^{201}Tl and ^{99m}Tc-MIBI Tumor Imaging

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INTRODUCTION

Tumor imaging comprises a significant portion of the practice of nuclear medicine.

Functional tumor imaging is a growing area in nuclear medicine with the development of both tumor-specific and non-specific radiopharmaceuticals as well as new instrumentation.

The imaging modality is applied in diagnosing and staging tumors, monitoring therapy, and detecting residual or recurrent tumors after therapy.

In this section, only non-specific tumor imaging agents-namely ^{201}Tl chloride and ^{99m}Tc MIBI or sestamibi (methoxy isobutyl isonitrile) are discussed.

1. Thallium-201 Chloride

Thallium-201 is a potassium analog and it has been used in the evaluation of myocardial perfusion since the 1970s. Recently, clinical data has indicated that ^{201}Tl can also play an important role in imaging a wide variety of tumor types. These include brain tumors, breast cancer, thyroid cancer, bone and soft tissue sarcomas, low grade lymphoma, etc.

1) Physical Characteristics and Dosimetry

Thallium is a metallic element. ^{201}Tl is produced by a cyclotron. It decays by electron capture with a half-life of 73 hours. A cluster of characteristic x-rays between 69 and 83 keV(94%) and gamma rays of 135(3%) and 167 keV(10%) are emitted. The kidney is the target organ and it received 3.6 rads/mCi. The whole body dose is 0.63 rads/mCi.

2) Mechanism of Tumor Uptake

The mechanism of ^{201}Tl tumor uptake is not clearly understood, but it appears to be affected by several factors. Sufficient blood flow within a tumor is one important requirement for successful ^{201}Tl delivery. Poor blood flow to a tumor results in decreased ^{201}Tl uptake. However, a sharp increase in blood flow does not necessarily induce a correspondingly high level of ^{201}Tl uptake. The effect of blood flow on ^{201}Tl tumor uptake is nonlinear.

Since ^{201}Tl is a potassium analog, it behaves, biologically, like potassium. Consequently, ^{201}Tl uptake is facilitated by the ATPase dependent sodium-potassium pump system in the cell membrane which actively expels sodium from the cells in exchange for ^{201}Tl. ^{201}Tl is accumulated by viable tumor tissue but not by necrotic tissue, perhaps because of the lack of a functional ATPase dependent pump system.

3) Limitations of ^{201}Tl Tumor Imaging

The major limitation of ^{201}Tl in tumor imaging is its low photon energy of 80 keV and limited photon yield from the maximum approved dose of 3mCi. These factors result in poor image resolution especially in SPECT studies. Thallium imaging of the thorax, abdomen, and pelvis is severely limited by high normal surrounding activities. SPECT must be performed in order to

detect tumors in these regions.

4) Imaging Method

The usual adult dose of 3 mCi is given intravenously. For planar or SPECT, the optimal imaging time is 10 to 30 minutes after injection. We prefer whole body imaging using a dual detector system at a slow speed followed by spot views. SPECT of the organ of interest requires at least 40-45 minutes of acquisition time using a triple detector system to insure sufficient count density.

5) Clinical Applications of ^{201}Tl Tumor Imaging

(1) Brain Tumor

^{201}Tl has been used in grading astrocytoma and in differentiating malignant from benign tumors. The higher the grade of astrocytoma, the greater the uptake of ^{201}Tl. ^{201}Tl brain SPECT can identify tumor viability whereas CT and MRI often cannot differentiate between active tumors and postoperative or postradiation changes. ^{201}Tl accumulation in brain tumors indicates tumor viability.

In the interpretation of ^{201}Tl brain SPECT, both a visual assessment and semi-quantitative method are utilized. A comparison of ^{201}Tl uptake in a tumor and in contralateral normal tissue (and/or skull and scalp) is commonly used in clinical practice. The semi-quantitative method involves drawing the region of interest over the highest pixel counts or averaging the pixel counts of ^{201}Tl tumor uptake. The counts are compared to average pixel counts from the contralateral regions mentioned above. A ratio above 1.6 usually indicates malignant glioma.

(2) Breast Cancer

Recent reports demonstrate that ^{201}Tl scintimammography has a high sensitivity in the detection of primary carcinomas of the breast. The highest target-to-background ratio occurs 15 minutes after injection, and imaging is most successfully performed in the prone lateral position. Benign lesions seldom depict ^{201}Tl uptake when uptake occurs, it is mild or diffuse. As mentioned previously, ^{201}Tl is not the imaging agent of choice because of its low photon energy and limited photon yield. Recently, ^{99m}Tc sestamibi has been explored as scintimammographic agent. Dr. Richard A. Holmes will discuss the efficacy of this agent in greater detail.

(3) Thyroid Cancer

Our laboratory considers ^{201}Tl to be an excellent alternative tracer to I-131 in thyroidectomized patients for well differentiated thyroid carcinomas(WDTC). ^{201}Tl imaging is performed while the patient contiunes in thyroid hormone therapy. Waxman and others have found ^{201}Tl to be more sensitive than I-131 in the detection of metastatic lesions of WDTC. The drawback is that ^{201}Tl is not specific for thyroid cancer. Patients should undergo whole body I-131 scans for consideration of I-131 therapy where a positive ^{201}Tl is accompanied by increased levels of serum thyroglobulin.

(4) Soft Tissue and Bone Sarcoma

^{201}Tl scintigraphy accurately depicts the extent of tumor involvement in primary bone tumors as well as in soft tissue sarcomas of the extremities. Also, ^{201}Tl imaging is valuable for following tumor response to chemotherapy. A significant decrease in ^{201}Tl occurs within weeks following successful chemotherapy. Multidrug resistance (MDR) of tumor prior to chemotherapy could be detected by scintigraphy using both ^{201}Tl and ^{99m}Tc-MIBI.

(5) Low Grade Lymphoma

Low grade lymphomas are better imaged with ^{201}Tl than with ^{67}Ga which is more effective in imaging high grade lymphomas. Again, ^{201}Tl appears useful in determining the efficacy of chemotherapy in low grade lymphomas.

2. ^{99m}Tc-Methoxy Isobutyl Isonitrile (MIBI, Sestamibi)

^{99m}Tc MIBI, a lipophilic cationic complex, is a technetium myocardial perfusion agent which has tumor imaging capabilities like ^{201}Tl. Sestamibi with a ^{99m}Tc label, however, has imaging advantages over ^{201}Tl, particularly in performing SPECT studies of tumors in various organs. ^{99m}Tc has an ideal energy of 140keV and an abundance of photon flux (20-30mCi). ^{99m}Tc sestamibi has been very useful in localizing parathyroid adenomas. Other tumors which have been evaluated successfully with MIBI include breast cancer, brain tumors, primary bone tumors, soft tissue sarcomas of the extremities, etc.

The multidrug-resistant P-glycoprotein (plasma membrane protein) encoded by the multidrug resistance gene(MDR1) is an important resistance mechanism of certain tumors against chemotherapeutic drugs. ^{99m}Tc MIBI, a substrate of Pgp, could be used in the detection of MDR in the tumor before chemotherapy. It is expected that a strong clinical effort will be made to study the presence of MDR in tumors by means of scintigraphy.

1) Mechanism of Tumor Uptake

The exact mechanism of ^{99m}Tc MIBI uptake in tumors is not completely understood. A recent study suggests that 90% of the tracer activity is localized in the mitochondria and the cytoplasm in response to elevated membrane potentials across the membrane bilayers of the cell and mitochondria. Tumors exhibit elevated potentials due to their increased metabolic rates. Like ^{201}Tl, an adequate blood flow within the tumor is essential for delivery of the tracer.

2) Imaging Method

The usual adult dose-between 20 and 30 mCi-is given intravenously. The optimal imaging time for scintimammography is 5 minutes after injection starting with 10 min. prone lateral views. For other tumors, planar or SPECT studies are performed 10 to 30 minutes after injection. Brain SPECT requires 30 to 35 minutes of imaging time which is about 10 minutes shorter than ^{201}Tl brain SPECT performed in our laboratory.

3) Clinical Applications

(1) Parathyroid Adenoma

Since the introduction of MIBI as a parathyroid imaging agent in 1989, ^{99m}Tc MIBI has been routinely used for localizing parathyroid adenomas by many nuclear medicine practitioners. Its ^{99m}Tc label has an imaging advantage over ^{201}Tl.

There is differential washout of MIBI from adenomas as compared with normal thyroid glands. MIBI washout is slower from the adenomas than from the thyroid with exception of oxyphilic adenomas which have a rapid washout. In our experience, MIBI imaging alone is sufficient to localize adenomas without having a baseline thyroid scan.

(2) Breast Cancer

^{201}Tl is not the imaging agent of choice because of its low photon energy and limited photon flux. Khalkhali and others at Harbor UCLA Medical Center have shown that ^{99m}Tc sestamibi scintimammography in prone lateral position exhibits a high sensitivity in the detection of breast cancer. This ability helps to reduce the number of unnecessary biopsies. This author has tried the imaging method at Ajou University Hospital in thirty patients with a high clinical or mammographic suspicion of breast cancer. In this selected patient population, the sensitivity of the imaging technique was close to 100 percent. Details of the technique will be discussed by Dr. Richard Holmes.

(3) Brain Tumors

Similar to ^{201}Tl, ^{99m}Tc sestamibi is useful in grading astrocytoma, diagnosing and detecting

CPA tumors, and detecting viable tumors following surgery or radiation therapy. This author has found that MIBI and ^{201}Tl SPECT studies are comparable in the evaluation of brain tumors with a few exceptional cases in which discordant SPECT findings have been noted. We believe ^{201}Tl avid and absent MIBI tumor uptake might be due to MDR. We superimpose the functional SPECT images of MIBI on morphologic studies such as MRI to more accurately localize the lesion for biopsy.

(4) Primary Bone Tumors and Soft Tissue Sarcoma

Recent data demonstrates that ^{99m}Tc sestamibi is equally sensitive as ^{201}Tl in the detection of primary bone tumors. Additional abnormal sites are better detected using MIBI.

An excellent correlation was noted between thallium and MIBI and biopsy findings in the evaluation of tumor response to chemotherapy prior to limb salvage procedures.