Advances in Positron Emission Tomographic Imaging of Lung Cancer

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Positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG) has been established as a useful tool in the management of patients with non-small cell lung cancer and promises to be as valuable in the clinical management of other cancers. PET imaging with FDG allows the assessment of tumor glucose metabolism *in vivo*; however, a number of other PET tracers are being used in oncologic research to assess changes in other cellular processes associated with malignant transformation of the cell. [^{11}C]-Labeled methionine and choline are being used to assess changes in cell membrane synthesis; however, small studies have not shown the added information from these tracers to be clinically useful. DNA synthesis can be assessed by measuring the uptake of the thymidine analog 3'-deoxy-3'-[^{18}F]fluorothymidine, which may be more specific for evaluating malignancy without the problem of false-positive results from inflammatory lesions, as seen with FDG. Tumor hypoxia imaging with copper-labeled diacetyl-bis(N(4)-methylthiosemicarbazone) or [^{18}F]fluoromisonidazole may provide a better method of predicting which tumors will respond best to conventional therapy. The role of PET will continue to evolve with further clinical studies using these and other new tracers.

Keywords: FDG; cell proliferation; cell hypoxia

Positron emission tomography (PET) has been established as a useful adjunct in the diagnosis and management of cancer for research and routine clinical use. PET is a molecular imaging technique that provides images of biochemical and physiologic processes within the body. PET provides quantitative *in vivo* measurements of the biodistribution of radiolabeled tracers. One of the attractive aspects of PET is the use of tracer molecules that can be labeled with short-lived radioisotopes of naturally occurring elements within the body. Thus, PET has a unique ability to detect and quantify physiologic receptor processes in the body.

The positron-emitting radionuclides used to label PET tracers decay by emitting positrons, which collide with nearby electrons after losing their kinetic energy and subsequently form two 511 keV annihilation photons that travel at approximately 180° from each other. The coincidence detection of the annihilation photons allows for high photon-detection efficiency and excellent resolution. In addition, when the PET examination incorporates a transmission scan, accurate correction for photon attenuation in the body is possible, allowing for precise quantification of the

regional distribution of the tracer. This is a major advantage of PET imaging over conventional single-photon emission tomography and other anatomic imaging modalities, such as computed tomography (CT). Several quantitative and semiquantitative methods can be used to quantify the radiotracer distribution. The most commonly used semiquantitative method clinically is the standardized uptake value, which is the radioactivity measured in a tissue region corrected for the dose of radioactivity injected and for body mass.

Because cancer cells exhibit derangement of a number of physiologic cell processes, different PET tracers have been developed to assay these processes *in vivo*. The most widely used radiotracer in clinical oncology is the glucose analog [^{18}F]fluorodeoxyglucose (FDG), which allows assessment of cellular glucose use. Other tracers are available that can be used to assess other cellular processes (e.g., cell membrane synthesis and DNA synthesis) or serve as proxies for cell proliferation and tumor hypoxia. These tracers may be used to differentiate the physiologic behavior of various tumors and their potential response to therapies.

GLUCOSE METABOLISM

FDG, a glucose analog, is taken up by the same glucose transporters that transport glucose into the cell, where it is phosphorylated by hexokinase to yield FDG-6-phosphate. FDG-6-phosphate is not a substrate for glucose-6-phosphate isomerase due to the position of the [^{18}F] label and thus is biochemically trapped intracellularly after phosphorylation. Measuring the uptake of FDG serves as a proxy for glucose metabolism, which is elevated in malignant cells. Studies have shown that malignant transformation of cells is associated with a higher glucose utilization rate compared with normal cells (1). Brown and colleagues (2) demonstrated that FDG uptake in untreated non-small cell lung cancer (NSCLC) is directly related to the expression of glucose transporter-1 expression, and Higashi and colleagues (3) suggested that the magnitude of this effect increases with higher grades of malignancy within a given tumor type. In general, more aggressive tumors demonstrate markedly increased glucose metabolism and hence are detected with much higher sensitivity than slower-growing, more indolent tumors, such as bronchoalveolar carcinomas and carcinoid tumors, which typically have a low glucose utilization rate (4–7). A number of nonmalignant conditions, particularly inflammatory and granulomatous diseases, can cause increases in FDG uptake as well, decreasing the specificity of using FDG uptake as a marker for malignancy in these settings (8).

Numerous studies have investigated the use of FDG-PET imaging in lung cancer, particularly in NSCLC (8–11). Evidence indicates that PET imaging with FDG is useful in diagnosing, staging, and restaging NSCLC (12–15). FDG-PET imaging is useful in demonstrating unsuspected extrathoracic disease, thereby reducing the number of futile thoracotomies and improving treatment planning by increasing the accuracy of staging this disease (10). Figure 1 (p. 512) demonstrates how FDG-PET can be useful in identifying mediastinal disease in addition to identifying the known primary tumor. FDG-PET is more sensitive

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and specific (85% and 90%, respectively) than CT (61% and 79%, respectively) for detecting mediastinal disease but is not accurate enough to replace mediastinoscopy (16). Several studies indicate that PET may provide useful prognostic information because higher-grade tumors, which are associated with poorer survival, exhibit highly elevated levels of FDG uptake (17–19).

Several recent studies have investigated the role of FDG-PET in determining treatment volumes for radiation therapy planning because CT may provide anatomic contours but may not be adequate in differentiating tumor from nontumor tissues. Bradley and colleagues (20) studied 26 patients with stages I–III NSCLC using FDG-PET and separately acquired CT simulation images as part of the radiation therapy treatment planning. Of 24 patients who were candidates for curative radiation therapy, 14 patients had altered therapy plans based on the contribution of the PET results, with three patients receiving a lower dose by excluding areas of atelectasis demonstrated on PET and 10 patients receiving higher doses to include unsuspected nodal disease. With the development of the PET-CT scanners, PET and CT images can be acquired almost simultaneously. Ashamalla and colleagues (21) used a PET-CT scanner and thermoplastic molded immobilization devices to ensure the same positioning in the PET-CT study and during treatment. They found that treatment volumes were increased by over 20% in 8 out of 19 patients. The metabolic information provided by FDG-PET may be used to provide a more accurate assessment of the active tumor burden, thus assisting in determining appropriate volumes for radiation therapy and leading to more effective therapy while decreasing morbidity associated with unnecessary radiation to nontumor tissues. Further prospective studies are required to assess the long-term efficacy of this technique.

The role of FDG-PET in monitoring response of NSCLC to therapy has been investigated in several studies (10). Ichiya and colleagues (22) showed that the decrease in metabolic response by FDG-PET correlated with pathologic response of the tumor, and MacManus and colleagues (23) showed that the tumor response after completion of treatment as measured by PET was a better predictor of survival than that measured by CT. Weber and colleagues (24) have shown that metabolic response early in the course of therapy, such as after one cycle of chemotherapy, as measured by PET may be predictive of subsequent tumor response (24), potentially offering earlier guidance in determining the most efficacious chemotherapy regimen.

Fewer data are available on the use of FDG-PET in small cell lung cancers (SCLC). However, preliminary studies indicate that FDG-PET may be useful in staging these cancers (25, 26). One retrospective study showed that 5 out of 15 patients with SCLC who underwent FDG-PET imaging at initial diagnosis were upstaged based on the PET findings, and in 25 patients who underwent restaging PET examinations, 8 showed more extensive disease than conventional imaging (26). PET was confirmed in 79% of lesions with discordant findings (26). These findings were extended in a prospective study involving 24 patients with SCLC. This study showed that not only was PET able to correctly identify the primary tumor, but it also identified unsuspected nodal disease in six of the patients and influenced subsequent treatment planning (25). Although these results are promising, larger prospective studies investigating the impact of PET on these management decisions are required to establish its role in the management of SCLC.

Because of the relatively limited specificity and possible false-positive findings with FDG-PET, primarily due to inflammatory or infectious processes, new radiotracers that are taken up by cellular processes more closely linked to the rapid cell proliferation seen in malignancies would be helpful. The development of new PET tracers in recent years to interrogate different cellular

processes may improve upon the specificity of detecting malignancy or assessing cell death.

CELL MEMBRANE SYNTHESIS

[¹¹C]-Labeled methionine and choline, which are incorporated into the cell membrane after being transported into the cell, have been recently developed and studied in lung cancer. Because malignant cells exhibit a high rate of cellular proliferation, these tracers theoretically should be more specific than FDG in identifying malignant cells without being taken up by other inflammatory processes. However, investigations using these two tracers have yet to show any benefit above or in conjunction with FDG-PET imaging. A small study of nine patients with solitary lung cancers who underwent targeted radiotherapy showed that [¹¹C]-methionine-PET provided essentially the same information as FDG-PET imaging (27). Another study of 17 patients that compared the ability of [¹¹C]-methionine and FDG to distinguish malignancy from benign tumors and correctly identify mediastinal involvement found similar sensitivities and specificities with both tracers (28).

Tian and colleagues (29) compared [¹¹C]-choline with FDG-PET imaging in a large series involving 126 patients with a variety of malignancies or suspected malignancies before treatment, including 16 lung lesions, 15 bone lesions, 25 brain lesions, and 23 soft-tissue lesions. Uptake of both tracers was increased in malignant tumors when compared with benign tumors (29). FDG uptake in the brain, head, neck, and lung malignancies was statistically significantly higher than [¹¹C]-choline uptake; however, brain tumors could be well visualized with [¹¹C]-choline due to the much lower physiologic uptake of this tracer in the normal brain and therefore higher target-to-background count ratio. Although they did not find any statistically significant improvement in the ability of [¹¹C]-choline to identify malignancies compared with FDG, their data did suggest that [¹¹C]-choline may be useful in distinguishing malignancy from benign tumors in certain body regions, such as in the brain and bone, which normally exhibit higher physiologic levels of FDG uptake (29). Larger studies are required to evaluate more thoroughly what role [¹¹C]-choline may play in the management of cancer.

DNA SYNTHESIS

3'-deoxy-3'-[¹⁸F]fluorothymidine (FLT) is a thymidine analog used to assess cell proliferation that is taken up and trapped intracellularly after phosphorylation by thymidine kinase 1 (30). Although FLT is not incorporated into the DNA, its uptake is thought to track DNA synthesis because the concentration of thymidine kinase 1 increases up to tenfold during DNA synthesis (31). In a recent study of an animal model of turpentine-induced inflammation, van Waarde and colleagues (32) demonstrated intense FDG uptake but no FLT uptake in inflammatory lesions. Therefore, this tracer has the potential to be more specific in identifying malignant cells than simply measuring increased glucose utilization with FDG.

Increased FLT uptake has been demonstrated in a number of malignancies, including colorectal cancer, melanoma, and breast cancer (33). Several recent publications demonstrate that FLT may improve the specificity of PET imaging in identifying lung malignancy. Buck and colleagues (34) prospectively studied 47 patients with suspicious lung nodules with FDG-PET and FLT-PET and found that, although the sensitivity of FDG-PET and FLT were similar (94% versus 90%) in detecting the primary lung tumor, the specificity of FDG-PET was much lower than FLT-PET (73% versus 100%). FDG and FLT had low sensitivity (77% and 67%, respectively) but were highly specific (100%

Figure 2. Pretherapy transaxial FDG-PET (left), ^{60}Cu -ATSM-PET (middle), and CT (right) images of the chest at the level of the patient's known NSCLC. The CT image shows increased soft tissue density in the left paratracheal space (arrow). There is markedly increased FDG uptake in this patient's known left paratracheal lung cancer (arrow) with mildly increased ^{60}Cu -ATSM uptake in the tumor (arrow). The ^{60}Cu -ATSM uptake is greater in the periphery of the lesion, whereas FDG uptake is uniform within the lung cancer.

specificity) in identifying nodal disease. Halter and colleagues (35) studied 28 patients prospectively using FLT-PET and FDG-PET before resecting lung nodules and found two false-positives with FDG-PET but no false-positives with FLT-PET. Although imaging with FLT does not improve upon the sensitivity of FDG-PET in the diagnosis and initial staging of lung tumors, it may serve as a useful adjunct to improve the specificity of FDG-PET imaging in staging these patients.

FLT as a cell-proliferation tracer is potentially more tumor specific than FDG and may be more useful in determining responsiveness to therapy than measurements of glucose metabolism, which may remain elevated in the inflammatory cells surrounding the treated tumor during and shortly after therapy. Several preclinical studies in mouse models for fibrosarcoma showed that the decrease in FLT uptake was more pronounced than the associated decrease in FDG uptake (36, 37). Larger prospective studies in humans are needed to assess the role of FLT in monitoring therapy.

HYPOXIA IMAGING

Numerous *in vivo* and *in vitro* studies have shown that the oxygen tension within solid tumors influences the cells' ability to respond to radiation therapy and some types of chemotherapy. However, noninvasive methods of determining the degree of hypoxia within these tumors are not available.

Copper-labeled diacetyl-bis(N(4)-methylthiosemicarbazone) (^{60}Cu -ATSM) is a recently developed tracer introduced by Fujibayashi and colleagues (38) that is taken up and trapped in hypoxic cells but quickly washes out of normoxic cells and can be labeled by several different radioisotopes of copper. Dehdashti and colleagues (39) studied 14 patients with NSCLC using PET imaging with ^{60}Cu -labeled ATSM (^{60}Cu -ATSM) and FDG before therapy (chemotherapy, radiotherapy, or chemoradiotherapy) to evaluate the potential role of ^{60}Cu -ATSM in predicting response to treatment. An example of the quality of the images obtained with ^{60}Cu -ATSM is shown in Figure 2. Eight patients responded (five with complete response and three with partial response) to therapy, whereas six patients did not respond to therapy and had disease progression. Nonresponders had significantly higher uptake of ^{60}Cu -ATSM than the responders ($p = 0.002$). A tumor-to-muscle ratio (T/M) of 3 or higher of ^{60}Cu -ATSM by 60 min after injection was predictive of poor response to therapy, and a T/M ratio less than 3 was predictive of good response to therapy. There was no significant difference in the degree of FDG uptake between responders and nonresponders. These preliminary results indicate that ^{60}Cu -ATSM may have great poten-

tial in identifying patients who are less likely to respond to conventional therapy.

^{18}F fluoromisonidazole (FMISO) is another tracer that is selectively taken up by hypoxic cells but has a slower washout from normoxic cells than does ^{60}Cu -ATSM. Eschmann and colleagues (40) recently examined whether FMISO uptake could predict tumor recurrence after radiation therapy in 14 patients with NSCLC and 26 patients with head and neck cancer. T/M or tumor-to-mediastinum ratios at 4 h after injection were used to quantify uptake, and the kinetics of FMISO uptake were described by time-activity curves that were used to stratify patients into a rapid washout, intermediate or delayed washout, or accumulation group. The authors found that a T/M cutoff of 1.6 or a tumor-to-mediastinum ratio cutoff of 2 could differentiate those who subsequently developed disease recurrence from those who did not. Only 3 out of 11 patients (27%) with ratios less than these cutoff values developed recurrent disease. In addition, the authors found that patients with tumors that had slow washout were more likely to develop recurrence compared with patients with tumors that had rapid washout.

Larger studies are needed to evaluate the accuracy of these tracers in predicting clinical response to therapy and outcome. However, with the development of new chemotherapeutic agents targeted to hypoxic cells (e.g., tirapazamine) that are toxic but would presumably have the greatest benefit for patients with hypoxic tumors, the use of hypoxia imaging tracers may be able to direct therapy and monitor the effectiveness of hypoxia-targeted therapy.

CONCLUSIONS

There is significant interest in characterizing the biological properties of individual cancers to better determine their behavior and thus select the best therapeutic approach as early as possible for management of these cancers. Although FDG-PET is accepted as a diagnostic imaging tool for the assessment of various cancers, the potential uses of PET in oncology extend beyond the imaging of glucose metabolism. PET imaging with various types of radiopharmaceuticals can target a number of events in tumors, including hypoxia, cell membrane synthesis, and DNA synthesis. These radiopharmaceuticals have the potential to allow assessment of specific cellular processes and to provide an effective means of monitoring the effect of drugs targeting these specific aspects of cancer cell biology. The role of these more targeted radiopharmaceuticals in clinical oncology will most certainly continue to evolve as their utility is clarified in future studies.

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References

- Warburg O. The metabolism of tumors. London: Arnold Constable; 1930.
- Brown RS, Leung JY, Kison PV, Zasadny KR, Flint A, Wahl RL. Glucose transporters and FDG uptake in untreated primary human non-small cell lung cancer. *J Nucl Med* 1999;40:556-565.
- Higashi K, Ueda Y, Sakurai A, Wang XM, Xu L, Murakami M, Seki H, Oguchi M, Taki S, Nambu Y, et al. Correlation of Glut-1 glucose transporter expression with [18F]FDG uptake in non-small cell cancer. *Eur J Nucl Med* 2000;27:1778-1785.
- Gupta NC, Maloof J, Gunel E. Probability of malignancy in solitary pulmonary nodules using fluorine-18-FDG and PET. *J Nucl Med* 1996;37:943-948.
- Detterbeck FC, Falen S, Rivera MP, Halle JS, Socinski MA. Seeking a home for a PET, part 1: defining the appropriate place for positron emission tomography imaging in the diagnosis of pulmonary nodules or masses. *Chest* 2004;125:2294-2299.
- Lowe VJ, Fletcher JW, Gobar L, Lawson M, Kirchner P, Valk P, Karis J, Hubner K, Delbeke D, Heiberg EV, et al. Prospective investigation of positron emission tomography in lung nodules. *J Clin Oncol* 1998;16:1075-1084.
- Higashi K, Ueda Y, Seki H, Yuasa K, Oguchi M, Noguchi T, Taniguchi M, Tonami H, Okimura T, Yamamoto I. Fluorine-18-FDG PET imaging is negative in bronchioloalveolar lung carcinoma. *J Nucl Med* 1998;39:1016-1020.
- Mavi A, Lakhani P, Zhuang H, Gupta NC, Alavi A. Fluorodeoxyglucose-PET in characterizing solitary pulmonary nodules, assessing pleural diseases, and the initial staging, restaging, therapy planning, and monitoring response of lung cancer. *Radiol Clin North Am* 2005;43:1-21 (ix).
- Hensing TA. Clinical evaluation and staging of patients who have lung cancer. *Hematol Oncol Clin North Am* 2005;19:219-235 (v).
- Vansteenkiste J, Fischer BM, Doooms C, Mortensen J. Positron-emission tomography in prognostic and therapeutic assessment of lung cancer: systematic review. *Lancet Oncol* 2004;5:531-540.
- Schrevers L, Lorent N, Doooms C, Vansteenkiste J. The role of PET scan in diagnosis, staging, and management of non-small cell lung cancer. *Oncologist* 2004;9:633-643.
- Wahl RL, Quint LE, Greenough RL, Meyer CR, White RI, Orringer MB. Staging of mediastinal non-small cell lung cancer with FDG PET, CT, and fusion images: preliminary prospective evaluation. *Radiology* 1994;191:371-377.
- Vansteenkiste JF, Stroobants SG, Dupont PJ, De Leyn PR, Verbeken EK, Deneffe GJ, Mortelmans LA, Demedts MG. Prognostic importance of the standardized uptake value on (18)F-fluoro-2-deoxyglucose-positron emission tomography scan in non-small-cell lung cancer: an analysis of 125 cases. Leuven Lung Cancer Group. *J Clin Oncol* 1999;17:3201-3206.
- Scott WJ, Schwabe JL, Gupta NC, Dewan NA, Reeb SD, Sugimoto JT. Positron emission tomography of lung tumors and mediastinal lymph nodes using [18F]fluorodeoxyglucose. The Members of the PET-Lung Tumor Study Group. *Ann Thorac Surg* 1994;58:698-703.
- Albes JM, Lietzenmayer R, Schott U, Schulen E, Wehrmann M, Ziemer G. Improvement of non-small-cell lung cancer staging by means of positron emission tomography. *Thorac Cardiovasc Surg* 1999;47:42-47.
- Gould MK, Kuschner WG, Rydzak CE, Maclean CC, Demas AN, Shigemitsu H, Chan JK, Owens DK. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. *Ann Intern Med* 2003;139:879-892.
- Higashi K, Ito K, Hiramatsu Y, Ishikawa T, Sakuma T, Matsunari I, Kuga G, Miura K, Higuchi T, Tonami H, et al. 18F-FDG uptake by primary tumor as a predictor of intratumoral lymphatic vessel invasion and lymph node involvement in non-small cell lung cancer: analysis of a multicenter study. *J Nucl Med* 2005;46:267-273.
- Sasaki R, Komaki R, Macapinlac H, Erasmus J, Allen P, Forster K, Putnam JB, Herbst RS, Moran CA, Podoloff DA, et al. [18F]fluorodeoxyglucose uptake by positron emission tomography predicts outcome of non-small-cell lung cancer. *J Clin Oncol* 2005;23:1136-1143.
- Sachs S, Bilfinger TV, Komaroff E, Franceschi D. Increased standardized uptake value in the primary lesion predicts nodal or distant metastases at presentation in lung cancer. *Clin Lung Cancer* 2005;6:310-313.
- Bradley J, Thorstad WL, Mutic S, Miller TR, Dehdashti F, Siegel BA, Bosch W, Bertrand RJ. Impact of FDG-PET on radiation therapy volume delineation in non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;59:78-86.
- Ashamalla H, Rafla S, Parikh K, Mokhtar B, Goswami G, Kambam S, Abdel-Dayem H, Guirguis A, Ross P, Evola. The contribution of integrated PET/CT to the evolving definition of treatment volumes in radiation treatment planning in lung cancer. *Int J Radiat Oncol Biol Phys* (In press)
- Ichiya Y, Kuwabara Y, Sasaki M, Yoshida T, Omagari J, Akashi Y, Kawashima A, Fukumura T, Masuda K. A clinical evaluation of FDG-PET to assess the response in radiation therapy for bronchogenic carcinoma. *Ann Nucl Med* 1996;10:193-200.
- MacManus MR, Hicks R, Fisher R, Rischin D, Michael M, Wirth A, Ball DL. FDG-PET-detected extracranial metastasis in patients with non-small cell lung cancer undergoing staging for surgery or radical radiotherapy: survival correlates with metastatic disease burden. *Acta Oncol* 2003;42:48-54.
- Weber WA, Petersen V, Schmidt B, Tyndale-Hines L, Link T, Peschel C, Schwaiger M. Positron emission tomography in non-small-cell lung cancer: prediction of response to chemotherapy by quantitative assessment of glucose use. *J Clin Oncol* 2003;21:2651-2657.
- Bradley JD, Dehdashti F, Mintun MA, Govindan R, Trinkaus K, Siegel BA. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. *J Clin Oncol* 2004;22:3248-3254.
- Blum R, MacManus MP, Rischin D, Michael M, Ball D, Hicks RJ. Impact of positron emission tomography on the management of patients with small-cell lung cancer: preliminary experience. *Am J Clin Oncol* 2004;27:164-171.
- Ishimori T, Saga T, Nagata Y, Nakamoto Y, Higashi T, Mamede M, Mukai T, Negoro Y, Aoki T, Hiraoka M, et al. 18F-FDG and 11C-methionine PET for evaluation of treatment response of lung cancer after stereotactic radiotherapy. *Ann Nucl Med* 2004;18:669-674.
- Nettelbladt OS, Sundin AE, Valind SO, Gustafsson GR, Lamberg K, Langstrom B, Bjornsson EH. Combined fluorine-18-FDG and carbon-11-methionine PET for diagnosis of tumors in lung and mediastinum. *J Nucl Med* 1998;39:640-647.
- Tian M, Zhang H, Oriuchi N, Higuchi T, Endo K. Comparison of 11C-choline PET and FDG PET for the differential diagnosis of malignant tumors. *Eur J Nucl Med Mol Imaging* 2004;31:1064-1072.
- Mankoff DA, Shields AF, Krohn KA. PET imaging of cellular proliferation. *Radiol Clin North Am* 2005;43:153-167.
- Sherley JL, Kelly TJ. Regulation of human thymidine kinase during the cell cycle. *J Biol Chem* 1988;263:8350-8358.
- van Waarde A, Cobben DC, Suurmeijer AJ, Maas B, Vaalburg W, de Vries EF, Jager PL, Hoekstra HJ, Elsinga PH. Selectivity of 18F-FLT and 18F-FDG for differentiating tumor from inflammation in a rodent model. *J Nucl Med* 2004;45:695-700.
- Been LB, Suurmeijer AJ, Cobben DC, Jager PL, Hoekstra HJ, Elsinga PH. [18F]FLT-PET in oncology: current status and opportunities. *Eur J Nucl Med Mol Imaging* 2004;31:1659-1672.
- Buck AK, Hetzel M, Schirrmeister H, Halter G, Moller P, Kratochwil C, Wahl A, Glatting G, Mottaghy FM, Mattfeldt T, et al. Clinical relevance of imaging proliferative activity in lung nodules. *Eur J Nucl Med Mol Imaging* 2005;32:525-533.
- Halter G, Buck AK, Schirrmeister H, Wurzig I, Liewald F, Glatting G, Neumaier B, Sunder-Plassmann L, Reske SN, Hetzel M. [18F] 3-deoxy-3'-fluorothymidine positron emission tomography: alternative or diagnostic adjunct to 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography in the workup of suspicious central focal lesions? *J Thorac Cardiovasc Surg* 2004;127:1093-1099.
- Barthel H, Cleij MC, Collingridge DR, Hutchinson OC, Osman S, He Q, Luthra SK, Brady F, Price PM, Aboagye EO. 3'-deoxy-3'-[18F]fluorothymidine as a new marker for monitoring tumor response to antiproliferative therapy in vivo with positron emission tomography. *Cancer Res* 2003;63:3791-3798.
- Leyton J, Latigo JR, Perumal M, Dhaliwal H, He Q, Aboagye EO. Early detection of tumor response to chemotherapy by 3'-deoxy-3'-[18F]fluorothymidine positron emission tomography: the effect of cisplatin on a fibrosarcoma tumor model in vivo. *Cancer Res* 2005;65:4202-4210.
- Fujibayashi Y, Taniuchi H, Yonekura Y, Ohtani H, Konishi J, Yokoyama A. Copper-62-ATSM: a new hypoxia imaging agent with high membrane permeability and low redox potential. *J Nucl Med* 1997;38:1155-1160.
- Dehdashti F, Mintun MA, Lewis JS, Bradley J, Govindan R, Laforest R, Welch MJ, Siegel BA. In vivo assessment of tumor hypoxia in lung cancer with 60Cu-ATSM. *Eur J Nucl Med Mol Imaging* 2003;30:844-850.
- Eschmann SM, Paulsen F, Reimold M, Dittmann H, Welz S, Reischl G, Machulla HJ, Bares R. Prognostic impact of hypoxia imaging with 18F-misonidazole PET in non-small cell lung cancer and head and neck cancer before radiotherapy. *J Nucl Med* 2005;46:253-260.