Chapter X: SPECT in the evaluation of brain tumors

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X-1 Brain tumors

A brain tumor is an intracranial neoplasm that has various pathologies (*1*).Using diagnostic information, a tumor can be classified as least aggressive (benign) to most aggressive (malignant). In most cases, a brain tumor is named for the cell type of origin or its location. Identifying the type ofbrain tumor helps to determine the most appropriate course of treatment.

There are three main types of brain tumors: intra-medullary, extra-medullary, and metastatic. Most intra-medullary tumors originate from glial cells and are called gliomas.A glioma is generally infiltrative into the brain parenchyma; therefore, a complete surgical excision is usually difficult. The prognosis of patients with a glioma depends on the malignancy grade of the tumor; although, it is generally poor. On the other hand, most extra-medullary brain tumors are benign and complete surgical removal results in a good prognosis. Metastatic brain tumors are always malignant and although the prognosis depends on a patient’s systemic condition, it is generally poor.

X-2 Diagnosis of brain tumors

The main symptoms of brain tumors are headache, paresis, and epileptic seizures. A progressive clinical course suggests a brain tumor. An accurate preoperative diagnosis of the tumor pathology and malignancy grade is often challenging. Most intra-medullary tumors are malignant; however, they may be benign; while, the majority of extra-medullary tumors are benign,but malignant tumors also exist. Selecting an appropriate treatment depends on the malignancy grade and prognosis of the tumor; thus, a correct preoperative diagnosis is important. The final diagnosis depends on the pathological analysis of the surgical specimen.

X-3 Radiological diagnosis of brain tumors

Brain magnetic resonance imaging (MRI) is the modality of choice for evaluating patients who have symptoms and signs suggesting a brain tumor and for assessing the tumor location and extent. Even if most clinical questions can be answered by MRI and computed tomography (CT), these techniques have limitations in the characterization of brain lesions, defining the tumor extent,

therapy monitoring, and in detecting the recurrence or progression of tumors. High contrast enhancement in a tumor means high blood flow but not necessarily malignancy. Meningioma and pituitary adenomas are typical benign extra-medullary tumors with high contrast enhancement. In addition, complete visualization of infiltrating malignant glioma cells is difficult, even with high resolution MRI.

The brain neoplasms are treated with various combinations of surgery, radiation, and chemotherapy. Changes that follow treatment may include edema and radiation necrosis, and it is often challenging to differentiate between tumor recurrence and such benign physical changes with CT or MRI(*2-5*). Nuclear medicine imaging allows *in vivo* investigation of tumor metabolism, given the wide availability of radiotracers, and plays a major role in the diagnosis and follow-up of patients with brain tumors.

X-4 SPECT for the diagnosis and evaluation of brain tumors

Single photon emission computed tomography (SPECT) is a valuable diagnostic modality for the evaluation of the brain tumor malignancy grade and activity.Thallium-201 (Tl) and two Technetium-99m labeled

radiopharmaceuticals (methoxyisobutylisonitrile (Tc-MIBI) and tetrofosmin (TF))have been clinically used with SPECT to evaluate brain tumors. SPECT has also been used with the radioactive labeled amino acid 3-[123I]iodo-a-methyl-L-tyrosine for the diagnosis of brain tumors and evaluation of tumor response to radiation therapy.

X-4-1 Tl SPECT

Tl, a potassium analog, is taken up by viable tumor cells but not by necrotic tissue or non-proliferating glial cells(*6*).It is cyclotron produced with a physical half-life of 73 hours. Tl has been used in myocardial scintigraphy and in evaluating lung carcinomas and brain tumors. Tl SPECT is useful for identifying the presence of a tumor (*7*), grading of the tumor malignancy(*3, 4, 6*),and distinguishing tumor recurrence from radiation necrosis (*2-4*)(**Figure 1**).The SPECT procedure involves imaging approximately 20-30 minutes following injection of 74-148 MBq of Tl. Occasionally, a 2-hour delayed Tl acquisition may be helpful as the abnormal tumor tissue would be expected to washout more slowly than normal brain tissue (*8, 9*).The SPECT imaging should be done using

a low energy general purpose collimator. The photopeak should be centered at 80 and 167 keV. The Tl index, the ratio of counts in the lesion region of interest (ROI) to counts in the contralateral ROI, is used to differentiate between low and high grade gliomas(*6*) as well as between recurrence and radiation necrosis (*11, 12*).The value of these ratios varies according to the identification of the ROI, the location and size of the lesion, and whether or not there is central necrosis. Some investigators recommend drawing the ROI over the highest pixel counts of Tl uptake; while, others recommend drawing it over the inner and outer border of the tumor and averaging the pixel counts. Ratios above 1.6-2.4 may indicate malignant lesions; while, lower ratios indicate either benign lesions or early recurrence (*13*).In a population of 90 patients with supratentorial brain tumors, the overall sensitivity and specificity of Tl in detecting the lesions were 71.7% and 80.9% respectively(*14*).Dynamic Tl SPECT is useful to evaluate tumor vascularity, histopathology, and malignancy (*15, 16*).The utility of Tl SPECT in differentiating toxoplasmosis from lymphoma in AIDS patients was demonstrated by Kessler et al.(*17*) with a sensitivity of 100% and specificity of 93%.

The utility of Tl SPECT as an early predictor of outcome in patients with recurrent gliomas has been shown by Vos et al.They reported that at baseline and follow-up, maximal tumor intensity by Tl SPECT was the strongest predictive variable and was inversely related to overall survival as well as progression-free survival. They also showed a progression of maximal tumor intensity after two courses of chemotherapy was a powerful predictor of poor outcome. For a Tl-avid lesion that has been treated and shown to be Tl negative on follow-up, any Tl uptake is an indicator of tumor recurrence(*13*).Glioma surgery may improve the prognosis, but this is controversial, possibly due to the method of evaluating glioma surgical extent. In a study from our group, we evaluated the glioma surgical extent using fusion images of preoperative Tl SPECT with postoperative MRI to predict the prognosis of the patients regarding the removal rate and postsurgical residual tumor. All patients received standard adjuvant radiation and chemotherapy after surgery. We found the fusion image of preoperative Tl SPECT and postoperative MRI was more useful for evaluating glioma removal extent than just MRI. Patients with partial removal had a poor prognosis; thus, the aim should be for maximum surgical removal using multimodal images including MRI and Tl SPECT. The total removal of Tl

SPECT positive lesions improves the prognosis and prevents early recurrence(*18*).

Inflammation after surgery or radiation is a major cause of false positives(*3, 4, 19-21*). Other inflammatory lesions, like brain abscesses, can be also a source of a false positive scan(*22*) (**Figure 2**). Using combined Tl and ^{99m}Tc–hexamethylpropyleneamine oxime (Tc-HMPAO) for brain tumors has been recommended to increase the specificity of Tl SPECT (*2, 23*). Carvalho et al. assessed the ability of sequential Tl and Tc-HMPAO SPECT to distinguish tumor recurrence from radiation changes after high-dose radiation therapy for malignant gliomas. The authors found Tc-HMPAO SPECT is useful for identifying the absence of solid tumor recurrence in patients with low to moderate Tl uptake (ratio 1.1 to 3.4) and low perfusion to that site (less than 0.5.)(*23*).

Some causes of false negative findings may include small tumor size; located centrally or adjacent to areas of physiological tracer uptake, such as choroid plexus; histological heterogeneity; and cystic or necrotic components (*24, 25*).Young et al.(*25*) reported that when using a Tl-index > 2 in lesions bigger

than 2 cm, Tl SPECT has a 100% sensitivity and 89% specificity for the differentiation between brain lymphoma and toxoplasmosis in patients with AIDS; while, the sensitivity and specificity were 50% and 82%, respectively, in lesions smaller than 2 cm.

Both central neurocytomas and gangliogliomas are benign gliomas with a high Tl uptake (*26*)(*27*). High cell density and high metabolic rate are thought to explain the high Tl uptake in these low proliferative tumors. In our series, one patient with a central neurocytoma showed high Tl uptake and no Tc-MIBI uptake (**Figure 3**). In this case, Tc-MIBI SPECT was more accurate than Tl SPECT to evaluate tumor malignancy. Pilocytic astrocytoma is one of the most benign gliomas and the Tl SPECT findings show variable uptake (*28*). Lower Tl uptake is also observed in early follow-up studies after surgical excisions and/or aggressive chemotherapy. This is due to granulation tissue and new vascularity associated with treatment(*13*)

X-4-2 Tc-MIBI SPECT

Tc-MIBI is a lipophilic cationic complex with a physical half-life of 6 hours, initially designed for myocardial perfusion SPECT. Tc-MIBI SPECT is also useful to diagnose brain tumor recurrence (*29, 30*);evaluate the biological characteristics of brain tumors(*31*), tumor volume, and survival (*32, 33*); and in the differential diagnosis of radiation necrosis(*5*). As with Tl imaging, the Tc-MIBI index can be used to differentiate between low and high grade gliomas (*34*) as well as recurrence and radiation necrosis (*29*), and to estimate the prognosis (*32, 33*). Tc-MIBI is concentrated in the mitochondria as the result of active diffusion due to increased metabolic needs (*29*). Its uptake is affected by tumor malignancy, viability, density, oxygenation, vascular supply, and blood brain barrier (BBB) disruption (*35*). These factors are not linearly correlated because glioblastoma, the most malignant form of glioma, is pathologically heterogeneous and includes internal necrosis.

In Tc-MIBI SPECT, tumor imaging occurs approximately 20-30 minutes following injection of about 740 MBq Tc-MIBI.Delayed images (2-4 h p.i.) have been also recommended. The SPECT imaging should be done using a low energy general purpose collimator and the photopeak should be centered at 140

keV. In the brain, Tc-MIBI is taken up by normal choroid plexus, scalp, the pituitary gland, and nasopharyngeal tissues (*36*).

With respect to the histological type, a higher Tc-MIBI retention index has been noted in glioblastoma multiforme compared with metastatic tumors. In addition, while Tc-MIBI SPECT shows high uptake and retention in malignant gliomas, washout from metastatic brain tumors is faster than from glioblastomas(*37*). Tc-MIBI has also been successfully used in high-grade gliomas to distinguish recurrent tumor from radionecrosis (*30*) and when the results of both CT and MRI are difficult to interpret, because of inflammation resulting from surgery or radiation, and offer only an imperfect indication of tumor viability(*38*). A false negative finding by MIBI SPECT may occur due to an intact BBB. (*30*). In a study on patients in the pre-surgical phase for interparenchymal brain tumors, Tc-MIBI SPECT identified tumors in the fronto-temporal regions more easily than in the temporal regions or in the posterior fossa (*36*). P-glycoprotein is a drug efflux pump in the cell membrane and it acts to remove Tc-MIBI from tumor cells (*40, 41*). Other studies have suggested that p-glycoprotein expression in malignant gliomas may cause false negative results in Tc-MIBI SPECT (*42-44*).However, the effect of p-glycoprotein expression on clinical Tc-MIBI

SPECT images has been investigated, and the effect was negligible in the diagnosis of brain tumor malignancy (*45*). Henze also reported that p-glycoprotein efflux does not contribute to falsely negative MIBI SPECT, since MIBI washout did not occur between the early and late SPECT scans (*46*).

Some of the false positive results were due to recent radiation induced local disruption of the BBB (*30*). Tc-MIBI shows early accumulation into the normal choroid plexus and good wash out from it. .Choroid plexus papillomas show slower tracer wash out than the normal choroid plexus;hence, the delayed MIBI index is higher than the early MIBI index(*47*).

X-4-2-1 Comparison of Tl and MIBI brain SPECT in patients with gliomas

The diagnostic values of brain Tl and Tc-MIBI SPECT have been evaluated by our group using sensitivities and specificities with arbitrary cut off values. The diagnostic ability of Tl SPECT and Tc-MIBI SPECT were directly compared for patients with an initial glioma using ROC analysis. The study population included 59 patients with gliomas. The benign group included patients with low grade astrocytomas and central neurocytomas; while,the malignant group included patients with anaplastic astrocytomas and glioblastomas. All patients

underwent Tl and Tc-MIBI SPECT and tumor/not-tumor (T/N) ratios were calculated. The area z-score(A_z) values were calculated from the areas under the ROC curves (**Figure 4**). The delayed Tc-MIBI had the highest A_z while the early MIBI had the lowest A_z. Both Tl and MIBI SPECT are considered useful imaging modalities for the evaluation of glioma malignancies. Delayed MIBI SPECT demonstrated better diagnostic value in patients with gliomas based on ROC analysis; although,the difference was not statistically significant(*48*).

Some studies have reported that Tc-MIBI SPECT has higher sensitivity and specificity than Tl SPECT for adult and childhood brain tumors and for the differential diagnosis of recurrence and radiation necrosis (*5, 33, 38*); however, other studies disagree(*37*). This discrepancy may be caused by small and heterogeneous patient populations and arbitrarily selected cut off values. In Tl SPECT, there is some normal brain uptake, which makes the T/N ratio low. Tc-MIBI has a high photon energy level and higher T/N ratio in comparison with Tl SPECT and yields clear SPECT images with high sensitivity for malignant brain tumors(*5, 29, 38*).

X-4-3 Tc-Tetrofosmin SPECT

TF is a lipophilic cationic tracer with a physical half-life of 6 hours that was initially used for myocardial perfusion SPECT. The utility of TF in evaluation of brain tumors has been demonstrated(*49-52*). Soricelli et al. (*49*) showed significant agreement among Tl and TF SPECT for the diagnosis of brain tumors; however, the image quality, contrast, and the definition of tumor margins obtained by TF were superior to those with Tl. TF is also useful for non-invasive grading. There was a striking difference between the TF index in low grade and high grade gliomas, which was not the case for Tl, Tc-MIBI, and 18F-FDG PET(*53*). TF can also distinguish tumor recurrence from radiation necrosis(*50-52*).We compared the radiological image findings from TF and Tl SPECT for 11 patients with brain tumors.The tracer uptakes of TF and Tl were almost matched. In the patients with meningioma, both TF and Tl early images showed high uptake and these tracers were washed out in delayed images (**Figure 5**). Both TF and Tl delayed SPECT images showed high uptake in tumors from patients with glioblastomas(**Figure 6**).

There is physiological TF uptake in the normal choroid plexus, which contributes to the spatial correlation between tumors and ventricles. TF SPECT is better and more useful than Tl SPECT to diagnose tumor location, extent, malignancy, viability, and effects from therapies(*54*).

X-4-4:3-[123I]iodo-a-methyl-L-tyrosine SPECT

3-[123I]iodo-a-methyl-L-tyrosine (123I-IMT) is an amino acid SPECT tracer for brain imaging.Tumors are imaged with SPECT approximately 10 minutes after the injection of 370-740 MBq 123I-IMT. To prevent the uptake of free iodine, the thyroid should be blocked with 400-600 mg sodium perchlorate 30 minutes before tracer application. The SPECT imaging should be done using a low energy high resolution collimator using a 20% energy window centered on the 159-keV photopeak.123I-IMT SPECT was directly compared with [methyl-11C]-L-methionine (MET) PET in 14 patients with cerebral gliomas(*55*). Visual comparison of the scans yielded no differences in tumor size and shape with both methods. The tumor to brain ratios of 123I-IMT SPECT and MET PET showed a significant correlation especially in the early, transport dominated phase at 15 min after injection.

Kuwert et al.(*56*) showed that 123I-IMT SPECT may aid in differentiating high-grade gliomas from histologically benign brain tumors and non-neoplastic brain lesions; however, this modality was inappropriate for distinguishing non-neoplastic from benign lesions. In this study, the sensitivity and specificity of 123I-IMT SPECT were 71% and 83%, respectively, for differentiating high grade from low grade gliomas, 82% and 100%, respectively, for distinguishing high-grade gliomas from non-neoplastic lesions, and 50% and 100%, respectively, for discriminating low-grade gliomas from non-neoplastic lesions(*56*).

The utility of 123I-IMT SPECT for determining tumor grade and prognosis of the disease is controversial(*56-60*). A strong correlation between tracer uptake and tumor proliferative activity was reported by Kuwert etal.(*59*). In contrast,Weber et al.(*61*) reported that 123I-IMT uptake appeared not to correlate with the biological aggressiveness of tumor cells in patients with unresectable high-grade gliomas. Nevertheless, the clear association between focal 123I-IMT uptake after tumor resection and poor survival suggests that 123I-IMT is a specific marker for residual tumor tissue(*61*).

It is very important to precisely determine the tumor extent for planning surgery or radiation. 123I-IMT is taken up in brain areas with an intact blood-brain barrier and IMT SPECT appears to be able to image the infiltrating tissue of cerebral gliomas like MET(*62*).In a study using IMT SPECT in addition to MRI for planning radiation therapy, a larger tumor volume was detected by 123I-IMT SPECT than by conventional MRI. The authors highlighted that IMT-SPECT investigations improved tumor detection and delineation in the treatment planning process (*63*).

Several studies yielded good sensitivity and specificity of IMT SPECT for the detection of viable tumor tissue in previously treated patients (*57, 58, 64*). Bader et al. showed that 123I-IMT SPECT was equivalent to a stereotactic biopsy in its ability to identify high-grade tumors at recurrence (*57*).The fusion of 123I-IMT SPECT images with MRI improves the interpretation of the findings and may increase the specificity of the investigation(*65*). In addition, 123I-IMT-SPECT was a promising complementary imaging tool for the detection of recurrences of non-astrocytic intracranial tumors and for distinguishing them from treatment induced changes(*66*). Several studies indicate the utility of 123I-IMT in the follow-up of patients with brain tumors (*57, 64, 67*). Patients with

recurrence had significantly higher ratios of 123I-IMT uptake in the tumor area to that in the background region than patients without recurrence. The majority of brain metastases exhibit high 123I-IMT uptake, which does not allow differentiation from gliomas. A combination of 123I-IMT and Tl SPECT, however, may be able to distinguish high-grade gliomas from other malignant brain lesions, like metastases, with high accuracy (*68*).

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