Review Article

Advancements and future directions in positron emission tomography-guided radiotherapy: a narrative review

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Background and Objective: Positron emission tomography (PET) imaging has been useful in delineating tumor volumes and allowing for improved radiation treatment. The field of PET-guided radiotherapy is rapidly growing and will have significant impact on radiotherapy delivery in the future. This narrative review provides an overview of the current state of PET-guided radiotherapy as well as the future directions of the field.

Methods: For this narrative review, PubMed was searched for articles from 2010–2023. A total of 18 keywords or phrases were searched to provide an overview of PET-guided radiotherapy, radiotracers, the role of PET-guided radiotherapy in oligometastatic disease, and biology-guided radiotherapy (BgRT). The first 300 results for each keyword were searched and relevant articles were extracted. The references of these articles were also reviewed for relevant articles.

Key Content and Findings: In radiotherapy, ^{18}F-2-fluoro-2-deoxy-D-glucose (F-FDG or FDG) is the major radiotracer for PET and when combined with computed tomography (CT) scan allows for anatomic visualization of metabolically active malignancy. Novel radiotracers are being explored to delineate certain cell types and numerous tumor metrics including metabolism, hypoxia, vascularity, and cellular proliferation. This molecular and functional imaging will provide improved tumor characterization. Through these radiotracers, radiation plans can employ dose painting by creating different dose levels based upon specific risk factors of the target volume. Additionally, biologic imaging during radiotherapy can allow for adaptation of the radiation plan based on response to treatment. Dose painting and adaptive radiotherapy should improve the therapeutic ratio through more selective dose delivery. The novel PET-linear accelerator hopes to combine these techniques and more by using radiotracers to deliver BgRT. The areas of radiotracer uptake will serve as fiducials to guide radiotherapy to themselves. This technique may prove promising in the growing area of oligometastatic radiation treatment.

Conclusions: Significant challenges exist for the future of PET-guided radiotherapy. However, with the advancements being made, PET imaging is set to change the delivery of radiotherapy.

Keywords: Positron emission tomography (PET); radiation oncology; biology-guided radiotherapy (BgRT); dose painting; adaptive radiotherapy

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Introduction

Positron emission tomography (PET) imaging has become a valuable tool in the field of oncology and has led to significant changes in patient management. A combined PET with computed tomography (CT) scan was introduced into clinical practice in 1998 (1). Since that time its role has grown to affect the initial staging, treatment, and surveillance of many disease sites. The process of a PET scan begins with intravenous injection of a radiotracer which is a radiopharmaceutical compound with a biologically active ligand. Based upon the characteristics of the ligand, the compound accumulates in certain areas of the body, and the PET scanner measures the positron emitting radioisotopes allowing for localization and visualization of the tumor (2).

18-F-2-fluoro-2-deoxy-D-glucose (F-FDG or FDG) is the major radiotracer for PET and provides an imaging correlate for cellular metabolism which is often upregulated in cancer cells. Significant efforts are being made into the development and testing of novel radiotracers which will allow for evaluation of certain cell types and numerous tumor metrics including metabolism, hypoxia, vascularity, and cellular proliferation. As a result, PET allows for both molecular and functional imaging. These radiotracers have the ability to dramatically change the practice of oncology (3).

PET imaging has been critical to the field of radiation oncology. Radiotherapy planning requires accurate identification of the tumor to determine the area to which the radiation will be delivered. By better identifying areas of gross tumor and tumor spread, FDG PET has allowed for more selective treatment volumes. In 2000, the concept of a "biologic tumor volume" (BTV) was coined to characterize these volumes that are derived from biologic imaging. At the time, the hypothesis was that biologic imaging would allow for more selective radiation dose delivery (4). Currently, significant progress is being made in the advancement of PET-guided radiotherapy. Many of these technologies and techniques are in their infancy, however they have the ability to change the way in which radiation is delivered (5).

This review article will focus on the ways in which PET may further guide radiotherapy volumes as well as the impact that the novel combined PET-linear accelerator (LINAC) may have on radiotherapy. With this narrative review, we first describe the fundamentals of current PET-guided radiotherapy and some of the current challenges of PET imaging. We then describe the ways in which PET imaging may change radiation planning and some of the trials that have utilized these techniques. Finally, we discuss the benefits and challenges of the novel combined PET LINAC and the impact it may have on treatment of oligometastatic disease. We present this article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-143/rc).

Methods

For this narrative review, we conducted a search in PubMed including articles from 2010–2023. The keywords searched were, "Positron Emission Tomography radiotherapy", "Positron Emission Tomography radiation oncology", "PET radiotherapy", "PET radiation oncology", "PET simulation radiotherapy", "PET simulation radiation oncology", "PET planning radiotherapy", "PET planning radiation oncology", "PET guided radiotherapy", "PET guided radiation oncology", "PET radiotherapy oligometastatic", "PET radiation oncology oligometastatic", "PET radiotherapy metastatic", "PET radiation oncology metastatic", "PET radiotracers radiotherapy", "PET radiotracers radiation oncology", "Biology guided radiotherapy", and "BgRT". The first 300 results for each keyword were reviewed. Only articles written in English were included. Articles were initially selected based on the title. The abstracts of the selected articles were reviewed for relevance to the review article. The relevant articles were considered for inclusion in the review article. Additionally, the bibliographies for these articles were reviewed for relevant publications which were also reviewed for inclusion in the manuscript. The methods for the literature search are listed in *Table 1*.

Fundamentals of PET imaging in radiation planning

The utilization of imaging in radiation therapy has grown over time and is now a crucial tool in guiding treatment planning. During the radiation treatment planning process, the radiation team must create a plan that delivers adequate dose to the tumor while sparing normal surrounding tissues. The field has advanced tremendously in the past two decades with the adoption of techniques such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT). These techniques have allowed for reduced normal tissue irradiation as well as dose

Table 1 Search strategy summary

Items	Specification
Date of search	Jun 15, 2023–Aug 1, 2023
Database	PubMed
Search terms used	"Positron Emission Tomography radiotherapy", "Positron Emission Tomography radiation oncology", "PET radiotherapy", "PET radiation oncology", "PET simulation radiotherapy", "PET simulation radiation oncology", "PET planning radiotherapy", "PET planning radiation oncology", "PET guided radiotherapy", "PET guided radiation oncology", "PET radiotherapy oligometastatic", "PET radiation oncology oligometastatic", "PET radiotherapy metastatic", "PET radiation oncology metastatic", "PET radiotracers radiotherapy", "PET radiotracers radiation oncology", "Biology guided radiotherapy", and "BgRT"
Timeframe	2010–2023
Inclusion criteria	Priority was given to more recently published articles given the rapid changes in this topic over the search criteria. Only English articles were included
Selection process	Studies were selected based on the relevance to the review article topic. Studies were initially chosen by the primary author (S.M.) and were reviewed by contributing author (C.Y.) and senior author (J.C.Y.)

PET, positron emission tomography; BgRT, biology-guided radiotherapy.

escalation of tumor volumes (6). However, these techniques rely on accurate target delineation which can be difficult on structural imaging such as CT or magnetic resonance imaging (MRI). Tumor seen on these modalities can have similar properties to surrounding normal tissue which can make borders between tumor and normal tissue difficult to discern (7,8). Functional imaging such as FDG PET can help to delineate tumor from surrounding tissue (2).

Malignant cells take up FDG, a glucose analogue, more so than normal tissue due to their increased glucose metabolism, a property utilized in FDG PET scans to identify active tumors (8). Despite the sensitivity of the PET scan in discerning active disease, anatomical information from a CT or MRI is still required to localize the area of metabolic activity (7). In the case of PET/CT, these areas of uptake on the PET scan are then overlayed onto a CT scan which is either acquired simultaneously or at a separate interval and then co-registered, allowing for anatomic visualization of metabolically active malignancy. Other radiotracers with different molecular characteristics can be utilized with PET/CT to target and visualize other tumor characteristics (8). There are also combined PET/MRI devices which allow for simultaneous imaging acquisition of both imaging sets, and anatomic localization of disease on the MRI. These devices are fairly limited, however they can improve tumor delineation for soft tissue targets (9,10).

Given the utility of PET imaging to better delineate tumor volumes, it is a useful tool in radiation planning (*Figure 1*). Dependent on the institution, the PET/CT may be used as the planning image, or a separate planning CT may be obtained and coregistered to the PET/CT. When coregistering a PET/CT to a planning CT, registration transformation can either be rigid or non-rigid (deformable). Rigid registration uses translation and rotation to align the image sets while deformable registration transforms the PET/CT to maximize similarity to the planning CT scan. Accurate coregistration is important for radiation treatment planning (1). Of note, if the PET/CT is used as the primary planning image the CT component must be a high-quality diagnostic CT for accurate treatment calculations. When completing a separate PET/CT scan for radiation planning, it is critical to use the same position and immobilization methods that will be used during treatment (1,11). Additionally, considerations should be made based on the location of the target. For example, for thoracic lesions, motion during respiration should be accounted for (2,5).

Utilization of FDG PET/CT in radiation planning

FDG PET/CT currently plays a role in many disease sites in oncologic care. Many studies and trials on radiation planning and treatment volumes using FDG PET/CT have involved lymphoma and non-small cell lung cancer (NSCLC). In lymphoma, treatment FDG PET/CT has allowed for risk adapted treatment which has allowed for more selective treatment approaches. The 5-point Deauville scale allows for evaluation of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL)

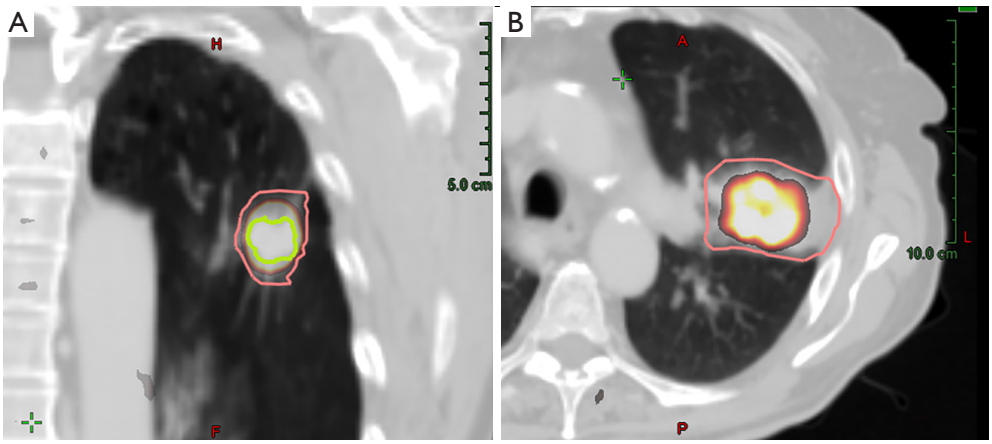

Figure 1 Utility of PET in radiation planning for lung tumors. (A) SBRT planning for NSCLC. Due to tumor movement with respiration, the PET signal (yellow-red gradient) appears larger than the GTV as seen on CT (green) and more accurately reflects the target volume within the lung, similar to the ITV (pink) created using 4D CT simulation images. (B) Definitive chemoradiation plan for a large cT3N0 NSCLC. PET signal (yellow-red gradient) helps distinguish active tumor and inactive atelectatic lung. This information can then be used to focally boost the active disease and/or reduce margin from ITV (pink) created using CT simulation images. PET, positron emission tomography; SBRT, stereotactic body radiotherapy; NSCLC, non-small cell lung cancer; GTV, gross tumor volume; CT, computed tomography; ITV, internal target volume.

through comparison of the metabolically active disease to the FDG avidity of the mediastinal blood pool or liver. This scale helps to determine initial staging and treatment response after systemic therapy. This tool has been used as a predictive imaging biomarker in PET/CT scans following chemotherapy to guide treatment (12). Modern international trials for early stage HL have attempted to utilize PET/CT after chemotherapy to determine whether patients with complete metabolic remission can forgo radiotherapy. These studies overall showed improved outcomes with the addition of radiotherapy, however given the excellent prognosis and the excellent salvage options for patients radiotherapy is sometimes omitted for these patients through this risk adapted approach (13-16). In advanced HL, radiotherapy is often used as consolidation therapy following chemotherapy. In limited stage indolent NHL, radiotherapy can be used definitively, and in advanced NHL the role of radiotherapy is often consolidative, or palliative based upon PET/CT risk adapted approaches to treatment. PET/CT has allowed for targeted radiotherapy for lymphomas through involved site radiotherapy which uses smaller field sizes to only include local disease sites visible on PET (17). This has dramatically reduced the radiotherapy field sizes for this disease and reduced normal tissue toxicity (12). International Lymphoma Radiation Oncology Group guidelines have reported on the use of PET/CT for target identification making its use standard of care in many lymphomas (18,19).

Regarding NSCLC, PET is useful in radiation planning particularly in locally advanced lung cancer (*Figure 1B*). Given the extent of disease, there is often atelectatic or collapsed lung volume encompassing the gross tumor volume which on a high-quality CT scan can appear contiguous with tumor. FDG PET allows for differentiation of tumor from normal lung and accurate gross tumor contouring (6). International groups have supported the routine use of FDG PET for radiation planning (20). The PET-Plan trial, a multicenter randomized control trial, evaluated the benefit of using FDG PET to reduce target volumes for locally advanced NSCLC in definitive chemoradiotherapy. All patients received a FDG PET and CT. Patients were thereafter randomized to Group 1: target volume delineation based on PET and CT imaging and elective nodal irradiation (conventional treatment group) or Group 2: target volume delineation based on FDG avid sites alone. Dose was prescribed to 60–74 Gy in 2 Gy per fraction based upon surrounding tissue tolerances. The risk of locoregional progression at one year of the FDG alone based target group was non-inferior and overall lower than that of the conventional treatment group [14% *vs.* 29%, hazard ratio (HR) =0.57; 95% confidence interval (CI): 0.30–1.06]. The FDG based target group was also

able to treat to higher doses (67.3 *vs.* 65.3 Gy, P=0.039) with comparable acute and long-term toxicity. Overall, this led to the conclusion that FDG PET planning could potentially allow for higher dose with comparable toxicity and improved local control (9,21).

FDG PET is utilized in other disease sites including breast, head and neck, gastrointestinal, gynecological, among others. The current use and advancement of PET in other disease sites has been extensively covered in a number of recent reviews and will not be investigated here (5,8-10,22-25). Prostate specific membrane antigen (PSMA) has also been increasingly utilized and will be discussed further in the novel radiotracers section.

General challenges to the further integration of PET with radiation treatment planning

Challenges exist to the widespread integration of PET in radiation treatment planning which limits its widespread use to guide treatment volumes. Radiotracer uptake can occur nonspecifically and can be taken up by tissues through normal physiologic processes or non-malignant pathologic processes. This can lead to false positive findings. This can commonly be seen in lymph nodes on FDG PET in patients with infection or granulomatous disease. Nonspecific uptake may limit tumor visualization and/or make certain radiotracers unsuitable for certain organ systems. In the case of FDG PET, it is difficult to visualize tumors in the brain, heart, kidney, and bladder due to baseline accumulation of FDG in these organs. Additionally, the acquisition of the PET scan itself has many variables which are difficult to standardize. Standard uptake value (SUV) is a widely adopted metric with SUV =1 indicating uniform uptake referenced to a standardized phantom and typically SUV =2 or higher indicative of abnormality or malignancy. However, SUV is by definition semiquantitative and is dependent on several patient-specific factors which include bodyweight, timing, biologic processes, reconstruction methods, and technical configurations of the scanner. These abundant variables make PET imaging difficult to standardize among institutions for RT planning (9,10).

The detection and visualization of disease of PET/CT also has limitations. The spatial resolution of a PET scan is approximately 4–7 mm which is a significant limitation of this imaging technique (1). Tumor that is smaller than this size may go undetected, resulting in a false negative scan (2). Fortunately, novel and more specific tracers such as those based on PSMA are becoming more widely available and are far more sensitive in detecting small volume disease in prostate cancer (26). An additional challenge is determining the spatial extent of the lesion, which is a process called segmentation. SUV is commonly used to quantitatively assess PET images and is often used in segmentation methods. Numerous methodologies of varying complexity exist for segmentation however there is no consensus for which method is superior (2,7,27). Examples include manual contouring, physician determination regarding the borders of the target, thresholding, use of a minimum SUV to identify the target, gradient edge detection, and delineation of the target based on change in signal across voxels (28). These many challenges make further use of PET in radiotherapy difficult to achieve due to the need for highly accurate imaging.

The establishment of a PET facility can logistically be challenging. This is highlighted in greater detail in the section below, "Challenges to BgRT". However, in brief, a PET program requires a specialized team of nuclear medicine and radiation safety personnel that is trained in the safe handling and administration of radiotracers. Given the government regulation of the radioactive compounds, the facility must closely work with state and federal regulatory offices. The facility must also have a dedicated infusion space and appropriate storage areas. These spaces require adequate shielding and a nearby washroom that is only used by patients receiving radiotracers. Furthermore, the transportation of the radiotracers can logistically be difficult. As a radioactive material, the shipping of the radiotracers requires additional precautions. Additionally, the short half-life can constrain the time frame in which radiotracers can be shipped and may require production near the PET facility (29,30).

Potential advancements of PET use in radiation planning

Novel radiotracers

Adoption of new radiotracers in clinical practice may allow for improved molecular or functional imaging and tumor characterization. This may improve radiation planning as well as identification of radioresistant areas which may facilitate dose painting and/or adaptive planning. Currently, FDG PET is the most common radiotracer although PSMA is also increasingly utilized (31). *Table 2* provides an overview of Food and Drug Administration (FDA)-approved and investigational radiotracers.

Table 2 PET radiotracers used in oncology

Tracer	Tumor type	Cellular target	Clinical application	Molecular basis	Advantages	Disadvantages
^{18}F-FDG	All tumor types, lung, head and neck, cancer, lymphoma	Glucose analogue	Target delineation, dose painting, adaptive radiation	Malignant cells have increased rates of glycolysis and overexpression of GLUT-1 and 3 receptors	Useful in tumor detection and staging; monitoring of treatment response	Nonspecific uptake. Has physiologic activity in brain, heart, kidneys/ bladder, liver
^{18}F-FMISO†	Lung, head and neck, brain tumors	Hypoxia	Hypoxic sub-volume delineation, dose painting, planning adaptive radiation	In hypoxic tumor cells, oxidation does not occur and ^{18}F-FMISO molecule accumulates in cell	Allows targeting of hypoxic areas	Clearance is slow, leaves radioactivity within blood pools and causes nonspecific uptake; has slow accumulation in tumor
^{18}F-FAZA†	Lung, head and neck, brain tumors	Hypoxia	Hypoxic sub-volume delineation, spatio-temporal variation	Hypoxic tumor cells, oxidation does not occur, and radiotracer molecule accumulates in cell	Allows targeting of hypoxic areas. Has faster clearance than 18F-FMISO after injection leading to earlier and improved hypoxia-normoxia contrast	Clearance is slow, leaves radioactivity within blood pools and causes nonspecific uptake
^{18}F-HX4†	Lung, head and neck	Hypoxia	Hypoxic sub-volume delineation, spatio-temporal variations	Hypoxic tumor cells, oxidation does not occur, and radiotracer molecule accumulates in cell	Allows targeting of hypoxic areas	Stability in detecting hypoxic fraction during treatments needs to be further assessed
^{18}F-FLT†	Lung, head and neck, gliomas, esophageal cancer	Proliferation	Serial proliferative tumor volume delineation before and during radiation	FLT is a structural analog of thymidine and enters proliferating cells	More specific to tumor proliferation than inflammation	Relative lack of data; concern for decreased uptake in neoplasms with lower proliferative indices
^{11}C-MET†	Primary and recurrent gliomas	Amino acid metabolism	Target delineation; prognostication	Increased rates of amino acid transport in malignant cells	Sensitive to areas of recurrence; more specific and accurate in detecting infiltrative subclinical disease	Has short half-life and thus requires on-site cyclotron
^{18}F-FET	Gliomas; brain metastasis	Amino acid metabolism	Target delineation and dose painting; prognostication; distinguishing progressive disease from pseudoprogression	Increased rates of amino acid transport	More specific to neoplasia over normally proliferative tissue (e.g., brain neoplasms); differentiate between pseudoprogression/ radiation necrosis *vs.* tumor recurrence; high diagnostic accuracy with histopathological validation	Clearance is slow and leaves radioactivity within pools causing nonspecific uptake
^{18}F-DOPA	Gliomas, paragangliomas, medullary thyroid carcinoma	Amino acid metabolism	Target delineation and dose painting; prognostication; distinguishing progressive disease from pseudoprogression	Increased rates of amino acid transport	Can help differentiate between low and high grade brain tumors; sensitive in detection of primary and recurrent brain tumors	Radiotracer availability

Table 2 (*continued*)

Table 2 (*continued*)

Tracer	Tumor type	Cellular target	Clinical application	Molecular basis	Advantages	Disadvantages
^{68}Ga-PSMA	Prostate	Type II membrane protein	Target delineation and planning dose painting	PSMA inhibitor	Prostate cancer staging, follow up and Lutetium-177 planning; growing evidence of high sensitivity in low PSA levels (<1 ng/mL); versatility in imaging of lesions (e.g., prostate, lymph nodes, soft tissue, bone)	PSMA is not specific to prostate cancer and can be physiologically expressed in salivary glands, proximal renal tubules, liver, spleen, small bowel
^{68}Ga-DOTATOC	Meningioma	Somatostatin receptor	Target delineation	Somatostatin receptors are overexpressed in many tumors	Staging, follow up, assessment for possible radioisotope therapy for neuroendocrine tumors and meningiomas	Pituitary gland is highly positive and limits precision of target volume definition in this area
^{68}Ga-DOTATATE	Meningioma	Somatostatin receptor	Target delineation	Somatostatin receptors are overexpressed in many tumors	Staging, follow up, assessment for possible radioisotope therapy for neuroendocrine tumors and meningiomas	Not specific, tumors and other inflammatory processes can express SSTRs; pituitary gland is highly positive and limits precision of target volume definition in this area; cannot identify microscopic disease due to limited spatial resolution. Cannot identify CTV with precision
^{18}F-NaF	Prostate, lung, breast	Bone metabolism	Staging; follow up of prostate cancer; bone metastasis	Increased bone turnover in lytic and blastic bone lesions	High sensitivity for bone metastasis; has greater accuracy for sclerotic lesions over lytic lesions	Nonspecific—has increased uptake in bone sites undergoing rapid remodeling (e.g., arthritis, broken bone, growth plate in pediatrics, neoplastic lesions); inadequacy to depict other findings beyond bone lesions
^{18}F-fluciclovine	Prostate	Amino acid transport	Biochemically recurrent prostate cancer	Increased rates of amino acid transport	Minimal activity in excreted urine (unlike PSMA), may be more useful in biochemically recurrent prostate cancer when there is equivocal findings in prostate bed on conventional imaging or PSMA; useful in ~10% of prostate cancers that are PSMA negative	Less likely to yield positive results in PSA <1 ng/mL

Table 2 (*continued*)

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Tracer	Tumor type	Cellular target	Clinical application	Molecular basis	Advantages	Disadvantages
^{11}C-CHO	Brain tumors, lung cancer, gastrointestinal or genitourinary cancers	Lipid metabolism	Staging; follow up of prostate cancer; target delineation and dose painting	Cancer cells use greater amounts of substrates for cell membrane synthesis	Sensitive to areas of recurrence	Not sensitive to hyperplastic *vs.* neoplastic disease (e.g., benign prostatic hyperplasia); short half-life of 20 minutes limits use in centers with an on-site cyclotron
^{64}Cu-DOTATATE	Neuroendocrine neoplasm	Somatostatin receptor	Staging; follow up; assessment for possible radioisotope therapy for neuroendocrine tumors	Somatostatin receptors are overexpressed in many tumors	Reproducible, highly accurate for detection of metastasis; flexible acquisition time window ranging from 1–3 hours after injection	Copper-64 has higher positron energy than Gallium-68, resulting in inferior spatial resolution
^{18}F-FES	Breast	Estrogen receptors	Detection of estrogen receptor positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer	Estrogen receptors are often overexpressed in breast cancer	Evaluate entire metastatic tumor burden; predict response to hormonal therapy in breast cancer; identifying and targeting oligoprogressive lesions	High liver physiological uptake so unable to detect liver lesions
^{18}F-DCFPyL	Prostate	Type II membrane protein	Prostate cancer staging; follow up; BCR evaluation	Enzymatic activity	Spatial resolution (due to shorter positron range in tissues compared with Gallium-68); better stability allowing for higher production capacity and use at more centers; higher tumor to background ratios leading to better detection of lower grade or smaller size prostate cancers; approved for patients with suspected metastasis who are candidates for initial definitive treatment as well as those with suspected recurrence based on elevated PSA level; growing evidence of high sensitivity in low PSA levels (<1 ng/mL); versatility in imaging of lesions (e.g., prostate, lymph nodes, soft tissue, bone)	PSMA is not specific to prostate cancer and can be physiologically expressed in salivary glands, proximal renal tubules, liver, spleen, small bowel

†, radiotracers that are not FDA-approved but are investigational drugs. PET, positron emission tomography; FDG, fluorodeoxyglucose; GLUT, glucose transporter; FMISO, fluoromisonidazole; FAZA, fluoroazomycinarabinoside; FLT, fluorothymidine; MET, methionine; FET, fluoro-ethyl-tyrosine; SSTR, somatostatin receptor; CTV, clinical target volume; PSMA, prostate specific membrane antigen; PSA, prostate specific antigen; CHO, choline; FES, fluoroestradiol; BCR, biochemical recurrence; FDA, Food and Drug Administration.

There has been significant interest in use of radiotracers in neuro-oncology. The PET-RANO group provided recommendations on the use of PET in glioma. Due to the high background signal of FDG in the brain, there has been interest in other radiotracers. It explored the use of F-FDG, O-(2-^{18}F-fluoroethyl)-l-tyrosine (F-FET), ^{11}C-methyl-L-methionine (C-MET), and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (F-FDOPA) (32). The recommendations and additional studies showed promise in F-FET at improving target delineation (33-35). A prospective phase II study on 22 patients evaluated use of F-FET to delineate and prescribe an integrated boost to F-FET PET avid glioblastoma. Integrated boost dose was 72 Gy in 30 fractions with 60 Gy in 30 fractions delivered

to visible disease on MRI. Median overall survival (OS) was 14.8 months and disease free survival was 7.8 months, which was not an improvement in outcomes over historical controls (36). Meningioma radiotracers targeting the somatostatin receptors such as Ga-DOTATOC and Ga-DOTATE have been explored and have shown potential to improve target delineation (37,38).

^{18}F-fluoromisonidazole (F-FMISO), ^{18}F-fluoroerythronitroimidazole (F-FETNIM), and ^{18}F-flortanidazole (F-HX4) are radiotracers that allow for identification of hypoxic tumors. Given that oxygen is a potent radiosensitizer, it has been theorized that hypoxic regions of tumor may be radioresistant (25,31). Given the function of F-FMISO, it has been proposed to identify areas of radioresistance that could receive an additional boost. RTEP 5 is a phase II study of patients with locally advanced NSCLC receiving chemoradiotherapy who were all evaluated with a F-FMISO-PET. Patients with a negative F-FMISO PET received 66 Gy in 33 fractions. Those patients with uptake were dose escalated if possible, considering normal tissue constraints. If dose escalation was feasible, patients were treated up to 86 Gy in 2 Gy per fraction with dosing based upon surrounding organ tolerances. Ultimately, the range of doses for the dose escalation arm ranged from 70–86 Gy. Among the F-FMISO positive arm, 24 patients could be dose escalated while 10 patients could not be due to normal tissue constraints. The F-FMISO positive patients overall had worse progression-free survival (PFS) (12 *vs.* 26.2 months, P=0.048). No significant difference was seen in median OS in the F-FMISO positive patients that received a greater dose relative to standard dose (26.5 *vs.* 15.3 months, P=0.71) (39,40). Although outcomes were not improved, this serves as a model for how hypoxia based radiotracers could be used to attempt to dose escalate subvolumes. Evaluation of these hypoxic radiotracers have also been explored to dose paint radioresistant volumes of head and neck cancers. This has been shown to be feasible but studies have not yet shown its benefit in this setting (41,42).

PSMA radiotracers are highly specific to prostatic tumoral tissue and have grown in use for PET imaging of prostate cancer particularly in the salvage and metastatic settings (31). A meta-analysis evaluating detection rates at different prostate specific antigen (PSA) levels showed that at levels of 0–0.2, 0.2–1, 1–2, and >2 ng/mL, the scans were positive at rates of 42%, 58%, 76%, and 95%, respectively (43). Additionally, studies have shown that PET PSMA is better at detecting bone metastases than bone scans (44-47). The role of PET PSMA in influencing contours has been explored in patient populations with biochemically recurrent prostate cancer with PSA ≤1.0 ng/mL following prostatectomy. Patients' scans were contoured based on radiation therapy oncology group (RTOG) guidelines and then contours were compared to PET PSMA imaging. Among the 270 patients, 132 had a positive PET PSMA with 52 of these patients having a lesion not covered by the RTOG based clinical target volume (CTV) (48). Future trials are investigating the role PET PSMA may have in radiation planning. Future directions of PET PSMA may allow for improved treatment volume delineation and the possibility for dose escalation through dose painting (31). Additionally, recent trials such as STAMPEDE, ORIOLE, and STOMP, have shown improved outcomes with treatment of oligometastatic disease (49,50). PET PSMA is being further explored in its role for treatment of oligometastatic disease (*Figure 2*) (34).

Several molecular agents have been approved for clinical use by the FDA with many more still in investigational phases. As the number of approved agents continues to grow and indications for use expand the PET/CT will become a more integral component of radiotherapy. With appropriate selection these radiotracers may improve treatment plans and improve the therapeutic ratio, ultimately improving outcomes for patients (51).

Dose painting

In radiation oncology, plans often have different dose levels based upon specific risk factors of the various target volumes. This variation in dose to target volumes is called dose painting (23). With the use of biologic imaging there is the possibility to identify heterogeneity within imaged tumors to identify radioresistant subvolumes. Through the improved identification of radioresistant populations these areas could receive a greater dose to achieve improved outcomes either through manual contouring of these heterogenous areas or through dose variations determined by the PET signal (1,52). There are a variety of dose painting strategies some of which include dose escalation and dose redistribution. In dose escalation the subvolumes are simply escalated in dose, while in dose redistribution dose is increased in the radioresistant areas and decreased in the surrounding tumor volume (6,23,53).

The PET-Boost phase II trial attempted to dose escalate tumor subvolumes with higher FDG uptake in patients with locally advanced lung cancer (inoperable stage II–

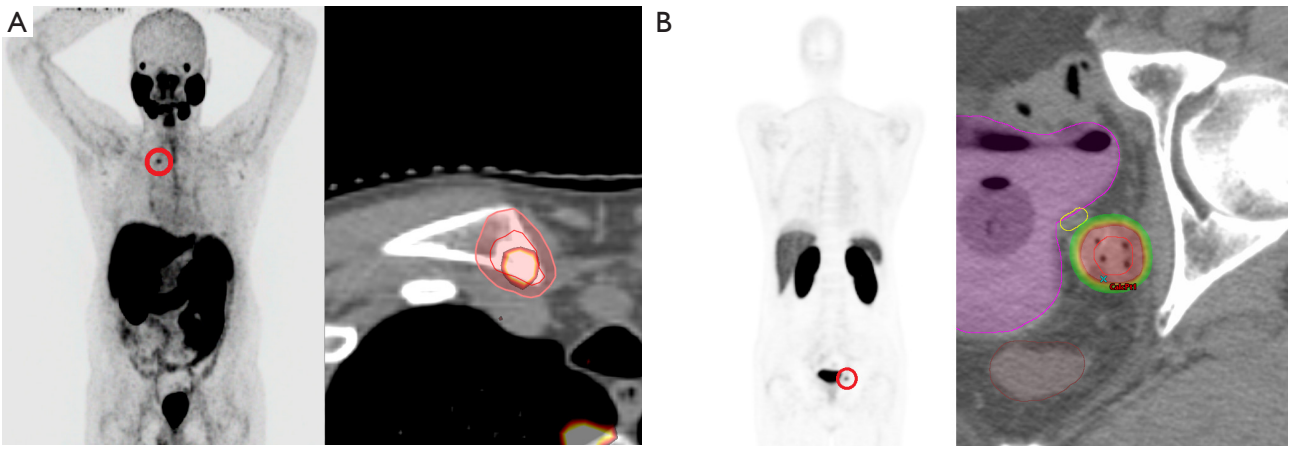

Figure 2 PSMA PET in guiding radiation for recurrent prostate cancer. Red circles represent PSMA avid lesions. (A) A 56-year-old male who underwent prostatectomy for localized high-risk prostate cancer followed by androgen deprivation and radiotherapy to the pelvis/prostate bed, found to have PSA elevation of 0.2 ng/mL 3 years later. PSMA PET showed a small uptake in the right clavicular head. SBRT 27/30 Gy [PTV (pink contour)/GTV (red contour)] in 3 fractions done as shown and he remains disease-free without further therapy 2 years after SBRT. (B) A 61-year-old male who underwent prostatectomy for localized high-risk prostate cancer followed by prostate fossa radiotherapy. Five years later, PSA 2.0 ng/mL, with PSMA PET showing small uptake in the left seminal vesicle remnant. Patient underwent interstitial HDR brachytherapy 36 Gy in 4 fractions [GTV (red contour)/bladder (purple contour)/rectum (brown contour)/ureter (yellow contour)]. Post treatment PSA down to 0.8 ng/mL. At 6 months post treatment, no signs of disease on PSMA PET. PSMA, prostate specific membrane antigen; PET, positron emission tomography; PSA, prostate specific antigen; SBRT, stereotactic body radiotherapy; PTV, planning target volume; GTV, gross tumor volume; HDR, high dose rate.

III NSCLC) (54,55). This was based on prior studies which have shown that areas with higher FDG uptake may correspond to areas of residual disease or local relapse after treatment with definitive chemoradiotherapy (56,57). In the study, 107 patients were randomized to receive 66 Gy in 24 daily fractions with an integrated boost to the whole tumor or an integrated boost to a subvolume defined as areas of the primary tumor with a SUV max of >50% on the pretreatment FDG PET scan. The integrated boost for both arms was escalated to at least 72 Gy in 24 daily fractions with the degree of dose escalation determined by normal tissue dose constraints. Involved lymph nodes were treated with 66 Gy in 24 fractions and elective nodal irradiation was not allowed (58). The median dose tumor in the whole tumor boost group was 79.2 and 84 Gy in the subvolume boost arm (54). The trial was closed early due to slow accrual but showed significant side effects with >G3 acute or long term toxicities in 54% and 53% respectively and G5 toxicities in 7% and 9% respectively (54,55). One year freedom from local failure was 97% and 91% respectively (54). Despite the significant toxicity of this trial, it provides a framework for how PET can be integrated into future clinical trials for subvolume dose escalation.

Treatment of suspected radioresistant volumes can become more complex than creating a SUV threshold at which to dose escalate. Thorwarth *et al.* (59) showed that this is technically and clinically feasible by utilizing a multi parametric functional image (MRI, Choline/PSMA/FMISO-PET/CT) of a patient with high risk prostate cancer to create a plan with a voxel-based prescription. With the functional imaging, they developed a probability based map of tumor aggressiveness and created a voxel based prescription based on this data which ranged from 75.3 to 93.4 Gy (59). Numerous trials are evaluating dose painting in different disease sites through the use of PET-guided radiotherapy (22). The overarching goal is that customization of dose painting based on PET will allow for personalized treatment and translate to improved clinical outcomes.

Adaptive planning

Given that PET is a functional form of imaging, PET can be prognostic and predictive of response to treatment during the course of treatment. As a result, there has been interest in completing biologic imaging during radiotherapy to inform on the response to treatment. With this information, plans can be adapted over the treatment course

to allow for improved outcomes and reduced radiation side effects. Such adaptations can include dose escalation to areas of radioresistance for increased chance of cell killing, improved dose conformity, and dose de-escalation to areas of radiosensitivity to reduce dose to surrounding structures to mitigate side effects. Additionally, adaptive imaging can allow for anatomical modification of radiation volumes should the tumor shift position. These adaptive treatments have already been explored with combined MRI LINACs (3,23).

Kong *et al.* (60) recently published an abstract of RTOG 1106, a phase II trial evaluating PET adaptive planning in locally advanced NSCLC patients receiving chemoradiotherapy. Patients received a mid-treatment FDG PET after approximately 40 Gy was delivered and plans were modified thereafter. Plan modification allowed for dose escalation and field reduction based upon the scan results with modified daily fraction size for the remainder of treatment varying from 2.2 to 3.8 Gy with a maximum dose delivered of 80.4 Gy in 30 fractions and median of 71 Gy. Dose escalation limits were based on normal tissue constraints of the lung. The control arm treated patients with 60 Gy in 30 fractions. Of note, no patients received consolidative immunotherapy. No statistically significant differences were found between the control arm and the adaptive arm in 3-year OS (49.1% *vs.* 47.5%, P=0.80), or 2-year local regional progression freedom (59.5% *vs.* 54.6%, P=0.66). There were no significant differences in cardiac or esophageal adverse events, however there were more G3 respiratory events in the adaptive arms (23.8% *vs.* 14.3%). Of note the 3-year OS of the adaptive arm of RTOG 1106 was improved over the dose escalation arm of RTOG 0617 (47.5% *vs.* 31.1%), potentially indicating that this method of dose escalation may be viable for future dose escalation studies (60,61). Adaptive planning is being evaluated among many disease sites in current clinical trials (22).

Another avenue in which adaptive planning is being explored is with PULSAR (personalized ultra-fractionated stereotactic adaptive radiotherapy). Through this treatment paradigm, patients receive multiple fractions of stereotactic radiotherapy with intervals of weeks to months between fractions. With each fraction patients receive new imaging studies which can include PET imaging to allow for an adapted plan. The significant advantage of PULSAR is that it allows for tumor change to occur between fractions which can better allow for adaptation and ideally more personalized care. Furthermore, PULSAR may allow for an immune-stimulatory effect when combined with immunotherapy (62,63).

Adaptive planning could also be of used to reduce dose to normal tissue should it show significant radiation effect. The use of PET is evolving to help detect acute and long-term complications of radiation. These side effects can have significant effects on patients. Not much research has been completed to assess radiation toxicity using PET during the course of radiotherapy. However, a few studies have evaluated radiation toxicity in the months following radiation. These studies were able to use PET following radiation to assess carotid vasculitis in head and neck cancer patients, parotid gland inflammation in head and neck cancer patients, and pulmonary inflammation in esophageal cancer patients (64-66). Further studies should occur to evaluate the use of PET during radiotherapy to assess, treat, and prevent radiation induced toxicity. Such research should incorporate additional radiotracers which may be more selective at detecting inflammation in certain organs. For example, sodium fluoride (NaF)-PET is effective at detecting atherosclerosis and could be used to evaluate carotid atherosclerosis in head and neck patients or coronary artery atherosclerosis in breast cancer patients (67). Furthermore, new radiation modalities such as proton therapy attempt to reduce radiation to normal tissue relative to photon-based radiotherapy. Use of PET could assist in evaluating toxicity differences between photons and protons.

Significant studies are underway to further explore PET-guided radiation. Several of the actively accruing studies on ClinicalTrials.gov looking at PET-guided radiation are listed in *Table 3*. Adaptive radiotherapy is in its infancy, however, its utilization can potentially improve the therapeutic ratio. The difficulty of adaptive therapy is replanning treatment weekly or daily to account for these changes. The novel combined PET/CT scanner which will be discussed next provides a solution to this problem.

Biology-guided radiotherapy (BgRT) with a combined PET-LINAC

A combined PET/CT scanner and 6 MV flattening-filter-free LINAC developed by RefleXion X1 (RefleXion Medical Inc., Hayward, CA, USA) has recently come to clinical use and is FDA cleared to deliver IMRT, stereotactic radiosurgery (SRS), and stereotactic body radiotherapy (SBRT). It enables a new modality for treatment with radiotherapy called BgRT (68). The unique aspect of this hybrid PET-LINAC is that it allows for dynamic targeting and real-time tumor tracking of multiple PET avid lesions.

Table 3 Ongoing phase II or III clinical trials using PET-guided radiation

Clinical study	Tracer	Tumor type	Study type	Clinical question	Primary outcome	Secondary outcome	Trial arms
METRO (NCT 04983095)	PSMA	Prostate	Phase III	In patients with hormone sensitive prostate cancer, with oligometastatic disease by PSMA-PET/CT, how does failure free survival compare after MD-SBRT plus standard treatment *vs.* standard treatment alone?	Failure free survival	Predictive value of investigated biomarkers in blood and imaging; acute and late toxicity after MD-SBRT; PROM at 3 months, 1, 3, and 5 years; overall survival; differences in outcome between patients by strata	Arm A: MD-SBRT in addition to standard treatment; arm B: standard treatment (GnRH-agonist or GnRH-antagonist)
PERYTON (NCT 04642027)	PSMA	Prostate	Phase III	Can oncologic outcomes in patients with post-prostatectomy recurrent prostate cancer be improved by increasing biological effective RT using hypofractionated schedule?	5-year PFS	Acute grade 2+ GI and GU toxicity; late grade 2+ GI and GU toxicity; QOL after radiation; metastasis-free survival; overall survival; PCSM	Arm 1: conventional salvage external beam radiation—total dose of 70 Gy in 35 fractions; arm 2: hypofractionation—60 Gy in 20 fractions
Intratreatment FDG-PET during RT for gynecologic and GI cancers (NCT 03403465)	^{18}F-FDG	Gynecologic and GI cancers	Phase II	What is the utility of adaptive PET/CT planning for GI and gynecologic cancers treated with radiation?	Number of subjects with benefit from intra-treatment PET/CT; pathologic complete response; locoregional control; freedom from distant metastasis; overall survival; PFS	Measure potential sparing of radiation dose to critical normal tissues	Single arm: interventional study. FDG-PET scan will be obtained prior to radiation as well as a second FDG-PET scan to be obtained 3–5 weeks after treatment has started
INTELHOPE (NCT 02757222)	Not specified	Head and neck cancers	Phase II	Is moderate escalation of radiation dose in advanced/poor prognosis oropharyngeal and laryngeal and hypopharyngeal cancers safe?	Number of patients with Grade 3+ adverse events related to dose escalation according to CTCAE	Efficacy of dose escalation in intermediate and high-risk oropharyngeal cancer and in lymph node positive, locally advanced laryngeal and hypopharyngeal cancer patients	Arm 1: standard dose—patients receive RT dose of 66 Gy in 30 fractions to PTV1 and 54 Gy in 30 fractions to PTV2 with concurrent platinum chemotherapy weekly; arm 2: escalated dose—patients receive 73.5 Gy in 30 fractions to boost target volume, 63 Gy in 30 fractions to PTV1 and 54 Gy in 30 fractions to PTV2 with concurrent platinum chemotherapy weekly
Radiotherapy planning using fluciclovine PET in patients with GBM (NCT 04840069)	^{18}F-fluciclovine	GBM	Phase II	Can use of PET in planning radiation reduce local failures?	Patterns of failure; defining tumor volume	Overall survival; PFS	Arm 1: no intervention, patients all receive MRI guided radiation; arm 2: MRI + fluciclovine PET guided radiation

Table 3 (*continued*)

Table 3 (*continued*)

Clinical study	Tracer	Tumor type	Study type	Clinical question	Primary outcome	Secondary outcome	Trial arms
18F-FDG PET guided reduced dose RT for nasopharyngeal cancer (NCT 04813705)	^{18}F-FDG	Nasopharyngeal cancer	Phase II	Does PET/CT guided dose reduced radiation maintain survival outcomes in patients with nasopharyngeal cancers?	Local-regional recurrence free survival	Overall survival; PFS; distant metastasis free survival; incidence of treatment related acute and late complications; overall response rate	Arm 1: reduced dose group—patients achieving complete metabolic response and more than 70% partial metabolic response at 25th fraction will receive reduced dose radiation for 30 fractions; arm 2: conventional dose group—patients who do not achieve complete metabolic response or 70% partial metabolic response at 25th fraction will receive conventional dose radiation for 33 fractions
PSMA SBRT-SIB (NCT 04402151)	PSMA	Prostate	Phase II	What is the clinical efficacy of PSMA PET/MR guided MR-LINAC based SBRT-SIB?	Recurrence free survival	Performance of PSMA PET/MRI to MRI alone at staging prostate cancer, identifying dominant intraprostatic nodules during RT planning; compare imaging biomarkers of interest on MRI and PSMA PET/MR; change in QOL; change in AUA symptom score; change in number of subjects with adverse events; change in RT doses received by normal structures and PTV; compare immunological changes during SBRT-SIB; compare changes in microbiome during SBRT-SIB	Single arm—patients will undergo PSMA PET/MRI prior to start of RT planning process
Flu-BLAST-PC (NCT 04175431)	PSMA, ^{18}F-fluciclovine	Prostate	Phase II	How well does PSMA or PET/CT direct therapy in treating patients with prostate cancer?	Undetectable PSA rate	Total testosterone; median time to reinitiation of ADT; overall survival; number of patients with abnormalities within prostate fossa with PSA <10	Arm 1: group 1—fluciclovine PET/CT; patients who had initial fluciclovine or PSMA PET/CT that did not show any abnormalities outside prostatic fossa will undergo PSA checks every 3 months and fluciclovine or PSMA PET/CT if PSA >2; arm 2: group 2—surgery, RT, abiraterone, prednisone (patients who undergo fluciclovine or PSMA PET/CT who have ≤3 regions of metastatic disease outside of prostatic fossa will have MD-therapy)

Table 3 (*continued*)

Table 3 (*continued*)

Clinical study	Tracer	Tumor type	Study type	Clinical question	Primary outcome	Secondary outcome	Trial arms
STARPORT (NCT 04787744)	Not specified	Prostate	Phase III	Does adding PET-directed local therapy improve disease control in patients with oligorecurrent prostate cancer on PET/CT?	CRPC-free survival	Radiographic PFS; clinical PFS; freedom from index lesion progression; new metastasis free survival; PCSS; CTCAE toxicity; patient reported QOL	Arm 1: standard systemic therapy; arm 2: standard systemic therapy + PET-directed local therapy. PET-directed local therapy can include surgery, RT, cryotherapy, HIFU
PATRON (NCT 04557501)	PSMA	Prostate	Phase III	Does PSMA PET/CT-guided intensification of RT or surgery improve cancer outcomes compared to conventional image guided radiation? How does toxicity and QOL compare? What is the cost effectiveness of PSMA PET/CT guided approach?	Failure free survival	Rates of toxicity; time to subsequent next line of therapy; QOL; new lesion detection yield on PSMA PET/CT; impact of PSMA PET/CT on RT or surgical management; cost effectiveness	Arm 1: standard of care treatment with surgery or RT (+/– hormone therapy); arm 2: patients undergo PSMA PET/CT prior to treatment and treatment is intensified based on image findings
TRAILOCLORI01 (NCT 05111197)	^{18}F-FDG	NSCLC	Phase III	What is the impact of ablative RT on overall survival in patients with NSCLC and oligometastatic lesions treated by immunotherapy first line	Overall survival	PFS; QOL	Arm 1: immunotherapy + SBRT (maximum of 5 residual hypermetabolic lesions); arm 2: immunotherapy alone
GlioMET (NCT 05608395)	^{11}C-MET	GBM	Phase II	What are the clinical outcomes for patients who undergo PET/CT guided RT to rapid early progression of GBM?	PFS	Rapid early progression incidence; overall survival; biomarkers; patterns of failure analysis; QOL	Single arm: patients will undergo 11C-MET PET/CT 2 weeks prior to chemo/radiation
Comparing 'salvage' RT and individualized PSMA PET targeted treatment in relapsing prostate cancer (NCT 004794777)	PSMA	Prostate	Phase III	In patients with biochemical recurrence of prostate cancer after surgery, how does PSMA PET/CT guided salvage RT compare with standard salvage treatment?	Primary PSA PFS	Time to metastasis; prostate cancer specific survival; time to secondary treatment; differences in QOL recorded using PROM	Arm 1: experimental arm—receives individualized therapy based on PSMA PET/CT results. For example, in group 1 (no uptake on PET/CT), patients will be treated with conventional salvage radiotherapy against prostate bed. For group 2 (uptake only in prostate bed), patients will receive IMRT including VMAT for prostate bed with SIB to PET positive uptake in prostate bed; arm 2: control arm—receives standard salvage radiotherapy

Table 3 (*continued*)

Table 3 (*continued*)

Clinical study	Tracer	Tumor type	Study type	Clinical question	Primary outcome	Secondary outcome	Trial arms
PET guided SBRT for treatment of oligoprogressive NSCLC, melanoma, and RCC	^{18}F-FDG	NSCLC, melanoma, RCC	Phase II	Is PET guided SBRT safe and effective in oligoprogressive NSCLC, melanoma and RCC compared to standard SBRT?	Feasibility and safety of PET adapted SBRT; if PET adapted SBRT allows for dose escalation through SIB resulting in improved LC	Duration of LC and distant control; utility of measuring ctDNA before, during, and after SBRT; identify genomic predictors to predict for distant progression; determine durability of current systemic therapy with SBRT to oligoprogressive sites	Arm 1: patients undergo 5 SBRT treatments EOD; also, patients undergo CT or PET/CT and blood collection throughout study; arm 2: patients undergo 3 SBRT treatments EOD during week 1, then undergo PET/CT and replanning 1 month after SBRT. Then, undergo two additional treatments with SIB. Patients undergo CT or PET/CT and blood collection throughout study
PSMA-SRT (NCT 03582774)	PSMA	Prostate	Phase III	The purpose of this trial is to evaluate the success rate of salvage radiotherapy for recurrence of PCa after prostatectomy with and without planning based on PSMA PET/CT	Success rate of SRT measured as BPFS after initiation of SRT	5-year BPFS rate from date of randomization; metastasis free-survival from date of randomization; initiation of additional salvage therapy after completion of SRT measured as rate of additional PCa therapy initiation-free survival; change in initial treatment intent	Arm 1: standard salvage radiotherapy; arm 2: PSMA PET/CT based salvage radiotherapy

On October 2023, we conducted a search of ongoing clinical trials listed on ClinicalTrials.gov using search terms including "PET" and "Radiation". Only phase II and III trials were reviewed. Only actively recruiting trials were reviewed. Only trials related to PET-guided radiation were included in this table. PET, positron emission tomography; PSMA, prostate specific membrane antigen; CT, computed tomography; MD-SBRT, metastasis-directed SBRT; SBRT, stereotactic body radiation; PROM, patient reported outcome measures; GnRH, gonadotropin releasing hormone; RT, radiation; PFS, progression-free survival; GI, gastrointestinal; GU, genitourinary; QOL, quality of life; PCSM, prostate cancer specific mortality; FDG, fluorodeoxyglucose; CTCAE, common terminology criteria for adverse events; GBM, glioblastoma multiforme; MRI, magnetic resonance imaging; MR, magnetic resonance; MR-LINAC, magnetic resonance-linear accelerator; SIB, simultaneous integrated boost; AUA, American Urologic Association; PTV, planning target volume; PSA, prostate specific antigen; ADT, androgen deprivation therapy; MD, metastasis directed; CRPC, castrate resistant prostate cancer; PCSS, prostate cancer specific survival; HIFU, high intensity focused ultrasound; NSCLC, non-small cell lung cancer; MET, methionine; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy; RCC, renal cell carcinoma; LC, local control; ctDNA, circulating tumor DNA; EOD, every other day; PCa, prostate cancer; SRT, salvage radiotherapy; BPFS, biochemical progression-free survival.

The machine has a direct feedback loop by which the PET scanner detects emission from the tumor and can deliver radiotherapy to the tracked lesion with sub-second latency. The dynamic treatment delivery modality allows for wide use in both inter and intra fraction motion management (69-71).

The clinical workflow differs significantly from that of standard radiotherapy. A patient with radiotracer avid disease first has a BgRT imaging only session which is subsequently used for treatment planning. Thereafter, the patient returns, and a PET scan is completed prior to treatment delivery to generate a predicted dose distribution which is compared to the dose distribution of the treatment plan. Should tumor identified by the PET scan fall within the set bounds of the treatment plan, BgRT can be delivered. To account for the unique aspects of this technology, additional contouring structures are needed to assist with treatment. The first is a biology-guidance margin (BgM) which is an expansion from a CTV to account for errors intrinsic to BgRT delivery such as latency time between tumor detection and treatment delivery. The second is biology-tracking zone (BTZ) which encompasses the motion extent of the lesion as well as patient set-up error. This region limits the area from which the device gathers PET emissions to guide radiotherapy, preventing detection of PET emissions from other structures within the body (69,72). A retrospective study has compared conventional IMRT/SBRT plans to BgRT generated plans on the same subset of patients. All plans were found to be clinically acceptable with all but three planning metrics being found to be equivalent or superior. Of note beam on times were found to be significantly longer for the BgRT plans relative to the conventional plans at all sites treated ($P<0.01$) (70). Treatment experiences with the RefleXion have been published on SBRT and IMRT treatments however the FDA only cleared treatment in 2023 with BgRT so data on this treatment technique is still pending (73).

Within the last few years, several studies have shown improved outcomes with ablative radiotherapy treatment of oligometastatic disease. Much of these studies have been completed in NSCLC and prostate cancer, however the SABR-COMET trial enrolled patients with a variety of histologies and showed a 5-year OS rate of 17.7% in the standard of care palliative treatment arm *vs.* a 42.3% rate in the arm in which 1–5 metastatic sites were treated with ablative doses of radiotherapy (74-77). A limitation of treatment of oligometastatic or metastatic disease sites are visualization of disease and toxicity from numerous treatment courses. As a result, one avenue of interest with this device is treatment of oligometastatic and metastatic disease. This would be feasible as a single radiotracer can allow for visualization and targeting of the full extent of disease (69,78). Complete metastatic ablation has been proposed as a possibility for this device given the ability to use each of these visible areas of disease as a fiducial to precisely and effectively ablate visible disease. Although extreme, this goal appears more achievable in the age of immunotherapy (79).

The recent PEMBRO-RT trial was designed under the premise that high dose radiotherapy may allow for tumor antigen release which would improve checkpoint inhibition agents. The study looked at patients with advanced NSCLC and randomized patients to pembrolizumab alone every 3 weeks or pembrolizumab every 3 weeks within 7 days after 24 Gy in 3 fractions of radiotherapy to a single site of disease. Among 76 total patients the overall response rate at 12 weeks was 18% in the pembrolizumab alone arm and 36% in the pembrolizumab and radiation arm ($P=0.07$). Although benefit was seen, the prespecified endpoint for benefit was not met; nonetheless, this study shows promise for the potential synergy or radiotherapy and immunotherapy in patients with metastatic disease (80). Combination of BgRT and immunotherapy could allow for improvements of this effect and treatment of metastatic disease.

Radiotracers can also depict normal tissues and non-malignant pathologies. In the case of radiotherapy, daily imaging of the patient with radiotracer could allow for visualization of radiation induced inflammation such as pneumonitis or esophagitis, potentially detecting radiographic abnormalities before side effects occur. Visualization of these secondary effects could allow for improved clinical management and appreciation of severity of side effects (6). Severity of esophageal toxicity and pulmonary toxicity correspond to uptake seen on FDG PET (81,82).

Challenges to BgRT

Given that BgRT is a new technology there are many challenges to its use. Due to its novelty there is no evidence as to whether this more precise form of radiotherapy will yield clinical benefits (78). There are many challenges to the integration of the technology into today's healthcare system and the execution of treatment using this machine. At the hospital level, the execution of BgRT will require close and complex coordination

between the nuclear medicine and radiation oncology department. Staff will require significant training in order to use these devices (83). The radiation safety team will have to develop new protocols for radiation safety and staff will need to be educated on safe procedures with this process and handling of radiopharmaceuticals. The facility itself will need to be designed to accommodate these patients and the radioactive materials. Areas which may be necessary would include specialized storage rooms for the radiotracers isolated holding areas to allow for injection of the radiotracer and to allow for the patient to wait until there has been sufficient uptake within the tumor. These rooms would require specialized shielding.

For the machine to accurately target the desired tumor volume, sufficient radiotracer must be present in the patient and in the tumor. The half-life of the most common radiotracer FDG is about 2 hours, and the half-life of other radiotracers may be shorter. This poses numerous challenges to its utilization during treatment. The center must have acquired the radiotracer with sufficient time prior to the patient's treatments to deliver an effective dose to the patients. This would require complex supply chain management. Treatment would have to occur within a specified timeframe following administration of the radiotracer for it to be effective for treatment. This would require delicate coordination by the treatment team. This complicated process would need to be repeated consistently for each treatment (84).

At a biologic level, the tumor would need to continue to consistently take up radiotracer for it to act as a fiducial during treatment. If radiotracer uptake were to be disrupted due to treatment response, this may cause problems with target delineation. Surrounding tissues may also take up radiotracer during the course of treatment in response to secondary effects of radiotherapy. This would make accurate tumor delineation more difficult (9,83). Furthermore, with the use of concurrent chemotherapy and/or immunotherapy, it is unclear whether this may affect radiotracers and functional imaging (3). A solution to the prior challenges would be a radiotracer with a longer half-life that can be used through multiple days of treatment. Regardless, the frequent administration of radiotracer would also add significant cost to the overall treatment (9). Given the logistical and economic burden this technology may pose, BgRT may be best administered for hypofractionated or stereotactic courses of radiotherapy to best balance clinical benefit and the challenges of the technology (78).

Strengths and limitations of review

The paper provides a strong overview of the current state of PET-guided radiotherapy and the future directions of the field. The PubMed search covered a wide variety of search terms, and the authors reviewed a significant number of papers with each search term. Additionally, sources of the papers were reviewed for additional material. Although the search likely provided a strong evaluation of the field, it is not as thorough as a systematic review and therefore may have left out relevant articles. As a review paper, the article provides significant breath of knowledge on the topic without significant depth into any of the subtopics.

Conclusions

Over the past decades, the field of radiotherapy has advanced through technologies and techniques that have allowed for more precise treatment of malignancies and reduced treatment of normal tissue. PET imaging has already allowed for improved delineation of tumors through the integration of FDG PET and other radiotracers into radiotherapy planning. Significant challenges still exist with the integration of PET with radiation treatment planning due to the unique logistical challenges of PET as well as the technologic challenges. Nonetheless, PET imaging is a rapidly growing field with significant resources being deployed into the development and utilization of novel radiotracers to provide molecular and functional imaging. The advancement of these radiotracers will allow for new radiation treatment paradigms for different disease sites with techniques such as dose painting and adaptive planning. The creation of a PET-LINAC and the ability to deliver BgRT presents a new opportunity for the field of radiotherapy to further enhance treatment. The technology is still in its infancy and will need time to determine the areas of best use. Numerous clinical trials are evaluating use of radiotracers to further guide radiotherapy. These trials will provide insight into the next stages of PET-guided radiotherapy. Overall, PET imaging is set to greatly change the future delivery of radiotherapy.

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Footnote

Reporting Checklist: The authors have completed the

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All clinical procedures described in this study were performed in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was not required for this article and accompanying images as the figures were sufficiently anonymized.

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