Clinical application of several tumor imaging agents

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Abstract Neoplasms is one of the main diseases for harming health. It is difficult to prevent the neoplasms because the factors of bringing out them are complex. To raise survival rate the early diagnosis of tumors is very important. Radionuclide imaging is useful to detect recurrent or residual disease and to identify benign or malignant tumor. Several tumor imaging agents as following have clinical significance in diagnosing tumors.
Keywords Tumor imaging agents, Neoplasms, Clinical application

1 ^{131}I- or ^{123}I-MIBG

1.1 Pharmacology and physiology

Structurally, MIBG resembled norepinephrine and guanethidine. MIBG images the adrenal medulla and sympathetic nervous tissue. It can be labelled with either ^{123}I or ^{131}I. The 159 keV photon of ^{123}I could be more easily collimated and images obtained were of higher quality. There was no demonstrable difference between ^{131}I and ^{123}I in detecting neuroblastoma. MIBG localized to storage granules in adrenergic tissue of neural crest origin. The uptake was proportional to the number of neurosecretory granules within the tumor. In childhood, extra-adrenal chromaffin tissue was abundant. After the age of 3 years, these extra-adrenal sites regressed except in sympathetic ganglia and the carotid bodies.

Usually the adrenals were not seen in ^{131}I-MIBG imaging, but may be faintly visualized in 10% to 20% on delayed images. For ^{123}I-MIBG, adrenals were seen in 30% of patients. Although the uptake was generally mild, it can be unilateral or asymmetric in up to 50% of cases. Confusion can then occur in differentiating this uptake from a pheochromocytoma. Unilateral uptake less than or equal to the liver can represent pheochromocytoma in 10% and 33% of cases, respectively. Unfortunately, 31% of normal adrenals were also visualized with uptakes less than or equal to the liver. In general, most pheochromocytomas demonstrated uptake more intense than the liver (80%).[1] Liver uptake was inversely related to catecholamine levels. Most ^{131}I-MIBG (about 85%) was excreted unchanged in the urine. There was variable excretion into the gut (1% to 4%). The whole body half-life was about 24 hours, but the agent was retained in sympathetic nervous tissue for a prolonged period of time.

1.2 Technique

MIBG was labelled with 18.5 MBq ^{131}I or 370 MBq ^{123}I. Imaging was performed at 1 and 3 days following ^{131}I-MIBG administration, and 6 and 24 hours after ^{123}I-MIBG administration. To block thyroid uptake of free iodine, Lugol's solution should be used and continued for 5 to 6 days. The critical organ was adrenal medulla (2.7×10^{-8}Gy/Bq for ^{131}I). Some drugs can interfere with MIBG uptake, such as cocaine, tricyclic antidepressants, catecholamine agonists, reserpine, antipsychotics, calcium channel blockers, adrenergic blockers and so on.

1.3 Clinical application

1.3.1 Pheochromocytoma. Pheochromocytomas arised from chromaffin cells in adrenal medulla, sympathetic ganglia, aortic and carotid chemoreceptors. Patients can present with paroxysmal hypertension(50%) or sustained hypertension(40%) associated with headache, sweating, palpitations, weight loss and hyperglycemia. Only was 0.05% of patients with hypertension found having pheochromocytomas. 10% pheochromocytomas were malignant (tend to be larger lesions), 10% were bilateral, 10% occued in pediatric patients, and 10% were extra-adrenal. Pheochromocytomas were associated with certain disorders, such as neurofibromatosis, von Hippel-Lindau, and Carney's syndrome. Extra-adrenal lesions occured in 10% of adults, and 30% in children.

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Extra-adrenal lesions generally located in the retroperitoneal sympathetic ganglia in the paracaval/aortic region. Other sites included the renal hilum, mediastinum, and urinary bladder. In adults, extra-adrenal lesions were malignant in 30% to 40% cases, and about 2% in children.

On CT most pheochromocytomas were usually soft tissue density and the center of lesion may be necrotic or completely cystic. Calcification was noted infrequently. On MRI, the lesion was usually slightly less intense than the liver on T1 images, but extremely bright on T2 images. Occasionally, lesions may be inhomogeneous, iso- or hypointense to the liver. Angiography was contraindicated unless absolutely necessary as it may provoke a hypertensive crisis. In such cases, premedication was required.

MIBG scan sensitivity for pheochromocytoma was 86% and specificity was 95% to 99%. In patients with biochemical abnormalities indicative of a pheochromocytoma, CT or MRI were more accurate in detecting primary tumors of the adrenal gland, but they were inferior to MIBG in detection of extra-adrenal tumors which accounted for about 10% of lesions.[2] On MRI, pheochromocytomas had a signal intensity similar to or slightly lower than that the liver had on T1 images, but were extremely hyperintense on T2 images. Unfortunately, due to the presence of necrosis within the lesion, over 20% of lesions would have an atypical appearance on T2 images.[3] Approximately 10% of pheochromocytomas were cystic, but these lesions were still endocrinologically active and would concentrate MIBG.

1.3.2 Neuroblastoma. Neuroblastoma was the most common extracranial solid malignant tumor of infants and children. About 50% of cases occured in children less than 2 years, and 90% were seen by 8 year of age. Males were affected slightly more than females. Symptoms of neuroblastoma included an abdominal mass, limp, nystagmus or inability to walk. Hypertension was found in 30% of patients and elevated urinary catecholamine level (VMA & HVA) was seen in 90%.

Metastases were present in 60% of patients with neuroblastoma. The skeleton was the most common site (60%). Metastases could also go to lymph nodes (40%), liver and intracranial. Prognosis was related to patient's age and tumor's grade. Sites of primary neuroblastoma 75% of cases were intraabdominal.

Sensitivity and specificity of ^{131}I- or ^{123}I-MIBG scan in the detection of neuroblastoma have been reported to be 90% and 100%.[3] The extent of metastatic bone and bone marrow lesion can be accurately defined by this method. ^{123}I-MIBG was more suitable for imaging and ^{131}I-MIBG for treatment. Bone scanning often grossly underestimated the extent of osseous metastases.[4] Liver metastases may be escaped with MIBG imaging. Small lesions may be obscured.[5] SPECT increased diagnostic certainty, but did not increase lesion detection with ^{123}I-MIBG.[6] ^{99m}Tc-MDP was concentrated in about 2/3 of primary lesions (related to presence of calcification). The localization of metaphyseal metastases can be difficult due to the adjacent physeal activity. A common finding on bone scan in patients with metaphyseal metastases was ill-defined increased activity in this area with loss of the sharp boundary between the growth plate and the metaphysis. On IVP there was typically inferior renal displacement rather than collecting system distortion. On CT neuroblastoma it appeared as a large complex mass which was often locally invasive into adjacent tissue and typically encaseds the great vessels, although a pseudocapsule might be seen.

2 ^{67}Ga

2.1 Chemistry and pharmacology

^{67}Ga has a physical half-life of 78 hours and a biologic half-life of 2 to 3 weeks. ^{67}Ga decays with the following gamma emissions: 93 keV(40%), 184 keV(24%), 296 keV(22%) and 388 keV(7%). ^{67}Ga has approximately a 12 hour half-life in blood. The Ga^{+3} ion resembled the ferric ion in atomic radius and charge. It bound to transferrin (in plasma), lactoferrin (in tissue) and ferritin, which was not protein bound and was either cleared by the kidneys or passeds into the extravascular space. Saturation of transferrin with iron. The patients with iron overload from repeating transfusions will result in altered biodistribution of ^{67}Ga, such as less liver uptake, greater renal activity and more rapid clearance. Renal excretion (10% to 30% of injected dose) occured mostly during the first

24 hours. Renal activity should not be seen on 72 hour images. Persistent activity implied renal disease. Gastrointestinal excretion was the predominant route after 24 hours, but a small amount of Ga^{3+} excreted via the liver and biliary tract. A laxative may be required prior to later imaging to clear colonic activity. Significant amounts of carrier will change the biologic distribution of ^{67}Ga in the body.

2.2 Technique

The typical dose of ^{67}Ga was 370 MBq for neoplasms (image at 48-72 hours after administration). When performing whole body scan, a slow scan speed (10 cm/min) was recommended in order to obtain adequate count densities. When performing scan of the abdomen, the liver should be shielded or placed out of the field of view. ^{99m}Tc-sulfur colloid imaging may be performed to subtract from liver activity. When imaging axillary abnormalities, the arms should be raised above the head to fully expose the axilla.

2.3 Clinical application

2.3.1 Lymphoma. ^{67}Ga scanning can be used in patients with Hodgkin's lymphoma in order to determine the extent of disease, for the evaluation of a residual mass, to monitor response in treatment, and to predict disease free survival. About 90% of Hodgkin's lymphomas were ^{67}Ga avid pretreatment. Lymphocyte predominant tumors (10% of cases) showed somewhat less ^{67}Ga avidity (79%). Overall sensitivity for detecting Hodgkin's lymphoma was about 85%, with a specificity of 90%. SPECT had a sensitivity of 95% and a specificity of 90% for the detection of mediastinal lesion. Mediastinal or hilar nodal involvement was more common in patients with Hodgkin's lymphoma (75%) than in non-Hodgkin's lymphoma (25%). Nodal involvement of the hila and mediastinum was usually asymmetric. The ^{67}Ga imaging was not useful for assessing splenic involvement. Its periportal area may also be difficult to assess. ^{67}Ga was very useful in detection of recurrent or residual disease. For recurrence, it was essential to image the entire body since about 25% of patients relapsed only in new sites.[7,8] Up to two-third of patients with initial mediastinal involvement will have persistent radiographic mediastinal abnormalities. Chemotherapy may suppress ^{67}Ga uptake. At least 3 week delayed after chemotherapy was recommended prior to re-imaging. Tumor irradiation may also result in transient or permanent loss of ^{67}Ga uptake since ^{67}Ga was a viability agent. It was taken up by cancer tissue and not by fibrotic or necrotic tissue at tumor site. When ^{67}Ga uptake was observed in a residual mass indicating viable tumor following treatment, further treatment should be done. The presence of residual ^{67}Ga uptake after treatment showed a poor prognosis in patients with Hodgkin's lymphoma. In Hodgkin's patients, 2 year survival rate decreased from 100% to 60% in patients with positive scans at the end of treatment, and decreased from 90% to 35% in non-Hodgkin's patients. Frequently, bilateral hilar nodal ^{67}Ga uptake can be seen in patients who have completed chemotherapy and may persist. This uptake was only very rarely associated with the presence of residual lymphoma. It may be related to the presence of a concomitant inflammatory disease or the chemotherapy. Unilateral hilar uptake post therapy was somewhat more concerning and raises the possibility of recurrent disease. If necessary, ^{201}Tl imaging may be useful.

^{67}Ga sensitivity was reported to be better (85%) for high grade tumors. Patients with high grade tumors generally had a poor prognosis. Its sensitivity for low grade tumors was poor. Detection of well differentiated lymphocytic lymphoma with ^{67}Ga was also poor (60%). A persistently positive ^{67}Ga exam was associated with a poor prognosis, while a negative scan implied a favorable prognosis. ^{201}Tl imaging can add useful information in the evaluation of non-Hodgkin's lymphoma. For both non-Hodgkin's and Hodgkin's lymphoma the response of sites of osseous involvement were best monitored with ^{67}Ga.[9]

2.3.2 Hepatocellular carcinoma. Approximately 90% of hepatomas were ^{67}Ga avid. About 50% of the lesions, the activity was greater than the adjacent liver, 30% had the uptake equal to the surrounding liver. For these reasons, it was essential to view the ^{67}Ga exam in conjuction with a ^{99m}Tc-sulfur colloid exam. Cold lesions on the sulfur colloid study which "fill-in" on the ^{67}Ga scan were highly suspicious for hepatoma.

2.3.3 Malignant melanoma. About 75% of lesions over 2 cm in size were ^{67}Ga avid. For le-

sions less than 2 cm in size, only 20% showed ^{67}Ga uptake. Overall sensitivity and specificity have been reported to be 82% and 99% , respectively.

2.3.4 Bronchogenic carcinoma. Squamous cell carcinoma had the highest detection rate (^{67}Ga avidity) , while adenocarcinoma had the lowest. Overall, ^{67}Ga had a sensitivity of about 90% for the detection of primary bronchogenic carcinoma. Scatter from adjacent structures reduced the detection rate of lesions near the mediastinum and the liver. Lesions smaller than 1.5 cm were also difficult to be detected. When a primary tumor accumulated ^{67}Ga and there was also extrapulmonary, the likelihood of extrapulmonary metastatic lesion was about 90%.

3 ^{201}Tl and ^{99m}Tc-MIBI

3.1 ^{201}Tl tumor imaging

^{201}Tl accumulated mainly within viable tumor tissue and lesser degree within connective tissue which contained inflammatory cells. Its accumulation was barely detectable in necrotic tissue. Localization of ^{201}Tl within tumors was likely multifactorial, involving blood flow, tumor viability, the sodium-potassium ATP-ase system, the non-energy dependent co-transport system, the calcium ion channel system, vascular immaturity with leakage, and increased cell membrane permeability . Cellular uptake of ^{201}Tl was not affected by steroids, chemotherapy, or radiation therapy. A baseline retreatment determination of a tumor's ^{201}Tl avidity was crucial to its efficacy in therapeutic response assessment. The optimal time for ^{201}Tl tumor imaging was 20 to 60 minutes post injection. For lymphoma, delayed images at 3 hours were recommended because the lesion to background ratio on the later images was good. The dose used for imaging is 111 to 148 MBq. The normal distribution of ^{201}Tl within the body was in the choroid plexus of the lateral ventricles, lacrimal glands, salivary glands, thyroid, myocardium, liver, spleen, splanchnic arease, kidneys and testes. Bone marrow activity should not be seen. There was little uptake in healing surgical wounds. The elimination of Tl was slow with a biologic half-life of 10 days. False-positive uptake has been seen in histiocytosis, benign bone tumors, stress fractures and inflammation.

Rapid washout of ^{201}Tl from central nervous system (CNS) neoplasms has been described, and lesions may be missed if only delayed images were performed. Normal brain uptake occured from the cerebrospinal fluid (CSF) and was related to neuronal activity. There was normally little or no ^{201}Tl uptake in the white matter. ^{201}Tl will not cross through intact blood brain barrier (BBB), yet disruption of the BBB was not the sole factor which affects ^{201}Tl accumulation within a primary CNS lesion as little ^{201}Tl accumulation was identified at sites of cerebral infarction. Uptake of ^{201}Tl in CNS tumors also likely depended on the ATP-ase activity of the sodium-potassium pump and active transmembrane transport via the k+/glucose co-transport system in viable tumor cells.[10] ^{201}Tl accumulated in residual recurrent tumor in proportion to the malignant grade and total viable tumor bulk. ^{201}Tl can also accumulate in benign tumors such as meningiomas and pituitary adenomas.[11] ^{201}Tl accumulation was minimal or negative at sites of radiation necrosis and resolving hematomas. Lesions less than 2 cm in size, centrally located, or adjacent to areas of normally high activity may be missed. Malignant gliomas and meningiomas were detected with high sensitivity, while pituitary and parasellor tumors, low grade gliomas, and brainstem tumors were detected with low sensitivity. ^{201}Tl accumulation was shown to be largely dependent on tumor grade, with low or no uptake in low grade tumors, and with intense uptake in high grade lesions. Quantitative assessmsent of lesion activity showed that most tumors had a tumor-to-normal brain ratio of greater than 2.5 and ratios less than 1.5 suggested a non-malignant lesion.[12] ^{201}Tl imaging could be used to aid in discriminating CNS lymphoma from toxoplasmosis. Lymphoma could avidly accumulate ^{201}Tl , while toxoplasmosis infection typically demonstrated only mild ^{201}Tl uptake. The lesion to -non-lesion uptake ratio was generally greater than 2.5:1 in cases of CNS lymphoma.[13]

^{201}Tl can be used to differential residual tumor from postoperative/post-radiation therapy changes for CNS neoplasms such as gliomas. Radiation necrosis occured 3 to 12 months following radiotherapy and can be associated with exuberant gliosis. ^{201}Tl uptake which increased

in comparison to the contralateral normal brain was highly suggestive of recurrence. Necrosis and inflammatory-infecatious processes may rarely showed increased uptake.[14]

The advantages of ^{201}Tl scintigraphy for imaging thyroid cancer included low radiation exposure compared to ^{131}I and patients did not need to be removed from thyroid hormone replacement therapy. Primary thyroid carcinoma metastases were detected using ^{201}Tl with a sensitivity between 35% and 95%. Unfortunately, ^{201}Tl uptake was not specific for thyroid cancer and did not give predictive information on the therapeutic of ^{131}I. Additionally, it was less sensitive than ^{131}I scanning in the detection of pulmonary metastases, bone metastases, and for metastases below the hemidiphragms.

In osteosarcoma, ^{201}Tl uptake usually decreased significantly which showed a histologic response to chemotherapy. Research indicated that patients with more than 90% necrosis following preoperative chemotherapy had a better prognosis.[15] SPECT images can be performed to permit co-registration with CT or MRI images. Unfortunately, ^{201}Tl accumulation in bone lesions was non-specific and was described in some benign lesions including fractures. ^{201}Tl was also used in the evaluation of soft tissue sarcomas. ^{201}Tl uptake within the lesion appeared to reach a maximum by about 1 hour after injection. Lesion to muscle ratio of greater than 3:1 was typically identified with sarcomas, while infection or inflammation had the ratios of below 1.0. ^{201}Tl uptake in pulmonary metastases was poor. Overall, ^{67}Ga was superior to ^{201}Tl in the evaluation of lymphomas. ^{201}Tl may be beneficial in evaluating the mediastinum for residual disease. Normally, no ^{201}Tl uptake was seen in the mediastinum. Gastrointestinal excretion of ^{201}Tl limited its usefulness for evaluation of abdominal lesions.[16]

Mammography has been accepted as the primary screening tool for breast cancer. Unfortunately, it was very difficult to mammographically distinguish benign from malignant lesions and the exma had a positive predictive value for cancer of only 15% to 30%. Studies had demonstrated the usefulness of ^{201}Tl in differentiating benign from malignant breast lesions. Benign lesions seldom demonstrated tracer accumulation, although highly cellular adenomas and papillomas may demonstrate uptake of tracer. Overall ^{201}Tl had a sensitivity between 67% and 96% in the differentiation of benign from malignant breast lesions, and a specificity of 91% to 93%. ^{201}Tl was not useful for the detection of axillary node metastases (sensitivity 50% to 60%). Lesion size may have a major effect on sensitivity. ^{201}Tl exam had a sensitivity of 67% for lesions greater than 1.5 cm in size, but only 20% for lesions below this size.[17~19]

3.2 ^{99m}Tc-MIBI tumor imaging

There were many advantages to use ^{99m}Tc rather than ^{201}Tl for scintigraphic imaging. Having shorter physical half-life permited the use of a higher dose of radiopharmaceutical. The gamma energy of ^{99m}Tc (140 keV) was optimal for detector crystal in gamma camera.

^{99m}Tc-MIBI has also been used to evaluate CNS neoplasms. ^{99m}Tc-MIBI uptake was a marker of mitochondrial oxidative capacity. In the patients responding to chemotherapy, ^{99m}Tc-MIBI uptake within the lesion frequently decreased and this felt to be reflective of damage to the mitochondrial oxidative capacity of the tumor. Unfortunately, ^{99m}Tm-MIBI uptake of choroid plexus limited its usefulness for CNS neoplasm imaging.

^{99m}Tc-MIBI has also been used to evaluate breast lesions, and may be more sensitive than ^{201}Tl in evaluation of breast lesions greater than 1.5 cm in size. The administration dose was approximately 740 MBq. Specially designed imaging systems have recently been developed to permit prone lateral imaging. Overall, ^{99m}Tc-MIBI had a sensitivity of 83% to 96% and a specificity of 72% to 100% for malignancy. The negative predictive value has been reported to be as high as 95% to 97%. False positive exams have been described with fibroadenomas, papillomas, epithelial hyperplasia, and fibrocystic breast disease.[19,20] It has been noted that 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.[19,20] Most false negative exams occured with lesions smaller than 1 cm in size or non-palpable lesions.[21,22]. It was generally accepted that ^{99m}Tc-MIBI was not accurate in the detection of malignant axillary adenopathy

(with a sensitivity of 50% to 60%), although its sensitivities as high as 84% was reported.[23]

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