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Single-photon agents for tumor imaging: ^{201}Tl, ^{99m}Tc-MIBI, and ^{99m}Tc-tetrofosmin

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This review aims at fostering comprehension and knowledge not only for expert physicians who can skillfully handle various techniques for tumor imaging but also for young practitioners in the field of nuclear medicine. As image processing software and hardware become smaller, faster and better, SPECT will adapt and incorporate these advances. A principal advantage of SPECT over PET is the more widespread availability of the equipment and lower cost for the introduction of the system in community-based facilities. Moreover, SPECT has become less dependent on a limited number of acknowledged experts for its interpretation owing to a variety of handy computer tools for imaging analyses. The increasing use of PET in tumor imaging is not necessarily proportional to the decline of SPECT. General physicians' attention to SPECT technology would also increase more by evoking their interest in "tracer imaging."

Key words: ^{201}Tl, ^{99m}Tc-MIBI, ^{99m}Tc-tetrofosmin, tumor imaging, SPECT

INTRODUCTION

NUCLEAR ONCOLOGY, shown here as a tool for tumor imaging [e.g. Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET)], involves a large variety of procedures to assess patients with already-known or unspecified neoplastic conditions. It has progressed with an enormous quantity of knowledge on molecular and clinical oncology becoming available, and some current topics, such as scintigraphic assay of multidrug resistance, are premised on gene concepts. One of the medically desirable minimum services required for radiologists and nuclear medicine physicians is a simple tool to divide lesions into two groups, namely tumor and non-tumor. At this moment, we can have a PET that appears to represent the only feasible solution to the above insistent demand. However, contrary to the advent of clinical PET as the state-of-the-art medicine, a large majority of hospitals based in local communities are reluctant to install PET scanners and baby-cyclotrons because of the fragile financial conditions and drastic reforms of the medical-care system in our country. Therefore, hospital finance committee's consideration of the renewal of nuclear medicine devices is inevitably weighted to the selection of combined PET/SPECT cameras. In this context, although it is certain that the era of clinical PET has arrived, the demand for tumor imaging by SPECT will not necessarily decrease. Owing to the new heights of popularity of clinical PET, we believe that the general physicians' attention to SPECT will also increase by evoking their interest in "tracer imaging." Therefore, we need to understand again the single photon imaging tracers used for current tumor imaging: ^{201}Tl, ^{99m}Tc-MIBI and ^{99m}Tc-TF.

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GENERAL INTRODUCTION

1. ^{201}Tl

As a help to the understanding of radioactive thallium-201 (^{201}Tl) used in nuclear medicine, general information on several isotopes of Tl, non-radioactive and radioactive, is provided here. In the periodic table, non-radioactive Tl [atomic number: 81, atomic weight: 204.3833, density:

11.8 g/cm^3, phase at room temperature: solid metal] occupies a position between mercury (Hg, atomic number: 80) and lead (Pb, atomic number: 82). The location of Tl is defined as group 13. Five elements [boron (B), aluminum (Al), gallium (Ga), indium (In) and Tl (Tl)] constitute group 13. They were classified into group III, which consists of two subgroups—group IIIa and group IIIb. A slight confusion of the description about ^{201}Tl in some nuclear medicine textbooks has been found; one defines ^{201}Tl as IIIa, and the other as IIIb. This confusion is attributable to the existence of two different group designations: Standard American Designation and International Designation. The group numbers used primarily in the United States (US) and most of the textbooks that have been written in the US over the past several decades have used the former, whereas the latter is recently used worldwide. Therefore, the description of ^{201}Tl in nuclear medicine books, following the former, is IIIa, and that following the latter is IIIb.

Historically, Tl (Greek *thallos* meaning "a green shoot or twig") was discovered by Sir William Crookes in 1861 in England. The name comes from its bright green spectral emission lines. Tl has 25 isotopes which have atomic masses that range from 184 to 210. ^{203}Tl and ^{205}Tl are the only stable isotopes and ^{201}Tl is employed in the field of nuclear cardiology and oncology. Although less well known, Tl, either radioactive or nonradioactive, has been used in various lines of fundamental scientific exploration about cell physiology including membrane, mitochondria, Golgi apparatus, and sarcolemma.[1–8]

Generally, Tl and its compounds, except for the medical use of ^{201}Tl, are highly toxic and should be handled with great care. This toxicity has led to its use (now discontinued in many countries) as a rodenticide (mouse poison). The distinctive effects of Tl poisoning are alopecia (loss of hair), and damage to peripheral nerves.[9,10] The mystery writer, Agatha Christie, who had worked as a pharmacist, used Tl as the agent of murder in her novel *The Pale Horse*—the first clue to the murder method coming from the hair loss of the victims. The 1996 film *The Young Poisoner's Handbook* was based on the crimes of *Graham Frederick Young* who killed at least three people with Tl in the 1960s and 1970s.

2. ^{99m}Tc-MIBI

Many lipophilic cationic technetium-99m (^{99m}Tc)-radiopharmaceuticals were initially developed for imaging myocardial perfusion. In 1989, Hassan et al. reported that benign and malignant lung tumors are depicted by abnormal uptake of ^{99m}Tc-MIBI.[11] Subsequently a number of investigators reported the diagnostic feasibility of it to depict a variety of tumors in the parathyroid, bone, brain, breast, and other organs.[12–22] As is well known, its advantages over ^{201}Tl are: lower radiation burden, higher spatial resolution of the image, and availability at a lower price than ^{201}Tl in some nations. It is striking that tumor imaging with ^{99m}Tc-MIBI, validated as a P-glycoprotein transport substrate, has been studied not only for diagnostic purposes but also for *in vivo* imaging as a predictive test of the tumor response to the anticancer agents.[23–27]

The multidrug-resistant P-glycoprotein (P-gp), a 170 kDa plasma membrane protein encoded by the mammalian multidrug-resistance gene (MDR1), has been documented in nearly all forms of human cancer, and could be one of the major mechanisms responsible for the lack of ^{99m}Tc-MIBI uptake in tumor cells expressing MDR. Therefore, negative or equivocal uptake of ^{99m}Tc-MIBI in an already-detected lesion (on CT and/or MRI) has been considered as having an important implication for cancer therapy; absent or less uptake may show that the lesion has already expressed the MDR character and the lesion may be resistant to some anticancer agents.

3. ^{99m}Tc-Tetrofosmin

^{99m}Tc-TF is a lipophilic diphosphine routinely used for myocardial perfusion imaging and currently proposed for oncological use. Its potential in tumor imaging was proposed after the demonstration of the clinical usefulness of ^{201}Tl and ^{99m}Tc-MIBI in tumor imaging. Its application in patients with breast cancer is based mainly on its similarities with ^{99m}Tc-MIBI, as demonstrated by clinical use in nuclear cardiology and by similar uptake mechanisms suggested in several *in vitro* studies.

In addition to uptake mechanisms, recent studies have also shown that the similarities encompass a wider aspect in that ^{99m}Tc-TF flows outwardly from the cells via MDR mechanisms like ^{99m}Tc-MIBI.[28–30] In our search of the literature, the number of papers focusing on tumor imaging and MDR assay is still biased toward ^{99m}Tc-MIBI compared to ^{99m}Tc-TF. However, the bias in data size in comparison between the two tracers does not show the superiority of ^{99m}Tc-MIBI; in particular, the difference of the two tracers concerning *in vivo* predictive assay has yet to be compared systematically.

UPTAKE MECHANISMS

1. ^{201}Tl

Several factors responsible for determining the level of uptake of ^{201}Tl by tumor cells have been studied and presented. Perfusion to malignant tissue appears important for delivery purposes.[31,32] Tumors with poor perfusion, especially if necrotic, appear to take up less than the same type of tumors with little or no necrosis. However, few reports have directly compared the vascularity of tumors with the degree of ^{201}Tl uptake. Nevertheless, with some exceptions, it seems definite that a high degree of positive correlation exists between tumor vascularization and intensity of ^{201}Tl uptake. Actually, anyone engaged in diagnostic work using CT or MRI knows that intense ^{201}Tl uptake would be observed in well-enhancing tumors; this is a sufficient piece of empirical evidence to prove the

above. Waxman et al. argued that the intensity of ^{201}Tl uptake in a tumor was more closely linked to cell type than other factors.[33] This finding was observed in a lymphoma model which demonstrated that highly vascularized aggressive tumors such as diffuse large-cell lymphomas had less ^{201}Tl uptake than slower-growing indolent tumors such as lowgrade lymphomas. In brief, the intense of ^{201}Tl uptake does not necessarily share a base of comparison with the grade of tumor perfusion.

^{201}Tl is considered to behave similarly to potassium with respect to biochemistry and physiology. The sodium-potassium ATPase system in the cell membrane is thought to play a key role in ^{201}Tl entry into tumor cells.[34,35] A high potassium concentration within the cell is maintained compared with the extra cellular space in large part due to sodium-potassium ATPase pump. Sessler and coworkers studied the cellular uptake of ^{201}Tl using Ehrlich ascites tumor cells. They found that the uptake of ^{201}Tl by the tumor cells was inhibited using ouabain, which is known to inhibit the sodium-potassium ATPase pump. The same group also confirmed that furosemide, an inhibitor of the cotransport system, also inhibited ^{201}Tl uptake. An additive effect of both furosemide and ouabain on the inhibition of ^{201}Tl uptake was also observed, leading to a conclusion that at least two transport systems were involved in the cellular uptake of ^{201}Tl. The cotransport system for ^{201}Tl was demonstrated to increase as the cells aged from the 6th day to 12th day while, in contrast, the ATP system fell as the cell became older. The dominant mode of cellular uptake of ^{201}Tl using this system was found to be in the furosemide-sensitive group, indicating that cotransport plays a dominant role in the cellular uptake of ^{201}Tl. After the inhibition of the sodium-potassium ATPase system, as well as the cotransport system, a minimal rest flow for ionic transport continued. This flow was attributable to a calcium-dependent ion channel.

In 1987, Ando et al. studied the biodistribution of ^{201}Tl in tumor-bearing animals and found ^{201}Tl to be accumulated mainly by viable tumor tissue with lesser concentration abilities noted in connective tissue which contained inflammatory cells and was barely detectable in necrotic tumor tissue.[36] Their findings suggest that ^{201}Tl is more specific for differentiating tumors from benign or inflammatory pathologies, as compared to ^{67}Ga. In this study, ^{201}Tl was observed mainly to exist in the free form in the fluid of the tumor, while a small fraction of ^{201}Tl was located in the nuclear, mitochondrial, and microsomal fractions in these tissues. In addition, ^{201}Tl was found to be bound to a protein in these subcellular fractions. It was also noted that the biodistribution of ^{67}Ga was different from that of ^{201}Tl, suggesting that the uptake mechanisms for ^{201}Tl and ^{67}Ga in tumor tissue were independent.

Although much evidence shows that the sodium-potassium ATPase pump plays a major role in the active transport across the cell membrane, the biological significance of ^{201}Tl uptake remains unclear. From the following speculations, we studied the biologic significance of ^{201}Tl uptake *in vitro*. First, despite intravenous direct contact between ^{201}Tl and red blood cells (RBC) expressing abundant sodium-potassium ATPase, ^{201}Tl uptake by RBC is quite low. If RBC were avidly labeled, ^{201}Tl myocardial perfusion scintigraphy would lose its basis because the separation of myocardium and ventricular lumen is insufficient. It is noteworthy that no mitochondria are present in RBC despite the abundant expression of membrane sodium-potassium ATPase. Actually, several investigators have presented data showing that mitochondrial function acts as a critical key for ^{201}Tl uptake by cells.[37–41] Therefore, we should reconfirm the important role played by mitochondria in ^{201}Tl uptake into the cells, and should not minimize the importance of the intracellular energy generator "mitochondria" based on Ando's experimental finding of intracellular ^{201}Tl being barely detected on organelles including mitochondria.

2. ^{99m}Tc-MIBI

Uptake mechanisms of ^{99m}Tc-MIBI in myocardial cells

The detailed mechanism responsible for ^{99m}Tc-MIBI uptake was elucidated by the experiments conducted on cultured embryonic chick ventricular myocardial cells.[42] Their transmembrane electrical potentials were altered by modifying the extracellular potassium concentration or using the potassium ionophore valinomycin or protonphores such as 2-4-dinitorphenol and a cyanide derivative. The membranes were also hyperpolarized using the K^+/H^+ ionophore nigericin and the ATP synthetase inhibitor rotenone. A clear relationship existed between the changes in the cellular uptake of ^{99m}Tc-MIBI and the electrical transmembrane potential alterations. In addition, a clear proof that this uptake mechanism differs from that of ^{201}Tl is that exposure to ouabain did not result in a decreased uptake, but rather in an increased uptake, a likely expression of the secondary hyperpolarization of the mitochondrial membrane in this condition. Therefore, ^{99m}Tc-MIBI uptake was considered to be via transmembrane diffusion allowed by the cationic charge.

It is well known that the electrically negative transmembrane potential is lower at the mitochondrial inner matrix than at the sarcolemmal level. Accordingly it can be expected that, ^{99m}Tc-MIBI preferentially accumulates within the mitochondrion which is the intracellular energy-production site.

Crane et al. also verified these findings in the guinea pig heart. Ten minutes after the *in vivo* injection of ^{99m}Tc-MIBI, the mitochondrial fraction of myocardial homogenates contained 80% to 90% of the overall ^{99m}Tc-MIBI cellular activity.[43] Direct proof of the intramitochondrial uptake of ^{99m}Tc-MIBI was provided by Backus et al.,[44] whose electron-probe X-ray analysis of freezed-dried cryosections of cultured myocardial cells showed an overconcentration of up to 1000 times in the mitochondria

relative to the extracellular medium. As an interesting demonstration, a transmembrane electrical potential sufficient to drive by itself the uptake of ^{99m}Tc-MIBI has been obtained with artificial unilamellar vesicles.[45] After having been electrically charged by being placed in a solution underconcentrated in potassium and containing ^{99m}Tc-MIBI, these artificial bags with lipid membrane accumulated ^{99m}Tc-MIBI in direct relation to the electrical potentials. These observations seem to support the contention that the mechanism of cellular uptake of ^{99m}Tc-MIBI is through passive diffusion since no ATP is directly consumed during this process.[46] However, *in vivo*, the transmembrane chemical and electrical gradients is the end result of metabolic activity and is mostly derived from ATP energy consumption. In other words, a part of this energy within cells is used to accumulate ^{99m}Tc-MIBI. Consequently, from a broader perspective, the mechanism of uptake corresponds to the so-called secondary active transport, although the passive diffusion is the manner of membrane passage.

Uptake mechanisms of ^{99m}Tc-MIBI in tumor cells

Following the inadvertent discovery of the uptake of ^{99m}Tc-MIBI in a lung cancer, *in vitro* experiments have confirmed its ability to truly overconcentrate in tumor cells.[20] The first experimental report originated from Delmon-Moingeon et al. in 1990.[47] In a series of nine human carcinoma cell lines and two normal cell lines, they observed maximal cellular concentrations of ^{99m}Tc-MIBI ranging between 5% to 28% of the external medium activity in the tumor cell lines, and of less than 2% in the normal cells. The maximum level was found after 1 hour, and the time to half-maximum was 10 min, kinetics similar to what is observed in cultured myocardial cells. Depolarization of plasma transmembrane potential induced by a high concentration of potassium ion in the incubation medium reduced the ^{99m}Tc-MIBI uptake by 60%. Incubation with valinomycin, an ionophore that dissipates the mitochondrial membrane electrical potential, eliminated 80% to 85% of ^{99m}Tc-MIBI uptake; incubation with nigericin, which increases this potential, also increased ^{99m}Tc-MIBI uptake. At this point, there was a strong suggestion that, as in the myocardial cells, uptake of ^{99m}Tc-MIBI in tumor cells could also be linked to the presence of mitochondria. In fact, ^{99m}Tc-MIBI shares some similarities with other lipophilic cations already used experimentally for the measurement of transmembrane plasma and mitochondrial potentials in living cells.[48] Since tumor cells have a higher mitochondrial density and probably also a higher transmembrane electrical potential than the surrounding epithelial cells, ^{99m}Tc-MIBI accumulates more intensely in tumor cells, and hence more intensely in malignant tumors than in their surrounding epithelial or connective tissues. But this nonspecific mechanism opens the possibility of an increased uptake in nontumorous cells with a higher metabolic activity or higher density of mitochondria, a situation encountered in atypical hyperplasia or especially-active, tumor-like granulation.

3. ^{99m}Tc-Tetrofosmin

Although bearing similarities to ^{99m}Tc-MIBI, whole of ^{99m}Tc-TF uptake mechanism are not understood. The possible role of mechanisms that are not necessarily dependent on mitochondria has been hypothesized. An intracellular distribution has been demonstrated and concentration is observed only in viable tissue and depends both on blood flow and metabolic status of the cells.[49,50] *In vitro* studies are conducted mainly on cultured cell lines, on both myocardiac cells and neoplastic cells, but experimental data about subcellular structures have been limited to isolated adult rat mitochondria.[50] One hypothesis is that the ^{99m}Tc-TF can penetrate into the cell membrane in a nonspecific manner that is dependent on its lipophilicity and driven by membrane potentials. Even if blood flow is considered a limiting factor,[49,51] tissue retention can only occur if these potentials are preserved, i.e., in viable and metabolically active cells.[52] Data regarding the possible role of sodium-potassium ATPase, i.e., of the main, albeit not exclusive, mechanism involved in ^{201}Tl uptake, is not univocal.[35,52–54] Moreover, different from ATPase systems, in an experiment using adult rat ventricular myocytes no significant effect on uptake was shown by sodium or potassium ion channel inhibitors.[54] In partial contrast with these data, Arbab, in the lymphoma B-cell line HBL2 and in the small-cell carcinoma of the adrenal cortex cell line SW-13, demonstrated that cell membrane (sodium-potassium transport) and mitochondrial potentials can modulate cellular ^{99m}Tc-TF uptake.[52] This paper is important because of its demonstration of the existence of a different mechanism between ^{99m}Tc-TF and ^{99m}Tc-MIBI. In this study, it was also observed that only a small fraction of ^{99m}Tc-TF accumulates inside the mitochondria while most of the ^{99m}Tc-MIBI has an intramitochondrial location. In my opinion, this difference with regard to intramitochondrial localization, between the two tracers, may be related to different clearance of the two from the clinical target regions. However, despite the small fractional rate, a primary role of mitochondria in the ^{99m}Tc-TF uptake is not negligible. Noticeable information comes from studies on isolated adult rat mitochondria, suggesting that the cellular uptake of ^{99m}Tc-TF is driven by the sarcolemmal and mitochondrial transmembrane potentials.[50] Metabolically active cells are required for an optimal uptake that cannot be explained on the basis of simple diffusion. Uptake is temperature-dependent, and is decreased by metabolic inhibitors, and reaches values exceeding those achievable with simple diffusion.[52,54] Although it was conducted on smooth muscle cell, namely non-tumor, Nakamura et al. recently reported slight inhibition of ^{99m}Tc-TF uptake by a calcium ion channel blocker.[55]

It has been demonstrated in different neoplastic cells culture systems that ^{99m}Tc-TF shares with ^{99m}Tc-MIBI the priority of being a substrate for P-glycoprotein, a membrane transport responsible for the multidrug resistance.[28,56] A similar behavior has also been hypothesized with respect to multidrug resistance-associated protein (MRP), an alternative transporter discovered by Cole.[57] Ballinger et al. studied ^{99m}Tc-TF and ^{99m}Tc-MIBI uptake in wild-type and doxorubicin-resistant variants of the rat MatB and human MCF-7 breast tumor cell lines.[28] Nakamura carried out experiments on human anaplastic thyroid carcinoma (KB3-1) and on two human recombinant cell lines: MDR1-transferred KB-G2, and MRP-transferred C-A500.[58] He also performed *in vivo* studies on cell lines implanted in athymic mice, concluding that both ^{99m}Tc-TF and ^{99m}Tc-MIBI can detect the functional expression mediated by P-gp as well as by MRP, although ^{99m}Tc-MIBI seems to be a more sensitive tool.

Between ^{99m}Tc-TF and ^{99m}Tc-MIBI in cell culture systems, direct comparisons were made by De Jong, who compared ^{99m}Tc-MIBI, ^{99m}Tc-TF, and ^{99m}Tc-Q12 in human breast adenocarcinoma MCF-7 and ZR-75 cell lines[59] and by Molteni, who evaluated the uptake of ^{99m}Tc-MIBI and ^{99m}Tc-TF, in MCF-7 cell lines both in basal conditions and during cell growth.[60] In the first paper ^{99m}Tc-MIBI showed the highest cellular uptake, following by ^{99m}Tc-TF and Q12. The uptake of ^{99m}Tc-MIBI and ^{99m}Tc-TF was inhibited at low temperatures, and the outflow processes of the radiolabeled compounds were similar.[59] Morteni demonstrated that ^{99m}Tc-TF uptake was lower in the logarithmic phase and higher in the plateau phase in the cell proliferation, while ^{99m}Tc-MIBI showed the opposite trend.[60]

Eventually, my possible hypothesis is that ^{99m}Tc-TF uptake mechanisms are similar to those of ^{99m}Tc-MIBI, depending mainly on blood flow and on the metabolic status of cells. Comparative studies have demonstrated that uptake of ^{99m}Tc-TF is lower than that of ^{99m}Tc-MIBI, probably reflecting differences in the responsiveness of the two tracers to membrane potentials.[26,52,59] Differences are related to the lower influence of mitochondrial activity on ^{99m}Tc-TF uptake and to the partial dependence of ^{99m}Tc-TF uptake on the sodium-potassium ATPase pump.

Despite differences at the molecular level, *in vivo* similarities between ^{99m}Tc-TF and ^{99m}Tc-MIBI have been clearly demonstrated. ^{99m}Tc-TF has a clinical role as a routine tracer for coronary artery disease with results overlapping with those obtained with ^{99m}Tc-MIBI.[61,62] A similar whole-body distribution and slight pharmacokinetic differences have been observed. For ^{99m}Tc-TF no significant cardiac washout and a more favorable clearance from the lungs and liver have been observed, allowing an earlier myocardial scan than with ^{99m}Tc-MIBI.[63–65] Faster hepatic clearance could be an advantage in the evaluation of tumors located in the breast or lung near the liver, determining a lower background, but data supporting this attractive propensity of ^{99m}Tc-TF have not yet demonstrated any clinical benefit.

^{201}Tl IN CLINICAL TUMOR IMAGING

^{201}Tl accumulates predominantly within viable tumor tissue, less within normal or inflammatory tissues and least in necrotic or non-active tissues. The optimal time for tumor imaging is 20 to 60 minutes post-injection of ^{201}Tl; in particular, images obtained just after ^{201}Tl injection are considered to reflect blood flow to the tumor. Delayed images at 2 to 3 hours are recommended in the case of lymphoma, lung cancer, and breast cancer because of primarily enhancing lesion-to-background ratio on the later images. Although the mechanisms have not been completely clarified, ^{201}Tl has a strong tendency of prolonged retention in the tumor lesion. This tendency is more prominent in malignant tumors than in benign ones, but there are some exceptions with regard to this assertion that delayed uptake is specific for malignancy. The normal, physiological uptake of ^{201}Tl are the choroid plexus of the lateral ventricles, lacrimal glands, salivary glands, thyroid, myocardium, liver, spleen, bowels, kidneys, and testes. The muscle uptake is also uniform and not intense compared to the above normal uptake sites. Bone marrow uptake should not be observed even in patients with solid cancer, and if noted indicates hyperplastic marrow or malignant spread. Healing wounds due to surgery have no or little uptake.

In my opinion, the clinical indications for ^{201}Tl in oncological use are: 1. a reliable device for making diagnosis of malignant disease, 2. a guide for grading malignant or proliferative potential, 3. monitoring the therapeutic effect, and 4. discriminating necrotic tissue from recurrent or residual tumor (especially in the brain and lung). The anatomic areas in which ^{201}Tl is practically useful are: 1. brain, 2. bone and soft-tissue sarcomas, 3. chest disease related to AIDS (Kaposi's sarcoma), 4. cervical nodes related to thyroid cancer, 5. cancer in the breast, lung and mediastinum, and 6. head and neck cancers including those of the skull base.

Primary Brain Tumors:

As is often the case with neoplastic diseases in the brain, rapid washout of tracer from the lesions interferes with the correct evaluation of the image, and lesions may be missed if only delayed scanning is performed. If possible, scanning at both early and delayed phases is preferable. There is normally little or no ^{201}Tl uptake in the white matter. ^{201}Tl will not pass through an intact blood-brain-barrier (BBB), yet disruption of the BBB is not the absolute factor regulating ^{201}Tl uptake within a lesion as little ^{201}Tl uptake is identified at sites of cerebral infarction. Uptake of ^{201}Tl in brain tumors is also likely dependent on the activity of sodium-potassium ATPase pump and active transmembrane transport via the potassium-glucose co-transport system in viable tumor cells.[66] How-

ever, convincing explanations of the abnormal intense uptake of ^{201}Tl in brain tumors, from the macroscopic viewpoint, include the enhancing perfusion to the tumor, disruption of BBB, and the presence of immature vessels with hyperpermeability. ^{201}Tl accumulates in residual or recurrent tumor in proportion to the malignant grade and total viable tumor bulk. Benign brain tumors such as meningiomas and pituitary adenomas can also accumulate ^{201}Tl.[67] Sites of radiation necrosis and post-surgical change have minimal or negative ^{201}Tl uptake. As a well-recognized false positive result, inflammatory demyelinating disease with high ^{201}Tl uptake mimics malignant pathologies.[68]

Even if using SPECT, lesions less than 2 cm in diameter, centrally located, or adjacent to areas of normally high activity may be easily missed. Malignant gliomas and meningiomas are well detected with high sensitivity, while pituitary and parasellar tumors, low-grade gliomas, and brainstem tumors are considered poorly sensitive on ^{201}Tl imaging. Ambivalent or intermediate results are observed with posterior fossa tumors, but application of SPECT with thin-slice technique improves the detectability. Infratentorial lesions (such as medulloblastoma) are incompletely labeled by ^{201}Tl; this may be related to the low-grade nature of these lesions. Quantitative assessment of ^{201}Tl uptake in the lesion has shown that most tumors, with malignant character or with high rate of proliferation, tend to have a tumor-to-normal brain ratio of greater than 2.5, while ratios less than 1.5 suggest a non-malignant or slowly proliferating lesion.[69] These indices should not be easily used without the foggiest notion of the difference in efficiency of imaging devices. Probably for the accurate diagnosis, all those who employ the semiquantitative indices must decide some appropriate diagnostic ratios in each institute. In any case, ratios are helpful for evaluating newly diagnosed, untreated lesions, but are not reliable for determining tumor grade when evaluating treated tumors. However, a higher ratio detected in the post-therapeutic context, either surgical or non-surgical, suggests the possibility of recurrent or residual tumor.

Brain Lymphoma:

In the immunocompromised host such as patients with HIV infection, ^{201}Tl imaging is available to aid in discriminating brain lymphoma (BL) from toxoplasmosis, although this has been a matter of diagnostic controversy in many cases. Epidemiologically a two-fold higher incidence of the BL is noted as compared to toxoplasmosis, but the number of HIV infection, either already diagnosed or not, multiplies rapidly. Hence, diagnostic dilemma in HIV patients with brain lesion is no longer an items of publication, rather a subject of routine practice. HIV-related lymphoma is said to be a high ^{201}Tl uptake lesion, while toxoplasmosis infection shows only mild uptake. Generally, a lesion to non-lesion ratio greater than 2.5 suggests AIDS-related BL. Diagnostically the most important point of differentiation is that BL will generally be ^{201}Tl and ^{67}Ga positive, while toxoplasmosis infection is ^{201}Tl negative, but ^{67}Ga positive. Additionally, for the purpose of the above discrimination, ^{123}I-IMP, a cerebral perfusion agent, is beneficial because it shows prolonged retention (more than 12 hours) in BL, in contrast to no retention in toxoplasmosis. High ^{201}Tl uptake is occasionally found in various benign infectious pathologies such as cytomegalovirus encephalitis, candidiasis, and bacterial abscess.[70] Therefore, evaluation of ^{201}Tl image in tandem with CT and MRI is a prerequisite. At least, in principle, we should use the delayed scan at 2–4 hours following injection to make the best possible use of ^{201}Tl imaging; early ^{201}Tl uptake within inflammatory lesions washes out, while uptake remains within tumors.[71]

Brain Tumor Recurrence:

To differentiate residual tumor from post-surgical/post-radiation changes is also a diagnostic dilemma, but ^{201}Tl can be a candidate for problem solving. Radiation therapy for brain tumor, is associated with a delayed necrosis. Necrosis usually occurs even when the irradiation dose is considered to be in the therapeutic range. The condition may be also delayed up to two or three months following radiation therapy. The necrotic area may also stimulate edema in the surrounding tissue. On CT or MRI, this diagnostic difficulty comes from the disruption of the BBB that makes an abnormal contrast enhancement area in both conditions. ^{201}Tl uptake, increasing in comparison to the contralateral normal brain, is highly suggestive of recurrence. Necrosis and inflammatory-infectious processes may rarely show increased uptake of ^{201}Tl.[72] Combined use of ^{201}Tl-^{99m}Tc-HMPAO has benefit to confirm or exclude recurrent tumor in some cases. ^{201}Tl uptake of the lesion is comparable to the scalp activity, while ^{99m}Tc-HMPAO uptake should be compared to cerebellar activity. A high likelihood of tumor recurrence was associated with a ^{201}Tl to scalp ratio greater than 3.5. A lesion, with ^{201}Tl uptake ratios between 1.1 to 3.4 and ^{99m}Tc-HMPAO ratio less than 0.5, was indicative of no sign of recurrence. For ^{201}Tl ratios between 1.1 to 3.4 and ^{99m}Tc-HMPAO ratios more than 0.5, the study was not accurate in predicting tumor recurrence.[73] Most published papers on diagnostic challenge with ^{201}Tl to discriminate recurrence from radiation necrosis, employed semiquantitative methods. However, setting ROIs, on contralateral or adjacent non-affected parenchyma and the lesion suspected of recurrence, is often a difficult task. Moreover, radiation therapy following surgical resection complicates the situation further. In such patients' brain, post surgical change coexists with parenchymal damage induced by irradiation, and these are often cystic with partial irregularity and abnormally enhancing circumference on conventional CT and MRI. Especially in the case of cystic change with enhancing wall, on CT or MRI with contrast agent, avid

^{201}Tl uptake of the lesion does not necessarily suggest tumor recurrence. In many our own cases of cystic radiation necrosis surgically diagnosed, a high concentration of ^{201}Tl is often detected in sampling cystic fluid through an Ommaya reservoir, compared to samples of CSF and blood. Through the disrupted BBB or fragile vasculature within the cystic wall, ^{201}Tl may leak into the cystic spaces and remain without elimination. Despite the evidence showing the merits of ^{201}Tl for the diagnosis of necrosis and recurrence after radiation therapy, we should adopt a cautious stance in numerous cases even when suspicious lesions show intense ^{201}Tl uptake.[74]

Intracranial Infection and Inflammation:
Inflammatory lesions can accumulate ^{201}Tl. Brain abscesses, inflammatory demyelinating diseases, and pulmonary actinomycosis are widely known as ^{201}Tl avid. Tuberculosis may occasionally accumulate ^{201}Tl. Moreover, ^{201}Tl uptake within both hilar and mediastinal adenopathy with sarcoidosis is not rare. Semiquantitative analysis using ROIs and comparison of early and delayed scan images provides beneficial information.

Cerebral Infarction:
Cerebral infarctions have little or no ^{201}Tl uptake within 5 days of onset. In general, the use of this tracer in cerebral infarction cannot be justified for any reason. However, we occasionally encounter cancer patients showing intracranial ^{201}Tl uptake despite no sign of brain metastasis confirmed by most recent neuroimaging diagnosis.

This unexpected finding is occasionally noted; it is not rare that malignant disease, either intracranial or not, and cerebrovascular accident coexist independently and simultaneously. Actually, as many readers already have experienced, delayed studies performed 2 to 3 weeks post-event may demonstrate some ^{201}Tl accumulation.[75–78]

Skull-Base Tumor:
The skull base is the most difficult area in which to scintigraphically detect lesions. Many pathologic conditions, derived from the bone, brain, and the soft tissue of otolaryngologic/ophthalmologic regions, can invade the skull base. Anatomical complexities and the need for spatial resolution of the diagnostic modality prevent the extension of scintigraphic techniques to this complicated area. From several studies on the feasibility of SPECT in this area by Larson and Yui, SPECT was found to be more sensitive and to provide better anatomical localization than planar imaging, and appeared useful in patients with a negative CT study.[79,80] ^{201}Tl, in this field, plays a major role in detecting tumors. CT and MRI often create an agonizing diagnostic dilemma as to whether lesion is a tumor or not. In such a case, abnormal ^{201}Tl uptake indicates the possibility of the lesion being neoplastic. If accessible to dual-isotope technique, simultaneous use of a bone scan agent (i.e. ^{99m}Tc-MDP/HMDP) and ^{201}Tl provides a convenient way to evaluate the skull-base abnormality.[81–83]

Breast Cancer:
Although the primary screening tool for breast cancer is mammography, the technique does not distinguish benign from malignant lesions. Actually, its positive predictive value for cancer is only 15 to 30%. Additionally, evaluation of a dense breast with this conventional technique often encounters difficulties; impossible to point out the suspicious lesions with radiological high density and irregular shape from the dense background. Studies have demonstrated the usefulness of ^{201}Tl in differentiating benign from malignant breast lesions, as well as its high detectability of the lesion in dense breasts. Benign lesions seldom demonstrate tracer uptake, although highly cellular adenomas and papillomas may demonstrate ^{201}Tl uptake. Overall, ^{201}Tl has sensitivity between 67 to 96% in the differentiation of benign from malignant breast lesions, and a specificity of 91–93%.[84] ^{201}Tl is not useful for the detection of metastasis in the axillar node because of insufficient sensitivity. Lesion size may have a major effect on ^{201}Tl sensitivity.[85] In one study, the ^{201}Tl scintimammography had a sensitivity of 67% for lesions greater than 1.5 cm in size, but only 20% for lesions below this size.[86] Although we do not know why, planar technique has been principally employed for scintimammography, and the use of SPECT in breast lesions is unstressed. In our institute, ^{201}Tl SPECT can correctly detect lesions less than 1.5 cm in a diameter, and threefold sensitivity concerning metastatic axillary node can be achieved.

Kaposi Sarcoma:
For decades Kaposi sarcoma (KS) was considered a rare disease that mostly affected elderly men of Mediterranean or Jewish heritage, organ transplant patients, or young adult African men. In the last 20 years, however, the vast majority of KS cases have developed in association with human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS), especially among homosexual men. Scintigraphically, ^{67}Ga is generally negative in KS, whereas lesions can be detected as intense ^{201}Tl uptake area. Lymphoma is generally positive on both ^{67}Ga and ^{201}Tl; but this pattern can be seen with tuberculosis (TB), and in KS patients with a superimposed opportunistic pulmonary infection. Common infection diseases are usually ^{67}Ga avid, but ^{201}Tl negative. ^{201}Tl uptake may uncommonly be seen in association with certain pulmonary infections; however, the uptake is usually transient, and delayed images will often demonstrate clearance of activity over time. Such clearance is typically not seen in association with ^{201}Tl uptake in malignant lesions. A possible explanation for this clearance of ^{201}Tl from inflammation is that ^{201}Tl uptake is

probably based on passive diffusion into the extravascular space with time, the tracer will diffuse back to the intravascular component.[87] The use of SPECT can enhance the detection of parenchymal KS.[88]

Lung Cancer:
Lung cancer is a well-studied target of ^{201}Tl tumor imaging. ^{201}Tl imaging has a high sensitivity reported of 91–100% for the detection. Probably the best lesion size for ^{201}Tl imaging is more than 2 cm in a diameter.[89] Although this tracer is universally recognized as a tumor imaging agent, a significant number of benign pathologies also demonstrate ^{201}Tl uptake including TB, pneumonia (organizing pneumonia), silicosis, radiation pneumonitis, sarcoidosis, and granulomas.[89,90] Delayed imaging can contribute to differentiate infect on from tumor because most malignant lesions will preserve ^{201}Tl as a prolonged retention, while it will wash out of benign, inflammatory lesions.[89] Owing to this property, we are inclined to place exaggerated hopes on ^{201}Tl. More noteworthy is that ^{201}Tl imaging can be positive in about 50% of bronchoalveolar cell carcinomas, which are characteristically not metabolically active on FDG imaging.[90] This may be because ^{201}Tl uptake is not directly related to cell glycolysis.[90] Another drawback of ^{201}Tl imaging is its poor sensitivity for the detection of nodal metastases.[91]

Lymphoma:
Generally, in cases of lymphoma, ^{201}Tl occupies a subordinate position to ^{67}Ga, for metastatic survey and lesion characterization. ^{201}Tl, however, has a high affinity for low-grade non-Hodgkin's lymphomas (which typically have low ^{67}Ga affinity). More variable ^{201}Tl uptake is noted in high or intermediate grade lymphomas, but these lesions typically demonstrate increased ^{67}Ga uptake. To evaluate the mediastinum for residual disease ^{201}Tl may be beneficial, but ^{67}Ga is probably surpass ^{201}Tl. Normally, no ^{201}Tl uptake should be seen in the mediastinum that appears photon deficient against the normal faint pulmonary activity. Gastrointestinal excretion of ^{201}Tl limits its usefulness for evaluation of abdominal lesions,[92] while ^{67}Ga is available under laxative premedication. ^{201}Tl may also be beneficial in differentiating thymic rebound from recurrent disease in post-chemotherapy children. The normal thymus is usually ^{67}Ga avid during or just after chemotherapy, but will be negative on the ^{201}Tl scan.

Scintigraphic diagnosis and post-therapeutic assessment should not be compared with other imaging modalities such as CT, MRI, and ultrasound. We should know that soluble interleukin 2 receptor (sIL-2R) has become the most reliable and non-invasive marker for management of malignant lymphoma.

Bone and Soft Tissue Tumors:
^{201}Tl is more accurate than ^{99m}Tc-MDP (or ^{99m}Tc-HMDP) and ^{67}Ga in determining the extent of involvement of primary bone tumors and in following the response to chemotherapy as it does not demonstrate activity secondary to bone regenaration.[93] ^{99m}Tc-MDP, a bone scan agent, is not specific to tumor tissue. Its uptake on bone scan shows the area in which bone diseases such as bone tumor (primary and metastasis), infection, and fracture destroy bony structure. Therefore, its uptake does not directly indicate tumor tissue. Especially, in cases of thyroid cancer, hepatic cancer, and multiple myeloma, those metastases to the bone often appear as cold lesions and the lesion can be positively detected when microfractures become evident. However, ^{201}Tl is considered more tumor-specific, and so bone and soft tumors are good candidates for this tracer imaging.

In osteosarcoma, ^{201}Tl uptake usually decreases significantly in tumors which have shown a histological response to chemotherapy. Research indicates that patients with more than 90% necrosis following preoperative chemotherapy have a better prognosis, and ^{201}Tl imaging can be used to assess the degree of necrosis.[94] SPECT images can be performed to permit co-registration with CT or MRI images. As well as other regions, ^{201}Tl uptake in bone pathologies is non-specific and has been described in some benign lesions including fractures. As an interesting example, ^{201}Tl myocardial perfusion image, conducted in patients rescued by life-saving maneuver including cardiac massage, occasionally shows hot spots along the ribs, corresponding to the iatrogenic fractures. In other bone pathologies, marked ^{201}Tl uptake has been described in Paget's disease, fibrous dysplasia, and acute osteomyelitis.

^{201}Tl serves the purpose of the evaluation of soft tissue sarcomas. Uptake within the lesion appears to reach a maximum by about 1 hour after injection. Lesion to muscle ratios greater than 3:1 are typically identified with bone malignancies, while those of benign non-tumorous disease below 1.0. Uptake in pulmonary metastases is poor. Although the intensity of ^{201}Tl uptake is not found to be predictive therapeutically, serial ^{201}Tl examinations and these comparisons during therapy are beneficial for assessing the therapeutic efficacy.[95]

Thyroid Cancer:
Advantages of ^{201}Tl for imaging thyroid cancer include the followings; low radiation exposure compared to ^{131}I diagnostic scan and needless to withdraw from thyroid hormone replacement therapy. However, studies suggest that TSH increases ^{201}Tl uptake by thyroid cells and that withdrawal of thyroid hormone has the potential to improve the sensitivity of ^{201}Tl scintigraphy for detecting thyroid remnant or cancer.[96]

Although iodine is said to be very sensitive to well differentiated thyroid cancer, one-quarter of metastases and recurrences from well-differentiated types may have negative iodine uptake.[97] Metastases from thyroid cancer

have been detected using ^{201}Tl with a sensitivity between 35% to 95%, with specificities between 94–97%. Therefore, this scintigraphic procedure should be used for already-detected lesions by other imaging modalities. For selected anatomic areas, ^{201}Tl scanning is probably at least as sensitive as ^{131}I in the detection of thyroid cancer, and ^{201}Tl imaging has been shown to be roughly equivalent to FDG-PET for lesion detection (although PET images have higher spatial resolution and better contrast).[98] ^{201}Tl is not recommended as the only modality for the follow-up of patients with thyroid cancer, but is probably best used to identify the presence of cervicomediastinal lymph node metastases.[99]

Unfortunately, ^{201}Tl uptake is not specific for thyroid cancer and does not provide predictive information on the therapeutic potential of ^{131}I. Additionally, it is less sensitive than ^{131}I scanning in the detection of residual thyroid tissue, diffuse pulmonary metastases, bone metastases, liver metastases, and for metastases below the diaphragm (due to the high background activity in the abdomen and pelvis). Probably the usefulness of ^{201}Tl scans is limited to the head, neck, and chest in order to obtain higher count density images of these regions.[99] In patients with Hurthle cell carcinoma of the thyroid, ^{201}Tl scanning should be performed as iodine scanning is invariably negative. ^{201}Tl scanning may also be beneficial in patients with elevated thyroglobulin levels, but sometimes negative ^{131}I scans.[100] In my opinion, patients with an elevated thyroglobulin level should initially undergo CT, MRI and ^{201}Tl scanning prior to ^{131}I imaging because the formers can minimize inconvenience to patient's daily life and does not need total thyroidectomy, but those advantages on diagnostic efficacy is not warranted.

Prostate Cancer:

Prostate cancer is a major cause of death from cancer in old-age men, and is rarely found in men younger than 40. Men at higher risk include black men older than 60, tire workers, painters, and men exposed to cadmium. The lowest incidence occurs in Japanese men and vegetarians. However, in Japan, it is expected to increase continuously reflecting the westernization of life-styles and rapid aging of the population. In this disease, nuclear medicine has two major missions: metastatic bone survey with bone scan technique and bone pain palliation with ^{85}Sr therapy, but the latter is now unapproved in Japan. Neither ^{201}Tl nor ^{99m}Tc-labeled tumor agents have diagnostic merit in the primary focus. There is an only Tsubuku's publication reporting diffuse bone metastases visualized by ^{201}Tl.[101]

^{99m}Tc-MIBI IN CLINICAL TUMOR IMAGING

A number of variables affect the uptake of ^{99m}Tc-MIBI in tumors. Washout of ^{99m}Tc-MIBI from tumor cells is related to the multi-drug-resistant energy dependent P-gp pump system.[102,103] Tumor cells with a higher concentration of this transmembrane protein demonstrate a faster rate of ^{99m}Tc-MIBI clearance (and hence, less tracer uptake).[102–104] ^{99m}Tc's shorter physical half-life permits the use of a higher administered dose as compared to ^{201}Tl, which translates to a higher count rate which will shorten imaging times and provide clear and better resolution images.[105] The gamma energy of ^{99m}Tc (140 keV) is optimal for use with the detector crystal used in the gamma camera and will undergo less attenuation and scatter. ^{99m}Tc is also readily available and produced daily from a Molybdenum generator in most Nuclear Medicine departments. Since its introduction, ^{99m}Tc-MIBI has been shown to be of value in the evaluation of many tumors.

As you well known, several ^{99m}Tc-labeled tracers such as ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin have been recognized as promising MDR substrate agents. In this context, to establish tailored anticancer therapy, we, front-line clinicians including nuclear medicine specialists, must intensively study *in vivo* MDR assay through our patients' scintigraphic results and final therapeutic outcomes, because MDR phenomena are mixed set-ups and dynamic movements in patients' bodies. These multifactorial, complicated *in vivo* responses to anti-cancer agents could not be estimated by means of gene analysis alone. Scintigraphic, quantitative data, on the uptake and washout phases, can show the dynamic pharmacokinetics within tumor tissue and tumor cells. Quantitative ROI technique offers a significant contribution for excluding the inhomogeneity of tumor tissue. ROI covers the entire tumor lesion on scanned images, which means that the ROI data can include the summation of tumor inhomogeneity. On the other hand, direct tissue or cell sampling needs a surgical intervention or a biopsy technique but they have to be constantly criticized for the problem of inhomogeneity. In this point, compared to genetic procedures we must recognize the superiority of scintigraphic *in vivo* MDR assay.

Bone and Soft Tissue Tumors:

An evaluation of the role of ^{99m}Tc-MIBI indistinguishing benign from malignant bone lesions has been reported, and both sensitivity and specificity shows more than 80%.[104] Compared to routine bone scan, ^{99m}Tc-MIBI is useful in evaluating whether the sites of fracture are malignant-pathologic or not, because non-pathologic fractures do not accumulate ^{99m}Tc-MIBI.[104] However, because some non-malignant pathologies including benign bone tumors can show false positive ^{99m}Tc-MIBI uptake, even ^{99m}Tc-MIBI can not exceed clinical expectations.

^{99m}Tc-MIBI is available for assessing response to therapy in patients with malignant bone or soft tissue tumor.[104] However, its use for the above purposes, either initial diagnosis or post-therapeutic assessment, should not be justified without doing an evaluation in advance using CT or MRI. Probably the usefulness of this tracer in this area is also shown as a clinical technique of MDR

assay, but in patients with osteosarcoma results of ^{99m}Tc-MIBI scan did not correlate with P-gp expression in the tumor tissue.[107] Nevertheless, most promising aspects of nuclear tumor imaging, without PET techniques, may be this field.

Brain Tumors:

As an example of the biological significance of ^{99m}Tc-MIBI uptake in brain tumors, a good correlation between mitochondrial malate dehydrogenase activity and ^{99m}Tc-MIBI uptake was shown by Carvalho et al.[108] The addition of the mitochondrial uncoupler (CCCP including cyanide) can release 85% of the ^{99m}Tc-MIBI. In clinical responders to chemotherapy, lesional uptake of ^{99m}Tc-MIBI frequently decreases reflecting chemotherapy-induced mitochondrial damage. However, this post-therapeutic observation is not limited to ^{99m}Tc-MIBI. ^{201}Tl and ^{99m}Tc-TF show the same pattern. Recent studies have shown that pediatric brain tumors are good candidates for ^{99m}Tc-MIBI imaging.[109] Tumor types diagnosable with ^{99m}Tc-MIBI included brain stem glioma, fibrillary astrocytoma, other low-grade astrocytomas, and glioblastoma multiforme. Most tumors with avid ^{99m}Tc-MIBI uptake were astrocytomas, including those in the brain stem, cerebellum, and cortex. Several tumors evident on MRI, including craniopharyngioma, medulloblastoma, and optic glioma were negative on ^{99m}Tc-MIBI SPECT. Kojima et al., using SPECT, compared ^{99m}Tc-MIBI uptake on pituitary adenomas and normal pituitary regions, and concluded that ^{99m}Tc-MIBI was taken up in the dorsum sellae or clivus but not the normal pituitary gland and had a strong affinity for the pituitary adenoma.[17] Their result implies that ^{99m}Tc-MIBI SPECT may be a useful new technique for identification of pituitary adenoma and would be expected to provide useful information for surgical planning. An interesting comparison between ^{99m}Tc-MIBI and ^{201}Tl brain SPECT in AIDS patients was conducted.[110] The study analyzed the diagnostic efficacy by the two tracers from the viewpoint of differentiating intracranial lymphoma from non-malignant lesions. Although the result is thought to be preliminary, ^{99m}Tc-MIBI was noted to be more helpful than ^{201}Tl.

Breast Cancer:

As the method of choice for the early detection of breast cancer, X-ray based mammography is widely known.[111] As a screening tool, mammography has a relatively high sensitivity of approximately 90%, but its specificity is only about 35–54%, even in specialized institutes.[111,112] As is well known, this technique often results in insufficient image in patients with glandular tissue and dense breasts. However, scintimammography with ^{99m}Tc-MIBI is uninfluenced by breast density.[113] Compared to ^{201}Tl, ^{99m}Tc-MIBI scan has high sensitivity in the evaluation of breast lesions greater than 1.5 cm in size. Early imaging (10 min after injection) is recommended as being more sensitive than delayed series because of significant washout of ^{99m}Tc-MIBI uptake from breast lesions by 1 hour.[114–116]

When combined with conventional mammography, the two exams have an overall improved sensitivity for cancer.[117] Overall sensitivity and specificity of ^{99m}Tc-MIBI in the diagnosis of breast cancer are 70–96% and 71–100%, respectively.[111–114,116–119] The diagnostic performance of ^{99m}Tc-MIBI is comparable and similar to that of FDG PET.[118] A review of the literature found a total average sensitivity of 84.5%, average specificity of 89%, average positive predictive value of 89%, average negative predictive value of 84%, and an average accuracy of 86%.[120] In the diagnostic performance, high negative predictive value is a noteworthy aspect in comparison with conventional mammography, ultrasonography, and MRI. Most false negative results, namely low or poor uptake, occur with lesions less than 1.5 cm in size or non-palpable lesions.[113,117,121] Unfortunately, in the evaluation of patients with non-palpable lesions, sensitivity of ^{99m}Tc-MIBI studies drops to 51% to 72%.[116,122–124] Curiously, larger lesions over 3 cm in size may be missed.[117,119]

The use of a high-resolution breast specific gamma camera improves the detection of smaller lesions.[121] False positives are observed in the case of fibroadenomas, fibrocystic disease, papillomas, epithelial hyperplasia, mastitis, scleradenitis, and fibrocystic breast disease.[86,116,119,125] In some reports, high-resolution images of the breasts with either ^{201}Tl or ^{99m}Tc-MIBI may demonstrate some normal glandular activity, but this is usually bilateral and non-localizing in character.[86,122] However, in our ^{201}Tl SPECT experience, no meddlesome uptake is found in the glandular breasts. Unlike ^{201}Tl, quantification of ^{99m}Tc-MIBI uptake has no value in differentiating benign from malignant lesions.[116] Superiority of ^{99m}Tc-MIBI over ^{99m}Tc-TF for the evaluation of breast cancer has been shown only in *in vitro* studies.[107] SPECT images provided better lesion contrast, but were less accurate in determining lesion localization.[126] ^{99m}Tc-MIBI is not accurate in the diagnosis of metastatic axillary adenopathy,[86,118,122] although sensitivities are around 80%.[127,128]

Articles regarding ^{99m}Tc-MIBI in the evaluation of breast masses encounter one criticism; the reported results were based on pre-selected patients, suggesting a possible selection bias.[129] Probably, ^{99m}Tc-MIBI has only a minor role in selected cases for the evaluation of patients with palpable masses suspected of being breast cancer.[130] In my opinion, the diagnosis of breast cancer with ^{99m}Tc-MIBI or ^{99m}Tc-TF, as a mass screening modality, is a dreamscape of nuclear medicine physicians. In the actual management of breast cancer, the effort of searching avid uptake of ^{99m}Tc-MIBI or ^{99m}Tc-TF in the breast, for the purpose of tumor diagnosis, is of little importance. With various technological advances including biopsy devices and ultrasound-guide systems, the demonstration of malignant cells from breast lesions has already become an

easy task, and the most important concern of imaging diagnosis has shifted toward the detection of intraductal spread. In this aspect, scintimammography cannot compete with other modalities.

However, diverse uptake patterns of ^{99m}Tc-MIBI or ^{99m}Tc-TF will hold a major significance for therapeutic prognosis. MDR is a major obstacle to effective cancer chemotherapy. Scintimammography with ^{99m}Tc-MIBI or ^{99m}Tc-TF could be complementary to mammography, but a major role of scintimammography with ^{99m}Tc-MIBI or ^{99m}Tc-TF in breast cancer management has received a lot of new attention recently. False negative cases and rapid washout cases can be related in part to the presence of MDR. A clinical study evaluated the role of ^{99m}Tc-MIBI kinetics in the prediction of pathologic tumor response to neoadjuvant chemotherapy in patients with locally advanced breast cancer.[131] As a conclusion, the washout rate of ^{99m}Tc-MIBI has proved to be a reliable index for predicting tumor response to neoadjuvant chemotherapy. In fact, negative findings, namely low washout cases, rule out chemoresistance, while positive findings, characterized as high washout, indicate a high risk of chemoresistance.

Parathyroid Diseases:

Taillefer et al. introduced their study on detection and localization of parathyroid adenomas in patients with hyperparathyroidism using ^{99m}Tc-MIBI.[132] Since then, a lot of studies using ^{99m}Tc-MIBI for this area showed that ^{99m}Tc-MIBI is a must for a professional survey in patients suffering from this metabolic disorder. Arbab et al. analyzed the correlation between ^{99m}Tc-MIBI uptake and histological types of the parathyroid lesions with special reference to the amount of oxyphilic cells in the lesions.[133] Their conclusion was that ^{99m}Tc-MIBI uptake in parathyroid foci was not dependent on the cell type but rather on either the size or functional state of the lesions. The independence of ^{99m}Tc-MIBI uptake from the oxyphilic cell component is considered an important feature of ^{99m}Tc-MIBI, different from ^{201}Tl. However, Carpentier et al. performed a study to assess the relation between oxyphilic cell content and early and delayed ^{99m}Tc-MIBI uptake.[134] Most of the lesions with an oxyphilic cell content > 25% showed positive late ^{99m}Tc-MIBI uptake, in comparison with a fair percentage of lesions with an oxyphilic cell content < 25% that showed no ^{99m}Tc-MIBI uptake. Moreover, they showed that early ^{99m}Tc-MIBI uptake was associated with higher serum calcium levels and larger lesions. In light of our own experience, it is not surprising to have negative delayed ^{99m}Tc-MIBI uptake in the evident presence of adenoma. In such a case with a rapid clearance of ^{99m}Tc-MIBI, a characteristic pathologic finding is often poor oxyphilic cell content.

In any case, parathyroid scan with ^{99m}Tc-MIBI, at present, seems to be a quite accurate tool in this field. Reality, however, is not that simple. Before undertaking to use ^{99m}Tc-MIBI for this area, we must consider the normal uptake in surrounding tissue, especially the thyroid. Increased thyroid uptake often disturbs the end sought; either the thyroid is normal or abnormal. ^{99m}Tc-MIBI uptake in the thyroid often suggests thyroidal illness such as medullary thyroid carcinoma, differentiated thyroid carcinoma, lymphoma, and benign adenoma.

Thyroid Cancer:

Thyroid cancer is a candidate for ^{99m}Tc-MIBI study, but overall sensitivity and specificity of this agent for detection of the cancer, range from 36% to 89% and 89% to 100%, respectively.[105] Early imaging (10–30 minutes after tracer administration) will detect more lesions. However, our experience of delayed imaging shows that no significant difference is observed between intra-thyroid lesion and surrounding normal thyroid tissue.

^{99m}Tc-MIBI may be sensitive for the detection of nodal metastases.[105] Nevertheless, ^{99m}Tc-MIBI has poor sensitivity for the detection of lung metastases and residual neck bed thyroid tissue. Nuclear medicine specialists have presented some evidence that ^{99m}Tc-MIBI is useful in the follow-up of high risk patients with elevated thyroglobulin and negative ^{131}I scans, and in patients with Hurthle cell or medullary carcinoma.[135–138] Nevertheless, with regard to the role of ^{99m}Tc-MIBI, a strong consensus among specialists of thyroid cancer has yet to be reached. From my clinical experience, compared to ^{99m}Tc-MIBI, ultrasound and CT are more helpful for the detection of thyroid lesions and for the assessment of regional nodal conditions.

^{99m}Tc-TETROFOSMIN IN CLINICAL TUMOR IMAGING

^{99m}Tc-TF accumulates in a variety of solid tumors and their metastases, and an inverse correlation between its uptake and status of P-gp has been confirmed. Like ^{201}Tl and ^{99m}Tc-MIBI, most clinical studies with this tracer have been carried out in patients with malignancies located in extraabdominal regions, since the tracer accumulates in a great quantity in the liver while showing rapid excretion to the digestive system. The usefulness of ^{99m}Tc-TF imaging in oncology is demonstrated in tumors located in the thorax (breast and lung cancer), neck, brain, and the *in vivo* predictive assay.

Brain Tumors:

^{99m}Tc-TF is a suitable imaging agent for intracranial lesions with SPECT, but better delineation of tumor margins and a higher contrast between tumor and normal brain parenchyma are required.[139,140] In this point, no difference was found between ^{99m}Tc-MIBI and ^{99m}Tc-TF. Choi et al. showed an excellent agreement between tumor-to-normal brain ratio on ^{99m}Tc-TF and ^{99m}Tc-MIBI.[139] Data gap between ^{99m}Tc-TF and ^{99m}Tc-MIBI exists in the

use for the diagnosis of radiation necrosis. ^{99m}Tc-MIBI has been used in some studies including those focusing on radiation necrosis, but its diagnostic usefulness in radiation necrosis has not been found. Actually, in our institute we have not used this tracer in the brain either. From an *in vitro* study using several glioma cell lines, the kinetics of ^{99m}Tc-TF is inversely proportional to the degree of MDRs including MRP/GS-X pump system.[141]

Thyroid Cancer:
In choosing among ^{99m}Tc-MIBI, ^{201}Tl, and ^{99m}Tc-TF, the two ^{99m}Tc-labeled agents result in better image quality and faster imaging than ^{201}Tl. Uptake mechanisms of ^{99m}Tc-TF in thyroid tumor and intracellular binding mechanisms have not been completely described but are likely dependent on blood flow and electric potentials of transmembrane and mitochondria.[142] The agent has been used for the detection of recurrent disease and metastases in patients being followed for thyroid cancer. Actually, ^{131}I-negative metastases can be detected with ^{99m}Tc-TF with more than 80% detectability of metastatic lesions. ^{99m}Tc-TF uptake in the non-malignant thyroid remnant can occur in up to 67% of cases and can make differentiation from local tumor recurrence difficult. However, other authors report poor sensitivity (33%) for the detection of residual non-malignant thyroid tissue.[105]

Early abdominal imaging (as soon as 5 minutes post-injection) is necessary for lesion detection as gut and biliary activity rapidly obscure detail in this region, but the current consensus is that these abdominal lesions are detectable with ^{131}I whole body scan and with optimal use of CT study. Generally speaking, for metastatic survey, we should not apply ^{99m}Tc-TF or ^{99m}Tc-MIBI. Similar to ^{201}Tl, ^{99m}Tc-TF is not necessarily an effective measure to identify pulmonary metastases.[100] Similarly the agent is less sensitive for the detection of osseous metastasis.[142,143] Unfortunately, ^{99m}Tc-TF uptake is not specific for thyroid cancer and does not provide predictive information on the therapeutic potential of ^{131}I. The agent may best be utilized in patients with elevated thyroglobulin levels but negative radioiodine scans, or in combination with radioiodine scanning.[100] At present, we believe that neither ^{99m}Tc-TF nor ^{99m}Tc-MIBI has sufficient advantages to convince any general specialists of thyroid diseases of the value of their routine use.

Lung Cancer:
Cancers with low uptake of ^{99m}Tc-TF likely have overexpression of MDR products such as P-gp, MRP, and so on. Furthermore, cancers characterized as having low uptake of ^{99m}Tc-TF are more likely to be associated with a poor response to certain chemotherapeutic agents.[144] Determination of MDR-Pgp at the time of diagnosis may provide information regarding which treatment protocol would be best for each individual patient, and would help in appropriately selecting therapeutic strategies in each patient. We analyzed a scintigraphic predictive assay using ^{99m}Tc-TF in patients with untreated lung cancer, and the *in vivo* scintigraphic prediction results were comparable to laboratory-based *in vitro* predictive assay.[145] Kinetics of ^{99m}Tc-TF in untreated lung cancer, semiquantitatively measured, could be a strong and independent predictor of their therapeutic outcomes, while ^{201}Tl could not have predictive power. Moreover, regardless of whether ^{99m}Tc-TF or ^{99m}Tc-MIBI was selected, therapeutic prediction is limited to the short-term outcome, and it is necessary to undertake some large-scale clinical trials to assess whether these scintigraphic findings may shed light on outcomes, namely patients' survival.

Parathyroid Disease:
In our search of the literature, the first case report describing the use of ^{99m}Tc-TF to depict parathyroid adenoma was published in 1995.[146] Subsequent preliminary studies using ^{99m}Tc-TF in hyperparathyroidism showed that ^{99m}Tc-TF is, like ^{99m}Tc-MIBI, a suitable agent for parathyroid scintigraphy.[147,148] A key distinguishing difference between ^{99m}Tc-TF and ^{99m}Tc-MIBI appeared evident in direct comparison of the two kinds of scan conducted on the same patients with hyperparathyroidism. On early images (5 min after injection), all the adenomas detected with ^{99m}Tc-MIBI were equally well visualized with ^{99m}Tc-TF and vice versa. However, on delayed imaging (3 hr after injection), the visualization of adenomas improved only in ^{99m}Tc-MIBI studies. The differential washout seen on ^{99m}Tc-MIBI images was not observed with ^{99m}Tc-TF. Hence, compared to ^{99m}Tc-MIBI parathyroid imaging, delayed imaging with ^{99m}Tc-TF has less impact diagnostically.

Breast Cancer:
Scintimammography using ^{99m}Tc-TF can detect breast cancer sometimes in situations in which there is considerable uncertainty, as with dense breast tissue. Dense breast tissue is particularly difficult to assess by standard mammography. Women with dense breasts have a high incidence of false positives with standard mammography—test results that appear "falsely" positive in the absence of cancer. The false positives lead to unneeded CT, MRI, and biopsies. ^{99m}Tc-TF scan is especially valuable in these women, who are often younger women who have not gone through menopause. Breast malignancies typically show increased uptake of ^{99m}Tc-TF as compared to benign growths. In my experience, ^{99m}Tc-TF scintimammography (using SPECT technique) had an accuracy of over 90%, while standard mammography yielded a significantly lower value.

The US Food and Drug Administration (FDA) has approved scintimammography with ^{99m}Tc-TF for the diagnosis of breast cancer. The technique is not meant to replace standard mammography or other current tests, but to be used in conjunction with them. Moreover, semi-

quantitative measurement of the tracer uptake and washout from breast cancer was proved to be an effective *in vivo* assay directly applicable to individuals.[149–151]

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