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Clinical Applications of Positron Emission Tomography/Computed Tomography Treatment Planning

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Positron emission tomography/computed tomography (PET/CT) has provided an incremental dimension to the management of cancer patients by allowing the incorporation of important molecular images in radiotherapy treatment planning, ie, direct evaluation of tumor metabolism, cell proliferation, apoptosis, hypoxia, and angiogenesis. The CT component allows 4D imaging techniques, allowing improvements in the accuracy of treatment delivery by compensating for tumor/normal organ motion, improving PET quantification, and correcting PET and CT image misregistration. The combination of PET and CT in a single imaging system to obtain a fused anatomical and functional image data is now emerging as a promising tool in radiotherapy departments for improved delineation of tumor volumes and optimization of treatment plans. PET has the potential to improve radiotherapy planning by minimizing unnecessary irradiation of normal tissues and by reducing the risk of geographic miss. PET influences treatment planning in a high proportion of cases and therefore radiotherapy dose escalation without PET may be futile. This article examines the increasing role of hybrid PET/CT imaging techniques in process of improving treatment planning in oncology with emphasis on non small cell lung cancer.
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According to the American Cancer Society (www.cancer.org), lung cancer is a common malignancy, and an estimated 213,380 new cases will be diagnosed in the United States in the year 2007. The standard imaging component used in the clinical staging of these patients is computed tomography (CT). Positron emission tomography (PET) using the radiopharmaceutical, ^{18}F-2-deoxy-D-glucose (FDG), a D-glucose analog labeled with Fluorine-18, compliments conventional radiologic assessment in the evaluation of patients with nonsmall cell lung cancer (NSCLC). This article will review the current applications of FDG-PET in patients with NSCLC and will discuss the utilization of this modality in radiotherapy planning.

Patients with NSCLC typically are staged before therapy according to the recommendations of the International Staging System for Lung Cancer.[1] This system describes the extent of NSCLC in terms of the primary tumor (T descriptor), lymph nodes (N descriptor), and metastases (M descriptor). The stage of the disease is identified anatomically using chest radiograph, CT with intravenous contrast over the chest and upper abdomen, together with contrast enhanced magnetic resonance imaging (MR) or CT of the brain.

Because the majority of NSCLC patients present with advanced disease, the identification of T4 lung cancer and the detection of contralateral nodal (N3) and or extrathoracic metastases (M1) are important as these patients are usually not surgical candidates and require additional chemotherapy and/or radiotherapy.

Utility of FDG-PET CT in Patients With NSCLC

Whole-body (base of skull to proximal thigh) FDG-PET has become an integral component of NSCLC staging because it improves the detection of nodal and distant metastases and frequently alters patient management.[2-7] The American Society of Clinical Oncology published evidence-based guidelines for the diagnostic evaluation of patients with NSCLC,[8] and its recommendations include FDG-PET complements radiologic findings and FDG PET imaging should be per-

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formed when there is no evidence of distant metastatic disease on CT. This was supported by the data of improved detection of nodal and distant metastases via FDG-PET. Clinically, FDG-PET is used together with CT because the relatively poor spatial resolution of FDG-PET limits its utility in the evaluation of the primary tumor and precise anatomic location of regions of focal increased FDG-uptake in nodes and metastatic lesions. The introduction of integrated PET-CT scanners with coregistration of PET and CT images overcomes limitations inherent to both modalities when used separately. In fact, staging of NSCLC has been reported to be more accurate with integrated PET-CT than when using visual correlation of PET and CT images performed separately.[3,9]

A recent review by Erasmus[10] concludes that FDG-PET for nodal staging is cost-effective and can reduce the likelihood that a patient with mediastinal nodal metastases (N3) that would preclude surgery will undergo attempted resection, decision analyses show that the number of false positive results due to infectious or inflammatory etiologies are too high to preclude mediastinoscopy. In this regard, the 2003 American Society of Clinical Oncology consensus regarding the positive predictive value of FDG-PET concluded that mediastinoscopy should be performed when the PET and CT findings are indicative of nodal metastases. Additionally, mediastinoscopy should be performed when the results of CT and PET are not congruent.[8] More recently, ultrasound-guided transesophageal and transbronchial biopsy of nodes, is performed to accurately determine the presence and location of nodal metastases in patients with NSCLC.[11] Nevertheless, FDG-PET/CT is not a perfect test, hence histologic verification is the safest route to ensure that patients are properly staged before therapy.

Utility of FDG PET in Radiotherapy Planning

Many studies have reported the impact of FDG-PET on radiation treatment volumes in NSCLC. Earlier series utilized a visual comparison of the PET and CT images, subsequent series incorporated computer software assisted registration of PET and CT data. Hebert[12] in a prospective series of 20 patients showed, 3 of 12 patients had CT/CXR changes larger than PET and 2 of 12 had PET volumes larger than CT/CXR. Kiffer[13] used coronal PET images with the anterior–posterior simulator image on which the RT volume had been marked. 4 of 15 patients would have had RT volume influenced by the PET findings. Nestle[14] in a retrospective study used CT-based planning with anterior–posterior portals encompassing the primary tumor and the mediastinum. PET findings would have contributed to a reduction in the radiation portals in 12 of 34 patients (35%). Munley[15] compared SPECT lung perfusion (n = 104) and FDG-PET (n = 35), which were registered with the CT of the thorax used to perform radiation therapy treatment planning. FDG-PET data influenced 34% (12 of 35) of the treatment plans examined, and resulted in enlarging portions of the beam aperture. Vanuytsel[16] performed a theoretical study to assess mediastinal nodes in patients with lung cancer. The GTV was defined based on CT and on PET-CT data. Pathology was the gold standard for comparison (988 lymph nodes). In 45 patients (62%), the information obtained from PET would have led to a change of the treatment volumes.

Erdi[17] performed a prospective study in which 11 patients with NSCLC were immobilized in a body cast (treatment position) during CT simulation and FDG-PET study. In 7 of 11 cases, they found an increase in PTV volume (19%) to incorporate nodal disease. In 4 patients, PTV was decreased an average of 18% mainly to exclude atelectasis and trimming the target volume to avoid delivering greater radiation to critical structures. The first study using an integrated PET/CT scanner, by Ciernick[18] studied 39 patients with various solid tumors. The CT and a FDG-PET were obtained in the treatment position and coregistered images were used for treatment planning. Overall, in 56% (22/39) of cases, the GTV delineation was significantly altered if PET imaging data were used. Interestingly, in 16% of cases, PET/CT showed distant metastases, changing the treatment strategy from curative to palliative. In summary, these various series demonstrated changes in treatment volumes from 15% to 60% if FDG PET information was used. More recent reviews on PET/CT utilization for radiotherapy planning in lung cancer maintained a range of 30 to 60% differences between PET derived contours versus CT only target volumes.[19]

An important and controversial issue is setting the threshold of the FDG-PET images when contouring the tumor volume. In the clinical setting, the physician can alter the volume of tumor significantly by varying the threshold or intensity setting. There is no validated standard threshold setting, but initial studies suggested that a 40% of the standard uptake value maximum approximated the tumor volume in peripheral lung tumors.[20-22] More recent studies confirm the anticipated inadequacy of a single threshold because of various factors such as tumor size, location, motion, heterogeneity of tumor uptake by FDG. Biehl et al[23] retrospectively reviewed 19 patients with NSCLC (20 tumor volumes) and the PETGTV at the 40% and 20% thresholds underestimated the CTGTV for 16 of 20 and 14 of 20 lesions, respectively. They concluded that no single threshold delineating the PET GTV provides accurate volume definition, compared with that provided by the CTGTV, for the majority of NSCLCs. Part of the solution is correction for breathing motion and multiple approaches have been developed not only for adequate tracking of the tumor, but to improve the quantification of the FDG PET images. Nemeh[24] used a camera-based respiratory gating system on the PET scanner, allowing more accurate tumor definition and FDG uptake quantification. The subsequent availability of hybrid scanners allowed the development of 4D CT technique, which uses a respiratory gating device to acquire a gated CT, which is used for attenuation correction. This compensates for tumor FDG uptake "smearing" allowing improved quantification and tracking of the tumor based on the CT study.[24] More recently, an average CT, which was acquired during tidal breathing, was used for attenuation correction allowing improved FDG quantification and image coregistration (correct misalign-

ment of PET and CT) with the acquired average CT scan.[25] This technique was also noted to be useful for better quantification and improved image registration in myocardial PET/CT scans.[26]

There are no definitive studies demonstrating superiority of outcome based on PET/CT radiotherapy planning versus CT alone. McManus in a cohort of 88 patients imaged before and after radical RT or chemoRT showed that a complete metabolic response on the FDG-PET provides superior freedom from local and distant relapse and late local relapse is common.[27] A recent study by Klopp[28] in 35 patients treated with definitive RT to FDG PET/CT positive regions showed a low rate of isolated out of field recurrences with a 2 year follow up period. It appeared that high standard uptake value (>13.8) is the best identifier of the region of interest that are at greatest risk of recurrence. A recent series of 35 patients in which the PET/CT RT volume delineation was compared with pathology showing concordance with prior studies in that >50% PET/CT volume contours alteration was noted compared with CT.[29] However, the pathology confirmed only 44% of the TNM stage changes indicated by PET again confirming that FDG PET is not infallible as it may miss microscopic disease or low uptake tumor.[10]

Novel PET Tracers

FDG is the only approved radiopharmaceutical for oncologic PET imaging, and numerous other radiotracers have been developed for evaluation of other metabolic parameters. ^{18}F-3′-deoxy-3′-fluorothymidine (FLT), which is a new tracer that images cellular proliferation by entering the salvage pathway of DNA synthesis but is not a direct marker of DNA proliferation.[30] A review by Shields highlights the fact that the greatest unmet need for PET imaging is in further developing and validating its use in the measurement of treatment response. FLT being one of the more promising tracers and further clinical trials are warranted.[31] In a recent study of 34 patients with NSCLC, FLT-PET showed better (although not statistically significant) specificity, positive predictive value and accuracy for N staging on a per-patient basis than FDG-PET. However, FDG-PET was found to have higher sensitivity for depiction of primary tumor than FLT-PET.[32] The same group showed in a preliminary study of 18 patients that, although FLT uptake correlated significantly with proliferative activity in NSCLC, the correlation was not better than that for FDG uptake.[33]

Tumor hypoxia plays an important role in biology of cancer cells through effects on signal transduction pathways, and the regulation and transcription of various genes involved in malignant growth and metastases. Well-oxygenated cells are more sensitive to the cytotoxic effects of ionizing radiation compared with hypoxic cells, and there is a preclinical evidence indicating that hypoxic cells are also resistant to the effects of chemotherapy, eg, by amplification of genes conferring drug resistance.[34,35] The PET tracer most widely used in a clinical setting of hypoxia is ^{18}F-fluoromisonidazole (^{18}F-FMISO). ^{18}F-FMISO PET scanning has been used for the noninvasive assessment of hypoxia in tumors, including NSCLC. The results appear mixed, because small studies showed promise, ie, FMISO PET allowed for the qualitative and quantitative definition of hypoxic sub-areas that may correspond to a localization of local recurrences.[36] In a recent series of 17 patients with NSCLC, The correlation between FMISO uptake, F-FDG uptake, and tumor markers of hypoxia and angiogenesis was poor.[37]

Several other radiolabeled markers of hypoxia have been developed that can be measured by PET scanning, including ^{60}Cu-ATSM and ^{62}Cu-ATSM.[38] Cu-ATSM has been studied and shown to have rapid uptake and selective retention in hypoxic cells, and clinical studies have been done for head and neck and cervical cancer.[39,40] A pilot study of 19 patients with biopsy-proven NSCLC were studied with PET and (60)Cu-ATSM before initiation of therapy. Response was evaluated in 14 patients; the mean T/M for (60)Cu-ATSM significantly lower in responders (1.5 ± 0.4) than in nonresponders (3.4 ± 0.8) ($P = 0.002$).[41]

Conclusions

FDG-PET and PET/CT imaging appears useful in improving radiotherapy treatment planning because of its greater accuracy in identifying nodal (N3) and distant metastatic disease, which precludes surgery and allows better RT delivery. The incorporation of the FDG-PET into treatment volume determination can increase or decrease the treated volume between 15 to 60%. FDG-PET imaging is not perfect and false positives and negatives should be taken into consideration during treatment planning. FDG-PET thresholding needs further study to optimize the levels depending on tumor size, location and heterogeneity. Solutions such as PET gating, 4DCT, and average CT techniques allow improvements in quantification and correct image misregistration. Follow-up data obtained from FDG-PET/CT for treatment planning shows promise, but the actual improvement in outcomes needs to be demonstrated. Novel tracers can be used to identify the hypoxic and presumed radioresistant volume of tumor, which may potentially benefit from more intense or higher doses of radiation to this tumor fraction with the hope of improving patient response or outcome.

References

1. Mountain CF: Revisions in the international system for staging lung cancer. Chest 111:1710-1717, 1997
2. Verboom P, Van Tinteren H, Hoekstra OS, et al: Cost-effectiveness of FDG-PET in staging non-small cell lung cancer: the PLUS study. Eur J Nucl Med Mol Imaging 30:1444-1449, 2003
3. Lardinois D, Weder W, Hany TF, et al: Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. N Engl J Med 348:2500-2507, 2003
4. Verhagen AF, Bootsma GP, Tjan-Heijnen VC, et al: FDG-PET in staging lung cancer: How does it change the algorithm? Lung Cancer 44:175-181, 2004
5. Reed CE, Harpole DH, Posther KE, et al: Results of the American College of Surgeons Oncology Group Z0050 trial: The utility of positron emission tomography in staging potentially operable non-small cell lung cancer. J Thorac Cardiovasc Surg 126:1943-1951, 2003
6. Vansteenkiste JF, Stroobants SG, De Leyn PR, et al: Lymph node staging in nonsmall-cell lung cancer with FDG-PET scan: A prospective study

on 690 lymph nodestations from 68 patients. J Clin Oncol 16: 2142-2149, 1998
7. Pieterman RM, van Putten JW, Meuzelaar JJ, et al: Preoperative staging of nonsmall-cell lung cancer with positron-emission tomography. N Engl J Med 343:254-261, 2000
8. Pfister DG, Johnson DH, Azzoli CG, et al: American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: Update 2003. J Clin Oncol 22:330-353, 2004
9. Antoch G, Stattaus J, Nemat AT, et al: Non-small cell lung cancer: Dual-modality PET/CT in preoperative staging. Radiology 229:526-533, 2003
10. Erasmus JJ, Macapinlac HA, Swisher SG: Positron emission tomography imaging in nonsmall-cell lung cancer. Cancer 110:2155-2168, 2007
11. Yasufuku K, Nakajima T, Motoori K, et al: Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. Chest 130:710-718, 2006
12. Hebert ME, Lowe VJ, Hoffman JM, et al: Positron emission tomography in the pretreatment evaluation and follow-up of non-small cell lung cancer patients treated with radiotherapy: Preliminary findings. Am J Clin Oncol 19:416-421, 1996
13. Kiffer JD, Berlangieri SU, Scott AM, et al: The contribution of 18F-fluoroseoxyglucose positron emission tomography imaging to radiotherapy planning in lung cancer. Lung Cancer 1998 19:167-177
14. Nestle U, Walter K, Schmidt S, et al: 18F-deoxyglucose positron emission tomograpy (FDG-PET) for the planning of radiotherapy in lung cancer: High impact in patients with atelectasis. Int J Radiat Oncol Biol Phys 1999 44:593-597
15. Munley MT, Marks LB, Scarfone C, et al: Multimodality nuclear medicine imaging in three-dimensional radiation treatment planning for lung cancer: Challenges and prospects. Lung Cancer 1999 23:105-114
16. Vanuytsel LJ, Vansteenkiste JF, Stroobants SG, et al: The impact of 18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) lymph node staging on the radiation treatment volumes in patients with non-small cell lung cancer. Radiother Oncol 2000 55:317-324
17. Erdi YE, Rosenzweig K, Erdi AK, et al: Radiotherapy treatment planning for patients with non-small cell lung cancer using positron emission tomography (PET). Radiother Oncol 2002 62:51-60
18. Ciernik IF, Dizendorf E, Baumert BG, et al: Radiation treatment planning with an integrated positron emission and computer tomography (PET/CT): A feasibility study. Int J Radiat Oncol Biol Phys 57:853-863, 2003
19. Greco C, Rosenzweig K, Cascini GL, et al: Current status of PET/CT for tumour volume definition in radiotherapy treatment planning for non-small cell lung cancer (NSCLC). Lung Cancer 57:125-134, 2007
20. Erdi YE, Rosenweig K, Erdi AK, et al: Radiotherapy treatment planning for patients with non-small cell lung cancer using positron emission tomography (PET). Radiother Oncol 62:51-60, 2002
21. Erdi Y, Mawlawi O, Imbriaco M, et al: Volume determination for metastatic lung lesions by adaptive PET image thresholding. Cancer 80: 2505-2509, 1997
22. Bradley J, Thorstad WL, Mutic S, et al: Impact of FDG-PET on radiation therapy volume delineation in non-small cell lung cancer. Int J Radiat Oncol Biol Phys 59:78-86, 2004
23. Biehl KJ, Kong FM, Dehdashti F: 18F-FDG PET definition of gross tumor volume for radiotherapy of non-small cell lung cancer: Is a single standardized uptake value threshold approach appropriate? J Nucl Med 47:1808-1812, 2006
24. Nehmeh SA, Erdi YE, Ling CC, et al: Effect of respiratory gating on quantifying PET images of lung cancer. J Nucl Med 43:876-881, 2002
25. Pan T, Mawlawi O, Nemeh SA, et al: Attenuation correction of PET images with respiration-averaged CT images in PET/CT. J Nucl Med 46:1481-1487, 2005
26. Pan T, Mawlawi O, Luo D, et al: Attenuation correction of PET cardiac data with low-dose average CT in PET/CT. Med Phys 33:3931-3938, 2006
27. Mac Manus MP, Hicks RJ, Matthews JP, et al: Metabolic (FDG-PET) response after radical radiotherapy/chemoradiotherapy for non-small cell lung cancer correlates with patterns of failure. Lung Cancer 49:95-108, 2005
28. Klopp AH, Chang JY, Tucker SL, et al: Intrathoracic patterns of failure for non-small-cell lung cancer with positron-emission tomography/computed tomography-defined target delineation. Int J Radiat Oncol Biol Phys 69:1409-1416, 2007
29. Faria SL, Menard S, Devic S, et al: Impact of FDG-PET/CT on radiotherapy volume delineation in non-small-cell lung cancer and correlation of imaging stage with pathologic findings. Int J Radiat Oncol Biol Phys, in press
30. Shields AF, Grierson JR, Dohmen BM, et al: Imaging proliferation in vivo with [F-18]FLT and positron emission tomography. Nat Med 4:1334-1336, 1998
31. Shields AF: Positron emission tomography measurement of tumor metabolism and growth: Its expanding role in oncology. Mol Imaging Biol 8:141-150, 2006
32. Yamamoto Y, Nishiyama Y, Kimura N, et al: Comparison of (18)F-FLT PET and (18)F-FDG PET for preoperative staging in non-small cell lung cancer. Eur J Nucl Med Mol Imaging, in press
33. Yamamoto Y, Nishiyama Y, Ishikawa S, et al: Correlation of (18)F-FLT and (18)F-FDG uptake on PET with Ki-67 immunohistochemistry in non-small cell lung cancer. Eur J Nucl Med Mol Imaging 34:1610-1616, 2007
34. Teicher BA, Lazo JS, Sartorelli AC: Classification of antineoplastic agents by their selective toxicities toward oxygenated and hypoxic tumor cells. Cancer Res 41:73-81, 1981
35. Rice GC, Hoy C, Schimke RT: Transient hypoxia enhances the frequency of dihydrofolate reductase gene amplification in Chinese hamster ovary cells. Proc Natl Acad Sci USA 83:5978-5982, 1986
36. Gagel B, Reinartz P, Demirel C, et al: [18F] fluoromisonidazole and [18F] fluorodeoxyglucose positron emission tomography in response evaluation after chemo-/radiotherapy of non-small-cell lung cancer: a feasibility study. BMC Cancer 6:51, 2006
37. Cherk MH, Foo SS, Poon AM, et al: Lack of correlation of hypoxic cell fraction and angiogenesis with glucose metabolic rate in non-small cell lung cancer assessed by 18F-fluoromisonidazole and 18F-FDG PET. J Nucl Med 47:1921-1926, 2006
38. Lewis JS, Welch MJ: PET imaging of hypoxia. Q J Nucl Med 45:183-188, 2001
39. Chao KS, Bosch WR, Mutic S, et al: A novel approach to overcome hypoxic tumor resistance: Cu-ATSM-guided intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys 49:1171-1182, 2001
40. Dehdashti F, Grigsby PW, Mintun MA, et al: Assessing tumor hypoxia in cervical cancer by positron emission tomography with 60Cu-ATSM: Relationship to therapeutic response-a preliminary report. Int J Radiat Oncol Biol Phys 55:1233-1238, 2003
41. Dehdashti F, Mintun MA, Lewis JS, et al: In vivo assessment of tumor hypoxia in lung cancer with 60Cu-ATSM. Eur J Nucl Med Mol Imaging 30:844-850, 2003