

《招請講演 I》

Expanding the Boundaries: Update in Nuclear Cardiology

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Nuclear cardiology has experienced explosive growth during the past decade, founded on the solid evidence that this discipline provides the clinician with an accurate assessment of patients with suspected ischemic heart disease. Myocardial perfusion SPECT imaging has superior sensitivity and specificity for the detection of coronary artery disease when compared with routine stress testing and provides information regarding the extent, severity, and location of coronary artery disease. The diagnostic value of perfusion imaging has further been improved by the use of gated SPECT and attenuation correction imaging. The latter method provides improved specificity, as well as an enhanced ability to detect multivessel disease.

The potential value of SPECT imaging has been extended to patients unable to perform maximal exercise with the use of pharmacologic testing. Adjunctive exercise in conjunction with vasodilator stress improves image quality and significantly reduces side effects. The ongoing development of specific A2a agonists will likely further improve safety and tolerability.

The ability of SPECT imaging to risk stratify patients that has served to define nuclear cardiology, as a tool beyond the establishment of a clinical diagnosis. This prognostic information permits the separation of a low-risk cohort of patients from those who are at a high risk for subsequent cardiac events. This information is incremental in nature to clinical and exercise data already available. The risk for myocardial infarction and cardiac death is magnified when high risk scintigraphic findings are present, such as transient ischemic dilation of the left ventricle. In addition to the prognostic applications of perfusion imaging in a general population, this technique has shown specific predictive value in subpopulations, including women and diabetic patients. Furthermore, MPI may be used successfully after acute coronary syndromes, following revascularization, before major surgery, and in patients with a cardiomyopathy.

The impact of the predictive value of perfusion imaging is also apparent when examining the cost-effectiveness of the technique. Data from a multitude of sources now suggest that perfusion imaging may be used to regulate invasive techniques and provide maximal benefit to patients who most require further intervention while doing so in a financially sound manner.

A new series of applications is approaching, using perfusion imaging not only to decide on treatment but also to evaluate the efficacy of these therapies. SPECT imaging has been used as an endpoint for studies examining novel methods of revascularization, such as with the use of laser techniques or angiogenic substances. Nuclear cardiology methods are also expanding beyond myocardial perfusion imaging and encompass a variety of molecular processing including, but not limited to the detection of necrosis and apoptosis, evaluation of adrenergic receptors, definition of atherosclerotic plaque morphology, and targeted imaging of angiogenesis.

In conclusion, myocardial perfusion imaging has clearly become a mainstay in the evaluation of patients with known or suspected ischemic heart disease. SPECT imaging offers critical diagnostic and prognostic data for a variety of patient groups and in many different clinical settings. Continued development regarding clinical applications and advances in cardiovascular molecular imaging offer great promise for the future of nuclear cardiology.

《招請講演 II》

PET Tumor Imaging Using Fluorine-18 Labeled Amino Acids

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[¹⁸F]fluoro-2-deoxyglucose ([¹⁸F]FDG) has been the most widely used PET agent for detecting brain and systemic tumors, and it is reported that the magnitude of uptake corresponds to tumor grade. [¹⁸F]FDG has also been used to assess radiation-induced tissue necrosis, response to treatment, and prognosis and survival. Although [¹⁸F]FDG has been shown to be an effective tumor imaging agent, [¹⁸F]FDG tumor imaging has several shortcomings. The interpretation of [¹⁸F]FDG images of solid tumors is often complicated by a number of conditions that increase glycolysis such as ischemic brain tissue resulting from stroke and the presence of inflammatory cells which show high [¹⁸F]FDG uptake. Secondly, [¹⁸F]FDG images of brain tumors are often difficult to interpret because of significant [¹⁸F]FDG uptake in adjacent normal brain gray matter which results in relatively low tumor to normal brain ratios. Thus, development of new PET radiopharmaceuticals to complement [¹⁸F]FDG are needed.

Similar to carbohydrates, amino acids are required nutrients for proliferating tumor cells. A variety of amino acids containing the positron emitting isotopes carbon-11 have been prepared and evaluated for potential use in clinical oncology for tumor imaging in patients with brain tumors and tumors outside the CNS. These amino acid candidates can be subdivided into two major categories. The first category is represented by radiolabeled naturally occurring amino acids such as L-[¹¹C]methionine (MET) and L-[¹¹C]tyrosine. The increased uptake and prolonged retention of these naturally occurring radiolabeled amino acids into tumors in comparison to normal tissue is due to significant and rapid regional incorporation into proteins. Of these radiolabeled amino acids, [¹¹C]MET has been the most extensively used clinically to detect tumors. Although [¹¹C]MET has been found useful in detecting brain and systemic tumors, it is susceptible to *in vivo* metabolism through multiple pathways giving rise to numerous radiolabeled metabolites. Thus, graphical analysis with the necessary accuracy for reliable measurement of tumor metabolic activity is not possible. An additional shortcoming for employing radiolabeled amino acids which accumulate in tumors via incorporation into proteins is that kinetic analysis of tumor uptake in humans strongly suggests that amino acid transport may provide a more sensitive measurement of tumor cell proliferation than protein synthesis.

The shortcomings associated with [¹¹C]MET may be overcome with a second category of amino acids. These are non-natural amino acids such as 1-[¹¹C]α-aminoisobutyric acid ([¹¹C]AIB), and 1-aminocyclobutane-1-[¹¹C]carboxylic acid ([¹¹C]ACBC). The advantage of [¹¹C]AIB, and [¹¹C]ACBC in comparison to [¹¹C]MET are that they are not metabolized. However, a significant limitation in the application of carbon-11 amino acids for clinical use is the short 20-minute half-life of carbon-11. In order to overcome the physical half-life limitation of carbon-11, we have recently developed several new fluorine-18 labeled amino acid analogs of ACBC and AIB which include *anti*-1-amino-3-[¹⁸F]fluorocyclobutyl-1-carboxylic acid ([¹⁸F]FACBC), *syn*- and *anti*-1-amino-3-[¹⁸F]fluoromethylcyclobutyl-1-carboxylic acid ([¹⁸F]FMACBC), *R*- and *S*-2-amino-3-[¹⁸F]fluoro-2-methylpropanoic acid (*R*- and *S*-[¹⁸F]FAMP) and *R*- and *S*-3-[¹⁸F]fluoro-2-methyl-2-(methylamino)-propanoic acid (*R*- and *S*-*N*-Me[¹⁸F]FAMP).

In this presentation, examples of the characterization, fluorine-18 radiolabeling, and PET imaging of non-natural amino acids developed in our laboratory showing good tumor uptake will be given.

《招請講演 III》

Radionuclide Therapy of Metastatic Bone Pain

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The use of radiopharmaceuticals in the palliative treatment of patients with painful bone metastases caused by cancer metastatic to bone has proven effective and safe. It has been in clinical use for several decades, with clinical benefit to thousands of patients. However, the current acceptance of the technique for the treatment of this large population of patients has not been as widespread as had initially been hoped. Two radiopharmaceuticals are in routine clinical use—Samarium-153 EDTMP and Strontium-89. In addition, Phosphorus-32 is approved for use in some jurisdictions.

As a rule of thumb, 70% of patients with painful bone metastases will respond to palliative therapy with radiopharmaceuticals, and approximately one third of these will become pain free. Duration of response is typically between 2 and 6 months, and re-treatment is perceived to be safe.

Recent data have shown that the effectiveness of the treatment can be improved by the use of adjuvant chemotherapy agents such as radiosensitizers, particularly Cisplatin.

The success of treating this population of patients is dependent upon patient selection and the careful attention to the administered dose. The requirements for patient selection criteria will be enumerated in this paper for radiopharmaceutical therapy, together with the infrastructure required to successfully support this venture. The involvement of the Nuclear Medicine Physician will be stressed at all stages of the management plan.

A comparison of the two routine radiopharmaceuticals will be made and the advantages and disadvantages of each will be discussed. In addition there will be a review of current radiobiological thinking for low dose and low dose rate radioisotope therapy and the relevance that these findings might have to the design of new protocols to establish the effectiveness of Samarium-153 EDTMP for the treatment of this group of patients. Possible interactions with treatment modifiers will be reviewed and future research directions and possibilities outlined.

Overall, radiopharmaceutical therapy for bone pain palliation is a safe and effective treatment, which requires considerable effort on the part of the Nuclear Medicine community to expand its role.

《招請講演 IV》

New Applications of Imaging in Research and Diagnosis in Parkinson's Disease

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Interest in objective biomarkers of Parkinson's (PD) and related disorders has intensified with new approaches to treatment which emphasize slowing down or reversing the progression of the disease. This interest has manifested in two ways; first, in using imaging biomarkers for research studies of disease progression and as a diagnostic screening tool for patient enrollment in trials of very early onset PD, and second in the more clinically-focused use of imaging to improve the timeliness and accuracy of diagnosis. Regarding the former, although no neuroprotective or neurorestorative treatments are available currently, the number of on-going clinical trials in neurodegenerative disorders suggests that such therapies may be feasible. Neuroprotection studies in PD are difficult to design and implement because the course of progression is slow, often variable between patients, and clinical assessments are confounded by concurrent symptomatic medications. In addition, the trials ideally enroll recent onset patients who must be followed for long duration of time (usually 2 years or more) to elucidate disease-modifying effects of protective therapies. In PD studies which have incorporated presynaptic dopaminergic imaging markers, there has been a discordance in a subset of patients between the initial criteria-based clinical diagnosis of PD and imaging measures which show no evidence of dopaminergic deficit. These patients have been termed "SWEDD" for subjects without evidence of dopaminergic deficit. In several studies involving very early PD subjects the rate of SWEDDs on the order of 10–15%. In order to understand whether imaging has a role in improving the accuracy of the enrolling neurologists for these studies we have initiated follow-up in these patients to clarify whether the initial clinical impression or the imaging findings were most accurate.

If the ongoing clinical PD studies demonstrate a disease-modifying intervention in the disorder, the need for an early and accurate means for identifying patients with Parkinson's suggests a role for imaging to maximize the early and accurate diagnosis in the difficult-to-diagnose early stages of disease. There have been a number of studies in PD evaluating the sensitivity and specificity of neuroimaging measures of presynaptic dopaminergic function including ^{18}F -dopa and dopamine transporter ligands using PET and SPECT. While all these studies have consistently demonstrated the diagnostic accuracy of these markers compared with the gold-standard diagnosis of a movement disorders specialist, these studies have not modeled the clinical scenario most commonly encountered in the use of imaging for diagnosis; specifically, what is the clinical value of imaging in patients for whom the diagnosis is uncertain?

In order to explore the practical application in most likely clinical scenario we compared the ^{123}I β -CIT SPECT with movement disorder specialist in the diagnostic evaluation of patients with suspected parkinson's syndrome (PS). For the purpose of this study, PS is defined as any extrapyramidal syndrome associated with nigrostriatal dopaminergic neuronal loss, including Parkinson's disease, progressive supranuclear palsy, multiple systems atrophy and CBGD. Twenty community neurologists from Connecticut, USA referred 94 patients for imaging in whom there was uncertainty regarding a diagnosis of PS. The community neurologists were asked to provide a 'best' clinical diagnosis of 'PS' or 'no PS' at the time of referral. Patients were evaluated by a movement disorders expert (MDE) who provided a baseline clinical

diagnosis of 'PS' or 'no PS'. Patients underwent imaging with [^{123}I] β -CIT SPECT and were assigned an imaging diagnosis based on a quantitative analysis. Follow-up clinical evaluation at 3–6 months and 12 months following the imaging study was performed by the MDE who remained blind to the imaging data. The 3–6 month clinical follow-up exam was considered the 'gold standard' diagnosis for this analysis. There was disagreement between the community neurologist and the 'gold standard' diagnosis in 32/94 (34%), between the MDE baseline evaluation and the 'gold standard' in 13/94 (14%) and between DAT imaging and the 'gold standard' in 10/94 (9.4%). Baseline DAT imaging most closely predicted the ultimate 'gold standard' diagnosis (sens = 0.86, spec = 0.95, auc = 0.90), compared to the community neurologist (sens = 0.84, spec = 0.37, auc = 0.61) and MDE evaluation at baseline (sens = 0.86, spec = 0.86, auc = 0.86). For the 16 subjects who have completed the 12-month follow-up visit, there was agreement between DAT imaging and the 'gold standard' in all (16/16) subjects.

There was substantial disagreement in the baseline clinical diagnoses assigned by the community neurologists experts compared with the 'gold standard' diagnosis. The quantitative DAT imaging diagnosis at baseline provided increased diagnostic accuracy compared to either the community neurologist or the movement disorders expert diagnosis suggest that imaging may be an important clinical tool in evaluation of PD, particularly as better therapeutics are developed.