Published in final edited form as:

Radiat Res. 2012 April ; 177(4): 436–448.

Application of Metabolic PET imaging in radiation oncology

Aizhi Zhu^a, David M. Marcus^{b,c}, Hui-Kuo G. Shu^{b,c}, and Hyunsuk Shim^{a,c,1}

^aDepartment of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, USA

^bDepartment of Radiation Oncology, Emory University School of Medicine, Atlanta, USA

^cWinship Cancer Institute, Emory University School of Medicine, Atlanta, USA

Abstract

Positron emission tomography (PET) is a noninvasive imaging technique that provides functional or metabolic assessment of normal tissue or disease conditions and is playing an increasing role in cancer radiotherapy planning. ¹⁸F-fluorodeoxyglucose PET imaging (FDG-PET) is widely used in the clinic for tumor imaging due to increased glucose metabolism in most type of tumors; its role in radiotherapy management of various cancers is reviewed. In addition, other metabolic PET imaging agents at various stages of preclinical and clinical development are reviewed. These agents include radiolabeled amino acids such as methionine for detecting increased protein synthesis, radiolabeled choline for detecting increased membrane lipid synthesis, and radiolabeled acetate for detecting increased cytoplasmic lipid synthesis. The amino acid analogs choline and acetate are often more specific to tumor cells than FDG, so they may play an important role in differentiating cancers from benign conditions and in the diagnosis of cancers with either low FDG uptake or high background FDG uptake. PET imaging with FDG and other metabolic PET imaging agents is playing an increasing role in complementary radiotherapy planning.

Radiation oncology plays an important role in cancer management. Radiation therapy is an effective non-invasive cancer therapy that can be given repetitively over a few to several weeks and can be targeted specifically at the area where treatment is needed, minimizing side effects for uninvolved normal tissues. Each year approximately 60% of cancer patients in the United States receive radiation therapy for definitive treatment, for palliation of symptoms, or as an adjunct to surgery or chemotherapy. Radiation therapy is commonly applied to control cell growth through DNA damage caused by Ionizing radiation of exposed tissue; furthermore, cancerous cells are more susceptible to death by ionizing radiation because many types of tumors have turned off their DNA repair machinery during the process of becoming cancerous. To spare normal tissues (such as skin or organs which radiation must pass through in order to treat the tumor), shaped radiation beams are aimed from several angles of exposure to intersect at the tumor, providing a much larger absorbed dose there than in the surrounding, healthy tissue. The field of radiation oncology changed dramatically with the wide introduction of computer-optimized intensity-modulated radiation therapy (IMRT) in the 1990's. IMRT is based on the use of numerous radiation beams with optimized nonuniform intensities resulting from inverse treatment planning, which can achieve much better dose conformity than conventional radiotherapy techniques. With this technique, high radiation doses to the primary tumor can be given while limiting the dose to radiation-sensitive normal tissues adjacent to the tumor. In the era of high-precision radiotherapy, accurate tumor volume delineation regarding tumor boundaries,

¹Address for Correspondence: Department of Radiology and Imaging Sciences, Emory University, 1701 Uppergate Drive, C5008, Atlanta, GA 30322, USA, Tel: +1-404-778-4564, Fax: +1-(404) 712-5813, hshim@emory.edu.

shape, and volume is crucial. For target volume selection and delineation, anatomic imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) remain the most widely used modalities. CT is widely available, does not have geometric distortion, and provides intrinsic information on the electronic densities of various tissues. However, CT lacks contrast resolution for normal soft-tissue structures and tumor extent, which has led to significant inter- and intra-observer variations in delineation of the gross tumor volume (GTV) in head and neck, lung, esophageal, prostate, breast, cervical, and brain tumors. MRI has been shown to be more accurate than CT for evaluating the soft-tissue or bone extent of nasopharynx, prostate, and brain tumors with smaller interobserver variations in delineation of the GTV. However, for pharyngeal–laryngeal tumors, both MRI and CT have limitations with significant interobserver variability in target volume delineation (1).

Over the last few decades, molecular imaging, particularly positron emission tomography (PET), has been widely used for cancer diagnosis, monitoring therapy response, and radiotherapy planning (2–4). As a highly sensitive and accurate nuclear medicine imaging technology based on molecular biology, PET has a unique ability to assess the functional and biochemical processes of the body's tissues, which are altered in the earliest stages of virtually all diseases. PET detects these changes — often before anatomical or structural changes have occurred or are evident on MRI or CT. It compares normal and abnormal tissues at a functional rather than morphologic level (MRI or CT). PET promises to improve the target definition by defining a metabolically active biological target volume (BTV). The target volumes defined by PET have been shown to be closest to the pathologic specimen compared with CT or MRI in laryngeal carcinoma (5). However, PET for radiotherapy planning has been limited by its lack of spatial resolution and relatively low specificity to locate a target to the degree of accuracy required in precision radiotherapy, such as IMRT. The advent of hybrid PET/CT scanners has allowed hardware fusion of functional and anatomic imaging. This provides better localization of the functional imaging and decreases the interobserver variations in identifying target volumes, which has proven to be a major advance for radiotherapy planning (3). ^{18}F -fluorodeoxyglucose (FDG) is the most commonly used and the only oncologic PET tracer approved by the Food and Drug Administration (FDA) for routine clinical use. More than 90% of oncologic PET imaging is performed by FDG-PET due to the increased metabolism of glucose by tumor cells in most lung, colorectal, esophageal, stomach, head and neck, cervical, ovarian, and breast cancers, as well as melanoma and most types of lymphoma. In addition to diagnosis, staging, restaging, and monitoring response to cancer treatment, FDG-PET can be useful for selection or delineation of radiotherapy target volumes. The use of FDG-PET for radiotherapy planning purposes has shown increasing importance, as more and more radiation oncologists believe that target volume selection and delineation cannot be adequately performed without the use of FDG-PET in certain cancer types. However, FDG is not a tumor specific substance; its accumulation in benign lesions, such as inflammation, causes false-positive results which lead to low tumor specificity(6). In addition to glucose, amino acids (the building block of protein) and choline (the building block of cell membranes), have also shown increased tumor consumption and tumor specificity; therefore, their radiolabeled radiotracers such as ^{11}C -methionine and ^{11}C -choline may have significant potential for tumor detection in organ sites with high glucose utilization resulting in an undesirable FDG-PET background such as with brain tumor or in tumors with low intrinsic FDG uptake such as prostate cancer. In addition, ^{11}C -acetate acts as a probe of tissue metabolism through entry into catabolic or anabolic metabolic pathways as mediated by acetyl–coenzyme A and is also a useful PET tracer for various cancer types, such as lung cancer, hepatocellular carcinoma, renal cancer, prostate cancer and astrocytomas (7–10), which makes it a potential substitute for FDG in target volume selection and delineation in radiotherapy planning (11).

Metabolic PET can provide information that impacts radiotherapy planning in several ways. First, PET may detect a tumor that is missed by CT or MRI. Second, PET may detect additional tumor regions outside the tumor volume as defined by CT or MR imaging. Third, PET may show subregions or foci with increased or altered metabolism within the gross tumor volume that could be preferentially targeted and treated with escalated radiation doses. The more precise 3D delineation of tumor volumes could translate into improved locoregional control with radiation therapy. A common issue in the use of FDG-PET for the delineation of radiation target volumes is the definition of a standardized uptake value (SUV) threshold for involved disease. There is no consensus definition of what constitutes metabolically active tumor as a function of SUV, and the definition of target volumes on PET is somewhat arbitrary. Generally, in order to define the metabolic target volume, contours based on multiple SUV thresholds are generated, and the radiation oncologist subsequently chooses the threshold that is believed to most accurately represent the burden of disease as determined by clinical exam and/or other imaging modalities. Contours from FDG-PET scans based on SUV thresholds should only be used to enlarge a target volume contour; using FDG-PET contours to shrink a pre-existing target volume would risk under-treating tissue that may be involved with tumor. For these reasons, FDG-PET contours based on SUV thresholds should generally be used as an adjunct to CT or MRI-based contours and not as a single modality method for defining a target volume.

Finally, FDG-PET may also have utility for following the response of tumors to radiation. In the short-term, oxidative stress induced by radiation therapy may reroute the utilization of glucose from glycolysis to the pentose phosphate pathway in a process regulated by ATM allowing production of NADPH as a response to the generation of reactive oxygen species (12). It remains unclear how this shift will alter overall glucose utilization and the signal seen on FDG-PET in the period during or immediately after a course of radiation therapy. However, over the long-term, decreasing cellular proliferation and inducing cell death with radiation will lead to an overall reduction in metabolism including reduced glucose consumption, protein synthesis/amino acid transport and DNA synthesis. Also, since inflammation is a common acute response to radiotherapy, FDG-PET signals may be confounded by inflammatory cells leading to limitations in the detection of early tumor responses to radiation. For these reasons, FDG-PET should not be performed until several months after completion of radiotherapy, while DNA analogs or amino acids and their analogs are more specific to tumor characteristics than FDG, which may be more suitable to monitor early radiotherapy response. Haubner reviewed the syntheses and biological characteristics of clinically tested PET tracers which may be useful in radiation treatment planning (13). This article will focus on the utility of FDG and other metabolic tumor PET imaging agents in radiotherapy planning for accurate delineation of the radiotherapy target volume and monitoring radiotherapy response of various tumors, including lung, head and neck, breast, esophageal, lymphoma, brain, and prostate cancers.

Lung cancers

Lung cancer is the leading cause of cancer death in both men and women. 80% of lung cancer is non-small cell lung cancer (NSCLC). While difficult to treat, the best opportunity to cure NSCLC is by radical surgical resection in the early stages of disease. FDG-PET has been widely used in evaluation of patients with lung cancer and has proven to be of immense value in the initial diagnosis of disease (14). The overall sensitivity, specificity, and accuracy of FDG-PET for detection of lung cancers are very high for primary, residual, and recurrent disease.

Radiotherapy is a key treatment modality in the curative treatment of patients with lung cancer. Recent progress in combined modality treatments incorporating chemotherapy and

radiation, with or without surgery, as well as technical advances in radiation delivery, has led to significant improvements in treatment outcomes. Accurate evaluation of nodal metastasis is crucial for planning curative radiotherapy. FDG-PET scan is more sensitive than CT in detection of lymph node involvement and distant metastases in NSCLC. In our own experience, a 73 year old female patient with Stage IIIA NSCLC was imaged by FDG-PET/CT (Figure 1). Axial CT alone images in both mediastinal and lung windowing could not show a clear profile of the tumors, while overlayed PET imaging clearly showed primary lung lesions and right paratracheal lymph node involvement (Figure 1A–D). The patient was treated on protocol with carboplatin/taxol + cetuximab with 3D conformal RT to 74 Gy based on the contour guided by FDG-PET/CT (Figure 1E–F). FDG-PET led to significant modification of treatment strategy and radiotherapy planning in NSCLC patients (15). PET-defined volumes were, in general, smaller than volumes defined by CT, thus leading to decreased radiation exposure of the lungs and esophagus sufficiently as to allow for radiation dose escalation (16). Faria reported that more than 50% major alterations in the GTV contoured on PET/CT compared with CT alone were found by oncologists. Figure 2 shows contour of a right lung tumor using PET/CT and CT had a GTV difference >30%. However, pathologic examination shows that PET is not always accurate; thus, histological examination should be obtained to confirm the findings of PET whenever possible (17). PET scans alone offer little additional advantage over CT or MRI scans for primary tumor staging; however, they have been observed to reduce the interobserver variability compared to CT alone (18), and integrated PET/CT improved variability even further (19). Additionally, PET/CT scans have been shown to detect distant metastases that are missed by conventional scans, which is of obvious benefit to patients who may require additional treatment.

In addition to its use in delineating the extent of a lung malignancy at the time of diagnosis, FDG-PET imaging is also used to monitor metabolic changes after radiotherapy (20, 21). MacManus et al. reported that metabolic response correlated well with radiotherapy outcome. Complete metabolic response (CMR) predicted good radiotherapy outcome: one-year survival for CMR and non-CMR patients was 93% and 47%, respectively, and 2-year survival was 62% and 30%, respectively (22). The degree of radiotherapy-induced change in tumor glucose metabolism as determined by FDG-PET is highly predictive for patient outcome and allows stratification of patients into groups with widely differing overall and progression-free survival probabilities.

FDG-PET/CT has led to the safe decrease of radiotherapy volumes by better delineation of tumor, enabling radiation dose escalation and, experimentally, allowing definition of regions of tumor at greatest risk for recurrence, permitting redistribution of radiation doses within the tumor to focus on these regions. In addition, FDG-PET/CT has proven to be a useful tool for monitoring treatment response in lung cancer patients. PET/CT imaging is rapidly being embraced by the radiation oncology community as a means to accurately define the target volume for treatment optimization and for following response to treatment in NSCLC.

Head and neck cancers

Head and neck cancers (HNC) account for approximately 4% to 5% of all malignant diseases in the United States. The majority of HNC are squamous cell carcinomas of head and neck (SCCHN), which often spread to lymph nodes of the neck at the time of diagnosis. FDG-PET has become widely accepted as a standard modality for evaluating SCCHN with good diagnostic performance in the overall pretreatment evaluation of such patients; however, it may have limitations in detecting micrometastasis, due to low FDG uptake of small tumors without hypoxia (23).

Radiotherapy is one of the primary treatments of HNC. FDG-PET/CT can play various roles in the treatment of HNC including staging, restaging, and defining biological tumor volume (BTV) for high-dose radiotherapy boost. The role of FDG-PET in planning radiotherapy of HNC has drawn great interest and has been reviewed in multiple publications (24–26). There can be significant variation in target volumes depending on whether conventional planning or PET-CT based planning is used. Conflicting reports have shown that CT-based gross tumor volumes (GTVs) were larger than PET/CT-based GTVs in some cases (27, 28), while a similar study of 22 HNC patients reported that GTV defined with the help of PET-CT was significantly larger than the CT-based volumes ($P < 0.0001$) (29). In addition, different threshold methods to delineate the target volume also lead to variations in target volumes. Moule *et al.* investigated two fixed threshold methods to delineate the target volume using FDG-PET/CT. Functional volumes were delineated according to the standard uptake value cut off (SUVCO) (2.5, 3.0, 3.5, and 4.0 bodyweight gram/mL) and percentage of the SUVmax (30%, 35%, 40%, 45%, and 50%) thresholds, and it was shown that SUVCO was more reliable to differentiate target volume from background than SUVmax (30). Furthermore, interobserver variations were decreased when identifying the target volume with FDG-PET/CT compared to CT alone (31). In our own experience, a 62 year old male with T2N2b squamous cell carcinoma of left base of tongue had radiotherapy planned out by FDG-PET/CT combined images (Figure 3). Figure 3A is the CT alone image, which did not show a clear profile of the tumors, while the FDG-PET/CT combined images (Figure 3B–D) were significantly more sensitive at delineating the extent of tumors. PET contour showed an area within the VOI with $SUV > 7$ in the primary tumor and left level IIA lymph nodes. This patient was treated with IMRT to 57 Gy to low risk nodal regions, 63 Gy to high risk nodal regions and 70 Gy to PET-avid disease defined by $SUV > 7 + 5\text{mm}$ margin.

FDG-PET can provide important complementary information for radiotherapy planning in head and neck cancer. Potentially, the GTV can be changed on the basis of PET information, facilitating sparing of nearby normal tissues and allowing dose escalation to relatively small subvolumes. In addition, biologic imaging using ^{18}F -FDG PET may identify areas of tumor spread not recognized by CT or MRI, potentially improving the accuracy of GTV definition. A comparison study of ^{11}C -acetate (ACE) and FDG-PET in ten patients indicated that ACE-PET may be more sensitive than FDG-PET for the detection of primary tumors and metastases in patients with SCCHN (10, 32).

In addition to playing a significant role in radiation treatment planning, FDG-PET is also used to evaluate treatment outcome in HNC. Pre-treatment FDG-PET is useful in predicting the response to treatment, and post-treatment FDG-PET is of value in identifying residual viable tumors. Kitagawa *et al.* reported that HNCs with high SUVs (mean, 9.75 mg/ml) prior to the treatment decreased significantly after the therapy (3.41 mg/ml, $P < 0.01$) and lower post-therapy SUV was significantly correlated with good histological results (no viable tumor cells, $n=16$) (33). Farrage reported that the overall survival (OS) and disease-free survival (DFS) were significantly different in good responders with a low SUVmax than poor responders with a high SUVmax (81 and 67% versus 50 and 40%, respectively), whereas there were no significant differences in CMRs and non-CMRs (34). In brief, FDG-PET has a profound impact on the treatment strategy for head and neck carcinomas.

Currently there is no significant evidence suggesting the use of one modality over the other in HNC radiotherapy planning. Attempts are being made to combine the benefits of multiple modalities to get more accurate representation of the tumor. However, to address the clinical value and possible shortcomings of these concepts, additional histological validation studies and properly designed clinical studies are needed.

Breast cancers

Breast cancer is the most common cancer in female patients, and carries a significant risk for recurrence and metastases. Breast cancer is the second leading cause of death in women. For localized cancers, the 5-year survival rate is more than 96%, but survival decreases dramatically with regional or distant metastatic disease. FDG-PET has been widely used in evaluation of patients with breast cancer, especially in those who have recurrent or locally advanced breast cancer. Strategies in managing breast cancer include using various combinations of surgery, radiation therapy and chemotherapeutic regimens. Radiotherapy is mainly applied in three areas: 1) adjuvant radiation therapy after breast surgery, 2) radiation therapy for isolated recurrence after surgery, and 3) radiation therapy for metastatic disease.

Published reports are limited in assessing the utility of FDG-PET in breast cancer radiotherapy planning. At present, FDG-PET has not shown significant utility in radiation planning after breast-conserving surgery. Postoperative inflammatory changes in the cavity will lead to increased FDG uptake; therefore, the FDG-PET-defined lumpectomy cavity was significantly larger than the CT-defined cavity, which could be covered by CT-determined volume without significant increase (35). However, FDG-PET can contribute in significant ways to the clinical management and radiation planning of patients who have suspected locoregional recurrences. The most common sites of locoregional recurrence among breast cancer patients that have undergone mastectomy and axillary node dissection are the chest wall and supraclavicular nodes. Patients who have locoregional recurrences are at high risk for synchronous or metachronous distant metastases (36). FDG-PET is able to differentiate recurrences from post-surgical scars and is much more sensitive at detecting metastasis than CT and/or MRI. The role of FDG-PET is especially prominent in the management of oligometastatic disease (a state of metastatic progression in which a limited metastatic spread of disease is potentially curable with local therapy), which is an area in which radiation therapy is emerging as an important treatment modality (34). In our own experience, a 56 year old female patient with infiltrating ductal carcinoma of the right breast (T2N3), treated with neoadjuvant chemo followed by mastectomy and radiation, developed a right internal mammary node (IMN) recurrence 2 ½ years after initial therapy (Figure 4A–B). The recurrence was treated to the IMN chain to 45 Gy in 25 fractions and was boosted to the PET-positive node with an additional 15 Gy in 3 fractions (Figure 4C); five months after treatment, FDG-PET imaging fused onto the original treatment planning CT showed complete resolution of PET-positive focus in Figure 4D.

In summary, the greatest clinical applications of FDG-PET in breast cancer are in the detection and definition of the extent of recurrent or metastatic disease, which can provide valuable information for determining treatment volumes and avoiding geographic misses, thus improving outcomes. At this point, there is little data available to support the use of FDG-PET to monitor tumor response to radiation; however, future studies may serve to increase the role of FDG-PET in the evaluation of breast cancer patients following their radiation treatment course.

Esophageal cancers

The incidence of esophageal cancer ranks in the top ten worldwide with a relatively high mortality rate. Esophageal cancers consist primarily of two subtypes, adenocarcinoma (comprising 50–80% of all esophageal cancer cases) and squamous cell carcinoma (comprising most of the remaining cases). FDG-PET is not generally used for the initial diagnosis of esophageal cancer due to significant FDG uptake in infectious esophagitis, Barrett's esophagus, inflammatory esophagitis, and other benign diseases. In addition, FDG-PET plays a limited role in the evaluation of regional nodal disease in patients with

esophageal cancer but has a high sensitivity for evaluation of local recurrence along with a high sensitivity and specificity for detection of distant disease occurring outside the initial surgical field. (37).

Like with many malignancies, radiotherapy is one of the primary treatments for esophageal cancer. Combined chemotherapy and radiation therapy has proven superior to either therapy alone as primary treatment for esophageal cancer. Overall, while radiation therapy alone can be used to treat localized cancer in patients who cannot tolerate surgery or chemotherapy, very few patients are actually cured with this approach. Radiation therapy alone can also be used to decrease symptoms associated with this cancer especially with more locally advanced disease in the setting of patients who are medically unable to receive surgery or chemotherapy or who have a recurrence after surgery.

Accurate delineation of GTV is a prerequisite for a successful treatment of esophageal cancer with radiotherapy. The use of FDG-PET/CT has been shown to change target volumes contoured by radiation oncologists in a considerable proportion of patients (20–90%) with consequent changes in treatment planning (38, 39). The tumor length evaluated by FDG-PET at an SUV cut off of 2.5 seemed most approximate to the pathological tumor length (40, 41). In addition, the inter- and intra-observer variability of GTV contours based on FDG-PET is decreased compared to CT-based planning in a few reports (42). However, evidence supporting the validity of the use of FDG-PET/CT in the tumor delineation process is very limited. No significant correlation between FDG-PET-based tumor length and pathological findings has been found, because using different methods to evaluate FDG-PET imaging results in variations in gross tumor lengths. Muijs *et al.* reported a systematic review on the role of FDG-PET/CT in tumor delineation and radiotherapy planning in patients with esophageal cancer and did not find a significant role of FDG-PET in radiotherapy (43).

FDG-PET has limitations in monitoring early therapy response because FDG-PET cannot clearly separate post-treatment inflammation from residual tumor in esophageal cancer (44). Most of the reports regarding the use of FDG-PET to evaluate treatment response in esophageal cancer include patients primarily treated with chemotherapy with very limited data on radiotherapy. A systematic review concluded that FDG-PET should not be used in routine clinical practice to guide neoadjuvant therapy decisions in patients with esophageal cancer due to its widely variable sensitivity and specificity, which have both been reported to range around 30–100% (45). Ngamruengphong *et al.* also reported their experience in this situation and found no difference in accuracy between early FDG-PET and FDG-PET after completion of neoadjuvant therapy (46). They concluded that FDG-PET added no significant information in monitoring therapy response in esophageal cancer.

In summary, FDG-PET can play a complementary role in radiation therapy planning to other modalities such as CT, MRI and endoscopic ultrasound (EUS) in the management of esophageal cancer. Due to the low sensitivity of FDG-PET in esophageal cancer, the irradiated volume should not be reduced based on a negative FDG-PET in a region with suspect nodes on other tests. However, due to the high specificity of FDG-PET, enlarging the irradiated volume based on a positive FDG-PET in a region without suspected lymph nodes on CT and/or EUS should be considered. This indicates a role for FDG-PET in radiotherapy planning for esophageal cancer.

Lymphomas

Lymphomas are the most common primary hematopoietic malignancy in the United States. Lymphomas often respond well to therapy, and survival rates are generally 90% or higher

when these diseases are detected at early stages, making it one of the most curable forms of cancer (47). The primary therapeutic modalities are chemotherapy and radiotherapy, as surgery does not often play a role in the management of this disease. Accurate imaging is crucial to treatment strategy, and FDG-PET has become a useful imaging modality in the staging and treatment evaluation algorithm for lymphoma by providing unique metabolic information.

FDG-PET is more powerful than CT or MRI in evaluating both non-Hodgkin's and Hodgkin's lymphoma (48). Currently, FDG-PET may be more accurate than anatomic imaging modalities in assessing treatment effects to correctly identify patients with residual disease and predict therapy outcome (49). FDG-PET information for defining target volumes for radiotherapy planning has also drawn great interest. Hutchings *et al.* reported that FDG-PET/CT results in larger treatment volumes for radiotherapy planning (50). Furthermore, the initial FDG-PET helped the delineation of involved-field radiotherapy for the nodal regions at risk by the identification of lymph nodes that were undetected on CT in 36% of the patients (51). Asakura *et al.* published a series describing radiotherapy planning based on FDG-PET delineation, which resulted in good therapeutic outcome without relapse in three months (52).

In addition to its utility in radiation treatment planning, FDG-PET has significant value in monitoring response to therapy and predicting outcomes for patients with lymphoma (53). Most reports concerning the use of FDG-PET in lymphoma after treatment were for monitoring chemotherapy response, and reports of monitoring radiotherapy response by FDG-PET are more limited. It is still not proven that the use of interim FDG-PET can improve patient outcomes (54); however, FDG-PET may have a role in determining prognosis for treated patients. Keller *et al.* reported that using weekly FDG-PET imaging during radiotherapy for non-Hodgkin's lymphoma showed that smaller initial tumor volume and late metabolic and volumetric response (after completion of radiation therapy) correlated well to eventual local control, whereas pretreatment FDG uptake and GTV volumes showed large variability and were not correlated with eventual response (55). In our own experience, FDG-PET imaging of a 32 year old male patient with stage IIIB nodular sclerosing Hodgkin's disease had very poor response to chemotherapy, but good response to radiation treatment. Initially, this patient received chemotherapy protocol of ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) $\times$ 8 cycles with continued PET positive disease in mediastinum; then he received reinduction with ICE (ifosfamide, carboplatin and etoposide) chemotherapy, which still left PET positive disease in same region. Finally, the patient was treated with radiation to the mediastinum followed by high dose chemotherapy with autologous stem cell rescue. Four months post radiation therapy and stem cell transplant FDG-PET/CT imaging showed significant therapy response; the focus in the pre-radiation therapy PET imaging was decreased in four month post-radiotherapy PET imaging (Figure 5A–B). The mild increase in FDG uptake that remained was felt to represent some diffuse inflammation caused by radiotherapy (Figure 5B).

In brief, the addition of FDG-PET information could improve the accurate delivery of radiation therapy in patients with Hodgkin's and non-Hodgkin's lymphoma, but to date there are no reports that have described correlation with disease outcomes. Additionally, in Hodgkin's disease, FDG-PET is essential for determining the extent of involved-field irradiation and leads to increased irradiation volumes while also decreasing geographic miss.

Brain tumors

Brain tumors include all tumors that arise inside the cranium, especially gliomas, which are inherently serious and life-threatening because of their invasive and infiltrative character in

the limited space of the intracranial cavity. Surgery, chemotherapy, and radiotherapy are the main treatment modalities for gliomas. Radiotherapy as a primary treatment modality is mainly reserved for the inoperable cases; however, radiation therapy is often employed in an adjuvant setting, particularly if there is residual tumor left behind after surgical resection. Normal brain cells consume large amounts of glucose due to their high metabolic demand; therefore, FDG-PET alone is not suitable for brain tumor evaluation. Multimodality images including MRI or CT and FDG-PET are essential for accurate evaluation of brain tumors. However, due to increased proliferation and protein synthesis, brain tumors also have increased amino acid uptake and up-regulated amino acid transporters. Radiolabeled amino acid and its analogs are a class of tumor imaging agents that may be more suitable for tumors with high FDG background imaging.

Most studies of the natural amino acids as PET tracers were performed using ^{11}C -labeled amino acids. The most prominent example is PET scanning with ^{11}C -labeled methionine (MET-PET). MET-PET has been used in the clinical management of cerebral gliomas for initial diagnosis, differentiation of tumor recurrence versus treatment effect, grading, prognostication, tumor extent delineation after biopsy/surgical resection or for radiotherapy planning, and assessment of response to therapy (56). MET-PET shows promising results in the detection and delineation of viable tumor, especially in low-grade gliomas. MET-PET is reported to be superior to CT alone, FDG-PET and ^{18}F -labeled fluorothymidine (FLT)-PET in delineating low grade gliomas (57, 58). In high grade gliomas, use of the ^{11}C -MET tracer results in PET images that increased the size of the GTV obtained by more standard approaches in patients treated with radiation therapy (59); furthermore, treatment planning using MET-PET-based tumor delineation versus CT/MRI images was associated with an improvement in survival (60, 61). In tumor delineation of meningiomas, MET-PET also led to a significant increase in the size of the GTV (Figure 6) (62). In addition, the high sensitivity of PET can further modify the planning target volume by, for instance, identifying some tumors not seen with CT/MRI, but visible in PET imaging. ^{11}C -labeled tyrosine (TYR) was reported to monitor protein synthesis rate in pituitary adenoma pre- and post-radiotherapy and showed great decrease in TYR accumulation after radiotherapy (63). However, due to the short half life of carbon-11, fluorine-18 labeled radiotracers are more preferred. ^{18}F -labeled 1-amino-3-fluomcyclobutane-1-carboxylic acid (FACBC), an unnatural amino acid, is in the clinical trial stage for brain tumor imaging. ^{18}F -FACBC PET was performed on a patient with residual glioblastoma multiforme and showed intense uptake in the left frontal region of the brain with very clear background one week after surgery, while 8 weeks after surgery FDG-PET scan also showed the residual tumor with high normal brain uptake (64).

In summary, PET imaging with radiolabeled amino acid ^{11}C -MET or other tracers in clinical trials, such as ^{18}F -FACBC, ^{18}F -FLT, and radiolabeled choline, are good options for functional imaging in brain tumor radiotherapy planning (2).

Prostate Cancers

Prostate cancer is an age-related disease and is most common in men age 65 and older. Approximately 1 in 6 males will be diagnosed with prostate cancer in their lifetime, making this the most common non-cutaneous malignancy among men in the United States. The natural history of prostate cancer is very slow and typically, patients with early stage disease will be asymptomatic. However, advanced stage prostate cancer with metastasis is life-threatening. Hormonal therapy, surgery and radiotherapy are the mainstays of prostate cancer treatment. For radiation therapy planning in prostate cancer patients, accurate mapping of the primary tumor, lymph nodes and possible distant metastatic sites is critical for delivering an effective treatment while minimizing treatment-associated morbidity. Due

to the low glucose metabolism of prostate cancer cells and due the physiologic urinary excretion of glucose that may interfere with imaging of the pelvis, FDG-PET has limitations in prostate cancer imaging. Given these limitations, the role of ^{11}C -choline-PET/CT is under investigation for target volume selection and delineation for radiation therapy of both primary and recurrent prostate cancers (11, 65).

The primary imaging tools to evaluate prostate cancer are ultrasound (US), CT and MRI. ^{11}C -choline-PET/CT is not suitable for the initial diagnosis of prostate cancer due to the fact that prostate cancer is often characterized by multiple foci that may be smaller than PET spatial resolution (approximately 5 mm). Furthermore, the low ^{11}C -choline-PET/CT accuracy in lymph nodal staging of prostate cancer makes it inappropriate to plan target volumes in the lymph nodes (66). However, ^{11}C -choline-PET/CT presents high values of sensitivity and specificity in detecting distant recurrent sites of the disease, especially at the level of lymph nodes (67–69). In radiotherapy planning, ^{11}C -choline-PET/CT may be considered to select and delineate target volumes at recurrent sites in lymph nodes.

In addition to ^{11}C -choline, ^{11}C -acetate (ACE) is also potentially a valuable PET tracer for imaging prostate cancer. ACE-PET has been studied for imaging both primary and metastatic sites in prostate cancer patients (70–72). The role of ^{11}C -acetate in image guidance for radiotherapy planning has been evaluated in patients with intra-capsular prostate carcinoma with promising results (73). The major limitation of ^{11}C -labeled tracers is the relatively short half-life of ^{11}C (approximately 20 minutes). Therefore, this presents difficulties for use in facilities without an on-site cyclotron. This limitation can be overcome by using longer half-life radioisotopes. For instance, ^{18}F -choline behaves in a similar manner to ^{11}C -choline in prostate cancer patients but has a much longer half life (approximately 110 minutes). Despite its advantages, however, ^{18}F -choline is subject to a high rate of urinary elimination, which presents significant challenges in imaging the pelvis. (74). In studies of radiotherapy dose escalation, ^{18}F -choline has been used to delineate gross tumor volume and to generate the planning target volume in patients with intra-prostatic lesions while attempting to reduce radiation dose to the bladder and the rectum (75). However, data are still limited to establish the role of ^{18}F -choline in radiotherapy planning.

In addition to the aforementioned substances, the radiolabeled amino acid analog anti-1-amino-3- ^{18}F -fluorocyclobutyl-1-carboxylic acid (anti- ^{18}F -FACBC) has shown promising results in diagnosing primary and recurrent prostate cancers (76–79). FACBC-PET is believed to be useful not only for the detection of prostate cancer but also for differentiating prostate cancer from inflammation and benign prostatic hyperplasia. Though FACBC has not been evaluated for radiotherapy planning to date, given its ability to differentiate cancer from some benign processes, it may have a role in planning prostate cancer radiotherapy.

In conclusion, limited data are currently available on the role of ^{11}C -choline-, ^{11}C -acetate- and ^{18}F -choline-PET/CT in target volume selection and delineation. According to the available literature, ^{11}C -choline-PET/CT is not clinically recommended to plan the target volume for either primary prostate treatment or for local recurrence. Nevertheless, promising data suggest a potential role of ^{11}C -choline PET/CT as an image guide tool for the irradiation of prostate cancer relapse. Anti- ^{18}F -FACBC may become a useful tool in prostate cancer radiotherapy planning based on promising results in prostate cancer imaging.

Conclusion

FDG-PET plays an increasingly important role in radiotherapy that goes beyond staging and selection of patients. Especially for NSCLC, FDG-PET has led to the safe decrease of radiotherapy volumes, enabling radiation dose escalation and, experimentally, redistribution

of radiation doses within the tumor, along with playing a significant role in monitoring radiotherapy response. FDG-PET can provide important complementary information for radiotherapy planning in head and neck cancer. In breast cancer, the greatest clinical applications of FDG-PET are in the detection and definition of the extent of recurrent or metastatic disease. In esophageal cancer, the main advantage of FDG-PET is the detection of unrecognized lymph node metastases. In lymphoma, FDG-PET is essential for involved-nodal irradiation and leads to decreased irradiation volumes while also decreasing geographic misses. In brain tumors, the role of functional imaging in radiotherapy planning is limited; however, ^{11}C -MET may play an increasingly important role in radiation planning in the future. In prostate cancer, ^{11}C -choline may have a potential role for recurrent prostate cancer radiotherapy planning. The role of anti- ^{18}F -FACBC in the radiotherapy management of prostate cancer may emerge in the near future.

Currently, besides for staging/restaging purposes, PET/CT is only playing a complementary role to other modalities such as CT and MRI for target volume delineation in radiotherapy. Standardized protocols should be established to better define what role PET and/or PET/CT scans should play in radiotherapy planning.

Acknowledgments

This study was supported by NIH P50 CA 128301-0002 (Shim, H.). We are grateful to Ms. Jessica Paulishen for careful reading of the manuscript and helpful remarks.

References

1. Gregoire V, Haustermans K, Geets X, Roels S, Lonnew M. PET-based treatment planning in radiotherapy: a new standard? *J Nucl Med.* Jan; 2007 48(Suppl 1):68S–77S. [PubMed: 17204722]
2. Zhu A, Lee D, Shim H. Metabolic positron emission tomography imaging in cancer detection and therapy response. *Semin Oncol.* Feb; 2011 38(1):55–69. [PubMed: 21362516]
3. Ford EC, Herman J, Yorke E, Wahl RL. ^{18}F -FDG PET/CT for image-guided and intensity-modulated radiotherapy. *J Nucl Med.* Oct; 2009 50(10):1655–65. [PubMed: 19759099]
4. Lammering G, De Ruyscher D, van Baardwijk A, Baumert BG, Borger J, Lutgens L, van den Ende P, Ollers M, Lambin P. The use of FDG-PET to target tumors by radiotherapy. *Strahlenther Onkol.* Sep; 2010 186(9):471–81. [PubMed: 20814658]
5. Daisne JF, Duprez T, Weynand B, Lonnew M, Hamoir M, Reychler H, Gregoire V. Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. *Radiology.* Oct; 2004 233(1):93–100. [PubMed: 15317953]
6. Strauss LG. Fluorine-18 deoxyglucose and false-positive results: a major problem in the diagnostics of oncological patients. *Eur J Nucl Med.* Oct; 1996 23(10):1409–15. [PubMed: 8781149]
7. Liu RS, Chang CP, Chu LS, Chu YK, Hsieh HJ, Chang CW, Yang BH, Yen SH, Huang MC, Liao SQ, Yeh SH. PET imaging of brain astrocytoma with 1- ^{11}C -acetate. *Eur J Nucl Med Mol Imaging.* Apr; 2006 33(4):420–7. [PubMed: 16404596]
8. Higashi K, Ueda Y, Matsunari I, Kodama Y, Ikeda R, Miura K, Taki S, Higuchi T, Tonami H, Yamamoto I. ^{11}C -acetate PET imaging of lung cancer: comparison with ^{18}F -FDG PET and $^{99\text{m}}\text{Tc}$ -MIBI SPET. *Eur J Nucl Med Mol Imaging.* Jan; 2004 31(1):13–21. [PubMed: 14574513]
9. Dimitrakopoulou-Strauss A, Strauss LG. PET imaging of prostate cancer with ^{11}C -acetate. *J Nucl Med.* Apr; 2003 44(4):556–8. [PubMed: 12679399]
10. Sun A, Sorensen J, Karlsson M, Turesson I, Langstrom B, Nilsson P, Cederblad L, Bertling J, Riklund K, Johansson S. 1- ^{11}C -acetate PET imaging in head and neck cancer--a comparison with ^{18}F -FDG-PET: implications for staging and radiotherapy planning. *Eur J Nucl Med Mol Imaging.* May; 2007 34(5):651–7. [PubMed: 17146654]
11. Picchio M, Giovannini E, Crivellaro C, Gianolli L, di Muzio N, Messa C. Clinical evidence on PET/CT for radiation therapy planning in prostate cancer. *Radiother Oncol.* Sep; 2010 96(3):347–50. [PubMed: 20708811]

12. Cosentino C, Grieco D, Costanzo V. ATM activates the pentose phosphate pathway promoting anti-oxidant defence and DNA repair. *EMBO J.* Feb 2; 2011 30(3):546–55. [PubMed: 21157431]
13. Haubner R. PET radiopharmaceuticals in radiation treatment planning - synthesis and biological characteristics. *Radiother Oncol.* Sep; 2010 96(3):280–7. [PubMed: 20724013]
14. Oyen WJ, Bussink J, Verhagen AF, Corstens FH, Bootsma GP. Role of FDG-PET in the diagnosis and management of lung cancer. *Expert Rev Anticancer Ther.* Aug; 2004 4(4):561–7. [PubMed: 15270660]
15. Pommier P, Touboul E, Chabaud S, Dussart S, Le Pechoux C, Giammarile F, Carrie C. Impact of ^{18}F -FDG PET on treatment strategy and 3D radiotherapy planning in non-small cell lung cancer: A prospective multicenter study. *AJR Am J Roentgenol.* Aug; 2010 195(2):350–5. [PubMed: 20651189]
16. Greco C, Rosenzweig K, Cascini GL, Tamburrini O. Current status of PET/CT for tumour volume definition in radiotherapy treatment planning for non-small cell lung cancer (NSCLC). *Lung Cancer.* Aug; 2007 57(2):125–34. [PubMed: 17478008]
17. Faria SL, Menard S, Devic S, Sirois C, Souhami L, Lisbona R, Freeman CR. 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.* Mar 15; 2008 70(4):1035–8. [PubMed: 17996383]
18. Mah K, Caldwell CB, Ung YC, Danjoux CE, Balogh JM, Ganguli SN, Ehrlich LE, Tirona R. The impact of ^{18}F -FDG-PET on target and critical organs in CT-based treatment planning of patients with poorly defined non-small-cell lung carcinoma: a prospective study. *Int J Radiat Oncol Biol Phys.* Feb 1; 2002 52(2):339–50. [PubMed: 11872279]
19. Steenbakkers RJ, Duppen JC, Fitton I, Deurloo KE, Zijp LJ, Comans EF, Uitterhoeve AL, Rodrigus PT, Kramer GW, Bussink J, De Jaeger K, Belderbos JS, Nowak PJ, van Herk M, Rasch CR. Reduction of observer variation using matched CT-PET for lung cancer delineation: a three-dimensional analysis. *Int J Radiat Oncol Biol Phys.* Feb 1; 2006 64(2):435–48. [PubMed: 16198064]
20. Ishimori T, Saga T, Nagata Y, Nakamoto Y, Higashi T, Mamede M, Mukai T, Negoro Y, Aoki T, Hiraoka M, Konishi J. ^{18}F -FDG and ^{11}C -methionine PET for evaluation of treatment response of lung cancer after stereotactic radiotherapy. *Ann Nucl Med.* Dec; 2004 18(8):669–74. [PubMed: 15682847]
21. Hicks RJ, Mac Manus MP, Matthews JP, Hogg A, Binns D, Rischin D, Ball DL, Peters LJ. Early FDG-PET imaging after radical radiotherapy for non-small-cell lung cancer: inflammatory changes in normal tissues correlate with tumor response and do not confound therapeutic response evaluation. *Int J Radiat Oncol Biol Phys.* Oct 1; 2004 60(2):412–8. [PubMed: 15380574]
22. Mac Manus MP, Hicks RJ, Matthews JP, Wirth A, Rischin D, Ball DL. Metabolic (FDG-PET) response after radical radiotherapy/chemoradiotherapy for non-small cell lung cancer correlates with patterns of failure. *Lung Cancer.* Jul; 2005 49(1):95–108. [PubMed: 15949595]
23. Wong RJ. Current status of FDG-PET for head and neck cancer. *J Surg Oncol.* Jun 15; 2008 97(8):649–52. [PubMed: 18493944]
24. Dandekar P, Partridge M, Kazi R, Nutting C, Harrington K, Newbold K. Challenges in integrating ^{18}F -FDG PET-CT into radiotherapy planning of head and neck cancer. *Indian J Cancer.* Jul-Sep; 2010 47(3):260–6. [PubMed: 20587900]
25. Gregoire V, Bol A, Geets X, Lee J. Is PET-based treatment planning the new standard in modern radiotherapy? The head and neck paradigm. *Semin Radiat Oncol.* Oct; 2006 16(4):232–8. [PubMed: 17010906]
26. Troost EG, Schinagel DA, Bussink J, Boerman OC, van der Kogel AJ, Oyen WJ, Kaanders JH. Innovations in radiotherapy planning of head and neck cancers: role of PET. *J Nucl Med.* Jan; 2010 51(1):66–76. [PubMed: 20009000]
27. Guido A, Fuccio L, Rombi B, Castellucci P, Cecconi A, Bunkheila F, Fuccio C, Spezi E, Angelini AL, Barbieri E. Combined ^{18}F -FDG-PET/CT imaging in radiotherapy target delineation for head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* Mar 1; 2009 73(3):759–63. [PubMed: 18834671]

28. Newbold KL, Partridge M, Cook G, Sharma B, Rhys-Evans P, Harrington KJ, Nutting CM. Evaluation of the role of ^{18}F FDG-PET/CT in radiotherapy target definition in patients with head and neck cancer. *Acta Oncol.* 2008; 47(7):1229–36. [PubMed: 18661420]
29. Deantonio L, Beldi D, Gambaro G, Loi G, Brambilla M, Inglese E, Krengli M. FDG PET/CT imaging for staging and radiotherapy treatment planning of head and neck carcinoma. *Radiat Oncol.* 2008; 3:29. [PubMed: 18801181]
30. Moule RN, Kayani I, Moinuddin SA, Meer K, Lemon C, Goodchild K, Saunders MI. The potential advantages of ^{18}F FDG PET/CT-based target volume delineation in radiotherapy planning of head and neck cancer. *Radiother Oncol.* Nov; 2010 97(2):189–93. [PubMed: 20570004]
31. Ciernik IF, Dizendorf E, Baumert BG, Reiner B, Burger C, Davis JB, Lutolf UM, Steinert HC, Von Schulthess GK. Radiation treatment planning with an integrated positron emission and computer tomography (PET/CT): a feasibility study. *Int J Radiat Oncol Biol Phys.* Nov 1; 2003 57(3):853–63. [PubMed: 14529793]
32. Sun A, Johansson S, Turesson I, Dasu A, Sorensen J. Imaging Tumor Perfusion and Oxidative Metabolism in Patients with Head-and-neck Cancer using 1- [^{11}C]-acetate PET during Radiotherapy: Preliminary Results. *Int J Radiat Oncol Biol Phys.* Jan 13.2011
33. Kitagawa Y, Sano K, Nishizawa S, Nakamura M, Ogasawara T, Sadato N, Yonekura Y. FDG-PET for prediction of tumour aggressiveness and response to intra-arterial chemotherapy and radiotherapy in head and neck cancer. *Eur J Nucl Med Mol Imaging.* Jan; 2003 30(1):63–71. [PubMed: 12483411]
34. Farrag A, Ceulemans G, Voordeckers M, Everaert H, Storme G. Can ^{18}F -FDG-PET response during radiotherapy be used as a predictive factor for the outcome of head and neck cancer patients? *Nucl Med Commun.* Jun; 2010 31(6):495–501. [PubMed: 20351599]
35. Ford EC, Lavelly WC, Frassica DA, Myers LT, Asrari F, Wahl RL, Zellars RC. Comparison of FDG-PET/CT and CT for delineation of lumpectomy cavity for partial breast irradiation. *Int J Radiat Oncol Biol Phys.* Jun 1; 2008 71(2):595–602. [PubMed: 18394814]
36. Hathaway PB, Mankoff DA, Maravilla KR, Austin-Seymour MM, Ellis GK, Gralow JR, Cortese AA, Hayes CE, Moe RE. Value of combined FDG PET and MR imaging in the evaluation of suspected recurrent local-regional breast cancer: preliminary experience. *Radiology.* Mar; 1999 210(3):807–14. [PubMed: 10207485]
37. Rohren EM, Turkington TG, Coleman RE. Clinical applications of PET in oncology. *Radiology.* May; 2004 231(2):305–32. [PubMed: 15044750]
38. Moureau-Zabotto L, Touboul E, Lerouge D, Deniaud-Alexandre E, Grahek D, Foulquier JN, Petenief Y, Gres B, El Balaa H, Kerrou K, Montravers F, Keraudy K, Tiret E, Gendre JP, Grange JD, Hourry S, Talbot JN. [Impact of computed tomography (CT) and ^{18}F -deoxyglucose positron emission tomography (FDG-PET) image fusion for conformal radiotherapy in esophageal carcinoma]. *Cancer Radiother.* May; 2005 9(3):152–60. [PubMed: 16023043]
39. Vrieze O, Haustermans K, De Wever W, Lerut T, Van Cutsem E, Ectors N, Hiele M, Flamen P. Is there a role for FGD-PET in radiotherapy planning in esophageal carcinoma? *Radiother Oncol.* Dec; 2004 73(3):269–75. [PubMed: 15588870]
40. Zhong X, Yu J, Zhang B, Mu D, Zhang W, Li D, Han A, Song P, Li H, Yang G, Kong FM, Fu Z. Using ^{18}F -fluorodeoxyglucose positron emission tomography to estimate the length of gross tumor in patients with squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys.* Jan 1; 2009 73(1):136–41. [PubMed: 18538492]
41. Han D, Yu J, Yu Y, Zhang G, Zhong X, Lu J, Yin Y, Fu Z, Mu D, Zhang B, He W, Huo Z, Liu X, Kong L, Zhao S, Sun X. Comparison of ^{18}F -fluorothymidine and ^{18}F -fluorodeoxyglucose PET/CT in delineating gross tumor volume by optimal threshold in patients with squamous cell carcinoma of thoracic esophagus. *Int J Radiat Oncol Biol Phys.* Mar 15; 2010 76(4):1235–41. [PubMed: 19910143]
42. Schreurs LM, Busz DM, Paardekooper GM, Beukema JC, Jager PL, Van der Jagt EJ, van Dam GM, Groen H, Plukker JT, Langendijk JA. Impact of 18-fluorodeoxyglucose positron emission tomography on computed tomography defined target volumes in radiation treatment planning of esophageal cancer: reduction in geographic misses with equal inter-observer variability: PET/CT improves esophageal target definition. *Dis Esophagus.* Aug; 2010 23(6):493–501. [PubMed: 20113320]

43. Muijs CT, Beukema JC, Pruim J, Mul VE, Groen H, Plukker JT, Langendijk JA. A systematic review on the role of FDG-PET/CT in tumour delineation and radiotherapy planning in patients with esophageal cancer. *Radiother Oncol*. Nov; 2010 97(2):165–71. [PubMed: 20541273]
44. Arslan N, Miller TR, Dehdashti F, Battafarano RJ, Siegel BA. Evaluation of response to neoadjuvant therapy by quantitative 2-deoxy-2-[¹⁸F]fluoro-D-glucose with positron emission tomography in patients with esophageal cancer. *Mol Imaging Biol*. Jul; 2002 4(4):301–10. [PubMed: 14537121]
45. Kwee RM. Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of ¹⁸F FDG PET: a systematic review. *Radiology*. Mar; 2010 254(3):707–17. [PubMed: 20177086]
46. Ngamruengphong S, Sharma VK, Nguyen B, Das A. Assessment of response to neoadjuvant therapy in esophageal cancer: an updated systematic review of diagnostic accuracy of endoscopic ultrasonography and fluorodeoxyglucose positron emission tomography. *Dis Esophagus*. Apr; 2010 23(3):216–31. [PubMed: 19515185]
47. Ferme C, Eghbali H, Meerwaldt JH, Rieux C, Bosq J, Berger F, Girinsky T, Brice P, van't Veer MB, Walewski JA, Lederlin P, Tirelli U, Carde P, Van den Neste E, Gyan E, Monconduit M, Divine M, Raemaekers JM, Salles G, Noordijk EM, Creemers GJ, Gabarre J, Hagenbeek A, Reman O, Blanc M, Thomas J, Vie B, Kluin-Nelemans JC, Viseu F, Baars JW, Poortmans P, Lugtenburg PJ, Carrie C, Jaubert J, Henry-Amar M. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med*. Nov 8; 2007 357(19):1916–27. [PubMed: 17989384]
48. Divgi C. Imaging: staging and evaluation of lymphoma using nuclear medicine. *Semin Oncol*. Feb; 2005 32(1 Suppl 1):S11–8. [PubMed: 15786021]
49. Kazama T, Faria SC, Varavithya V, Phongkitkarun S, Ito H, Macapinlac HA. FDG PET in the evaluation of treatment for lymphoma: clinical usefulness and pitfalls. *Radiographics*. Jan-Feb; 2005 25(1):191–207. [PubMed: 15653595]
50. Hutchings M, Loft A, Hansen M, Berthelsen AK, Specht L. Clinical impact of FDG-PET/CT in the planning of radiotherapy for early-stage Hodgkin lymphoma. *Eur J Haematol*. Mar; 2007 78(3):206–12. [PubMed: 17253974]
51. Girinsky T, Ghalibafian M, Bonniaud G, Bayla A, Magne N, Ferreira I, Lumbroso J. Is FDG-PET scan in patients with early stage Hodgkin lymphoma of any value in the implementation of the involved-node radiotherapy concept and dose painting? *Radiother Oncol*. Nov; 2007 85(2):178–86. [PubMed: 17719110]
52. Asakura H, Togami T, Mitani M, Takashima H, Yokoe K, Yamamoto Y, Nishiyama Y, Monden T, Toyama Y, Ohkawa M. Usefulness of FDG-PET imaging for the radiotherapy treatment planning of pyothorax-associated lymphoma. *Ann Nucl Med*. Dec; 2005 19(8):725–8. [PubMed: 16445000]
53. Yao H, Cen XN, Liang ZY, Ou JP, Qiu ZX, Wang WS, Xu WL, Li Y, Yin Y, Wang MJ, Dong YJ, Wang LH, Ren HY. Application of SPECT/PET to 70 patients with lymphoma: monitoring response to therapy. *Zhonghua Xue Ye Xue Za Zhi*. Oct; 2010 31(10):667–70. [PubMed: 21223716]
54. Hutchings M, Barrington SF. PET/CT for therapy response assessment in lymphoma. *J Nucl Med*. May; 2009 50(Suppl 1):21S–30S. [PubMed: 19380407]
55. Keller H, Goda JS, Vines DC, Lockwood G, Tsang R. Quantification of local tumor response to fractionated radiation therapy for non-Hodgkin lymphoma using weekly ¹⁸F-FDG PET/CT imaging. *Int J Radiat Oncol Biol Phys*. Mar 1; 2010 76(3):850–8. [PubMed: 19515502]
56. Singhal T, Narayanan TK, Jain V, Mukherjee J, Mantil J. ¹¹C-L-methionine positron emission tomography in the clinical management of cerebral gliomas. *Mol Imaging Biol*. Jan-Feb; 2008 10(1):1–18. [PubMed: 17957408]
57. Jacobs AH, Thomas A, Kracht LW, Li H, Dittmar C, Garlip G, Galldiks N, Klein JC, Sobesky J, Hilker R, Vollmar S, Herholz K, Wienhard K, Heiss WD. ¹⁸F-fluoro-L-thymidine and ¹¹C-methylmethionine as markers of increased transport and proliferation in brain tumors. *J Nucl Med*. Dec; 2005 46(12):1948–58. [PubMed: 16330557]
58. Kaschten B, Stevenaert A, Sadzot B, Deprez M, Deguelldre C, Del Fiore G, Luxen A, Reznik M. Preoperative evaluation of 54 gliomas by PET with fluorine-18-fluorodeoxyglucose and/or carbon-11-methionine. *J Nucl Med*. May; 1998 39(5):778–85. [PubMed: 9591574]

59. Miwa K, Shinoda J, Yano H, Okumura A, Iwama T, Nakashima T, Sakai N. Discrepancy between lesion distributions on methionine PET and MR images in patients with glioblastoma multiforme: insight from a PET and MR fusion image study. *J Neurol Neurosurg Psychiatry*. Oct; 2004 75(10): 1457–62. [PubMed: 15377696]
60. Grosu AL, Weber WA, Franz M, Stark S, Piert M, Thamm R, Gumprecht H, Schwaiger M, Molls M, Nieder C. Reirradiation of recurrent high-grade gliomas using amino acid PET (SPECT)/CT/MRI image fusion to determine gross tumor volume for stereotactic fractionated radiotherapy. *Int J Radiat Oncol Biol Phys*. Oct 1; 2005 63(2):511–9. [PubMed: 16168843]
61. Grosu AL, Weber WA, Riedel E, Jeremic B, Nieder C, Franz M, Gumprecht H, Jaeger R, Schwaiger M, Molls M. L-(methyl-¹¹C) methionine positron emission tomography for target delineation in resected high-grade gliomas before radiotherapy. *Int J Radiat Oncol Biol Phys*. Sep 1; 2005 63(1):64–74. [PubMed: 16111573]
62. Grosu AL, Weber WA, Astner ST, Adam M, Krause BJ, Schwaiger M, Molls M, Nieder C. ¹¹C-methionine PET improves the target volume delineation of meningiomas treated with stereotactic fractionated radiotherapy. *Int J Radiat Oncol Biol Phys*. Oct 1; 2006 66(2):339–44. [PubMed: 16765533]
63. van den Bergh AC, Pruim J, Links TP, van der Vliet AM, Sluiter W, Wolffenbuttel BH, Langendijk JA, Hoving EW, Dullaart RP. Tyrosine positron emission tomography and protein synthesis rate in pituitary adenoma: different effects of surgery and radiation therapy. *Radiother Oncol*. Feb; 2011 98(2):213–6. [PubMed: 21296442]
64. Shoup TM, Olson J, Hoffman JM, Votaw J, Eshima D, Eshima L, Camp VM, Stabin M, Votaw D, Goodman MM. Synthesis and evaluation of [¹⁸F]1-amino-3-fluorocyclobutane-1-carboxylic acid to image brain tumors. *J Nucl Med*. Feb; 1999 40(2):331–8. [PubMed: 10025843]
65. Chiti A, Picchio M. The rising PET: the increasing use of choline PET/CT in prostate cancer. *Eur J Nucl Med Mol Imaging*. Jan; 2011 38(1):53–4. [PubMed: 21103870]
66. Schiavina R, Scattoni V, Castellucci P, Picchio M, Corti B, Briganti A, Franceschelli A, Sanguedolce F, Bertaccini A, Farsad M, Giovacchini G, Fanti S, Grigioni WF, Fazio F, Montorsi F, Rigatti P, Martorana G. ¹¹C-choline positron emission tomography/computerized tomography for preoperative lymph-node staging in intermediate-risk and high-risk prostate cancer: comparison with clinical staging nomograms. *Eur Urol*. Aug; 2008 54(2):392–401. [PubMed: 18456393]
67. Rinnab L, Simon J, Hautmann RE, Cronauer MV, Hohl K, Buck AK, Reske SN, Mottaghy FM. [¹¹C]choline PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy. *World J Urol*. Oct; 2009 27(5):619–25. [PubMed: 19234708]
68. Fuccio C, Castellucci P, Schiavina R, Santi I, Allegri V, Pettinato V, Boschi S, Martorana G, Al-Nahhas A, Rubello D, Fanti S. Role of ¹¹C-choline PET/CT in the restaging of prostate cancer patients showing a single lesion on bone scintigraphy. *Ann Nucl Med*. Jul; 2010 24(6):485–92. [PubMed: 20544323]
69. Tuncel M, Souvatzoglou M, Herrmann K, Stollfuss J, Schuster T, Weirich G, Wester HJ, Schwaiger M, Krause BJ. [¹¹C]Choline positron emission tomography/computed tomography for staging and restaging of patients with advanced prostate cancer. *Nucl Med Biol*. Aug; 2008 35(6): 689–95. [PubMed: 18678354]
70. Oyama N, Miller TR, Dehdashti F, Siegel BA, Fischer KC, Michalski JM, Kibel AS, Andriole GL, Picus J, Welch MJ. ¹¹C-acetate PET imaging of prostate cancer: detection of recurrent disease at PSA relapse. *J Nucl Med*. Apr; 2003 44(4):549–55. [PubMed: 12679398]
71. Soloviev D, Fini A, Chierichetti F, Al-Nahhas A, Rubello D. PET imaging with ¹¹C-acetate in prostate cancer: a biochemical, radiochemical and clinical perspective. *Eur J Nucl Med Mol Imaging*. May; 2008 35(5):942–9. [PubMed: 18338167]
72. Morris MJ, Scher HI. ¹¹C-acetate PET imaging in prostate cancer. *Eur J Nucl Med Mol Imaging*. Feb; 2007 34(2):181–4. [PubMed: 17238014]
73. Seppala J, Seppanen M, Arponen E, Lindholm P, Minn H. Carbon-11 acetate PET/CT based dose escalated IMRT in prostate cancer. *Radiother Oncol*. Nov; 2009 93(2):234–40. [PubMed: 19766336]

74. Husarik DB, Miralbell R, Dubs M, John H, Giger OT, Gelet A, Cservenyak T, Hany TF. Evaluation of [^{18}F]-choline PET/CT for staging and restaging of prostate cancer. *Eur J Nucl Med Mol Imaging*. Feb; 2008 35(2):253–63. [PubMed: 17926036]
75. Weber DC, Wang H, Cozzi L, Dipasquale G, Khan HG, Ratib O, Rouzaud M, Veas H, Zaidi H, Miralbell R. RapidArc, intensity modulated photon and proton techniques for recurrent prostate cancer in previously irradiated patients: a treatment planning comparison study. *Radiat Oncol*. 2009; 4:34. [PubMed: 19740429]
76. Schuster DM, Savir-Baruch B, Nieh PT, Master VA, Halkar RK, Rossi PJ, Lewis MM, Nye JA, Yu W, Bowman FD, Goodman MM. Detection of Recurrent Prostate Carcinoma with anti-1-Amino-3- ^{18}F -Fluorocyclobutane-1-Carboxylic Acid PET/CT and ^{111}In -Capromab Pendetide SPECT/CT. *Radiology*. Jun; 2011 259(3):852–61. [PubMed: 21493787]
77. Savir-Baruch B, Schuster DM, Jarkas N, Master VA, Nieh PT, Halkar RK, Nye JA, Lewis MM, Crowe RJ, Voll RJ, Camp VM, Bellamy LM, Roberts DL, Goodman MM. Pilot Evaluation of Anti-1-amino-2- ^{18}F fluorocyclopentane-1-carboxylic acid (anti-2- ^{18}F FACPC) PET-CT in Recurrent Prostate Carcinoma. *Mol Imaging Biol*. Oct 26.2010 DOI: 10.1007/s11307-010-0445-3.
78. Schuster DM, Votaw JR, Nieh PT, Yu W, Nye JA, Master V, Bowman FD, Issa MM, Goodman MM. Initial experience with the radiotracer anti-1-amino-3- ^{18}F -fluorocyclobutane-1-carboxylic acid with PET/CT in prostate carcinoma. *J Nucl Med*. Jan; 2007 48(1):56–63. [PubMed: 17204699]
79. Oka S, Hattori R, Kurosaki F, Toyama M, Williams LA, Yu W, Votaw JR, Yoshida Y, Goodman MM, Ito O. A preliminary study of anti-1-amino-3- ^{18}F -fluorocyclobutyl-1-carboxylic acid for the detection of prostate cancer. *J Nucl Med*. Jan; 2007 48(1):46–55. [PubMed: 17204698]

Fig. 1.

A 73 year old female patient with stage IIIA NSCLC. **A**, Axial image of CT alone under mediastinal windowing; **B**, Axial image of integrated PET/CT under mediastinal windowing; **C**, Axial image of CT alone under lung windowing; **D**, Axial image of integrated PET/CT under lung windowing. PET autocapture includes areas of SUV>5 in primary RLL lesion & R paratracheal lymph node. Patient was treated on protocol with carboplatin/taxol + cetuximab with 3D conformal RT to 74 Gy.

Fig. 2. Contour of right lung cancer according to computed tomography (CT) scan (Right). Fusion of positron emission tomography (PET) and CT of same tumor, at same level, but with gross tumor volume (GTV) according to PET (Left). The Difference between both GTVs was >30%.

Fig. 3. FDG-PET/CT imaging of a 62 year old male with T2N2b squamous cell carcinoma of L base of tongue. **A**, Axial image of CT alone; **B**, Axial image of integrated PET/CT; **C**, Sagittal image of integrated PET/CT; **D**, Coronal image of integrated PET/CT. PET contour shows area within VOI with SUV>7 in primary tumor and left level IIA lymph nodes. Pt treated with IMRT to 57 Gy to low risk nodal regions, 63 Gy to high risk nodal regions and 70 Gy to PET avid disease>7 SUV 5mm.

Fig. 4.

A 56 year old female with infiltrating ductal carcinoma of the right breast developed a right internal mammary node (IMN) recurrence 2 ½ years after initial therapy. **A**, Axial image of CT alone; **B**, Axial image of integrated PET/CT with mediastinal windowing is shown with PET positive node; **C**, Axial CT with boost dose cloud overlay, contour around lesion is with $SUV > 5$; **D**, Axial image of integrated PET/CT 5 months after recurrence treatment. Patient was treated to the IMN chain to 45 Gy in 25 fractions and was boosted to the PET positive node with an additional 15 Gy in 3 fractions. 2nd PET obtained approximately 5 months after treatment fused onto original treatment planning CT showed complete resolution of PET positive focus.

Fig. 5.

A 32 year old male patient with stage IIIB nodular sclerosing Hodgkin's disease. Before radiation treatment, this patient received ABVD x 8 cycles with continued PET positive disease in mediastinum; then he received reinduction with ICE chemotherapy, which still left PET positive disease in same region. Finally, the patient was treated with radiation to mediastinum followed by high dose chemotherapy with autologous stem cell rescue. **A**, Axial image of FDG-PET/CT before radiotherapy; **B**, Axial image of FDG-PET/CT 4 months after treatment with radiation to mediastinum followed by high dose chemotherapy with autologous stem cell rescue. 4 months post radiation therapy and stem cell transplant FDG-PET/CT imaging showed significant therapy response. PET was windowed at same level.

Fig. 6.

Computed tomography and magnetic resonance imaging treatment planning scans of Patient 1 showing a large meningioma of the right cerebellopontine angle with brainstem compression. (A) Discordant gross tumor volumes (outlined in pink and green) based on these computed tomography/magnetic resonance imaging scans drawn by two independent observers. The infiltration of cavernous sinus is unclear (red arrow). (B) Concordant reduction of the gross tumor volume with the availability of ^{11}C -methionine positron emission tomography/magnetic resonance imaging/computed tomography image fusion.