《International Symposium》

Current Status and Perspective of Nuclear Oncology

Junji Konishi
Graduate School of Medicine, Kyoto University
Kayoko Nakamura
Keio University School of Medicine

The incentive for organizing this symposium was the realization that nuclear medicine is destined to play an increasing important role in oncology.

Needless to say, nuclear medicine has provided much physiological and molecular information. The information leads to the clue which therapies should be selected and how therapies are going on for patients.

Some innovations have occurred in Nuclear Oncology, and all of them are going towards the goal for the managements of patients. The innovations have consisted of the approval of FDG in Japan, radioimmunotherapy in the USA, and sentinel node concepts in the world: The detection of lung cancer by FDG at its early stage would be much helpful for the cancer to be cured. Radioimmunotherapy of cancer has been a long enthusiasm to be achieved in Nuclear Oncology. Sentinel node detection would not be developed without aid of radiopharmaceuticals. The innovations also have encouraged the development of new radiopharmaceuticals for characterizing tumor physiology and for palliating tumor pain: The detection of hypoxic area *in vivo* is of special interest for all oncologists, since this physiological characteristics affects not only radiation therapy but also chemotherapy. We have learned that targeting of Sr-89 or Sm-153 has been successful for the palliation, and now we need more.

This symposium is designed to present these innovations not only to the nuclear medicine physician but also to the oncologist in various clinical fields. Each speaker has been asked to introduce his/her subject with this in mind. Speakers will describe many of more important topics of the role of nuclear medicine in the oncology. All presentations show clearly that understanding present clinical and experimental status will be essential for the nuclear medicine specialist in the near future. We view this symposium as one important step in providing what we should do in the Nuclear Oncology.

《International Symposium》

1. Imaging of Hypoxia in Tumours

James R. Ballinger

Department of Nuclear Medicine, Addenbrooke's Hospital, Cambridge University, UK

It has been known for many years that hypoxia affects the response to radiotherapy in human cancers. Hypoxic regions can develop as a tumour grows beyond the ability of its blood supply to deliver oxygen to the full extent of the tumour, exacerbated by vascular spasm or compression due to increased interstitial fluid pressure. This is particularly common in cancers of the uterine cervix, breast, lung, and soft-tissue sarcoma. However, hypoxia is heterogeneous and tumours that appear identical by clinical and radiographic criteria can very greatly in their extent of hypoxia. The inability to measure hypoxia diluted the power of early clinical trials of hypoxia-directed interventions due to the inadvertent inclusion of patients who could not be expected to benefit from such interventions. Several invasive procedures to measure hypoxia in tumours have now been developed and are predictive of response to therapy, but none of these is in routine clinical use due to technical complexity, inconvenience, and inability to obtain repeated measures. Non-invasive imaging with a hypoxia-directed radiopharmaceutical could be of great clinical utility. Most such radiopharmaceuticals under development use 2-nitroimidazole as the targeting moiety. 2-Nitroimidazole, which is selectively reduced and bound in hypoxic tissues, has been labelled with F-18, Cu-64/67, I-123, and Tc-99m. Of these, F-18-fluoromisonidazole (FMISO) and I-123-iodoazomycin arabinoside (IAZA) have been most widely studied clinically. The Tc-99m-labelled 2-nitroimidazoles BMS181321 and BRU59-21 show excellent properties *in vitro* but their lipophilic nature results in extensive hepatobiliary excretion which prevents them from being used to image tumours in the abdomen. Non-nitro-containing bioreductive complexes such as the Cu-60/62/64 thiosemicarbazone ATSM and Tc-99m butylene amineoxime (BnAO or HL91) have also been evaluated. Cu-ATSM is particularly promising; its accumulation is very rapid, as is its blood clearance, allowing the use of short-lived generator-produced Cu-62. Tc-99m-BnAO offers the advantage of extensive renal elimination. In preliminary clinical studies, I-123-IAZA and Cu-60-ATSM have shown correlation with response to radiotherapy. In addition, Cu-60-ATSM has been used to guide intensity-modulated radiation therapy to deliver a higher radiation dose to the hypoxic subregion of the tumour. However, more preclinical studies comparing imaging with validated invasive methods and clinical studies with outcome measures are required. Nuclear medicine is poised to play an important role in optimising therapy of patients with hypoxic tumours.

《International Symposium》

2. The Role of PET Scanning in the Evaluation of Lung Carcinoma

Theresa C. McLoud
Massachusetts General Hospital, USA

Solitary Pulmonary Nodules

Positron emission tomography with F-18 2-fluoro-2-deoxy-D-glucose (FDG), a glucose analog labeled with positron-emitting fluorine-18 is a useful imaging modality for evaluating patients with lung cancer. Most malignant tumors are characterized by increased glucose metabolism. Because tumors are metabolically active, tumor cells take up increased amounts of FDG relative to normal lung tissue. Therefore, FDG is highly sensitive in the identification of malignant tumors.

Positron emission tomography previously was available only in institutions with an on-site cyclotron. F-18 2-fluoro-2-deoxy-D-glucose now is distributed commercially, and PET imaging for lung cancer has been approved for reimbursement by most third-party payors.

Positron emission tomography with fluorodeoxyglucose has become an additional option for the evaluation of solitary pulmonary nodules and other focal lung lesions. Reported sensitivities for the detection of lung cancer have ranged in various reports between 83% and 100%, with specificities of 63% to 90% using standard uptake values of equal to or greater than 2.5. False-negative studies, however, can occur in tumors with low metabolic activity, such as bronchioloalveolar carcinoma and carcinoid tumors, and in small nodules that are smaller than 1 cm in diameter. False-positive studies may occur in benign nodules or lesions with high metabolic rates, such as active inflammatory processes. These include infectious granulomas, sarcoidosis, and other infections.

The negative predictive value of a PET study is clinically useful. Patients with focal lung lesions without significant FDG uptake can be followed because a negative finding is highly suggestive of a benign abnormality. The positive predictive value is lower, and such lesions frequently require biopsy; however, the positive predictive value for FDG-PET is 90% in patients over 60 years of age. The FDG-PET scan also should be interpreted in conjunction with the clinical likelihood of lung cancer in a given patient and other radiologic features of focal lesions, such as growth rate, morphologic features, and the presence or absence of contrast enhancement.

Staging of Lung Cancer

Positron emission tomography recently has proved useful in the staging of lung carcinoma, specifically in the determination of the presence of nodal disease and distant metastases. In several studies up to 18% of patients considered to be resectable have more advanced disease demonstrated by PET imaging.

Regarding nodal staging, the sensitivity of PET has been reported in the range of 76 to 100% and specificity in the range of 82 to 100%. Nearly all studies have demonstrated the superiority of FDG PET over CT scanning in the evaluation of nodal disease. A recent study by Peterman et al. of 102 patients with nonsmall cell lung cancer demonstrated a sensitivity for PET in the detection of nodal disease of 91% with a specificity of 86%. Despite the superiority of PET over CT scanning, the resolution of PET makes determination of the

extent of tumor and involvement of individual lymph node groups difficult although this should improve with the advent of combined CT PET scanners.

In addition positron emission tomography seems to improve the noninvasive detection of extrathoracic disease. Whole body PET can stage intrathoracic and extrathoracic disease in a single examination and has an overall greater accuracy than conventional imaging. Whole body PET can detect unsuspected extrathoracic metastases in up to 10% of patients when CT scanning fails to detect them, and also alters management in up to 40% of cases.

《International Symposium》

3. Application of Sentinel Node Concept for Gastrointestinal Malignancy

Kunihiko Yokoyama

Department of Nuclear Medicine, Kanazawa University Hospital

Sentinel lymph node is functionally and theoretically defined as the node(s) which lymphatic flow reach firstly from cancer site. For breast cancers and melanomas, sentinel lymph node biopsy become a standard procedure. Thus, we attempted to apply the sentinel node concept to gastrointestinal (GIT) and prostate cancers.

We compared three radiopharmaceuticals: Tc-99m-human serum albumin, Tc-99m-tin colloid and Tc-99m-phytate for breast cancer. Lymphoscintigraphy was performed at 15, 60 min and 3 hr after subdermal peritumoral injection and the patients were operated upon the following day. The surgical gamma probe and patent blue dye were used for sentinel node mapping. Tc-99m-human serum albumin visualized the sentinel lymph nodes in 35 out 49 (71.4%) cases. However, it traveled so rapid that the number of lymph nodes might be more than the actual number. Tc-99m-tin colloid in contrast was so large in size that it could only image the sentinel lymph nodes in 18 out of 33 (54.5%) cases. Tc-99m-phytate detected sentinel lymph nodes in 70 of 76 (92.1%) cases, thus it is considered better than the other 2 compounds. The kinetics of these radiopharmaceuticals was different owing to the molecular size. For GIT cancers, we used endoscopies in conjunction with Tc-99m-phytate to inject into the submucosa of the peritumoral areas. Twenty-four cases consisted of 11 gastric and 13 colorectal cancer patients were enrolled in the study. All the resected lymph nodes were measured in a well-type scintillation counter and pathologically examined. The mean numbers of hot nodes detected intraoperatively for gastric and colorectal cancers were 4.6 and 3.8, respectively. These numbers were not significantly different from those detected by the dye for colorectal and gastric cancers: 5.2 and 4.0. When the tumors located in the inferior part of the rectum, the dye method could not find the sentinel nodes because of the surgeon's field of view. All of the nodes with micrometastases from 4 cases showed higher radioactivity than the rest of the regional nodes.

The conventional Anger-type gamma cameras have been used to image sentinel node. Compared to intraoperative probing with a gamma-detector, scintigraphy depicted sentinel nodes in less number of patients. Although the radioactivity in the injection sites hindered scintigraphic detection, lymphoscintigrams provided surgeons with a valuable navigation, helping search the appropriate area including the sentinel node. A mobile gamma camera has been recently introduced and it gives another option of sentinel node detection, intraoperative imaging. We could carry the mobile gamma camera to the operating room and obtain the lymphoscintigrams there. Moreover, we have developed a hand-held gamma camera. The detector was consisted of CZT semiconductors, therefore, the sensitivity and resolution were better than those of conventional Anger-type camera. The weight of the camera was approximately 800 g. This palm camera has the advantage over both probe and mobile camera.

The sentinel node concept could be applied not only to breast cancers and melanomas but also to the GIT and prostate. The palm-sized gamma camera helped investigate broader area comparing the pinpoint view with a gamma probe.

《International Symposium》

4. Radioimmunotherapy of non-Hodgkin's Lymphoma: A Clinical Reality

Janet F. Eary
University of Washington Medical Center, USA

This is an exciting time for the field of Nuclear Medicine. Our field continues to change and evolve to translate the best in clinical and basic research scientific findings into effective patient care strategies. This is the situation for radioimmunotherapy of non-Hodgkin's lymphoma. As one of the original groups investigating radioimmunotherapy approaches to non-Hodgkin's lymphoma therapy, we continue to investigate treatment strategies which began development over 16 years ago. Lymphoma still presents to us same difficult problems today. Intensification of treatment regimen does not result in increased cure rates, but does result in increased rates of treatment related toxicity and mortality. The search for effective radioimmunotherapy is based on the premise that it would be expected to increase specific disease treatment using directed radiotherapy, without commonly associated toxicity. This has been shown to be a correct hypothesis for our work using high dose radioiodine labeled antibody and chemotherapy combined treatment with stem cell rescue. Objective responses in low and intermediate grade lymphomas were observed in 86% percent of patients with complete response rates observed for that group at 79%. Fifty percent of these patients remain in continuous complete remission for over 5 years. The maximally tolerated dose to any normal organ is now set at 27 Gy for treatment. This is an approach designed for patents who are stem cell rescue candidates and requires labor intensive imaging and dosimetry studies for patient dose estimation for treatment. The new non-myeloablative radioimmunotherapy strategy for non-Hodgkin's lymphoma commercially available in the United States utilizes a chimerized anti-CD-20 antibody and Y-90. In addition to the therapeutic effect of the beta particle emission from Y-90, anti-CD-20 antibodies exert an immune mediated anti-tumor effect as well. The synergy of these anti-tumor mechanisms result in programmed cell death (apoptosis) for the tumor cell population. This is the first such radioimmunotherapy product available commercially. It and others to be released in the future for non-Hodgkin's lymphoma and other disease indications will have a great impact on the emphasis in therapy in nuclear medicine practice. Radioimmunotherapy for non-Hodgkin's lymphoma is now a clinical reality. We now have another excellent opportunity to contribute to effective patient care in the field of nuclear oncology. Our challenge will also be to additionally provide new imaging approaches to provide data for treatment choice, outcome from treatment prediction, and treatment response monitoring.

《International Symposium》

5. New Approaches to the Use of Unsealed Source Radionuclide Therapy for Skeletal Metastases

V. R. McCready and J. M. O'Sullivan

Institute of Cancer Research & Royal Marsden Hospital, UK

In this presentation I will discuss some of the ways in which the therapeutic benefit of bone seeking radionuclides may be enhanced and we hypothesis on future research directions, which might be used in treatment strategies designed to prolong survival as well as provide relief from pain.

There are a variety of approaches, which should be effective including increasing the local dose to the individual metastases, changing the dose rate, and using prior or concomitant chemotherapy.

Increasing the local dose to the metastases

The simplest approach to increasing the local dose is to administer higher activities. We have escalated activities of Rhenium-186 HEDP up to 5000 MBq in hormone refractory prostate cancer metastatic to bone and with minimal soft tissue metastases.[1] In a phase 2 trial 16 patients have received 5000 MBq, with PSA responses in 40%.

Activity based on whole body doses

An alternative to fixed activity administration is to prescribe an activity based on a whole body dose, which has been shown to be safe and effective in the treatment of paediatric neuroblastoma using activities up to 31 GBq.[2] The gamma emission of Rhenium-186 would enable dosimetry to be carried out.

The number and size of metastases

Preliminary studies suggest that the uptake of radionuclide in individual metastases (corrected for area on the planar scan) is independent of the number of metastases.[3,4] In a study comparing large and small metastases, smaller lesions disappeared more often than large metastases.[5] A possible explanation is that the range of the beta particles is limited and the region of the highest dose is probably confined to a thin layer of soft tissue adjacent to the area of osteoblastic reaction. Thus smaller metastases are more likely to respond than larger lesions where the distance between bone and tumour is increased.

Enhancement of radionuclide uptake in metastases

The local dose to individual metastases is related to the uptake, and retention in the lesion. Improvements in the effectiveness of unsealed source radiotherapy for bone metastases could involve osteoblastic reaction stimulation using androgens to increase the uptake in the tumours (the 'flare' phenomenon).

Use of chemotherapy and radionuclides

There is evidence that chemotherapy and radiation can be synergistic. Tu et al. studied the addition of strontium-89 to chemotherapy.[6] Seventy-two patients (after induction chemotherapy) were randomised to receive doxorubicin with or without strontium-89. There was a statistically significant difference in the median survival for the group receiving strontium-89 (27.7 versus 16.8 months, $p = 0.0014$). This is one of the few randomised trials in advanced prostate cancer that shows a survival advantage.

Treatment of very early metastases

As many as 30% of patients with clinically localised prostate cancer and a normal isotope bone scan, will eventually relapse with bone metastases suggesting the

presence of metastases in bone at a very early stage.[7] Presumably there is a bone reaction at this stage (although it is not visible on bone scans) and so it is likely that short-range beta emitters would be more effective when the tumour is confined to a thin layer of tissue close to bone. The preferential response of small bone metastases would support this hypothesis.[5] There is also an argument for administering radionuclide therapy in patients where there is a high risk of spread based on clinical stage, Gleason score, and PSA level.

It is likely that small metastases are more amenable to the treatment using the short-range beta particles that emanate from the bone reaction surrounding the soft tissue tumour cells. Our studies using high activities of ^{186}Re HEDP suggest that the onset of new metastases in patients with hormone refractory disease is greatly reduced.

Repeated administrations

In external beam radiotherapy there is a trend towards using higher doses at shorter intervals. There is an argument to repeat the administration of unsealed source therapy as frequently as possible at an activity level that does not produce cumulative marrow damage to minimise tumour cell growth. Kasalicky and Krajska[8] have shown good results with patients receiving up to 5 administrations of ^{89}Sr with increasing pain relief periods. The repeated administrations could work by irradiating the layer of tissue closest to bone which then dies leaving the next accessible rather like peeling an onion.

Other radionuclides and cocktails

Short lived ^{188}Re HEDP has been used relatively little. It is generator produced and would be cheaper than the other radionuclides. It has a rapid urinary excretion resulting in a low whole body dose but the local dose to metastases is high.[9] ^{188}Re HEDP has been used successfully for pain relief from metastases from prostate carcinoma. As in other situations where radionuclide therapy is being given the concept of radionuclide cocktails should be considered. In the case of bone seekers a combination of alpha emitters, beta emitters and repeated administrations would enhance the ‘onion peeling’ effect.

Conclusions

Unsealed source radionuclide therapy for bone metastases is now well established. Now is the time to consider the next stage in the use of this modality. This presentation has indicated some new approaches which could go further than producing pain palliation and actually ablate the metastases, hopefully improving the survival of patients with widespread bone disease.

Reference List

1. O’Sullivan J, McCready VR, Flux GD, Norman AR, Buffa FM, Chittenden S. *British Journal of Cancer* 2002; in press.
2. Matthay KK, Panina C, Huberty J, Price D, Glidden DV, Tang HR, et al. *J Nucl Med* 2001; 42 (11): 1713–1721.
3. McCready VR, O’Sullivan J, Dearnaley D, Treleaven J. *Radiology* 2001; 221 (P): 344.
4. McCready VR, O’Sullivan J, Buffa F, Cook G, Flux GD, Dearnaley D, et al. *Eur J Nucl Med* 2001; 28 (8): 1054.
5. McCready VR, Dearnaley D, Treleaven J. *Eur J Nucl Med* 2000; 27 (8): 965.
6. Tu SM, Millikan RE, Mengistu B, Delpassand ES, Amato RJ, Pagliaro LC, et al. *Lancet* 2001; 357 (9253): 336–341.
7. Schellhammer PF. *Urology* 1988; 31 (3): 191–197.
8. Kasalicky J, Krajska V. *Eur J Nucl Med* 1998; 25 (10): 1362–1367.
9. Liepe KKJ, Hiscs R, Runge F, Knapp FF, Franke WG. *Eur J Nucl Med* 2000; 27: 266P.