The Use of Positron Emission Tomography Imaging to Guide Radiation Therapy

Bridget F. Koontz, MD, FASTRO[1]; and Mohit S. Kasibhatla, MD[1]

[1]Department of Radiation Oncology, Brody School of Medicine, East Carolina University, Greenville, North Carolina

Corresponding author:
Mohit S. Kasibhatla, MD
524 Moye Blvd
Vidant Radiation Oncology
Greenville, NC 27834
Tel: (252) 551-6300
Fax: (252) 329-0325
Email: KasibhatlaM19@ecu.edu

Abstract: Positron emission tomography (PET)-based biologic radiation planning has the potential to improve tumor control by improving the accuracy of radiation delivery, allow for rational adaptive treatment, and decrease the likelihood of both acute and late side effects. ^{18}F-fluorodeoxyglucose (FDG) PET is a widely used and effective diagnostic tool for many metabolically active tumors, including lymphoma and lung, head and neck, gastrointestinal, and gynecologic cancers. For these tumors, PET evidence has initially focused on more accurate staging but is evolving to allow for the escalation or deescalation of the radiotherapy dose depending on the PET-determined response to initial therapy. For gliomas and prostate cancer, novel tracers offer opportunities to improve tumor targeting of areas not well identified by traditional FDG PET. These tracers may also identify functional regions of healthy organs, allowing for more effective sparing of normal tissue.

Keywords
FDG PET, positron emission tomography, radiation therapy

Introduction

Positron emission tomography (PET)-based biologic radiation planning has the potential to (1) improve tumor control by enhancing the accuracy of radiation delivery; (2) allow for rational adaptive planning; and (3) decrease the likelihood of both acute and late side effects. Diagnostic imaging has long been used to aid in radiation therapy (RT) field design. PET offers higher-quality imaging of viable tumors and has been applied as a radiation oncology tool to improve the therapeutic index via better tumor coverage and sparing of normal tissue. As an example, in addition to delineating a site of bone metastasis, PET can be used to identify and therefore avoid active bone marrow, decreasing the risk of cytopenia during treatment.

Although most early studies incorporated ^{18}F-fluorodeoxyglucose (FDG) PET into radiation decision-making and planning, dramatic advances have occurred in the field of theranostics, with new radioactive tracers that can be used for both diagnosis and therapy. Targeted radiopharmaceuticals, such as lutetium-177 (^{177}Lu)-dotatate and ^{177}Lu prostate-specific membrane antigen (PSMA), have demonstrated benefits in patients whose disease has progressed on

first-line treatment for foregut neuroendocrine cancer and prostate cancer, respectively. These, along with other upcoming tracers, increase the utility and specificity of PET imaging.

Our goal in this review is to describe the evidence evaluating PET-based radiation treatment planning for the definitive treatment of tumors originating from various primary sites. As RT becomes more conformal and precise in its delivery, PET-based imaging modalities become increasingly valuable in the design of radiation treatment fields. Future PET tracers may identify metabolic features within a tumor that predict a lack of response or the development of resistance to treatment. Therefore, PET may be valuable in the adaptive replanning of radiation treatment or the rational addition of targeted agents to improve response and reverse resistance.

Imaging for Radiation Planning

As a local therapy, radiation planning has always required visualization of the target fields. Prior to the development of computed tomography (CT) in the 1970s, visualization of skin anatomic references and knowledge of anatomy, combined with plain films, were the backbone of treatment planning. With such crude tools, fields were often quite large to ensure coverage of the tumor. Large fields included significant amounts of adjacent healthy tissues and contributed to the toxicity burden of RT. As CT became available, followed by magnetic resonance imaging (MRI), 3-dimensional imaging of internal structures allowed much more precise delineation of the target and avoidance structures, with the concomitant smaller fields and lower toxicity burden for the same control rate. Modern radiation tumor targeting is based on gross tumor volume as determined by imaging techniques such as CT and MRI. This volume is expanded to the clinical target volume, which includes sites of possible microscopic tumor spread, and incorporates motion characteristics of the tumor in order to generate a planning target volume. The traditional goal of radiation planning is to deliver a homogeneous dose to the entire planning target volume because heterogeneity in tumor viability or radiation sensitivity is difficult to identify with conventional imaging. Additional technology that allows for the tracking of organ motion has provided the ability to reduce the size of uncertainty margins through an internal target volume, once again focusing on providing dose homogeneity within the target volume.[1]

PET offers a different type of target localization. It is coregistered with CT, thus providing a 3-dimensional anatomic reference. In addition, PET provides functional imaging by detecting glucose metabolism. Ling and colleagues originally proposed the concept of a biologic target volume, which further refines a tumor target by highlighting heterogeneity within the tumor volume. FDG PET, for example, identifies areas of higher tumor metabolism, whereas PET using 124 Iododeoxyuridine (IUdR) can identify regions of proliferation, and ^{18}F misonidazole can identify hypoxic regions, which are typically radioresistant.[2] Areas of greater tumor proliferation or hypoxia may benefit from a higher radiation dose to specific portions of the tumor. Advances in radiation technology, such as intensity-modulated RT (IMRT), have made this differential dose distribution, or "dose painting," possible.

Newer tracers, including both PSMA PET and DOTATATE PET, provide biologic characterization, including the identification of transmembrane receptors or the targeting of small molecules that are specific to a type of tumor. Biologic and functional assessment of the tumor with PET is a method of personalizing cancer care, with potential benefit from higher doses or alternate radiation schedules for tumors that exhibit more biologic activity.

In 2008, radiation oncology and nuclear medicine experts assembled by the International Atomic Energy Agency produced a report on guidelines for incorporating PET into radiation treatment planning.[3] At that time, few studies had formally evaluated PET specifically for radiation planning, but its promise to improve radiation treatment was evident via: (1) identifying lesions not appreciated on MRI or CT; (2) protecting atelectatic portions of lung uninvolved by tumor from treatment; (3) identifying heterogenous uptake within the tumor that may allow for partial tumor dose escalation to improve outcome; and (4) adapting treatment by identifying areas of metabolic response vs progression. However, realization of this promise requires formal protocols for coregistration of PET, an understanding of how to apply PET standard uptake value (SUV) activity levels to contouring a gross target volume, and the accurate incorporation of tumor motion when combining CT and PET.

Lymphoma

FDG PET has been an essential component of lymphoma staging and treatment response assessment since 2007, when the International Harmonization Project included PET as part of pretreatment staging and post-treatment assessment (Table).[4] Criteria for interim response and end-of-treatment response were created in 2014 to guide decision-making (ie, the Deauville 5-point diagnostic PET classification).[5] Because of PET's ability to distinguish between metabolically active tumor and treated residual anatomic abnormalities with no viable tumor, it has become the major factor in escalation or deescalation after

Table. Evidence-Based Uses for PET by Cancer Type

Cancer Type	Tracer	Uses
Lymphoma	FDG	Initial and posttreatment staging Allows downsized radiation fields to involved site Favorable DLBCL with PET CR may avoid RT
Small cell lung cancer	FDG	Initial and recurrence staging
Non–small cell lung cancer	FDG	Initial and recurrence staging Allows downsized radiation fields to involved node
Head and neck cancer	FDG	Initial and posttreatment staging PET CR after radiation/systemic therapy may avoid resection Study underway to evaluate ability to deescalate RT dose based on early PET response
Cervical cancer	FDG	Initial and recurrent staging Study underway to evaluate ability to reduce RT fields based on early PET response
	FAZA FETNIM ATSM	Study underway to utilize these hypoxia markers for prognostication
Gastrointestinal cancers	FDG	Initial staging
Glioma	FDOPA FET	RT treatment volume delineation
	MET	Prognostic of outcome after treatment
	FACBC	Recurrence staging versus radionecrosis
Prostate cancer	FACBC	Recurrence staging RT treatment volume planning for postoperative biochemical recurrence
	PSMA	Initial and recurrence staging Study underway for RT planning for postoperative biochemical recurrence Study underway evaluating ability to guide dose escalation

ATSM, diacetyl-bisN4-methylthiosemicarbazone; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FACBC, anti-1-amino-3-[18F] fluorocyclobutane-1-carboxylic acid; FAZA, fluoroazomycin-arabinoside; FDG, ^{18}F-fluorodeoxyglucose; FDOPA, 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine; FET, O-(2-[18F]-fluoroethyl)-l-tyrosine; FETNIM, ^{18}F-fluoroerythronitromidazole; MET, 1C-methyl-L-methionine; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RT, radiotherapy.

initial chemotherapy for curable Hodgkin and aggressive non-Hodgkin lymphomas.

The first beneficial effect FDG PET has had on RT planning is the more accurate delineation of the tumor. FDG PET is more accurate than CT, with one study showing that up to 30% of patients were downstaged or upstaged.[6] Radiation planning should be designed based on the initial staging extent of disease, and with more accurate staging by PET, there has been a shift from involved-field RT to involved-site RT.[7] Involved-field RT typically included the ipsilateral nodal region, whereas involved-site RT includes all originally involved nodes as well as the adjacent nodal beds. Ongoing efforts continue to evaluate the ability of further volume reduction to treat only the involved nodes, but that continues to be investigational.

In addition, recent trials have shown the ability to forego radiation for certain early-stage lymphomas when there is a favorable treatment response by PET. The Lymphoma Study Association/Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang (LYSA/GOELAMS) conducted a study from 2005 through 2014 of 334 patients with favorable stage I/II diffuse large B-cell lymphoma, no bulky disease, and a complete response by PET. Patients were randomly assigned to receive 4 to 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with or without RT.[8] The 5-year event-free survival rate was noninferior (preset threshold of 8%) in the arm with R-CHOP plus RT vs that in the R-CHOP–alone arm, at 92% vs 89%, respectively (hazard ratio [HR], 0.61; 95% CI, 0.3-1.2; *P*=.18). Most recently, the German Hodgkin Study Group HD17 trial randomly assigned 1100 patients with early-stage unfavorable Hodgkin lymphoma and a complete response to chemotherapy to either standard chemotherapy followed by RT or chemotherapy alone.[9] This study found that the 5-year progression-free survival (PFS) rate was noninferior in the RT arm to that in the control arm, at 97% vs 95%, respectively (HR, 0.52; 95% CI, 0.23-1.2).

Lung Cancer

FDG PET also has been instrumental in RT planning for both small and non–small lung cancer (NSCLC) in similar ways as lymphoma—as an important staging tool that guides appropriate field design. One example is the landmark multicenter prospective PET-PLAN trial performed by Nestle and colleagues,[10] which demonstrated the utility of FDG PET in defining primary and nodal treatment volumes for patients with locally advanced NSCLC treated with definitive RT and chemotherapy.

In this study, 311 patients with locally advanced NSCLC who were candidates for definitive RT and chemotherapy were randomized to PET-directed RT or traditional, CT-guided treatment. In both arms, a dedicated PET/CT was obtained within 3 weeks of treatment and used to delineate the primary lung tumor and regional nodal targets. PET-avid regions received a total dose of 60 to 74 Gy in both arms. Patients randomized to CT-based treatment received at least 50 Gy in 25 fractions to lymph nodes enlarged by CT criteria (>1 cm) and areas of atelectasis, even if these were not PET-avid.

Extensive quality assurance of PET-only and CT-based target volume delineation was performed both prior to treatment delivery and retrospectively to assure adherence to study protocol guidelines.

After a median follow-up of 29 months, patients with PET-only volumes had a noninferior likelihood of local regional progression than those who were treated with CT-based volumes, at 14% vs 29%, respectively (HR, 0.57). There was no difference in overall survival (OS) or PFS between the 2 arms, and both arms had the same rate of out-of-field progression.

The authors concluded that PET-based planning has the potential to improve cancer outcomes without increasing either acute or late toxicity in patients with unresectable NSCLC treated with chemoradiation therapy (CMT). As in PET-PLAN, future studies evaluating the benefits of dose escalation utilizing PET-based treatment planning should include rigorous prospective and retrospective quality assurance.

Although adaptation of radiation fields or doses has not been studied as rigorously in small cell lung cancer (SCLC) as in NSCLC, some data exist to corroborate the overall prognostic significance and utility of PET in SCLC. A post-hoc analysis of the CONVERT trial, which was a randomized trial of once- vs twice-daily CMT, found that patients who received planning with PET had lower normal tissue radiation dose.[11] A systematic review also noted improved diagnostic accuracy of FDG PET compared with CT.[12]

More accurate PET-based radiation planning for tumors in the lung and abdomen can be achieved with the use of 4-dimensional PET/CT, which combines biological information with tumor motion during the respiratory cycle.[13,14]

Head and Neck Cancer

FDG PET is also an important tool in the staging of patients with head and neck cancer, including those with an unknown primary tumor. Although performance varies by tumor histology, a meta-analysis found that PET added 25% to the detection rate of a primary site.[15] Multiple studies have shown a high negative predictive value of PET (97%-100%) for residual viable nodal disease, thus establishing PET as a tool to determine complete clinical response without the need for a neck dissection.[16] It is important to note that the use of PET imaging less than 8 weeks after treatment completion is associated with a higher rate of false-positive results than scans obtained at 12 weeks or later owing to treatment-associated inflammation early after completion.[16]

More recently, PET response has been evaluated as a strategy for adaptive radiation planning of the primary tumor site and regional lymph nodes. Allen and colleagues investigated the feasibility and toxicity outcomes of PET-directed RT in patients with human papillomavirus (HPV)-associated head and neck cancer treated with deescalated CMT.[17] In this prospective phase 2 trial, a mid-treatment PET scan was used to determine if patients would proceed to the planned dose of 70 Gy in 35 fractions or stop at 54 Gy in 27 fractions. The decision to deescalate was based on whether patients had a PET complete response. Of the 59 patients enrolled, 28 met the FDG PET deescalation criteria and therefore received a 20% to 30% lower radiation dose to the tumor and regional organs at risk.

Primary outcomes are still pending, but interim toxicity analysis at 3 months showed significantly higher rates in those who received full compared with deescalated treatment, including greater weight loss (median loss, 13% vs 5.8%; $P<.001$) and more aspiration events (33% vs 8%, $P=.037$). If the excellent oncologic outcome is preserved for the dose-deescalated arm, then PET/CT-based biologic assessment of disease response may prove a rational method to decrease the toxicity of treatment in early-stage HPV-associated cancers of the head and neck (Figure).

Cervical Cancer

FDG PET is a key part of cervical cancer staging, as well as delineating the extent of disease for radiation treatment targeting. Because cervical cancer nodal involvement can extend to the paraaortic nodes without further distant spread, PET staging is associated with a change

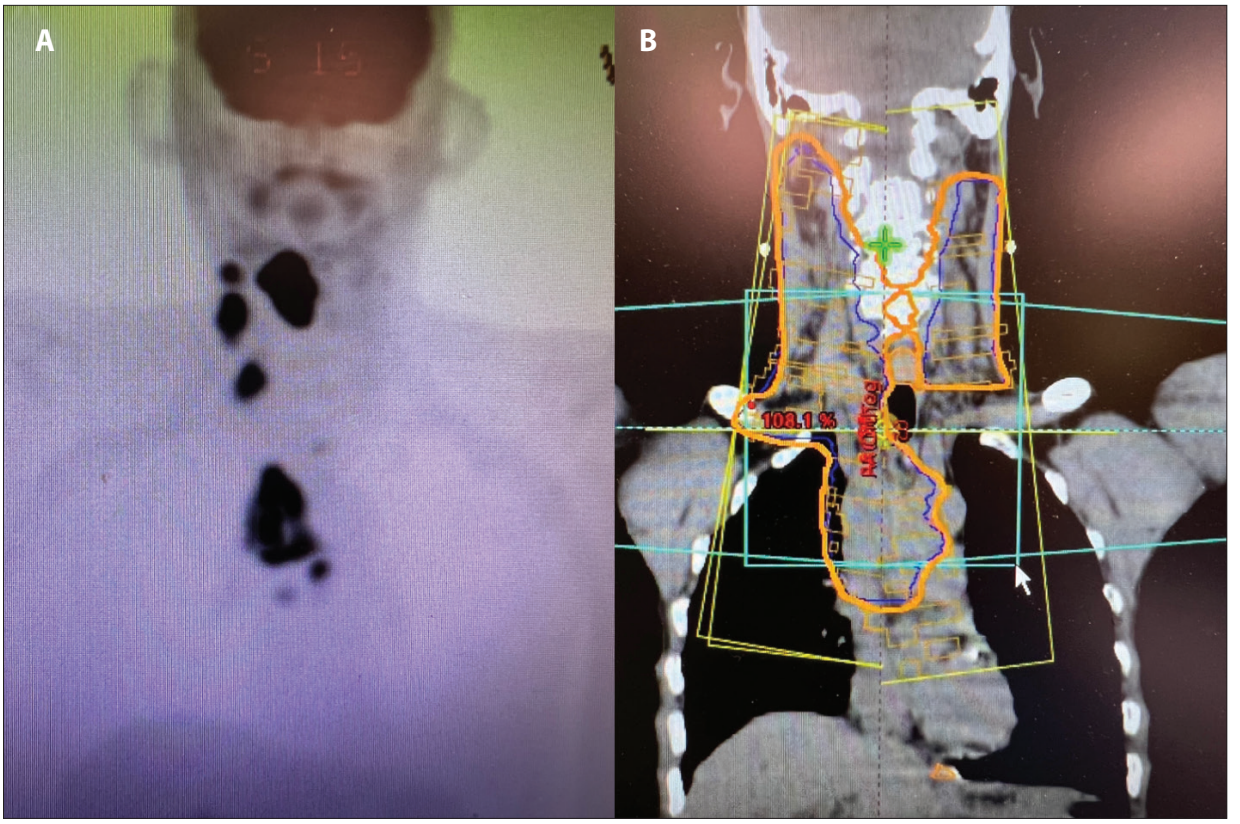

Figure. A representative image of ^{18}F-fluorodeoxyglucose positron emission tomography of a patient with head and neck and esophageal cancer (A). The radiation treatment plan shows inclusion of all PET-positive areas in the high-dose treatment fields (blue outline). The orange outline indicates the lower-dose elective nodal coverage delineated by the treating physician (B).

in management up to 18% of time, although MRI was better able to describe the extent of primary disease.[18]

PET response is prognostic in cervical cancer. Grigsby and colleagues found that patients with a complete response after CMT had a 5-year cause-specific survival of 80% compared with 32% for those with persistent uptake on PET a median of 3 months after treatment completion.[19] Consideration of adaptive RT based on PET response is currently under assessment in a trial comparing diagnostic PET pretreatment with a PET after 3 weeks of CMT to evaluate for changes in biological target volume (NCT03403465). This trial uses PET to adapt treatment based on PET changes, with the hypothesis that this adaptation will reduce normal tissue irradiation and toxicity.

Cytopenia, which occurs in 23% to 48% of patients receiving pelvic RT, can result in a treatment delay or a reduction of concurrent chemotherapy that may reduce cure rates. Bone marrow–sparing pelvic RT has been shown in a meta-analysis to decrease the likelihood of acute hematologic toxicity in women being treated with RT for cervical cancer.[20]

Williamson and colleagues evaluated whether PET-based bone marrow–sparing IMRT yielded lower rates of hematologic toxicity compared with standard IMRT in the phase 2/3 international INTERTECC trial.[21] Women with stage IB to IVA cervical squamous cell carcinoma being treated with RT with or without chemotherapy were randomized to standard IMRT or IMRT using PET-based bone marrow sparing (PET-BMS-IMRT). Although the trial was terminated early, 101 patients were followed for a median of 39 months. There was no difference in clinical disease endpoints between the 2 arms. Women in the PET-BMS-IMRT arm had a lower rate of grade 3 or higher neutropenic toxicity compared with those in the IMRT group, whereas there was no difference between the 2 arms for lymphocytopenia.

PET has been used to evaluate the oxygenation status of tumors through tagged hypoxia markers. These tracers include ^{18}F-fluoromisonidazole (^{18}F-FMISO), ^{60}Cu-diacetyl-bisN4-methylthiosemicarbazone (^{60}Cu-ATSM), ^{18}F-fluoroerythronitromidazole (FETNIM), and ^{18}F-fluoroazomycin-arabinoside (^{18}F-FAZA). The latter 3 tracers potentially have better uptake kinetics and associations with clinical outcomes.[22] These tracers have been used for cervical and other highly metabolic tumors as alternative

imaging that show differential characteristics than FDG for a more complex understanding of tumor metabolism and viability.

Although PET treatment guidance has been the most widely studied in cervical cancer among all gynecologic cancers, a small nonrandomized prospective study of PET adaptive RT for vulvar cancer noted a reduction in the dose received by nearby critical organs.[23]

Gastrointestinal Tumors

External beam RT with chemotherapy is the standard definitive treatment for patients with advanced cervical and anal canal cancer. Similar to lymphoma and head and neck cancers, PET imaging is key to accurate staging and identifying the extent of disease for most gastrointestinal cancers. Several studies have utilized PET response to neoadjuvant CMT as a decision point for proceeding to surgery[24] or changing the chemotherapy regimen.[25]

Likewise, there is now a trend for testing the role of PET response in adapting radiation. In a prospective planning study by Mantello and colleagues, the use of PET in addition to MRI for radiation treatment planning was evaluated in 37 patients with anal canal cancer.[26] The authors identified positive lymph nodes in 14 patients on PET that were not detected by MRI (38%). The majority of nodes identified solely on PET vs MRI were in the inguinal and sacral regions. MRI was superior to PET in the detection of involved mesorectal lymph nodes, but the addition of PET changed treatment planning volumes or dose in 14% of patients. The authors concluded that PET may identify involved lymph nodes not seen on CT or MRI, allowing for adequate nodal coverage and dose escalation that may improve local control and outcomes in anal canal squamous cell carcinoma.

Patient-specific PET-defined bone marrow sparing was evaluated in a phase 2 trial conducted by Arcadipane and colleagues, which included 21 patients with anal canal cancer who were treated with definitive CMT.[27] Areas of increased FDG activity in the marrow were contoured for each patient in 3 distinct regions of the pelvis: the iliac, the lower pelvis, and the lumbosacral regions. These regions were designated as hematopoietically active if the SUV was above the mean SUV of the liver for each patient. Volumetric modulated arc therapy plans were generated to treat the target volumes and protect the patient-specific FDG-defined bone marrow regions. Only 4 of 21 patients (19%) in the study experienced acute grade 3 or higher hematologic toxicity, which is significantly lower than historical controls.[28] The authors were encouraged by the results, and future studies will likely address the promise of individualized FDG PET–defined areas of bone marrow in pelvic substructures.

Central Nervous System Tumors

For gliomas, single-photon emission computerized tomography and MRI have long been used to delineate tumors from healthy brain tissue. A challenge with FDG PET has been the high baseline glucose metabolism. However, there are promising agents beyond FDG that do have differential uptake, including 3,4-dihydroxy-6-[18F] fluoro-L-phenylalanine (FDOPA), α-[11C]-methyl-L-tryptophan (AMT), anti-1-amino-3-[18F]fluorocyclobutane-L-carboxylic acid (FACBC or fluciclovine), O-(2-[18F]fluoroethyl)-L-tyrosine (FET), 11C-methyl-L-methionine (MET), and mitochondrial translocator protein (TSPO).[29]

The Mayo Clinic performed a dose-escalation study utilizing FDOPA, with tumors delineated by PET uptake receiving 76 Gy and those delineated by CT/MRI receiving 60 Gy.[30] The median PFS was improved compared with historical controls (8.7 vs 6.6 months; P=.17). Radionecrosis was diagnosed in 13% of the 75 patients in the study.

FET PET was tested in the DualFETboosT trial, a prospective study of radiation dose escalation in 17 patients with glioblastoma, conducted by Harat and colleagues.[31] Patients were planned with both MRI and dual timepoint FET PET study obtained at 10 and 60 minutes after injection. The thalamus or basal ganglia, areas known to show activity even without disease on FET PET, were included if deemed clinically involved or at risk. The biologic target volume was defined as the T1 + contrast abnormality + surgical bed + FET PET volume. A 2.3-cm expansion of this volume was treated to 60 Gy in 30 fractions, and a 0.3-cm expansion of the biological target volume was synchronously treated to 78 Gy.

After a median follow-up of 37 months, the median OS was an impressive 24 months, with a 1-year OS of 73% and a 2-year OS of 43%. The authors found moderate agreement in tumor volume delineation between MRI and FET PET. Local failure typically occurred at the boundary of the FET PET and MRI volumes, suggesting that this is a region that likely would benefit from further dose escalation. However, 7 patients in the study experienced radiation necrosis requiring surgery. Therefore, the simultaneous integrated boost approach likely needs modification in future studies. Nonetheless, as noted in these 2 studies, RT that included a biological target volume defined by PET in combination with MRI for glioblastoma yielded a promising median OS.

PET may be a more accurate prognostic test after treatment completion compared with MRI. A study evaluating MET PET after CMT for glioma found that residual actively metabolic regions 3 months after treatment were associated with worse PFS.[32]

PET may also play a role in differentiating between radionecrosis and tumor progression. The amino acid radiotracer ^{18}F-fluciclovine is a sensitive and specific marker for prostate cancer but may also play a role in differentiating intracranial tumor progression from radionecrosis.[33] Unlike FDG PET, amino acid PET radiotracers show limited uptake in normal brain tissue, and studies have confirmed that metabolically active glioma cells take up fluciclovine.[34]

Chao and colleagues prospectively evaluated whether PET/CT with the radiotracer ^{18}F-fluciclovine could distinguish between radionecrosis and progressive tumor in 15 patients with equivocal results on MRI after stereotactic radiosurgery treatment of brain metastases.[35]

Among the 20 lesions evaluated, 16 were due to radiation necrosis and 4 were due to tumor progression based on either biopsy or serial MRI evaluation. Higher maximum SUV (SUVmax) of ^{18}F-fluciclovine was a predictor of tumor progression vs radiation necrosis. Using an SUVmax cutoff of 4.3 yielded 100% sensitivity and 63% specificity in predicting tumor progression compared with necrosis. Other predictors of tumor progression included lesions with higher SUV mean, SUV peak, and SUV peak-to-normal brain.

Similarly, Goodman and colleagues prospectively evaluated ^{18}F-fluciclovine PET in 8 patients with 15 biopsy-proven gliomas or metastatic brain metastases previously treated with stereotactic radiosurgery.[36] Patients underwent ^{18}F-fluciclovine PET after standard-of-care MRI showing lesion enhancement. Approximately half of the lesions were biopsied, and the remaining were followed with serial MRI to distinguish progressive tumor from radionecrosis. At a time point of 30 minutes, there was 100% accurate differentiation of tumor progression compared with radionecrosis for patients with an ^{18}F-fluciclovine SUVmax threshold of 1.3 compared with contralateral brain. The accuracy declined with time, as ^{18}F-fluciclovine was gradually taken up by areas of radionecrosis.

Both studies demonstrate the potential for PET with ^{18}F-fluciclovine to accurately distinguish between radiation necrosis and tumor progression. Both groups seek to investigate this imaging modality further in larger, prospective trials.

Prostate Cancer

PET imaging has revolutionized prostate cancer treatment, defining an entire subset of oligometastatic disease that was previously unrecognized. Prostate cancer is not particularly FDG-avid, but in recent years, a number of other tracers have become available. ^{11}C-choline and ^{18}F PET were standards for many years but were challenged by limitations in the breadth of uptake, with one being primarily avid in soft tissue and the other in bony disease. More recently, prostate cancer–specific targeted tracers such as FACBC PET and multiple PSMA tracers have become available. PSMA PET is significantly more sensitive to metastatic disease than conventional imaging, with one prospective trial noting a sensitivity of 85% vs 38%, respectively, and a specificity of 98% vs 91%, respectively.[37]

There are 2 main roles PET plays in RT for prostate cancer. The first is in the management of biochemically recurrent disease. The EMPIRE-1 trial was a landmark study evaluating the impact of FACBC PET–based RT planning on patient outcomes.[38] A total of 165 patients with biochemical recurrence after prostatectomy were randomized to standard radiation treatment fields or radiation treatment based on FACBC PET results. Authors tracked changes in management, noting a change in the treatment plan for 35% of patients.[39] At 3 years, event-free survival was significantly improved in the PET-directed planning group (76% vs 63%; P=.03). EMPIRE-2 is now underway, repeating the study design but with ^{68}Ga-PSMA PET (NCT03762759).

A study involving ^{18}F DCFPYL (PYL) PSMA PET also noted changes in management driven by PET, most typically an increase in nodal coverage or concurrent androgen deprivation.[40] The ongoing PERYTON trial is utilizing PSMA PET to stage men eligible for salvage prostate bed hypofractionated RT, hoping to show improved results owing to both the biological dose escalation from hypofractionation and better PET staging (NCT04642027).

The second aspect of PET radiation planning is in the management of metastatic disease itself. Whether diagnosed at the time of recurrence or, for PYL PSMA and ^{68}Ga PSMA-11, the primary diagnosis space, PET has led to the classification of small volume "early" metastatic disease. Although systemic therapy can be used for these patients, there is also a role for RT to delay systemic therapy and extend PFS. Better delineation of nodal or metastatic disease often leads to changing treatment management. STOMP[41] and ORIOLE[42] were two phase 2 prospective trials that both randomized patients to observation vs metastasis-directed RT. Both studies noted promising outcomes with extended PFS. In STOMP, the 3-year androgen deprivation–free survival was 21 months for those receiving RT and 13 months for those being observed. In ORIOLE, progression at 6 months occurred in 19% of those receiving RT vs 61% of those being observed. Larger studies are being performed to evaluate the use of RT in this subset of patients with metastatic prostate cancer to delay the need for systemic therapy.

There is also a developing role for PSMA PET to direct treatment intensification. Several studies are evaluating the

ability of PSMA PET to change treatment management, similar to EMPIRE-1 described earlier, but also to dose escalate within target areas seen on conventional planning imaging. An ongoing trial[43] used PSMA PET to both identify new lesions for patients with high-risk, recurrent, or oligometastatic disease and to dose escalate up to 66 Gy for involved nodes and 72 Gy for the prostate bed with standard fractionation. Although long-term results are not yet available, investigators have noted that PSMA imaging resulted in treatment intensification in up to 52% of patients and reasonable early toxicity data.

Conclusion

As PET became more widely utilized in the diagnostic space, it quickly proved useful to radiation oncologists to better design treatment fields to accurately target tumors and avoid critical normal tissues. FDG PET was the first broadly successful and remains most utilized for both staging and evaluation of treatment response. Application to the field of radiation oncology first began as a complementary diagnostic tool providing more accurate delineation of tumor but has evolved to guide adaptation of "standard" radiation dose, even to the point of foregoing RT altogether after complete response in certain lymphomas. Likewise in a number of squamous cell cancer types, dose reduction for early responders shows potential to provide the same chance of cure with lower risk of toxicity.

What comes next? PET is a challenging co-registration image because the functional image is not perfectly correlated with anatomy. Computer-assisted analysis of SUV and the anatomic volumes most likely to contain active tumor will be invaluable as the field pushes for smaller treatment volumes to allow high-dose short courses with few side effects.

As noted in our brief review of gliomas and prostate cancer, more options for PET tracers that target tumor cell types, or functional information such as hypoxia, cell kinetics, or RT/chemotherapy resistance are becoming available. We need to better understand how we can further adapt treatment with this added information to further personalize and optimize cancer treatment.

Disclosures

Dr Kasibhatla has no disclosures. Dr Koontz has received advisory board honoraria from Blue Earth Diagnostics, Lantheus, and Rythera.

References

1. Evans PM. Anatomical imaging for radiotherapy. *Phys Med Biol*. 2008;53(12):R151-R191.
2. Ling CC, Humm J, Larson S, Amols H, Fuks Z, Leibel S, Koutcher JA. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. *Int J Radiat Oncol Biol Phys*. 2000;47(3):551-560.
3. MacManus M, Nestle U, Rosenzweig KE, et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006-2007. *Radiother Oncol*. 2009;91(1):85-94.
4. Cheson BD, Pfistner B, Juweid ME, et al; International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579-586.
5. Cheson BD, Fisher RI, Barrington SF, et al; Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphoma Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.
6. Cheson BD, Meignan M. Current role of functional imaging in the management of lymphoma. *Curr Oncol Rep*. 2021;23(12):144.
7. Wirth A, Mikhaeel NG, Aleman BMP, et al. Involved site radiation therapy in adult lymphomas: an overview of International Lymphoma Radiation Oncology Group Guidelines. *Int J Radiat Oncol Biol Phys*. 2020;107(5):909-933.
8. Lamy T, Damaj G, Soubeyran P, et al; LYSA Group. R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. *Blood*. 2018;131(2):174-181.
9. Borchmann P, Plütschow A, Kobe C, et al. PET-guided omission of radiotherapy in early-stage unfavourable Hodgkin lymphoma (GHSG HD17): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(2):223-234.
10. Nestle U, Schimek-Jasch T, Kremp S, et al; PET-Plan study group. Imaging-based target volume reduction in chemoradiotherapy for locally advanced non-small-cell lung cancer (PET-Plan): a multicentre, open-label, randomised, controlled trial. *Lancet Oncol*. 2020;21(4):581-592.
11. Manoharan P, Salem A, Mistry H, et al. ^{18}F-fludeoxyglucose PET/CT in SCLC: analysis of the CONVERT randomized controlled trial. *J Thorac Oncol*. 2019;14(7):1296-1305.
12. Martucci F, Pascale M, Valli MC, et al. Impact of ^{18}F-FDG PET/CT in staging patients with small cell lung cancer: a systematic review and meta-analysis. *Front Med (Lausanne)*. 2020;6:336.
13. Guerra L, De Ponti E, Elisei F, et al. Respiratory gated PET/CT in a European multicentre retrospective study: added diagnostic value in detection and characterization of lung lesions. *Eur J Nucl Med Mol Imaging*. 2012;39(9):1381-1390.
14. Wang YC, Tseng HL, Lin YH, Kao CH, Huang WC, Huang TC. Improvement of internal tumor volumes of non-small cell lung cancer patients for radiation treatment planning using interpolated average CT in PET/CT. *PLoS One*. 2013;8(5):e64665.
15. Rusthoven KE, Koshy M, Paulino AC. The role of fluorodeoxyglucose positron emission tomography in cervical lymph node metastases from an unknown primary tumor. *Cancer*. 2004;101(11):2641-2649.
16. Goel R, Moore W, Sumer B, Khan S, Sher D, Subramaniam RM. Clinical practice in PET/CT for the management of head and neck squamous cell cancer. *AJR Am J Roentgenol*. 2017;209(2):289-303.
17. Allen SG, Rosen BS, Aryal M, et al. Initial feasibility and acute toxicity outcomes from a phase 2 trial of ^{18}F-fluorodeoxyglucose positron emission tomography response-based de-escalated definitive chemoradiotherapy for p16+ oropharynx cancer: a planned interim analysis. *Int J Radiat Oncol Biol Phys*. 2023;117(1):171-180.
18. Belhocine T, Thille A, Fridman V, et al. Contribution of whole-body 18FDG PET imaging in the management of cervical cancer. *Gynecol Oncol*. 2002;87(1):90-97.
19. Grigsby PW, Siegel BA, Dehdashti F, Rader J, Zoberi I. Posttherapy [18F] fluorodeoxyglucose positron emission tomography in carcinoma of the cervix: response and outcome. *J Clin Oncol*. 2004;22(11):2167-2171.
20. Zhou P, Zhang Y, Luo S, Zhang S. Pelvic bone marrow sparing radiotherapy for cervical cancer: a systematic review and meta-analysis. *Radiother Oncol*. 2021;165:103-118.
21. Williamson CW, Sirák I, Xu R, et al. Positron emission tomography-guided bone marrow-sparing radiation therapy for locoregionally advanced cervix cancer: final results from the INTERTECC phase II/III trial. *Int J Radiat Oncol Biol Phys*. 2022;112(1):169-178.

22. Lyng H, Malinen E. Hypoxia in cervical cancer: from biology to imaging. *Clin Transl Imaging*. 2017;5(4):373-388.
23. Shenker R, Eckrich C, D'Anna R, et al. Adaptive positron emission tomography radiation therapy in patients with locally advanced vulvar cancer: a prospective study. *Adv Radiat Oncol*. 2023;8(4):101208.
24. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol*. 2007;8(9):797-805.
25. Goodman KA, Ou FS, Hall NC, et al. Randomized phase II study of PET response-adapted combined modality therapy for esophageal cancer: mature results of the CALGB 80803 (Alliance) trial. *J Clin Oncol*. 2021;39(25):2803-2815.
26. Di Carlo C, di Benedetto M, Vicenzi L, et al. FDG-PET/CT in the radiotherapy treatment planning of locally advanced anal cancer: a monoinstitutional experience. *Front Oncol*. 2021;11:655322.
27. Arcadipane F, Silvetti P, Olivero F, et al. Concurrent chemoradiation in anal cancer patients delivered with bone marrow-sparing IMRT: final results of a prospective phase II trial. *J Pers Med*. 2021;11(5):427.
28. Salama JK, Mell LK, Schomas DA, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: a multicenter experience. *J Clin Oncol*. 2007;25(29):4581-4586.
29. Galldiks N, Niyazi M, Grosu AL, et al. Contribution of PET imaging to radiotherapy planning and monitoring in glioma patients - a report of the PET/RANO group. *Neuro-oncol*. 2021;23(6):881-893.
30. Laack NN, Pafundi D, Anderson SK, et al. Initial results of a phase 2 trial of ^{18}F-DOPA PET-guided dose-escalated radiation therapy for glioblastoma. *Int J Radiat Oncol Biol Phys*. 2021;110(5):1383-1395.
31. Harat M, Blok M, Miechowicz I, Wiatrowska I, Makarewicz K, Małkowski B. Safety and efficacy of irradiation boost based on 18F-FET-PET in patients with newly diagnosed glioblastoma. *Clin Cancer Res*. 2022;28(14):3011-3020.
32. Miller S, Li P, Schipper M, et al. Metabolic tumor volume response assessment using (11)C-methionine positron emission tomography identifies glioblastoma tumor subregions that predict progression better than baseline or anatomic magnetic resonance imaging alone. *Adv Radiat Oncol*. 2019;5(1):53-61.
33. Gusman M, Aminsharifi JA, Peacock JG, Anderson SB, Clemenshaw MN, Banks KP. Review of ^{18}F-fluciclovine PET for detection of recurrent prostate cancer. *Radiographics*. 2019;39(3):822-841.
34. Bogsrud TV, Londalen A, Brandal P, et al. 18F-fluciclovine PET/CT in suspected residual or recurrent high-grade glioma. *Clin Nucl Med*. 2019;44(8):605-611.
35. Tom MC, DiFilippo FP, Jones SE, et al. ^{18}F-fluciclovine PET/CT to distinguish radiation necrosis from tumor progression for brain metastases treated with radiosurgery: results of a prospective pilot study. *J Neurooncol*. 2023;163(3):647-655.
36. Parent EE, Patel D, Nye JA, et al. [^{18}F]-fluciclovine PET discrimination of recurrent intracranial metastatic disease from radiation necrosis. *EJNMMI Res*. 2020;10(1):148.
37. Hofman MS, Lawrentschuk N, Francis RJ, et al; proPSMA Study Group Collaborators. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet*. 2020;395(10231):1208-1216.
38. Jani AB, Schreibmann E, Goyal S, et al. ^{18}F-fluciclovine-PET/CT imaging versus conventional imaging alone to guide postprostatectomy salvage radiotherapy for prostate cancer (EMPIRE-1): a single centre, open-label, phase 2/3 randomised controlled trial. *Lancet*. 2021;397(10288):1895-1904.
39. Jani A, Schreibmann E, Goyal S, et al. Initial report of a randomized trial comparing conventional- vs conventional plus fluciclovine (^{18}F) PET/CT imaging-guided post-prostatectomy radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2020;108(5):1397.
40. Ng M, Guerrieri M, Wong LM, et al. Changes in management after ^{18}F-DCFPyL PSMA PET in patients undergoing postprostatectomy radiotherapy, with early biochemical response outcomes. *J Nucl Med*. 2022;63(9):1343-1348.
41. Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol*. 2018;36(5):446-453.
42. Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. *JAMA Oncol*. 2020;6(5):650-659.
43. Petit C, Delouya G, Taussky D, et al. PSMA-PET/CT-guided intensification of radiation therapy for prostate cancer (PSMAgRT): findings of detection rate, effect on cancer management, and early toxicity from a phase 2 randomized controlled trial. *Int J Radiat Oncol Biol Phys*. 2023;116(4):779-787.