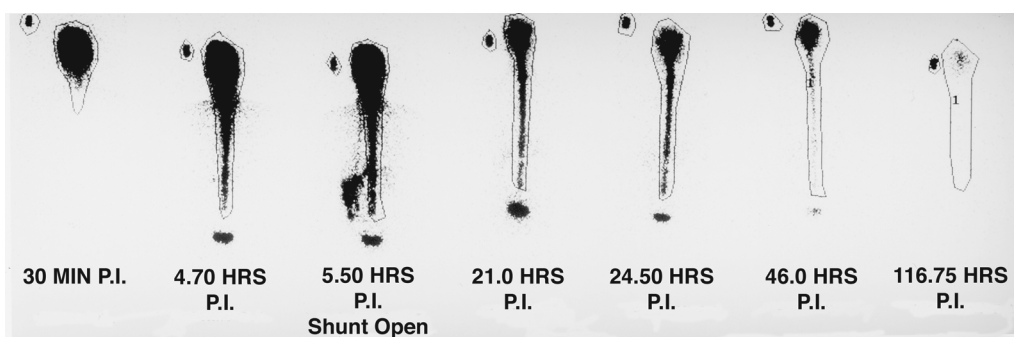
Figure 2–3. Whole-body images of a patient suffering from leptomeningeal metastasis from breast cancer. As part of an evaluation of the patency of CSF, she was injected with 0.5 mCi ^{111}In-DTPA via an Ommayo reservoir, which was connected with a ventriculoperitoneal shunt via an on–off valve. The dotted line encircling each image indicates where the level of radioactivity was measured for the one-compartment model. The valve was in the closed position for the first 5 hours. Initial effective half-life was 40 hours. Upon opening the valve, radioactivity is seen along the shunt and in the abdomen. The effective half-life after opening the valve was 7 hours, indicating communication between the CSF and extrathecal space P.I., postinjection.

lack of insurance reimbursement. With PET, after initial electronic gating for coincidence, tomographic images are obtained using reconstruction algorithms (and iterative methods) similar to those used in CT and MRI. Successful application of PET depends on effective utilization of the scanner, careful choice of PET radiopharmaceuticals, and the relevant interpretation of physiologic and pathologic findings. Currently, there are only a handful of available PET scanner models (GE, Seimens, Philips, and Imagtron). These models basically evolved from similar designs, and their performance depends on a combination of hardware that is used to collect high temporal and spatial resolution and software that is used to present the collected images in a meaningful fashion.

The latest generation of a PET multiple-slice scanner with the highest resolution available was developed at the M. D. Anderson Cancer Center. Called the MDAPET, it has a resolution down to 2.8 mm in plane and 2.9 mm axial (Uribe et al., 1999; Wong et al., 1996). This scanner was designed to use an innovative quadrant-sharing scheme to deploy detectors (Wong et al., 1993). Initial brain phantom studies show details similar to those derived from a low-end MRI. The development of other high-resolution PET scanners with similar detector schemes is being undertaken by several vendors in the industry. Furthermore, the development of combined CT-PET instruments is close to the marketing stage with the enticement of contemporaneous acquisition and registration of anatomic images (by CT) and metabolic images (by PET).

The study of human brain tumors using PET began in the 1970s. Gross pathology at the vascular level, such as perfusion abnormalities, was reported using ^{15}O-water PET (Ito et al., 1982). Breakdown of blood–brain barriers were reported with ^{68}Ga-PET (Yamamoto et al., 1977). Differential vascular responses between vessels in tumor versus brain were demonstrated via adenosine pharmacologic stimulation using ^{15}O-water PET (Baba et al., 1990). Vascular responses to physiologic stimulation have been assessed in patients with brain tumors for the purpose of identifying motor and sensory representation in brain parenchyma, data that have been used as a clinical tool for presurgical planning (Nariai et al., 1997). Since the 1970s, the regional perfusion of tumors has been investigated at cellular and subcellular levels, with particular attention being paid to oxygen consumption and glucose utilization. Although other specific PET tracers have been synthesized to study in situ cancer metabolism of sugar, lipid, amino acid, and nucleotides, [18]Fluorine (^{18}F)-fluoro-2-deoxy-D-glucose (FDG) remains the most commonly used tracer. It has gained federal approval for reimbursement in the clinical evaluation of lymphoma, melanoma, lung, esophageal, and colorectal tumors.

Tumor grading and staging are important tasks for the clinical oncologist. In the 1980s, increased ^{18}F-FDG uptake in gliomas was correlated with tumor

grades (Di Chiro et al., 1982; Di Chiro, 1987). Because of its uptake by the normal cerebrum, ^{18}F-FDG is still the main tracer used to study the brains of patients with and without tumors. Despite the popular use of FDG in PET, the mechanism of action of FDG is not fully understood. Putative mechanisms include increased hexose kinase activity (Weber, 1977), increased uptake by surrounding macrophages (Kubota et al., 1994), and increased levels of glucose transporters in tumors (Fulham et al., 1994).

Tomographic images are typically acquired between 40 and 60 minutes after intravenous injection of 5 to 10 mCi of FDG followed by the acquisition and evaluation of qualitative images. Semiquantitative evaluation may involve measuring the standard uptake value (SUV), which is the measured radioactivity calibrated for injected dose and body weight. The SUV approach is applicable to all tracers and is more effective than visual inspection of the images alone. Exact quantification requires multiple image sessions over short durations along with arterial catheterization to obtain the arterial input function for deconvolution of the measured pharmacokinetic and pharmacodynamic parameters. Application of this approach is illustrated by a study of ^{11}C-*N*-methyspiperone (NMSP) used to compare the quantification of dopamine receptors on pituitary adenomas with postmortem in vitro binding data (Yung et al., 1993). However, the marginal gain achieved in clinical benefit from this type of vigorous maneuvering has not been established and at the moment is perhaps best suited to a research setting.

The clinical utility of PET resides in extrapolation of its results to treatment planning. Most PET studies of brain tumors are of primary brain tumors (i.e., gliomas) with the findings directing subsequent treatment plans, such as continuing chemotherapy, further surgery, or observation. The usefulness of FDG-PET in the routine clinical evaluation of brain tumors other than gliomas, however, is not known. Meningiomas and metastases have only been scantily investigated vis-à-vis PET because treatment is directed by surgery for meningiomas and directed by treatment of the primary tumor for metastases. The use of PET is also limited in both meningiomas and metastases because of their variable uptake of FDG, which ranges from hypermetabolism to hypometabolism. With gliomas, a group of brain tumors of varying grade, there is an apparent trend of a higher uptake by higher grade tumors. Few studies, however, have delineated specific FDG uptake by specific glioma histology.

FDG-PET remains useful for differentiating recurrent tumor and post-treatment necrosis. In contradistinction, MRI of post-treatment patients often reveals persistent contrast enhancement. This is due to alterations in the architecture of normal brain parenchyma caused by the tumor or by the treatment for the tumor. Thus, grossly abnormal CT and MRI signals, including contrast enhancement, remain whether there is or is not recurrent tumor. In PET, necrotic tissues often have low FDG uptake, whereas tumors have a markedly elevated uptake. Immediately after radiation treatment, FDG uptake by brain and tumor may increase slightly, return to baseline, but then become subnormal after a few weeks (Valk et al., 1988). Surgery and administration of systemic steroids produced no significant changes in FDG uptake in the few days that followed in this study. Determining the location of a metabolic lesion (e.g., in gray matter versus in white matter) may help to distinguish recurrent tumor from post-treatment necrosis because there is a preferential and variable physiologic uptake of FDG by the gray matter. Some might argue that the PET findings are not necessary because a patient with primary glioma is expected to have multiple foci of tumor and infiltrating tumor fronts that spread throughout the entire brain, including in post-treatment necrotic tissues. A recent trend in this area has been to assess the temporal change of ^{18}F-FDG uptake in tumors. One study took measurements using a 3 hour window after injection. Uptake in the tumor rose in contrast to a pattern of steady or decreasing uptake in inflammation (Zhuang et al., 2000). Preliminary studies have indicated that rising FDG uptake over time correlates with the presence of tumor. Whether this finding is relevant to brain tumors is unknown.

Although the use of ^{11}C-methionine PET has been restricted mainly to research centers, it is a promising alternative to ^{18}F-FDG PET. Because there is minimal background activity in the brain, the lesions are well enhanced. The technology is, however, limited by a very short synthesis time due to the short half-life of ^{11}C-methionine (20 minutes). Occasionally, post-treatment necrosis also exhibits high uptake of the tracer. In one series of 29 patients, ^{11}C-methionine PET was reported to have better sensitivity (90%

versus 80%) than ^{18}F-FDG PET, although their specificities were comparable (70%) (Haynie et al., 1993; Wong, 1993). The search for tumor-specific markers in PET continues, with increasing emphasis on tumor-specific molecules such as essential amino acids (e.g., L-^{11}C-methionine) (O'Tuama et al., 1988), nucleotides such as ^{124}I-IUDR (Carnochan and Brooks, 1999), dopamine D2 receptors (Yung et al., 1993), and peripheral benzodiazepine receptors. A recent emphasis has been the development of ^{18}F-labeled compounds for tumor imaging. Tumor-related hypoxia may be studied using ^{18}F-labeled imidazole analogues (Yang et al., 1995). ^{18}Fluoro-ethyl-L-tyrosine (FET) is a new PET agent used for detection of tyrosine transporters on human brain tumors, producing results that compare favorably with those from ^{11}C-methionine (Derlon, 1989). ^{18}F-(3′-deoxy-fluorothymidine), or FLT, is a tracer that is retained in the cell after phosphorylation by thymidine kinase in a manner analogous to the relationship between FDG and hexose kinase. Tumor uptake of FLT is markedly elevated against background activities on PET (Dohman et al., 2000). ^{18}F-labeled PET tracers have the obvious advantage of a longer physical half-life, which allows regional distribution shortly after synthesis from the cyclotron to imaging facilities in the vicinity up to 100 miles away. Confirmation of the usefulness of these tracers awaits large-scale human studies of various tumor types to determine specificity.

Although the application of PET in the routine care of neuro-oncology patients is still under development, advances in PET technology have been furthered through the development of PET instrumentation with high spatial and temporal resolutions, along with novel specific PET metabolic tracers percolating down from the laboratory to the clinical arena. Recent efforts to co-register anatomic images with metabolic images permits exact determination of the location of metabolic lesions. With established co-registration algorithms (Woods et al., 1993), MRI and PET images are fused, pixel to pixel, so that the metabolic lesion is clearly identified on the anatomic image, as seen in Color Figure 2–4. Research in this area has been bolstered by an infusion of federal research money for clinical studies, ushering in a new era in PET technology for use in oncology. These developments, along with supported research, are creating vast opportunities for improved patient care, as well as state-of-the-art clinical and basic research in neuro-oncology.

RADIONUCLIDE THERAPY IN NEURO-ONCOLOGY

External beam radiation therapy with various schemes to achieve high target to nontarget delivery remains in the mainstream of radiotherapy. The use of radionuclides in therapy nevertheless may prove advantageous in selected types of cancer. Beta-emitters (in contrast to gamma-emitters) with their short millimeter ranges and high radiation absorbed dose deposited in a small volume are theoretically useful in cancer treatment. However, except for thyroid cancers and their cerebral metastases, systemic administration does not deliver enough radioactivity to brain tumor sites (usually <0.1% of injected dose/gram) to be effective and simultaneously subjects the rest of the body to excessive toxicity.

Interestingly, for systemic applications outside of the central nervous system, two beta-emitters have been shown to be effective and have received FDA approval for the palliation of painful osseous metastasis. ^{89}Strontium (^{89}Sr) chloride (Metastron) (Nair, 1999) and ^{153}Samarium-EDTMP (^{153}Sm-EDTMP) (Quadramet) (Resche et al., 1997) have physical half-lives of 50 days and 2 days, respectively. They bind to osteoblastic centers in osseous metastases and serve as a localized irradiation source against metastatic tumors. As many as 80% of patients receive sustained relief of pain from osseous metastasis for several months or longer. Empirically, the onset of pain relief is faster (in 2 to 3 days) with ^{153}Sm-EDTMP than with ^{89}Sr (2 to 3 weeks). The faster onset of action of ^{153}Sm-EDTMP is probably related to its quick deposit of one-half of its radiation within a shorter duration.

There are few similar examples of effective radiopharmaceuticals to treat brain tumors. The approach is usually locoregional (Akabani et al., 2000a). Brachytherapy using ^{125}I seeds has been reported with mixed results that showed a benefit primarily in smaller glioblastoma tumors (Mehta and Sneed, 1997). Injection of ^{32}P-colloid is another approach with limited success in cystic glioma, and it also has been limited by producing systemic toxicity (reviewed by Harbert, 1996b). Direct injection of a small amount (0.5 mCi) of ^{201}Tl into experimental intracerebral gliomas in rats resulted in eradication of the tumors by Auger electrons (Sjoholm et al., 1995), but no human studies have been reported. More recently, intracavitary brachytherapy using inflatable double-

lumen balloons filled with ^{125}I-iodo-hydroxybenzene sulfonate (Iotrex) in amounts as high as 532 mCi and as long as 16 hours of exposure has had few incremental adverse effects (deGuzman et al., 2000). A phase I study of intralesional continuous infusion into a glioma mass of ^{131}I-labeled chimeric antibodies against DNA/histone complexes has also been reported and demonstrates quadruple tracer retention through multiple-catheter injection (Spicer et al., 2000).

An Italian study of intralesional injection of monoclonal antibodies (BC4) against tenascin into patients with glioblastoma multiforme reported improved survival with ^{90}Y-labled BC4 and ^{131}I-labeled BC4. The overall median survival rates for ^{90}Y-BC4 in this study were 17 and 32 months for bulky disease and small remnant disease, respectively, and 14 months and 24 months, respectively, for ^{131}I-BC4 (Riva et al., 2000). The study population was composed of patients who had multiple previous failed therapy regimens, including radioimmunotherapy. Studies in more stratified patient populations are necessary to confirm the significance of results obtained thus far.

Alpha-emitters may provide a higher radiation absorbed dose to a more confined volume. This occurs because a high level of energy is emitted from the massive particle and delivered at a close range that is less than 0.1 mm in diameter. In theory, one particle is sufficient to destroy a cell. Such a high potential for destruction can also engender nonspecific toxicity because essentially all tissues in the immediate vicinity are subject to destruction along with tumor tissue. The clinical use of alpha-emitters will require specific knowledge of dosimetry at organ, tissue, cellular, and subcellular levels (microdosimetry). Despite these potential barriers, the clinical applications of alpha-emitters will increase because of their greater availability following the Cold War. In fact, the use of postsurgical intracavitary injection of up to 10 mCi of [213]Bi-81C6 antibodies in human glioma has been reported to cause low systemic toxicity in a phase I human study (Akabani et al., 2000b). Dosimetric estimates have also been derived (McLendon et al., 1999), confirming a high absorption of radiation in tumor contrasted with low levels of radiation absorption by the rest of the body.

Locoregional use of gold radiocolloid for intrathecal treatment of leptomeningeal metastasis has had partial success, limited by hematotoxicity, myelopathy, and radiculopathy, the last being due to sequestration of colloid in the thecal sac (Harbert, 1996a). Several groups reported the use of intrathecal ^{131}I-labeled monoclonal and polyclonal antibodies to treat leptomeningeal metastasis (Bigner et al., 1995). Using a ^{131}I dosage as high as 140 mCi with 60 mg proteins, scientists reported promising results, with hematotoxicity as the dose-limiting factor. However, what contribution antigen–antibody binding makes to the effectiveness of this treatment has not been established. In fact, this hypothesis may be in doubt because of the multiple biologic barriers that antibodies must overcome to reach and remain bound to the limited supply of antigens. The radiation dosimetry in CSF from this class of radiopharmaceuticals is only marginally better than that from ^{131}I-sodium iodide (Wong et al., 2000b) or ^{131}I-labeled human serum albumin (Johnston et al., 1972; Stabin and Evans, 1999), both of which have no tumor binding affinity.

The disadvantages of monoclonal antibodies (MoAbs) include their limited availability, the presence of foreign protein in the CSF, and the prolonged retention of ^{131}I that directly correlates with hematotoxicity (Wahl et al., 1998). One recent study employed ^{90}Y-labeled biotin in postsurgical cavities, with and without pre-targeting with biotinylated antitenascin MoAbs to treat glioblastoma patients. The preliminary results have demonstrated slight improvement in outcome with MoAb (one more patient in partial remission) but no difference in survival (Bartolomei et al., 2000). In fact, our laboratories are studying whether intrathecal application of beta-emitting radiopharmaceuticals with no tumor affinity is sufficient for treating leptomeningeal metastasis. Earlier simulations have demonstrated a promising radiation dose delivery to tumors in the CSF, with little effects on the brain and spinal cord (Wong et al., 2000c). A phase I human study is underway at M. D. Anderson Cancer Center. It is hoped that the results from this trial will show that locoregional application of nonspecific beta-emitters in the CSF may provide sufficient radiation to treat tumor cells in the CSF and surrounding leptomeninges.

With the availability of more radionuclides, a better understanding of radiation biology, and establishment of more precise dosimetric measurements, the use of alpha- and beta-emitters in neurooncology therapy may prove to be desirable alternatives after conventional therapeutic avenues have been exhausted.

CONCLUSION

Both nuclear medicine and neuro-oncology have shared in the benefits derived from the explosive growth of medical knowledge during the last few decades. Along with a constant flux of theoretical and empirical changes in medicine, the role of nuclear medicine in neuro-oncology has continued to evolve. Its initial role in evaluation of anatomic integrity has been transformed into a confirmatory role of physiologic and pathologic anomalies in brain tumors in which anatomic alterations have already been established. An increased understanding of how radionuclides interact with tissues has also enabled beta-emitters, and possibly alpha-emitters, to be used in cancer therapy. Whereas one of the current trends in medicine is to provide more specific diagnostic insights and therapeutic strategies aimed at the molecular level, nuclear medicine techniques have become invaluable in the practice of oncology and neuro-oncology. Nuclear medicine applications will play increasingly important roles in the future of clinical medicine because of the advantages of picomolar sensitivity and low chemical perturbation, along with the development of new instruments for monitoring and new molecular markers that can be used as probes on the organ level as well as on a subnucleotide level.

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