Acta Oncologica Vol. 33, No. 3, pp. 323-327, 1994

POSITRON EMISSION TOMOGRAPHY

A new tool for characterization of malignant disease and selection of therapy

WUI-JIN KOH, THOMAS W. GRIFFIN, JANET S. RASEY and GEORGE E. LARAMORE

Present therapy for cancer patients is based primarily on tumor histology and anatomy. Despite treatment advances, clinicians have often been frustrated by their inability to assess tumor biology. Metabolic imaging by positron emission tomography is a promising new technology that has opened up a whole realm of study in oncology. Glucose metabolism, hemodynamics, oxygen utilization, protein synthesis and thymidine incorporation may yield valuable data regarding tumor aggressiveness and stage, and allow assessment of tumor response early during treatment, before morphological changes are detectable. Other metabolic determinations, including tumor hypoxia and estrogen receptor density, may predict tumor response to therapy, and lead to selection of more appropriate treatment regimens, such as with neutrons or hypoxic cell sensitizers for documentably hypoxic tumors. While further clinical validation is required, positron emission tomography promises to provide vital information complementary to present anatomical imaging modalities that will aid oncologists in optimal management of their patients.

At present, state-of-the-art cancer therapy is primarily based on tumor histology and anatomy. Histology is obtained from pathologic evaluation of biopsy specimens. Tumor anatomy, which describes size, shape, location and tumor-normal tissue structural relationships, is obtained by physical examination and various radiographic tests including computed tomography (CT) and magnetic resonance imaging (MRI). With these factors taken into consideration, a cancer patient will then be treated with surgery, radiotherapy, or chemotherapy, or with a combination of treatment modalities.

Unfortunately, knowledge of tumor histology and anatomy alone does not allow the oncologist to confidently predict tumor response to treatment, especially when using chemotherapy and/or radiation. The oncologist is limited to conventional management approaches without the ability to select specific treatments based on a more detailed knowledge of individual tumor metabolism. Additionally, the routine assessment of tumor response to therapy using standard anatomic measurements is often difficult to interpret, and is usually attempted after all, or a substantial amount, of treatment has already been delivered. The presence of significant normal tissue changes secondary to radiation and chemotherapy often obscures anatomic evaluation. The early assessment of tumor response based on metabolic changes which occur prior to measurable anatomic effects would thus be useful in re-directing therapy for patients who are not responding to initially selected treatment.

While it is currently used principally as a research tool in the study of tumor physiological and biochemical processes, positron emission tomography (PET) is a promising technology which may eventually gain routine clinical acceptance in determining prognosis and predicting, as well as assessing, tumor response to therapy, leading to better selection of cancer treatment. Positron-emitting radioisotopes, such as ^{11}C, ^{13}N, ^{15}O, and ^{18}F, can be incorporated

Received 3 June 1993.
Accepted 7 September 1993.
From the Department of Radiation Oncology, RC-08, University of Washington Medical Centre, 1959 N.E. Pacific St., Seattle, WA 98195, USA.
Correspondence to: Dr Wui-Jin Koh, Department of Radiation Oncology, RC-08, University of Washington Medical Center, 1959 N.E. Pacific Street, Seattle, WA 98195, USA.
Presented at the Nordic Conference on Neutrons in Research and Cancer Therapy, 29-30 April, 1993, Linköping, Sweden.

 ISSN 0284-186X

into biologically significant molecules, such as glucose, thymidine, and amino acids. After injection of a radiolabeled biomolecule into a patient, PET provides high-resolution, in vivo, and quantitative detection of tumor radiotracer uptake, which, when combined with blood sampling and appropriate mathematical modeling, allows derivation of metabolic parameters of interest, depending on the biochemical used. Unlike many other assays of tumor metabolism, PET imaging information can be obtained from deep-seated tumors in a non-invasive manner. Additionally, because of the short half-lives of the above radiolabels (2–110 min), multiple sequential studies can be performed in a patient in a single day to assess different tumor metabolic parameters.

Although its clinical efficacy remains to be fully proven, the potential impact of PET in oncology is being explored by various research groups. Measures of tumor metabolism such as glucose utilization, hypoxia, blood flow and oxygen utilization, protein synthesis, thymidine incorporation into deoxyribose nucleic acid (DNA), and hormone receptor density are promising areas of investigation that may soon achieve wide clinical utility (1–3).

Glucose metabolism

The accelerated glycosis of tumor cells, even under conditions of adequate oxygenation, was first described by Warburg in 1930 (4). The exact mechanisms for this observation remain to be fully elucidated. Nevertheless, of all the physiological and biochemical parameters measurable by PET, imaging of tumor glucose utilization has gained the greatest clinical acceptance. The radiotracer most widely used is ^{18}F-fluorodeoxyglucose (FDG), an analog of glucose that is readily transported across the cell membrane and then rapidly phosphorylated by hexokinase. However, unlike glucose, further metabolism is halted, and ^{18}F activity within tissues in the form of FDG-phosphate can be imaged by PET and modeled to calculate regional glucose metabolic rates of tumor and normal tissues (5).

FDG PET imaging has been most extensively studied in patients with malignant gliomas. Di Chiro et al. have shown that FDG uptake, evaluated both visually and quantitatively as glucose metabolic rate, correlated in a strong and linear fashion with tumor grade, which would permit determination of tumor differentiation in patients whose malignancies cannot be adequately sampled surgically (6). A follow-up study showed that FDG PET imaging provided additional prognostic information beyond that obtained by histopathologic review of the gliomas. In 45 patients with high-grade astrocytomas (grades III and IV), patients who had high glucose metabolic rate ratios (>1.4 when compared to contralateral non-tumor cortex) had a median survival of 5 months, compared to a median survival of 19 months in those having a lower utilization, a statistically significant finding that was independent of the actual tumor grade (7). Furthermore, these investigators found that PET imaging of FDG uptake was useful in differentiating tumor recurrence from radiation or chemotherapy-induced cerebral necrosis in cases where conventional anatomical imaging such as CT and MRI provided indeterminate results (8).

In addition to primary brain tumors, there have been recent investigations into the role of FDG PET imaging in the management of patients with soft tissue sarcomas (3), non-Hodgkin's lymphomas (9), head and neck, colorectal, and breast cancers (10, 11). These studies have focused on the correlation of FDG uptake and histologic grade of the tumor, or on the ability of FDG to identify early tumor recurrence following definitive therapy at a time when clinical evaluation was inconclusive. In an intriguing preliminary report, Goodman et al. (12) used FDG PET imaging to help in tumor localization of a patient undergoing pion radiotherapy for malignant glioma, and obtained follow-up PET scans after radiation (without FDG) to detect the short-lived radioactive breakdown products of pions and hence confirm that the volume irradiated adequately encompassed the tumor.

Tumor hypoxia

It has been recognized for over 50 years that oxygen plays an important role in modifying the biological effects of radiation. In controlled laboratory experiments, fully oxygenated cells are approximately three times more sensitive to conventional sparsely-ionizing radiation as compared to anoxic but viable cells. Based on the histological observations of lung cancers by Thomlinson & Gray (13), as well as numerous experiments documenting the existence of hypoxic elements in animal solid tumor systems, it has been inferred that hypoxia exists, and limits radiotherapeutic cure, in many human malignancies (14). More recently, direct oxygen electrode measurements of human tumors have shown the presence of hypoxic regions in patients with cervical and head and neck cancers, and several of these studies have shown a correlation between tumor hypoxia and outcome following radiotherapy (15–18). Unfortunately, oxygen electrode measurements are invasive, technically demanding, and limited to accessible tumors.

Despite the relative paucity of documentation regarding the existence of viable hypoxic cancer cells in humans, this concept has remained at the forefront of experimental and clinical radiotherapy for over three decades. Multiple trials have used a variety of approaches aimed at overcoming the presumed cure-limiting effect of hypoxic cells in patients receiving radiation, including hyperbaric oxygen, correction of anemia, oxygen-mimetic hypoxic cell sensitizing drugs such as the nitroimidazoles, and densely-ionizing high linear energy transfer (LET) radiation, particularly with neutrons. While there has been some limited success,

the majority of these clinical trials showed no improvement in outcome for patients receiving 'tumor hypoxia-directed' therapy over conventional radiotherapy alone (14, 19–21). It would therefore seem that hypoxia may be a cure-limiting factor in only a proportion of human cancers, and the primarily negative clinical efforts to date result from the non-selective inclusion of patients in hypoxic tumor trials, without knowledge of their tumor oxygenation status (21).

A promising recent development in the assessment of human tumor hypoxia began with the recognition that nitroimidazoles bind to intracellular macromolecules in the absence of oxygen, and that an appropriately radiolabeled form could be detectable by external camera imaging to provide a 'positive' image of hypoxia (22). A quantitative, although non-linear, inverse relationship between nitroimidazole binding and oxygen tension has been described, and its retention in cells varies most markedly over the same range of oxygen concentration that most impacts radiosensitivity (23). After extensive study using in vitro and in vivo animal systems, our laboratory at the University of Washington has characterized ^{18}F-fluoromisonidazole (FMISO), in conjunction with PET imaging, as a promising hypoxia probe for in vivo human studies (21).

Based on extensive normal tissue data from animals and initial human FMISO PET imaging studies, Koh et al. (21, 24), in attempting to quantify the extent of hypoxia, consider any tumor region with a tumor:blood FMISO ratio $\geqslant 1.4$ by two or more hours after radiotracer injection as having detectable hypoxia, and have defined the fractional hypoxic volume (FHV) as the fraction of the imaged tumor volume with a tumor:blood ratio above this 'threshold' value of 1.4. They have reported the non-invasive assessment of tumor hypoxia in 26 patients prior to radiotherapy, including 10 patients with non-small cell lung cancers, 9 with head and neck malignancies, 4 with prostate adenocarcinomas, and one each with renal, breast, and rectal cancers. Five tumors showed no evidence of hypoxia, while the remaining 21 had FHVs ranging from 1–91% with a median FHV of 23%. Normal tissues such as muscle and brain rapidly equilibrated with blood FMISO levels, yielding ratios around 1.0. Seven patients with pretreatment FMISO PET studies documenting tumor hypoxia underwent repeat scans in the latter half of their fractionated radiotherapy courses, with 5 of the patients showing complete reoxygenation and no residual hypoxia (24). Preliminary analysis of clinical outcome suggests a slight correlation between tumor response and preradiation FHV, but further follow-up is needed for confirmation. Other investigators have also reported possible early promise in the use of FMISO PET imaging to assess hypoxia in human gliomas (25).

While further validation, particularly with regard to clinical correlation, is required, FMISO PET imaging holds significant promise as a predictor of response to conventional radiotherapy, and may eventually be used to select patients who would best benefit from further efforts aimed at overcoming tumor hypoxia, such as with high LET radiation or hypoxic cell sensitizers.

Hemodynamics and oxygen utilization

The sequential inhalation of $C^{15}O_2$, ^{11}CO and $^{15}O_2$ combined with PET imaging allows calculation of tumor blood flow, blood volume, oxygen metabolic rate, and oxygen extraction fraction. The extremely short half-lives of the radioisotopes used (O-15 = 2 min, C-11 = 20 min) permit such multiparameter assessment within a single short study session, typically lasting less than an hour.

While the quantification of hemodynamics is important for incorporation into more complex models in which substrate delivery to the tumor is an important consideration, such as with glucose, amino acids, and thymidine, these parameters have been found useful as independent measures of tumor physiologic status. Regional blood flow within tumors may be markedly heterogenous, but on average, is increased in comparison to adjacent normal soft tissues, and may be useful in delineating tumor extent for patients undergoing radiotherapy (1, 5). Additionally, blood flow measurements within a tumor may have important implications in predicting adequate vascular delivery of chemotherapeutic agents.

It has been suggested that measures of tumor blood flow and oxygen metabolism may provide an indirect measure of tumor hypoxia. However, such an approach would be suboptimal for detection of small areas of hypoxia within a tumor that also has regions of hypervascularity. In this context, FMISO, as discussed above, would be a better probe, as it would provide a 'positive' image of tumor hypoxic zones, as opposed to the 'negative' images of hypoxia that may be obtained by blood flow and oxygen utilization. Various patterns of change in tumor hemodynamics and oxygen metabolism during and after radiotherapy have been observed, and these measures may eventually be used to assess early tumor response before morphological changes are apparent (1, 5).

Protein synthesis

Tumors have accelerated amino acid uptake and protein synthesis compared to normal tissues. This characteristic can be exploited using PET imaging of radiolabeled amino acid accumulation, of which the most widely investigated is ^{11}C-methionine. Pilot studies have included assessment of patients with brain tumors, lung cancers, breast cancers, non-Hodgkin's lymphomas, and head and neck malignancies. While there is some disagreement over the relationship between quantitative uptake of ^{11}C-methionine and the histologic grade of cancer, it appears that tumors can be reliably imaged with this tracer. PET imaging of

^{11}C-methionine accumulation may find utility in accurate localization of tumor extent and aid conventional anatomic imaging modalities in the delineation of tumor volume for precise radiotherapy treatment planning (9, 26).

Thymidine uptake, DNA synthesis and tumor proliferation

Tumors generally have an increased cellular proliferation rate compared to slowly-cycling normal tissues. The uptake of thymidine for measurement of DNA synthetic rate and tumor proliferation has been described as a useful tool for predicting disease aggressiveness and response to chemotherapy (27). To date, this technique has required ex vivo analysis of biopsy samples, and is subject to problems associated with sampling inadequacy and a complex, time-consuming methodology. Using PET imaging of ^{11}C-thymidine uptake and appropriate modeling, it has been shown that tumor DNA synthetic rate may be calculated non-invasively (28). Current studies are ongoing to define the role of ^{11}C-thymidine PET imaging in staging malignancies, and in predicting their response to therapy.

Hormone receptor density

Using PET and ^{18}F-fluoroestradiol (FES), hormone receptor density has been studied primarily in patients with breast cancer. The concentration of estrogen receptors (ER) in a tumor not only has prognostic implications, it also predicts response to anti-estrogen therapy, which forms a major part of the oncologic armamentarium in the treatment of breast cancer, particularly for patients with metastatic disease. Presently, ER status in breast cancer requires surgical removal of a tumor sample, with ER levels then determined ex vivo using techniques such as radioimmunoassay (RIA). This approach for determining ER status and subsequent hormonal therapy is confounded by heterogeneity and sampling error within a given tumor mass, and, in the context of a patient with metastases, does not readily permit evaluation of multiple disease sites. While relatively uncommon, there is known incongruence between tumor ER status and response to anti-estrogen therapy, as well as site-to-site variability in response of patients with metastatic disease.

Investigators using PET imaging of FES uptake in breast cancer patients who subsequently underwent surgical resection of their tumors have noted a very strong linear correlation ($r = 0.96$) between FES accumulation and ER content as determined by RIA. Several patients with axillary lymph nodes of uncertain clinical significance were determined to have metastatic nodal disease on the basis of PET imaging, which was later confirmed on pathological review (29). This suggested that ER status can be determined non-invasively in multiple tumor sites using PET, and that this technique may also aid in staging of patients with ER positive tumors. These researchers have also performed sequential PET imaging studies in patients with metastatic disease undergoing anti-estrogen therapy before and after initiation of hormonal treatment. FES PET imaging may provide early assessment of the efficacy of therapy by measuring the magnitude of decrease in FES uptake following hormonal manipulation (30).

Metabolic imaging by PET has opened up a whole new realm of study in oncology that may yield valuable data regarding tumor grade, stage, prognosis, and potential and early response to conventional therapy. Clinical validation is required for the various physiological and biochemical parameters currently actively investigated, and improvements in modeling and comparisons of the different radiotracers are necessary to determine optimal feasibility (31). Nevertheless, PET promises to provide information complementary to present anatomical and pathological diagnostic methods that will eventually allow better selection of patients for clinical trials, as well as better delivery of therapy for individual patients based on their unique tumor characteristics.

ACKNOWLEDGEMENTS

This work was supported in part by NIH (NCI) grant No. CA42045 and the American Cancer Society Career Development Award No. 91-175 (WJK).

REFERENCES

1. Beaney RP. Positron emission tomography in the study of human tumors. Semin Nucl Med 1984; 14: 324–41.
2. Hawkins RA, Phelps ME. PET in clinical oncology. Cancer Metast Rev 1988; 7: 119–42.
3. Larson SM. Positron emission tomography in oncology and allied diseases. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Principles and practice of oncology, Vol. 3, No. 2—update. Philadelphia: Lippincott Co., 1989.
4. Warburg O. The metabolism of tumours. London: Constable and Co., 1930.
5. Brownell GL, Kairento A-L, Swartz M, Elmaleh DR. Positron emission tomography in oncology—the Massachusetts General Hospital experience. Semin Nucl Med 1985; 15: 201–9.
6. Di Chiro G. Positron emission tomography using [18F]-fluorodeoxyglucose in brain tumors: a powerful diagnostic and prognostic tool. Invest Radiol 1987; 22: 360–71.
7. Patronas NJ, Di Chiro GD, Kafta C, et al. Prediction of survival in glioma patients by means of positron emission tomography. J Neurosurg 1985; 62: 816–22.
8. Di Chiro G, Oldfield E, Wright DC, et al. Cerebral necrosis after radiotherapy and/or intraarterial chemotherapy for brain tumors: PET and neuropathologic studies. Am J Radiol 1988; 150: 189–97.
9. Leskinen-Kallio S, Ruotsalainen U, Nagren K, Teras M, Joensuu H. Uptake of carbon-11-methionine and fluorodeoxyglucose in non-Hodgkins lymphoma: a PET study. J Nucl Med 1991; 32: 1211–8.
10. Chaiken L, Rege S, Hoh C, et al. Positron emission tomography with fluorodeoxyglucose to evaluate tumor response and control after radiation therapy. Int J Radiat Oncol Biol Phys 1993; 27: 455–64.
11. Hawkins RA, Hoh CK, Glaspy J, et al. PET-FDG imaging in cancer. Appl Radiol 1992; May: 51–7.

12. Goodman GB, Lam GKY, Harrison RW, Bergstrom M, Martin WR, Pate BD. The use of positron emission tomography in pion radiotherapy. Int J Radiat Oncol Biol Phys 1986; 12: 1867–71.
13. Thomlinson RH, Gray LH. The histological structure of some human lung cancers and the possible implications for radiotherapy. Br J Cancer 1955; 9: 539–49.
14. Hall EJ. The oxygen effect and reoxygenation. In: Hall EJ, ed. Radiobiology for the radiologist, 3rd ed. New York: Lippincott Co., 1988.
15. Gatenby RA, Kessler HB, Rosenblum JS, et al. Oxygen distribution in squamous cell carcinoma metastases and its relationship to outcome of radiation therapy. Int J Radiat Oncol Biol Phys 1988; 14: 831–8.
16. Hockel M, Knoop C, Schlenger K, et al. Intratumoral pO2 predicts survival in advanced cancer of the uterine cervix. Radiother Oncol 1993; 26: 45–50.
17. Kolstad P. Intercapillary distance, oxygen tension and local recurrence in cervix cancer. Scand J Clin Lab Invest 1968; 106 (Suppl. 1): 145–66.
18. Lartigau E, Le Ridant A, Lambin P, et al. Oxygenation of head and neck tumors. Cancer 1993; 71: 2319–25.
19. Dische S. A review of hypoxic cell radiosensitization. Int J Radiat Oncol Biol Phys 1991; 20: 147–52.
20. Griffin TW. Fast neutron radiation therapy. Crit Rev Oncol Hematol 1992; 13: 17–31.
21. Koh W-J, Rasey JS, Evans ML, et al. Imaging of hypoxia in human tumors with [F-18]fluoromisonidazole. Int J Radiat Oncol Biol Phys 1992; 22: 199–212.
22. Chapman JD, Franko AJ, Sharplin J. A marker for hypoxic cells in tumors with potential clinical applicability. Br J Cancer 1981; 43: 546–50.
23. Rasey JS, Nelson NJ, Chin L, Evans ML, Grunbaum Z. Characterization of the binding of labeled fluoromisonidazole in cells in vitro. Radiat Res 1990; 122: 301–8.
24. Koh W-J, Rasey JS, Evans ML, et al. Fractional hypoxic volume and reoxygenation in human tumors (abstract). Radiother Oncol 1992; 24 (Suppl): S112.
25. Valk PE, Mathis CA, Prados MD, Gilbert JC, Budinger TF. Hypoxia in human gliomas: demonstration by PET with fluorine-18-fluoromisonidazole. J Nucl Med 1992; 33: 2133–7.
26. Leskinen-Kallio S, Nagren K, Lehikoinen P, Ruotsalainen U, Teras M, Joensuu H. Carbon-11-methionine and PET is an effective method to image head and neck cancer. J Nucl Med 1992; 33: 691–5.
27. Costa A, Bonadonna G, Villa E. Labeling index as a prognostic marker in non-Hodgkin's lymphoma. J Natl Cancer Inst 1981; 66: 1–5.
28. Shields AF, Lim K, Grierson J, Link J, Krohn KA. Utilization of labeled thymidine in DNA synthesis: studies for PET. J Nucl Med 1990; 31: 337–42.
29. Mintun MA, Welch MJ, Siegel BA, et al. Breast cancer: PET imaging of estrogen receptors. Radiology 1988; 169: 45–8.
30. McGuire AH, Lyss AP, Brodack JW, et al. Positron emission tomographic assessment of 16-α-[F-18]-fluoro-estradiol (FES) uptake in metastatic breast carcinoma: effect of antiestrogen therapy (abstract). J Nucl Med 1989; 30: 788.
31. Kubota K, Ishiwata K, Kubota R, et al. Tracer feasibility for monitoring tumor radiotherapy: a quadruple tracer study with fluorine-18-fluorodeoxyglucose or fluorine-18-fluorodeoxyuridine, L-[methyl-^{14}C]methionine, [6-^{3}H]thymidine, and gallium-67. J Nucl Med 1991; 32: 2118–23.