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Chapter 8

PET – Assessment of Oncologic Treatment Response

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Additional information is available at the end of the chapter

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1. Introduction

Positron Emission Tomography (PET), particularly with 18-Fluorodeoxyglucose (FDG), continues to define and expand its role in oncologic management. Beyond tumor size, as definable by computed tomography (CT), PET provides a measure of metabolic activity in tumors and is integral in initial workup for multiple disease sites including head/neck squamous cell carcinoma, non-small cell lung cancer (NSCLC), lymphoma, and many others. For head and neck cancers, FDG PET imaging facilitates early detection of persistent and recurrent head/neck squamous cell carcinoma after chemoradiotherapy, increasing deferral of surgical neck dissection to the salvage setting in many cases. In the setting of non-small-cell lung cancer, PET is further considered standard of care for radiotherapy treatment planning. Post-treatment PET has further shown to facilitate assessment of treatment response, with metabolic response seen on PET pre-dating CT-based radiographic response. Though routine post-therapy PET after definitive non-surgical management is standard management for head/neck squamous cell carcinomas, evidence to support this routine use for other subsites is lacking and thus currently not recommended for various organ sites including lung. This chapter herein discusses various PET imaging techniques and assessment variables that have been used to investigate assessment of response to oncologic treatment. In particular, assessment of response with early and late post-radiotherapy PET imaging for head and neck, NSCLC, rectal cancer, esophageal cancer, and lymphoma are discussed. Recent research involving on-treatment PET imaging as well as future work are further presented.

2. PET technique

2.1. ^{18}F-FDG

PET is a medical imaging technique employing the unique parameters of decay of positron-emitting isotopes. Today, PET is routinely used in conjunction with computed tomography (CT) in a combined medical imaging device, PET-CT, allowing anatomic image correlation with the functional imaging obtained by PET.

A number of PET radiotacers have been used in oncology, though ^{18}F-Flourodeoxyglucose (FDG) is FDA-approved and most commonly employed. Other agents including ^{18}F-FMISO (^{18}F-Fluoromisonidazole), ^{18}FLT (^{18}F-Fluorothymidine), 16b-^{18}F-Fluoro-5a-Dihydrotestosterone (^{18}F-FDHT), ^{60}Cu-ATSM (Copper-diacetyl-bis(N4-methylthiosemicarbazone)), ^{18}F-FES (16a-^{18}F-fluoro-17b-estradiol), ^{11}C-MET (11C-methionine), show significant potential to monitor the response to therapy before, during, or after therapeutic intervention[1].

^{18}F-FDG chemically is 2-deoxy-2-^{18}F-fluoro-D-glucose, a glucose analog. On ^{18}FDG, the positron-emitting radioactive isotope fluorine-18 is substituted at the 2' position of the glucose molecule preventing glycolysis, which requires a hydroxyl group at the 2′ position. It has significantly increased uptake in tissues with increased metabolic activity, in particular, most malignancies [2]. With increased demand for gluose, tumors tend to have increased expression of glucose transport proteins at the cellular membrane as well as increased hexokinase [3]. With its relatively short half-life of 110 minutes, in tissues with rapid uptake, the ^{18}F decay occurs primarily when trapped intracellularly, helping visualize these areas on PET. Malignancies with moderate to high ^{18}F-FDG uptake include most lung cancers, colorectal cancers, esophageal cancers, gastric cancers, head and neck cancers, cervical cancers, ovarian cancers, breast cancers, lymphomas, and melanoma [4]. Hepatocellucar carcinoma, testicular cancers, renal cancers, sarcomas, and neuroendocrine tumors have variable ^{18}F-FDG uptake [4]. Prostate adenocarcinoma, the most common cancer in males, has generally low metabolic activity, rendering ^{18}F-FDG particularly less helpful for this malignancy in the primary setting, leading to potential false negative interpretation [5–7]. As ^{18}F-FDG undergoes physiologic excretion through the bladder hinders evaluation of both bladder and prostate malignancies. Overall, ^{18}F-FDG has been the most used oncologic tracer, but its applicability is not universal across all malignancies, nor is its uptake specific to only neoplasm. Though aberrant tumor growth in malignancy routinely results in increased ^{18}F-FDG avidity, it is not tumor specific other benign tissue and benign conditions can also have variable uptake of ^{18}F-FDG (e.g. inflammation or hyperplastic bone marrow) potentially leading to false positive findings [4,7]. As bone marrow hyperplasia and inflammation are not uncommon consequences after oncologic treatment including surgery, radiation therapy, and/or chemotherapy, ^{18}F-FDG PET has limitations particulary in post-therapeutic assessment.

2.2. Other radiotracers

Beyond ^{18}F-FDG, other markers exploit other cellular mechanisms for biologic imaging with PET. Other markers have been used to assess tumor proliferation with markers of DNA

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synthesis. As thymidine is unique to DNA, this has been exploited with various radiotracers including ^{11}C-thymidine—which is limited by the short half-life of ^{11}C—as well as thymidine analogs ^{18}F-FLT and ^{8}F-FMAU with the longer half-life of ^{18}F [8]. ^{18}F-FLT acts as a substrate of cytosolic thymidine kinase 1 (TK1), a key enzyme for salvage DNA synthesis, and ^{8}F-FMAU is a substrate of thymidine kinase 2 (TK2), located in mitochondria, resulting in different distributions of these markers in tissue [9,10]. Although tumors tend to be less avid of ^{18}F-FLT in comparison go ^{18}F-FDG, tumor delineation from background tissue can be superior with ^{18}F-FLT in regions such as the brain, mediastinum, and intestines, where normal physiologic uptake of ^{18}F-FLT in these areas are much lower, yielding a high tumor-to-background ratio [1,11–13]. In a head-to-head comparison of ^{18}F-FLT to ^{18}F-FDG to assess chemotherapy response in patients with breast cancer who had imaging with both radiotracers, change in FLT uptake after one cycle of chemotherapy better predicted late changes in tumor marker levels and correlated well with eventual radiographic tumor response [14]. Though less employed in comparison to ^{18}F-FLT, ^{18}F-FMAU has shown ability to visualize breast, brain, lung, and prostate tumors. As ^{18}F-FMAU shows low uptake in normal bone marrow—as opposed to ^{18}F-FLT, which has high bone marrow uptake—^{18}F-FMAU is more suitable for visualization of metastatic prostate cancer.

Radiolabeled Cu-ATSM ($^{60/62/64}$Cu-ATSM) and ^{18}F-FMISO are currently the two primary radiotracers employed for imaging tissue hypoxia—correlated with decreased sensitivity to treatment—and has been with worse clinical outcomes [15,16]. ^{60}Cu-ATSM has been found to predict aresponse to therapy for NSCLC and predict both recurrence and survival outcomes for cervical and rectal cancers [17–19]. Clinically, pretreatment ^{18}F-FMISO has been shown to predict survival in patients with head and neck cancer and glioblastoma multiforme [20,21].

Various amino acid radiotracers have been used, with ^{11}C-MET (a methionine analog) the most common. It has found a niche in CNS malignancies. In malignant gliomas, decreased uptake during temozolomide therapy has shown improved time to progression; areas of uptake have shown areas at high risk of recurrence, and has helped distinguish post-radiation necrosis versus recurrent malignancy [22–24].

An additional class of radiotracers have aimed to assess hormone receptors, as receptors play an integral role in malignancies, paticulary prostate and breast cancers. ^{18}F-FES is the most commonly used, showing correlation with estrogen receptor (ER) levels as well as response to aromatase inhibitors [25,26]. Ultimately, pretreatment uptake values have shown to predict patients who would or would not respond to therapy [25]. For prostate cancer, ^{18}F-FDHT is an analog of 5α-dihydrotestosterone. Correlation with treatment response has not as well been shown in prostate cancer with this marker, though ^{18}F-FDHT uptake has been associated with high PSA levels [27].

Single-phase / Dual-phase / Dynamic PET

Historically, PET imaging was obtained with a single static set of images obtained up to 1 hour after injection of ^{18}F-FDG. As noted previously, a diagnostic limitation of PET imaging for oncologic diagnosis are the false positive findings secondary to inflammation quite commonly associated to therapeutic response. As ^{18}F-FDG uptake and retention kinetics are potentially

different between tumor and normal tissue inflammation, people have investigated more dynamic methods of acquiring metabolic PET data.

In a series of 21 patients with head and neck carcinomas, dual-time-point ^{18}F-FDG PET studies helped differentiate malignancy from inflammation [28]. Standard uptake values (SUVs) of tumors were shown to increase on the second (delayed) study by mean of 12% in comparison to matched contralateral normal tissue which showed a mean decrease of 5% on delayed imaging ($p<0.05$) [28]. Inflammatory sites showed relatively stable uptake over the two scans; time interval between scans correlate with tumor SUV increase; and interval of greater than 30 minutes was recommended for separation [28].

For evaluation of pulmonary nodules, an early study of 36 patients siwht 38 pulmonary nodules, malignant or benign, underwent dual-time-point PET at 70 and 123 minutes post-injection [29]. A similar trend was seen with mean increase of tumor SUV of 20% (from 3.7 to 4.4) in malignant lesions from early to delayed scan ($P<0.01$); benign lesions showed stable and lower mean SUVs (1.1 on both early and delayed imaging) [29]. They determine a threshold of 10% increase from early to delayed imaging as the best predictor, reaching sensitivity of 100% and specificity of 89% [29]. Other data have shown similar trends of increased ^{18}F-FDG uptake from first to second scan in malignant tissue and stable to decreased uptake in benign lesions [30].

In a study of 47 patients with suspected pancreatic cancer, patients had dual-time-point ^{18}F-FDG PET imaging acquired 1 and 2 hours after injection; further, some patients had a third scan at the 3-hour time point after injection [31]. Twenty-two lesions were malignant, whereas 20 were benign. With a constant SUV threshold, the initial 1-hour PET was found to be 95% sensitive, missing one of 22 malignant lesions, and 83% accurate. With addition information of 2-hour PET imaging, retention characteristics of ^{18}F-FDG increased diagnostic accuracy to 91.5%, with no decrease in false negatives [31]. The additional information provided by a 3-hour PET did not improve diagnostic accuracy beyond the dual-phase imaging obtained at the 1-hour and 2-hour time points [31].

With these potential diagnostic advantages from dual-phase PET-CT (with 2 PET scans separated by a time interval) has grown increasingly common. With the extra information provided with dual-phase imaging, people have further investigated 'dynamic PET' imaging, obtaining continuous PET data over time rather than at discrete or brief time spans, adding further breadth of data to kinetic profiles of uptake. Early work used dynamic continuous imaging to model discrete time-point imaging, showing linear change over time in patients with breast cancer. A recent study utilized dynamic PET imaging with ^{18}F-FCho (^{18}F-labelled fluoromethylcholine) to assess time-activity curves of space occupying brain lesions [32]. Another recent study used a dynamic PET-CT approach to assess cervical adenopathy in patients with oral/head and neck cancer; consecutive imaging at nine time points with PET/CT were obtained from 60-115 minutes after injection [33]. At our institution, we have recently initiated an adaptive radiation therapy protocol for patients with head/neck cancer in which patients receive weekly dynamic PET imaging over approximately 90 minutes during the course of treatment.

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Though PET imaging acquires three-dimensional (3D) data, as CT technology has advanced to enable four-dimensional (4D) imaging with full 3D CT image sets corresponding to various portions of a respiratory cycle, so now have 4D-PET-CTs come into clinical use, with potential to reduce image smearing, improve accuracy of PET-CT co-registration, and increase the measured SUV [34,35]. A study evaluating 57 pulmonary lesions showed particular benefit in characterizing smaller tumors, with 4D studies showing higher differences in SUVmax percent difference in comparison to 3D studies ($p<0.05$) assessment of smaller lesion lung lesions, with better characterization [36]. A recent study illustrated utility of respiratory-correlated 4D-PET-CT for target delineation of squamous cell carcinoma of the esophagus, further indicating SUV threshold of 20% or 2.5 for autocontouring the gross tumor volume (GTV) [37]. Algorithms for semiautomatic contouring have also been proposed for pulmonary lesions with minimal difference (0.1 ± 0.1 mm) on phantom studies and 0.8 ± 0.2 mm on patient tumors [38]. Four-dimensional PET/CT has been reported to facilitate planning stereotactic radiotherapy of liver metastases [39] and pulmonary tumors [40].

3. PET parameters

From an oncologic standpoint, PET imaging is notably quite useful in its ability to quantitate parameters associated with PET uptake. An assortment of quantitative values can be obtained from each scan and from multiple-time-point scans, as well as across different scans obtained at different time points with respect to treatment (e.g. pre-treatment versus post-treatment), providing valuable information for treating physicians.

A common measurement of PET images for clinicians is the semi-quantitative value referred to as "standardized uptake value (SUV) [41]." Standardized uptake values are calculated throughout the three-dimensional array of CT regions, with variable SUVs throughout an image. SUV provides an index of regional tracer uptake and is a function of local radioactivity concentration, injected activity, and patient's weight. ^{18}F-FDG SUV can help differentiate tumor from tissue, and when used, corrections to calculation are recommended [42]. A common method of correction accounts for a patient's lean body mass "SUV_{lbm}," commonly written as "SUV_{lbw}" (lbw="lean body weight"), "SUV_{lean}," or "SUL."[43]

$$SUV_{lean} = \frac{Radioactivity(\mu C_i / mL)}{Dose(mC_i) / lean\,body\,mass(kg)} \tag{1}$$

$$SUV_{lean} = SUV_{lbm} = SUV_{lbw} = SUL \tag{2}$$

Within a region of interest (ROI) on a PET-CT, various PET quantitative factors can readily be obtained. The most commonly reported value from PET-CT oncologic imaging the maximum SUV value (SUV_{max}). SUV_{max} values are measured and reported at areas concern-

ing for malignancy (e.g. a primary tumor and associated regional lymph nodes and distant metastases as well as other highly avid areas that may represent inflammation or reactive changes). Pre-treatment SUV_{max} with ^{18}F-FDG has been reported to be prognostic for many organ sites including lung [44–46], head and neck [47], esophagus [48,49], gastroesophageal junction [49] gastric [50], pancreas [51] cervix [52], rectum [53,54], lymphoma [55], and soft tissue sarcoma [56].

Beyond SUV_{max} of an ROI, the arithmetic mean SUV (SUV_{mean}) of voxels within the ROI have been used for oncologic assessment [57–59]. New parameters, which show promise in oncologic assessment, include the metabolic tumor volume (MTV) and total glycolytic activity (TGA) [60–63]. The MTV is defined as the tumor volume based on PET uptake and can be particularly helpful in comparison to CT-imaging when background density is similar to tumor density on CT. The boundary of MTV can be defined manually or with various parameters such as a fixed SUV threshold, percentage of SUV_{max} (e.g. 38%, 50%, and 60%), and gradient. On pre-treatment imaging prior to radiotherapy the volume delineated by PET-fusion to planning CT effectively corresponds to the MTV, which is utilized for biologically-targeted radiotherapy [64–66]. Such methods have been used extensively for lung radiotherapy planning, where PET staging is recommended [67]. MTV has shown to predict overall survival in lung cancer [61], head and neck cancer [60], and esophageal cancer [68].

Total glycolytic activity (TGA), defined as the (MTV) x (SUV_{mean}), is the primary PET parameter that includes both both anatomic (size) as well as metabolic parameters (e.g. with ^{18}F-FDG). In an analysis of TGA and MTV in 45 patients with oral or oropharyngeal SCC, stage, on univariate cox regression, MTV and TGA were the most associated with progression-free survival (PFS) and overall survival (OS) (p=0.002 and p=0.006, respectively), moreso than tumor grade (p=004) and SUVmax (p=0.56) [69].

$$TGA = MTV \ x \ SUVmean \tag{3}$$

Retention index (RI) is a dynamic parameter that can be calculated with dual-time-point (early and delayed) PET imaging, where RI is the difference of SUVmax on two scans divided by initial SUVmax. Rate of decline of RI during lung irradiation has shown to predict locoregional recurrence [70]. Further, in an analysis of 68 women with breast cancer, in comparison to other parameters including early and delayed SUV_{max}, RI showed best relation to biologic parameters including grade, Ki-67, and c-erbB-2 expression [71].

$$RI = \frac{SUV\max_{delayed} - SUV\max_{early}}{SUV\max_{early}} \tag{4}$$

From an oncologic standpoint, beyond the importance of baseline PET imaging for staging and radiotherapy planning, subsequent PET scans, whether during treatment or subsequent,

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are used for assessment of treatment response. From such data, inter-PET analysis can be performed (e.g. comparison of a pre-treatment scan to a post-treatment scan), not to be confused with factors such as the RI which are measured across two different scans performed during two time points of a single PET (e.g. early and delayed scans). Inter-PET parameters include the difference or change in (delta, Δ) values of parameters already previously discussed as well as "percent of" (e.g. percent of baseline), percent reduction from baseline, and rate of change (velocity "VEL"). Examples of such variables comparing a new PET to a baseline PET are as indicated below, where *t* is the time between PETs..

$$\Delta SUV\max = SUV\max_{new} - SUV\max_{baseline} \tag{5}$$

$$SUV\max_{\%Baseline} = \frac{SUV\max_{new}}{SUV\max_{baseline}} x100 \tag{6}$$

$$SUV\max_{\%reduction} = 100\% - SUV\max_{\%baseline} \tag{7}$$

$$VEl_{SUV\max} = \frac{SUV\max_{new} - SUV\max_{baseline}}{t} \tag{8}$$

4. Response criteria

Various methods for assessing and categorizing response of tumors based on radiographic imaging have been proposed, including the World Health Organization (WHO) criteria, the Response Evaluation Criteria in Solid Tumors (RECIST), and RECIST 1.1 [72–75]. Such criterica, depend on radiographic imaging, which may not best assess the biologic response, particularly given that metabolic response on PET routinely anatomic radiographic response on CT [76]. Accordingly, methods of categorizing response with PET have been developed, namely the European Organization for Research and Treatment of Cancer (EORTC) criteria and newer PET Response Criteria in Solid Tumors (PERCIST, version 1.0) [43,77]. A separate metric of response definitions using ^{18}F-FDG PET has been developed for lymphoma response and used for clinical trials [78]. Definitions of criteria are delineated in Table 1, Table 2, Table 3, Table 4, and Table 5.

RECIST 1.1 (2009) [75] (Anatomic)	EORTC (1990) [77] (Metabolic)	PERCIST (2009) [43] (Metabolic)
Measurable lesions have minimum size of 10 mm by CT scan,10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable), or 20 mm by chest X-ray. All other lesions are considered non-measurable	Tumor regions defined on pretreatment scan should be drawn on region of high ^{18}F-FDG uptake representing viable tumor. Whole tumor uptake should also be recorded. Uptake measurements should be made for mean and maximal tumor ROI counts per pixel per second calibrated as MBq/L. Partial volume may affect measurement of ^{18}F-FDG uptake. Tumor size from anatomic imaging in relation to PET scanner resolution should be documented where possible.	Measurable target lesion is hottest single tumor lesion SUV_{lbw} of ''maximal 1.2-cm diameter volume ROI in tumor" (Peak SUV_{lbw}). Peak SUV_{lbw} is at least 1.5-fold greater than liver SUV_{lbw} mean +2 SDs (in 3-cm spherical ROI in normal right lobe of liver). If liver is abnormal, primary tumor should have uptake > 2.0 SUV_{lbw} mean of blood pool in 1-cm-diameter ROI in descending thoracic aorta extended over 2-cm z-axis. Uptake measurements should be made for peak and maximal single-voxel tumor SUV_{lbw}. Other SUV metrics, including SUV_{lbw} mean at 50% or 70% of Peak SUV, can be collected as exploratory data; TLG can be collected ideally on basis of voxels more intense than 2 SDs above liver mean SUL

RECIST, Response Evaluation Criteria in Solid Tumors, European Organization for Research and Treatment of Cancer; PERCIST, PET Response Criteria in Solid Tumors; CT, Computed Tomography, ROI: Region of interest, SD, standard deviation.

Table 1. Evaluation of baseline lesions

	Target Lesions	Non-Target Lesions
CR	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
PR	≥ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.	N/A
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.	N/A
PD	≥ 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.	Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is considered progression.
Non-CR/ Non-PD	N/A	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Adapted from Eisenhauer *et al*. (2009) [75]. CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; N/A, Not Applicable

Table 2. RECIST 1.1 (Non-metabolic) response criteria

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Response	IWC[79]	IWC+PET[80]
CR	- no detectable clinical or radiographic evidence of disease - no disease-related symptoms - no biochemical abnormalities - negative BMB (if positive before treatment) - lymph nodes >1.5 cm at baseline regress to ≤ 1.5 cm - lymph nodes 1.1-1.5 cm at baseline regress to ≤ 1.0 cm	-CR by IWC with a completely negative PET - CRu, PR, or SD by IWC with a completely negative PET and negative BMB if positive prior to therapy - PD by IWC with a completely negative PET and CT abnormalities (new lesion or increasing size of previous lesion) ≥ 1.5 cm (≥ 1.0 cm in the lungs) and negative BMB if positive prior to therapy
CRu	- same as CR but either residual lymph mass > 1.5cm transverse diameter that has regressed > 75% or indeterminate BMB	- CRu by IWC with a completely negative PET but with an indeterminate BMB
PR	- ≥ 50% reduction in SPD of the six largest dominant nodes or nodal masses - no increase in size of spleen, liver, or other nodes - no new sites of disease	- CR, CRu, or PR by IWC with a positive PET at the site of a previously involved node/nodal mass - CR, CRu, PR, or SD by IWC with a positive PET outside the site of a previously involved node/nodal mass - SD by IWC with a positive PET at the site of a previously involved node/nodal mass that regressed to < 1.5 cm if previously > 1.5 cm, or < 1 cm if previously 1.1-1.5 cm
SD	- less than PR but not PD	- SD by IWC with a positive PET at the site of a previously involved node/nodal mass
PD	- applies only to patients with PR or nonresponders - ≥ 50% increase in the SPD from nadir of any previously identified abnormal node - any new lesion	- PD by IWC with a positive PET finding corresponding to the CT abnormality (new lesion, increasing size of previous lesion) - PD by IWC with a negative PET and a CT abnormality (new lesion, increasing size of previous lesion) of < 1.5 cm (< 1.0 cm in the lungs)
RD	- applies only to patients with CR or Cru - ≥ 50% increase in size of previously involved sites or - ≥ 50% increase in greatest diameter of any previously identified node > 1cm in short axis or - ≥ 50% increase in the SPD of ≥ 2 nodes or - any new lesion	(not defined)

Adapted from Juweid *et al.* (2005) [79]. IWC, International Workshop Criteria; PET, positron emission tomography; CR, complete remission; CRu, unconfirmed complete response, BMB, bone marrow biopsy, CT, computed tomography; PR, Partial Response; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease; RD, relapsed disease

Table 3. IWC+PET-based response definitions for lymphoma based on IWC designations and PET findings

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR, or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed Disease or PD	Any new lesion or increase of previously involved sites by ≥ 50% from nadir.	Appearance of a new lesion(s) > 1.5 cm in any axis, 50% increase in SPD of more than one node, or > 50% increase in longest diameter of a previously identified node >1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy.	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

From Cheson *et al.* Revised Response Criteria for Malignant Lymphoma (2007) [78]. CR, Complete Remission; FDG, ^{18}F-fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR = Partial Remission, SPD = sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Table 4. PET response definitions for clinical trials

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Response	EORTC	PERCIST 1.0	PERCIST Comment
Metabolic CR (CMR)	Complete resolution of ^{18}F-FDG uptake within tumor volume so that it was indistinguishable from surrounding normal tissue.	Complete resolution of ^{18}F-FDG uptake within measurable target lesion so that it is less than mean liver activity and indistinguishable from surrounding background blood-pool levels. No new ^{18}F-FDG-avid lesions in pattern typical of cancer. Disappearance of all other lesions to background blood-pool levels.	Percent reduction in SUV_{lbw} should be recorded from measurable region and time (weeks) after treatment initiated (i.e., CMR 290, 4). If anatomic progression by RECIST, must verify with follow-up.
Metabolic PR (PMR)	Reduction of minimum of 15% ± 25% in tumor ^{18}F-FDG SUV after 1 cycle of chemotherapy, and >25% after >1 treatment cycle. Reduction in extent of tumor ^{18}F-FDG uptake is not a requirement for PR.	≥ 0.8 and ≥ 30% reduction of Peak* ^{18}F-FDG SUV_{lbw} in target measurable tumor. No new lesions. SUV_{lbw} measurement is obtained from the most active lesion also present at baseline (even if a different lesion than measured at baseline). No increase > 30% in SUV_{lbw} or size of target or nontarget lesions.	Measurement is of the single most active lesion after treatment that was also present at baseline (e.g. may be a different lesion). Percent reduction in SUV_{lbw} should be recorded and time in weeks after treatment initiated (i.e., PMR -40, 3). If anatomic progression by RECIST, must verify with follow-up. Reduction in extent of tumor ^{18}F-FDG uptake is not requiremed.
Metabolic SD (SMD)	Increase in tumor ^{18}F-FDG SUV <25% or decrease of < 15% and no visible increase in extent of ^{18}F-FDG tumor uptake (20% in longest dimension).	No CMR, PMR, or PMD.	Peak SUV_{lbw} in metabolic target lesion should be recorded, as well as time (weeks) from initation of most recent therapy, in weeks (i.e., SMD -15, 7).
Metabolic PD (PMD)	Increase in ^{18}F-FDG tumor SUV of >25% within tumor region defined on baseline scan; visible increase in extent of ^{18}F-FDG tumor uptake (20% in longest dimension) or appearance of new ^{18}F-FDG uptake in metastatic lesions.	(1) >30% and >0.8 increase in ^{18}F-FDG Peak* SUV_{lbw} from baseline in pattern typical of tumor and not of infection/ treatment effect. Or (2) Visible increase in extent of ^{18}F-FDG tumor uptake (75% in TGA volume with no decline in SUV_{lbw} Or (3) New ^{18}F-FDG-avid lesions that are typical of cancer and not related to treatment effect or infection.	PD other than new visceral lesions should be confirmed on follow-up study within 1 month unless clearly associated with PD by RECIST 1.1. Should report percent change in Peak SUV_{lbw}, time elased since treatment (weeks) and whether new lesions are present/absent and their number (i.e., PMD, 135, 4, new: 5).

Adapted from Wahl *et al*.[43]. TLG, total lesion glycolysis; CMR, complete metabolic response; PMR, partial metabolic response; PD, progressive disease; SMD, stable metabolic disease; PMD, progressive metabolic disease; CR, complete remission; PR, partial remission.

*Single-voxel SUV_{lbw} (e.g. "SUV_{max}") is commonly used but has been reported to be less reproducible than Peak SUV_{lbw}, especially with very small single-voxel values. Peak SUV_{lbw} represents the highest mean value of a 1.2-cm-diameter spherical volume within a lesion and reduces variability secondary to voxel-to-voxel noise. It is suggested, but not required, that lesions assessed on PERCIST be larger than the 1.5-cm-diameter volume ROI used to minimize partial-volume effects.

Table 5. Metabolic Objective Response Assessment with ^{18}F-FDG PET: EORTC & PERCIST 1.0

4. Clinical relevance of treatment response assessment

4.1. Head & neck cancer – Definitive/preoperative chemoradiation

^{18}F-FDG PET has found a particularly significant role in treatment of head and neck cancers. It has long shown promise in its ability to prognosticate; in 37 patients from 1991-1994 with head and neck squamous cell carcinomas (HNSCC) receiving baseline ^{18}F-FDG PET, SUV_{max} showed correlation with aggressive disease and potential prediction for survival [81].

Beyond prognostication, ^{18}F-FDG PET is now routinely used to adapt treatment management, particularly in obviating surgical neck dissection in patients with complete response to initial radiation or chemoradiation therapy. Early studies have supported observation and omission of planned dissection after definitive radiotherapy for node-positive HNSCC with complete response on CT imaging, though at least selective nodal dissection was routinely practiced for residual neck masses [82,83]. With implementation of ^{18}F-FDG PET, its negative predictive value has further supported omission of planned neck dissection, including in patients with residual neck mass/lymphadenopathy [84–88].

In an early study by Yao *et al.* [84], 41 patients from 2000-02 with locally-advanced HNSCC received radiation therapy with or without chemotherapy as upfront treatment had pretreatment and follow-up CT and ^{18}F-FDG PET, with follow-up imaging 2.5-6 months (usually 3-4 months) post-treatment. Those without residual lymphadenopathy were observed. Twelve of 41 had residual lymphadenopathy; all had pathological testing, four with fine needle aspiration (FNA) biopsy, and eight had neck dissection. Follow-up ^{18}F-FDG PET correlated better than follow-up CT for residual disease, and SUV_{max} cutoff of < 3.0 had 100% negative predictive value and 80% positive predictive value, serving as a good "rule-out" test for residual disease and potential to forego planned neck dissection in favor of initial observation, thus decreasing overall toxicity [84].

In a further analysis, Yao *et al.* (2005) [85] reviewed findings in 53 patients (70 heminecks; 17 patients with bilateral disease) with N2A or higher HNSCC with complete response to radiation therapy (± chemotherapy). Forty-two had clinically positive (exam or CT) lymphadenopathy but negative PET; this group had option to pursue dissection; 17 were observed, and 4 had negative neck dissection. The remaining 7 heminecks had clinically and PET-positive lymphadenopathy, six had neck dissection, one FNA; three were positive and four were negative for residual disease. No regional recurrences had occurred after median follow-up of 26 months (range 12-57 months). Negative predictive value of PET was 100% and positive predictive value 43%. They conclude that observation is safe if both CT and PET-negative 12 weeks after treatment and potentially also if CT reveals small (e.g. <2-3 cm) but PET-negative lymphadenopathy.

Porceddu *et al*. [88] analyzed a select cohort of 39 patients with HNSCC treated with definitive radiotherapy (± chemotherapy) with (a) complete regression of the primary HNSCC, (b) clinical evidence of residual neck mass by exam or CT imaging 8 weeks after treatment, (c) a follow-up ^{18}F-FDG PET (median 12 weeks), and (d) either pathologic confirmation of neck status or > 12 months follow-up. Seven patients had residual PET uptake in the mass and proceeded to neck dissection (five were positive). Of the 32 with no residual tumor uptake, five had neck dissection (all pathologically negative), and 27 were observed (median follow-

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up of 34 months). One of the 27 observed patients had recurrence, yielding 97% negative predictive value. They conclude that in patients with a residual neck mass that is PET-negative 12 weeks after definitive radiotherapy (± chemotherapy), neck dissection is not required, and patients can be safely observed.

Such studies support timing of follow-up ^{18}F-FDG PET to be 12 weeks post-treatment [84,85,88]. High negative predictive value (91%) has been shown at 16 weeks [86] post-treatment, though early time points (e.g. 4 weeks) have shown increased false positives [87]. Metaanalyses support PET ≥ 12 weeks after completion of definitive therapy for moderately higher diagnostic accuracy. An added benefit of ^{18}F-FDG PET at this early follow-up interval is the potential to spare neck dissection in patients who show early distant metastatic disease [88,89].

Despite lack of any randomized prospective studies, significant retrospective evidence has continued to show similar findings. Recent metaanalyses [90–92], discuss 26, 27, and 51 studies including up to 2335 patients [92], overall supporting the high negative predictive value (approximately 95%) of follow-up PET and its value in omitting planned neck dissection. Further, despite the increased costs of PET imaging, PET-guided management in patients with complete response at the primary site has shown to be the more cost effective than CT-guided management or planned neck dissection [93].

4.2. Rectal cancer – Preoperative chemoradiation

Similar to HNSCC, first line treatment for locally-advanced rectal cancer includes upfront chemoradiation. In this setting, however, subsequent planned surgery remains standard of care. This multimodality neoadjuvant approach has shown to decrease local recurrence and improve overall survival [94,95]. Furthermore, neoadjuvant treatment has shown to increase sphincter-preserving surgery, conferring decreased surgical morbidity and improved quality of life [96–98].

Deferring subsequent surgical intervention in this disease site has similarly been investigated. In a cohort of 71 patients with distal rectal carcinoma considered resectable prior to concurrent chemoradiation with subsequent complete clinical response treated subsequently with observation alone (no planned surgery), five-year overall and disease-free survivals were 100% and 92%, respectively.

Improving restaging methods after neoadjuvant chemotherapy provides clinicians with increased information to guide management. Radiographic imaging modalities, however, are less sensitive to assessment of pathologic response, which is better characterized by metabolic imaging with ^{18}F-FDG PET [54,99,100].

A number of studies have attempted correlation of ^{18}F-FDG PET with tumor downstaging and response to neoadjuvant chemoradiation [100–105]. In a study by Capirci *et al.* [100] including 81 patients with locally-advanced rectal cancer, percent reduction of SUV_{max} from baseline to follow-up ^{18}F-FDG PET at 5-6 weeks after concurrent chemoradiation was most predictive of responders (71% reduction) versus non-responders (38% reduction) based on Mandard's criteria. They propose a cutoff of 65% reduction, yielding 85% sensitivity, 80% specificity, 81% positive predictive value, 84% negative predictive value, and 81% accuracy.

Notably, surgery is routinely planned approximately 6 weeks after neoadjuvant treatment, as surgery at 6-weeks was shown to have more tumor downstaging than at 2 weeks [106]. However, further tumor response and increased survival has been noted with intervals > 7 weeks [107]. A recent similar study by Perez *et al.* (2012) [105] of 91 patients with follow-up ^{18}F-FDG PET at 6 weeks but also again at 12 weeks showed best separation of good responders (49%) versus bad responders (51%) at 12 weeks (SUV_{max} of 9.1 in bad responders vs. 4.3 in good responders, $p<0.001$) rather than at 6 weeks (SUV_{max} of 6.4 in bad responders versus 5.8 in good responders, $p=0.5$). Good responders were more likely to have complete clinical response (38% vs. 7%, $p=0.001$) complete or near-complete pathologic response (45% vs. 16%, $p=0.008$) and smaller pathologic size (3.3 vs. 4.4, $p=0.03$). Increase from early-phase (1 hour after injection) to delayed-phase PET (3 hours after injection) at the 6 –week time point was 67% accurate of predicting good vs. bad responders. A good responder was considered anyone with $SUV_{12week} < SUV_{6week}$. They conclude that approximately half of patients will have continued improved response beyond 6 weeks, whereas approximately half will have increased metabolic activity. Dual-phase imaging at the 6-week point may help stratify the two groups, which may help guide clinicians in best timing for planned surgery.

In rectal cancer, ^{18}F-FDG PET restaging does show promise in potentially affecting treatment management; prospective studies investigating its role in this setting are awaited.

4.3. Lymphoma

^{18}FDG-PET finds various roles in management of lymphoma. For staging in Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), PET with CT (PET-CT) has been shown to improve sensitivity and specificity in evaluation of nodal and extranodal sites in comparison to contrast-enhanced CT without PET [108,109]. It has further shown to be 92% sensitive for bone marrow involvement in HL [110]. Beyond staging, PET has been used for post-chemotherapy restaging, assessing response during chemotherapy at initial diagnosis, and also during salvage treatment. In current NCCN guidelines for both HL & NHL, PET-CT has variably been incorporated into staging, restaging during chemotherapy, and restaging after chemotherapy; routine PET-CT in the surveillance setting, however, is recommended against secondary to false-positive risk [111,112].

Restaging

The role for PET in lymphoma is clearest in the setting of restaging, either during or subsequent to treatment. PET has a very high negative predictive value (88-100%, see Table 6) [113]. Further, after treatment, PET is superior to CT for distinguishing residual mass with versus without residual viable disease (e.g. post-treatment fibrosis) [114]. Spaepen *et al.* report on two cohorts, one with HL [115] and one with NHL [116] who were assessed with PET at baseline and after completion of chemotherapy. In the HL cohort [115] of 60 patients, 55 were PET- (PET negative) after chemotherapy and 5 were PET+ (PET positive). All 5 PET+ patients had relapse of disease. Of the PET- patients, 91% remained without recurrence after median follow-up of 32 months. Two-year PFS rates were 91% vs. 0% for PET- vs. PET+ patients ($p<0.0001$). Similarly, in the NHL cohort [116] of 93 patients, all 27 PET+ patients after chemotherapy had relapse (median 2.4 months), whereas 84% of the PET- patients remained in remission (median

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21 months). Two-year PFS rates were 85% vs. 4% for PET- vs. PET+ patients (p<0.0001). Halasz *et al.* (2011) [117] report a summary of post-chemotherapy and interim PET results. They further report a cohort of 59 patients with NHL, receiving 36 Gy (median) consolidative in-field radiation therapy (RT) (all patients) and R-CHOP chemotherapy (58 of 59 patients). Median follow-up was 47 months. In the 66% with negative PET after chemotherapy, 3-year PFS was 97%. However, with this treatment including RT, 3-year PFS was 90% in those with positive PET after chemotherapy (p-value not reported).

Author	Year	n	PPV (%)	NPV (%)
HL				
Spaepen [115]	2001	60	100	91%
Cerci [118]	2010	130	92%	100%
Engert [119]	2012	728	N/A	95%
NHL				
Bangerter [120]	1998	89	90%	98%
Jerusalem [114]	1999	35	43%	100%
Zinzani [121]	1999	31	93%	100%
Mikhaeel [122]	2000	45	60%	100%
Naumann [123]	2001	15	86%	88%
Spaepen [116]	2001	93	70%	100%
Gigli [124]	2008	42	75%	94%
Cashen [125]	2011	50	80%	92%

Adapted from Cheson [113]. HL, Hodgkin Lymphoma; NHL, Non-Hodgkin Lymphoma; PPV, positive predictive value; NPV, negative predictive value

Table 6. Positive and negative predictive value of PET-CT in lymphoma staging

Interim (during-chemotherapy) PET

More research has investigated interim (during chemotherapy) ^{18}FDG-PET for assessment of treatment response and prognostication (see Table 7). Cerci *et al.* [126] assessed interim PET after 2 cycles of ABVD (coxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy in 104 patients with early and advanced Hodgkin lymphoma. Negativity vs. positivity at interim PET significantly predicted event-free survival (EFS), 91% vs. 53% at 3 years for PET- vs. PET+ patients (p<0.001). On univariate analysis, interim PET was the best prognosticator of event-free survival (p<0.001), more so than stage, bulky disease, and international prognostic score (IPS) (p=0.24, p=0.15, p=0.99, respectively). It however failed to prognosticate survival (p=0.2), which was better predicted by age (cutoff 45 years, p=0.01) and IPS (0-2 vs. 3-7, p=0.04).

Author	Year	n	FU (months)	# cycles	Interim PET Response	Outcomes	p-value
HL							
Hutchings [127]	2005	85	40	2-3	74% PET- 11% PET+ 15% MRU	97% 2y PFS 46% 2y PFS	<0.001
Hutchings [109]	2006	77	23	2	79% PET- 21% PET+	96% 2y PFS 0% 2y PFS	<0.001
Kostakoglu [128]	2006	23	21	1	74% PET- 26% PET+	100% 2y PFS 13% 2y PFS	<0.001
Zinzani [129]	2006	40	18	2	80% PET- 20% PET+	97% PFS 12% PFS	<0.001
Gallamini [130]	2007	260	26	2	81% PET- 19% PET+	95% 2y PFS 13% 2y PFS	<0.001
Markova [131]	2009	50	25	4	72% PET- 28% PET+	100% PFS 28% PFS	NR
Cerci [126]	2010	104	36	2	71% PET- 29% PET+	91% 3y EFS 53% 3y EFS	<0.001
NHL							
Jerusalem [114]	2000	28	18	3	82% PET- 18% PET+	62% 2y PFS 0% 2y PFS	<0.001
Spaepen [132]	2002	70	36	2-3	53% PET - 47% PET +	16% progressed 100% progressed	<0.001
Haioun [133]	2005	90	24	2	60% PET - 40% PET +	82% 2y EFS 43% 2y EFS	<0.001
Mikhaell [134]	2005	121	29	2-3	41% PET - 43% PET + 16% MRU	88% 5y PFS 16% 5y PFS 59% 5y PFS	<0.001
Ng [135]	2007	45	31	1-5	69% PET - 31% PET +	15% relapsed 61% relapsed	<0.001
Han [136]	2009	40	24	2-4	68% PET - 32% PET +	10% progressed 71% progressed	NR
Pregno [137]	2009	88	26	2-4	72% PET - 28% PET +	85% 2y PFS 72% 2y PFS	0.048
Safar [138]	2009	112	38	2	63% PET - 37% PET +	84% 3y PFS 47% 3y PFS	<0.001
Cashen [125]	2011	50	15	2-3	52% PET - 48% PET +	85% 2y PFS 63% 2y EFS	0.031
Zinzani [139]	2011	91	50	variable	62% PET- 39% PET+	75% 4y EFS 18% 4y EFS	<0.001

HL, Hodgkin Lymphoma; NHL, Non-Hodgkin Lymphoma; PET, positron emission tomography; FU, Follow-up; n, number of patients in study with interim PET scan; EFS, event-free survival; PFS, progression-free survival; MRU, minimal residual uptake; # cycles, number of cycles of chemotherapy completed prior to interim PET; NR, not reported

Table 7. Prognostication of interim PET in lymphoma

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Drug salvage

In the setting of relapsing/refractory Hodgkin lymphoma, interim PET after 2 cycles of salvage high-dose chemotherapy has been assessed. Limited retrospective data from Castagna *et al*. [125] has shown similar prognostic potential, reporting 2-year progression-free survival of 93% (PET-negative) versus 10% (PET-positive, $p<0.001$).

PET Response-Adapted radiotherapy

In the German Hodgkin Study Group HD15 trial (2012) [119,140] with over 2,000 patients with advanced-stage Hodgkin lymphoma, 3 BEACOPP chemotherapy regimens were compared in a non-inferiority randomized trial. Radiotherapy was implemented with a "PET-guided" adaptive approach based on post-chemotherapy response regardless of treatment arm. If a PET-positive persistent mass 2.5cm or larger was present after completion of chemotherapy (median 21 days), 30Gy local radiation therapy was administered for consolidation. Negative predictive value for post-chemotherapy PET was 94% at 12 months follow-up. In the 3 arms, five-year freedom from failure ranged from 84%-89%, and five-year survival ranged from 92-95%. Consolidative radiotherapy was not randomized and was administered to 11% of patients (compared to 71% in HD9 [141]). With such excellent outcomes with this PET-guided radiotherapy approach, the authors indicate this approach as their current standard of care. Longer follow-up and prospective clinical trials assessing need for consolidative radiotherapy are still awaited.

4.4. Esophageal cancer – Definitive/preoperative

The role of multimodality therapy for esophageal and gastroesophageal cancer has historically not been well defined. Resection has been considered standard treatment for patients with resectable/localized disease without strong evidence supporting neoadjuvant therapy, despite significant risk for local and distant recurrences yielding poor 5-year survival rates ranging from 15-39%[142]. Neoadjuvant treatment is increasingly becoming adopted as standard of care for locally-advanced disease, with use continuing to increase [143,144]. Multiple prospective trials did not report survival benefit with neoadjuvant chemoradiotherapy [145–147], and randomized studies supporting neoadjuvant treatment are scarce. Walsh *et al.* (1996) [148] showed increased 3-year overall survival from 6% to 32% with neoadjuvant treatment ($p<0.01$) in a study of 113 patients. In the recently published CROSS trial [149] with 366 patients, addition of neoadjuvant chemoradiation increased R0 resection (resection with negative pathologic margins) from 69% to 92% ($p<0.001$) and more than doubled median overall survival from 24 to 49 months (hazard ratio = 0.66, $p=0.003$).

In patients receiving neoadjuvant chemoradiation, a portion—29% in the Dutch CROSS study—are found to have pathologic complete response on subsequent surgery. In a single-institution review, pathologic complete response from neoadjuvant treatment was associated with higher 5-year and overall survival (48% vs. 18% and 50 months vs. 28 months, respectively) in comparison to patients without complete response [150]. With treatment response bearing significant prognostic potential, assessment of response to neoadjuvant treatment for esophageal cancer has been an area of increasing research [150–163].

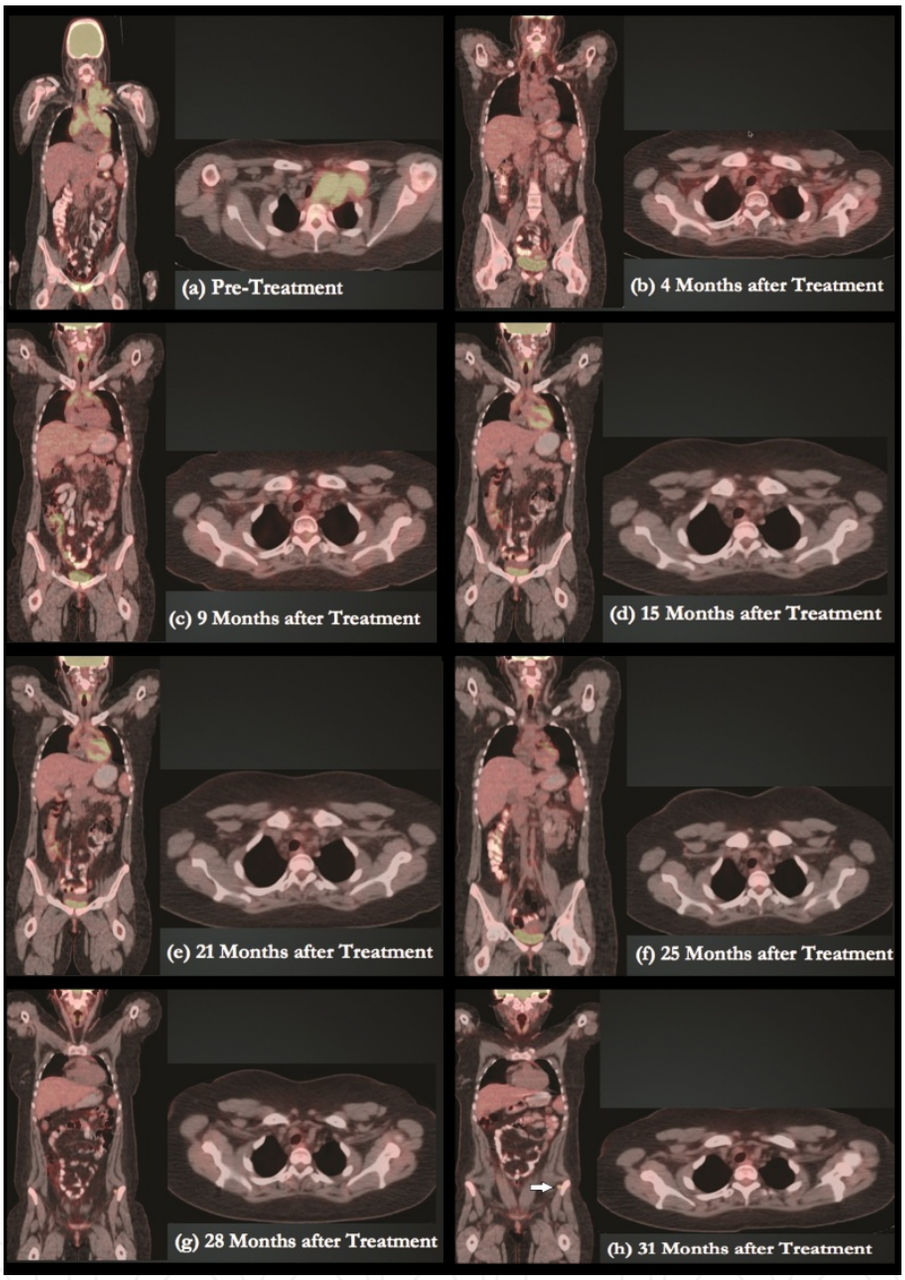

Figure 1. This is a 12-year-old female with a history of Stage IIB bulky nodular sclerosing Hodgkin lymphoma involving the bilateral cervical chain and mediastinum. She had achieved a complete response with 6 cycles of COPP-ABV chemotherapy. She then received a total radiation dose of 3060 cGy in 17 fractions of 180 cGy to the cervical and mediastinal lymph nodes. As seen in the serial PET/CT images (b-f above), the mediastinal and cervical lymph nodes responded well. However, by 28 months post-treatment, a left iliacus muscle lymph node became suspicious for lymphoma involvement (g – max SUV 5.0). By 31 months post-treatment, this node had increased further (h – max SUV 7.7).

In an early study by Weber *et al.* (2001) [151] in forty patients receiving neoadjuvant chemotherapy (without radiotherapy) for esophageal cancer, patients had ^{18}FDG-PET both pretreatment and after 14 days of treatment (during chemotherapy). Metabolic response was considered decrease of 35% from baseline, which was associated with 93% sensitivity and 95%

specificity for prediction of clinical response. Responders had longer time to progression/ recurrence and overall survival.

In a follow-up study [152], patients had three ^{18}FDG-PET scans: one pretreatment, one during treatment (2 weeks after starting), then 3-4 weeks preoperatively (but after neoadjuvant treatment. Responders had more decrease at 2 weeks (44% vs. 21%, $p<0.01$) and preoperatively (70% vs. 51%, $p=0.01$). During-treatment PET had higher power than the preoperative PET treatment to predict response (area under curve (AUC) of receiver operator characteristic (ROC) 0.78 vs. 0.88), though difference was not statistically significant ($p=0.40$). Best cutoff for response in this cohort was 30% reduction from baseline (93% sensitive, 88% accurate), who all proceed to have R0 resection. Responders by this PET criteria had higher survival (median 38 vs. 18 months; 2-year rates 79% vs. 38%, $p<0.01$).

Analysis of gastroesophageal junction tumors again showed improved prognostic potential with PET using percent reduction of SUV_{max} 2 weeks after treatment start ($p=0.03$) versus after completion of neoadjuvant treatment ($p=0.09$) [153]. Though percent reduction is routinely used to assess response, thresholds of decrease of SUV_{max} (e.g. decrease of ≥10) from before to after neoadjuvant treatment have shown to predict significant histopathologic response [158].

More recent studies have showed other metrics as better predictors of response. In a comparison of SUV_{max}, MTV based on fixed threshold of 2.5 SUV, and SUV_{mean} (of MTV), and TGA, MTV and TGA were both 91% sensitive in predicting histopathologic response when also using CT, but MTV increase specificity from 90% to 93%. Most predictive was TGA (AUC=0.95) followed by MTV (AUC=0.92), SUV_{max} (AUC=0.84), and SUV_{mean} (AUC=0.82) [159]. Further, metabolic response criteria (e.g. PERCIST) have shown better assessed response in comparison to non-metabolic methods (e.g. RECIST and WHO) [159,163].

With various studies showing prognostic potential of ^{18}FDG-PET early during treatment, there is question as to the utility of PET to potentially facilitate treatment modification [152]. Kwee (2010) [160] performed a metaanalysis of 20 PET-response studies including 849 patients; it however showed wide ranges of sensitivity and specificity with overall AUC of 0.78. Based on the pooled data, PET was not recommended for routine clinical use to guide neoadjuvant treatment. Furthermore, in a retrospective single-institution review [164], patients treated with neoadjuvant chemotherapy followed by surgery had similar freedom from local failure ($p=0.92$) and overall survival ($p=0.15$) in comparison to patients receiving definitive chemoradiation who attained metabolic CR (SUV<3). Furthermore, in this retrospective study, though not statistically significant, rate of death in the definitive chemoradiation group was higher than in the surgical group despite worse baseline characteristics.

Similar to head and neck cancer, prospective studies are awaited to formally assess necessity of surgical management after complete metabolic response to neoadjuvant chemoradiation therapy in operable/resectable patients.

4.5. Non-Small Cell Lung Cancer (NSCLC)

^{18}FDG-PET is currently recommended by NCCN guidelines for routine staging of stage I-III NSCLC [67]. Radiotherapy planning with PET fusion has further been recommended for

biologically-targeted radiotherapy in which 3D-PET fusion is implemented for tumor delineation, with PET performed with minimal delay between PET and start of treatment, given propensity for rapid disease progression [64–66,165]. Metabolic (PET) response to treatment has been shown to pre-date radiographic (CT) response. Despite increasing data showing utility of PET for assessing treatment response in NSCLC and predicting outcomes including survival, guidelines currently do not recommend PET in this setting [44,45,67,76,166–177].

In an early study of 15 patients receiving chemotherapy for IIIB-IV NSCLC, patients received weekly PET starting at initiation of chemotherapy until completion of 2 cycles (6 weeks later) [171]. Reduction of SUV_{max} by 50% week 1 to week 3 was predictive of survival of > 6 months, thus facilitating prediction of response to treatment. Those with less reduction died within 6 months. In patients without early response, management may thus be altered to forego futile chemotherapy. In an early study [167] of 15 stage I-III patients receiving radiotherapy, patients received 3 PETs: one pre-treatment, one during treatment after approximately 45 Gy, and one 3 months post-treatment. Response during treatment was shown to correlate with overall response after treatment (p=0.03), and SUV during treatment correlated with SUV 3 months after (p<0.001). A number of studies with prospective PET data with cutoffs are listed in Table 8.

Author	Year	n	Stage	Criteria	Outcome	p
Vansteenkiste [172]	1985	15	IIIA	50% decrease	OS	0.03
MacManus [173]	2003	73	I-III	CMR	OS	<0.01
Weber [174]	2003	57	IIIB-IV	20% decrease	OS	<0.01
Hellwig [175]	2004	47	IIB-III	SUV < 4	OS	<0.01
Eschmann [176]	2007	70	III	CMR or 80% decrease	OS	<0.01
de Geus-Oei [177]	2007	51	IB-IV	35% decrease	OS	0.02
Nahmias [171]	2007	16	IIIB-IV	50% decrease from week 1 to week 3	OS	<0.01
Tanvetyanon [178]	2008	89	IB-IIIB	CMR	OS	NS
Mangona [45]	2012	129	IA-IB	At 12 months		
				SUV ≥ 3.9	LF*	<0.01
				60% decrease	LF*	<0.01
				SUV ≥ 6.0	LF†	<0.01
Mangona [70]	2012	16	IIB-IIIB	During treatment		
				30% decrease	CSS	<0.01
				decrease ≥ 4	LRR	<0.01

Adapted from Hicks *et al.* [170]. CMR, complete metabolic response; OS, overall survival; LF, local failure; CSS, cause-specific survival; LRR, locoregional recurrence; NS, not statistically significant.*100% sensitive. †100% specific.

Table 8. PET Cutoffs/Criteria and Outcomes in NSCLC

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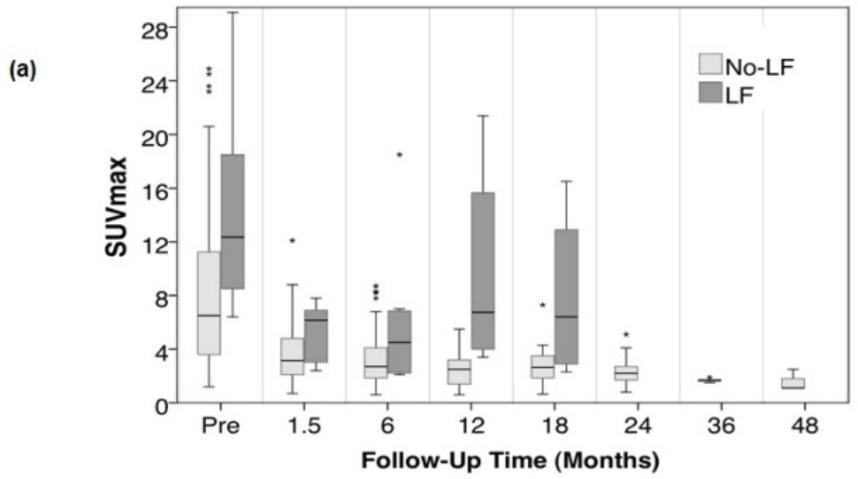
SBRT

Stereotactic body radiotherapy (SBRT), employing modern techniques including 4-D treatment planning and image-guided radiotherapy (IGRT) has been shown to be an effective, cost-efficient, treatment option for definitive management of early-stage NSCLC as well as lung metastases from other organs with excellent tumor control rates; in comparison to medically-operable patients who are treated with resection, retrospective data of primarily medically-inoperable patients with poor pulmonary function suggests excellent tumor control with SBRT with rates similar to that of sublobar resection and minimal toxicity [179–191].

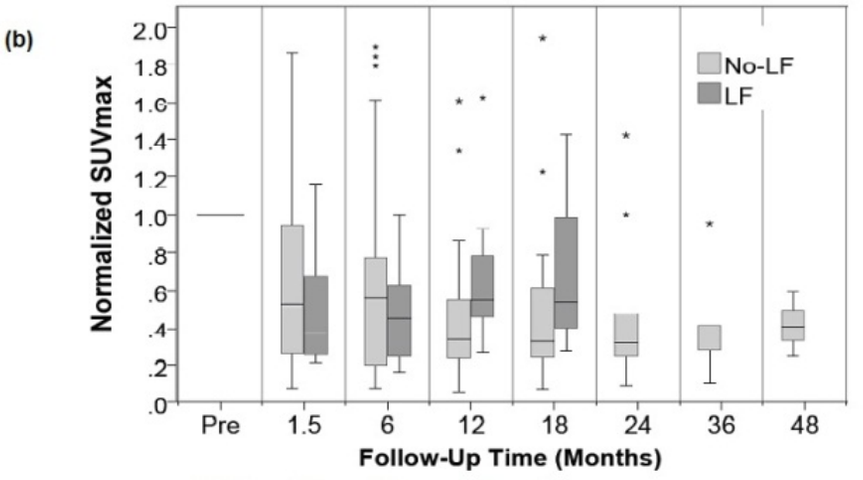
In a large single-institution analysis [45] of 129 consecutive NSCLC tumors treated with SBRT, 58% enrolled on a prospective phase II protocol, patients had baseline and serial follow-up PET imaging. Sixteen patients additionally had weekly on-treatment 4D-PET-CT. Median follow-up was 19 months and median time until local failure (LF) of 15 months. A total of 475 PETs were obtained. Change in SUV from pre-treatment to follow-up are seen in Figure 1 and stratified by status of LF vs. no-LF based on last follow-up. Though baseline SUV_{max} was higher in the LF group (12.4 vs. 6.5, p=0.0001), difference was not significant at 1.5 and 6 months, as both groups responded. SUV at 12 months, however, was significantly higher for the LF vs. no-LF group (6.8 vs. 2.5, p=0.02). Cutoffs predictive of LF were 12-month SUV ≥ 3.9 (100 sensitive), 12-month SUV ≥ 6 (100 specific), and 12-month SUV ≥ 40% of baseline (see Table 8). Analysis of SUV_{max} velocity showed trend for higher velocity at 12 months (+0.18 SUV/month vs. -0.03 SUV/month, p=0.058). On multivariate logistic regression, 12-month SUV was most predictive of LF (p=0.057).

Hyperfractionated radiotherapy

In a cohort of 16 patients with locally-advanced NSCLC enrolled on a phase II protocol, patients had PET at baseline, weekly during treatment, and at follow-up [70,192] (see Figure 2). Patients received hyperfractionated radiation therapy 1.5 Gy BID with concurrent chemotherapy either as definitive treatment (n=12) or as neoadjuvant treatment (n=4) delivering RT with daily online cone-beam CT for image guidance and intensity modulated radiotherapy (IMRT) to minimize potential normal tissue toxicity [190,193,194]. After potential follow-up of 20 months (range 12-28), 7 had locoregional recurrence (LRR), and 8 died (5 of disease). Interestingly, there was trend for higher SUV_{max} at baseline in those without LRR (the no-LRR group) than in those with LRR (19.0 vs. 11.9, p=0.08), an inverse relationship than expected. The rate of SUV decrease in the LRR group during RT was 1.6 per week, significantly faster than the no-LRR group (0.23 per week, p=0.02) such that SUV values were similar for both groups by the 4^{th} on-treatment PET (p=0.95) (see Table 9). A during-RT decrease of less than 4 from baseline was predictive of LRR (p<0.01), and a during-RT decrease less 30% from baseline was predictive of death from disease (p<0.01). Velocity of retention index from PET1 to PET-FU predicted overall survival (+1.6%/week in those who died vs. -1.7%/week in those alive, p=0.03).



		Pre	1.5	6	12	18	24	36	48
LF	Median	12.4 (n=10)	6.2 (n=8)	4.5 (n=8)	6.8 (n=8)	9.3 (n=5)	-	-	-
	IQR [25%-75%]	[8.3-19.6]	[2.8-7.2]	[2.2-6.9]	[4.0-16.8]	[2.9-18.0]	-	-	-
No LF	Median	6.5 (n=119)	3.2 (n=108)	2.7 (n=88)	2.5 (n=46)	2.7 (n=20)	2.2 (n=13)	1.7 (n=5)	1.1 (n=3)
	IQR [25%-75%]	[3.6-11.4]	[2.1-4.8]	[1.8-4.1]	[1.4-3.3]	[1.8-3.5]	[1.5-2.9]	[1.6-1.8]	[1.1-1.1]
p	(LF vs. no-LF)	0.001	0.033	0.203	0.024	0.097	-	-	-



		Pre	1.5	6	12	18	24	36	48
LF	Median	1.00 (n=10)	0.36 (n=8)	0.45 (n=8)	0.55 (n=8)	0.55 (n=5)	-	-	-
	IQR [25%-75%]	[1.00-1.00]	[0.23-0.75]	[0.22-0.66]	[0.46-0.85]	[0.40-1.04]	-	-	-
No LF	Median	1.00 (n=119)	0.53 (n=108)	0.56 (n=88)	0.33 (n=46)	0.32 (n=20)	0.31 (n=13)	0.37 (n=5)	0.41 (n=3)
	IQR [25%-75%]	[1.00-1.00]	[0.25-0.95]	[1.8-4.1]	[1.4-3.3]	[1.8-3.5]	[1.5-2.9]	[1.6-1.8]	[1.1-1.1]
p	(LF vs. no-LF)	-	0.365	0.501	0.044	0.875	-	-	-

Assessment of response for NSCLC with serial ^{18}FDG-PET. 129 node-negative non-small-cell lung tumors were treated with stereotactic body radiation therapy (SBRT) and followed with routine follow-up imaging. SUV for tumors with eventual local failure (LF) and no local failure (no-LF) at last follow-up are compared. (a) Plot of SUV_{max} vs. time, with baseline PET SUV_{max} at t=0. Tumors with resulting LF show higher SUV_{max} both at pre-treatment and at 12-months follow-up, though SUV_{max} at 1.5 and 6 months were similar. (b) Plot of normalized SUV_{max} (baseline normalized SUV = 1). Normalized SUV_{max} is higher at 12 months in the LF group but similar at other time points. Values are plotted as box plots with thick black line representing the median value, lower box border the 25th percentile, upper box border the 75th percentile, and outliers with points. PET SUVs subsequent to any treatment for recurrence (e.g. chemotherapy) were excluded; thus, the no-LF group had data at longer follow-up (e.g. 24, 36, and 48 months).

Figure 2. SUV kinetics after stereotactic body radiotherapy for NSCLC

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		PET0	PET1	PET2	PET3	PET4	PET-FU	Velocity during RT
SUV_{max}	LRR	11.9	9.5	11.4	10.6	9.8	6.7	-0.23/week
	no-LRR	19.0	17.3	16.3	12.8	9.4	4.6	-1.60/week
	p	*0.08*	*0.02*	*0.13*	*0.32*	*0.95*	*0.66*	*0.02*
$SUV_{delayed}$-SUV_{early}	LRR		1.90	2.00	2.15	1.30	0.95	-0.05/week
	no-LRR	-	4.20	2.80	1.60	1.55	0.61	-0.68/week
	p		*0.02*	*0.15*	*0.82*	*0.55*	*0.82*	*0.15*
Retention Index	LRR		23.3%	22.5%	22.8%	14.3%	18.4%	-0.8%/week
	no-LRR	-	27.1%	19.8%	18.5%	15.3%	17.6%	-3.4%/week
	p		*0.92*	*0.88*	*0.16*	*0.57*	*0.76*	*0.04*

Patients had PET-CT before treatment for staging/planning (PET0), weekly during treatment (PET1, PET2, PET3, and PET4), and at 6-12 weeks follow-up (PET-FU); RT, Radiation Therapy; LRR, locoregional recurrence; no-LRR, no locoregional recurrence at last follow-up.

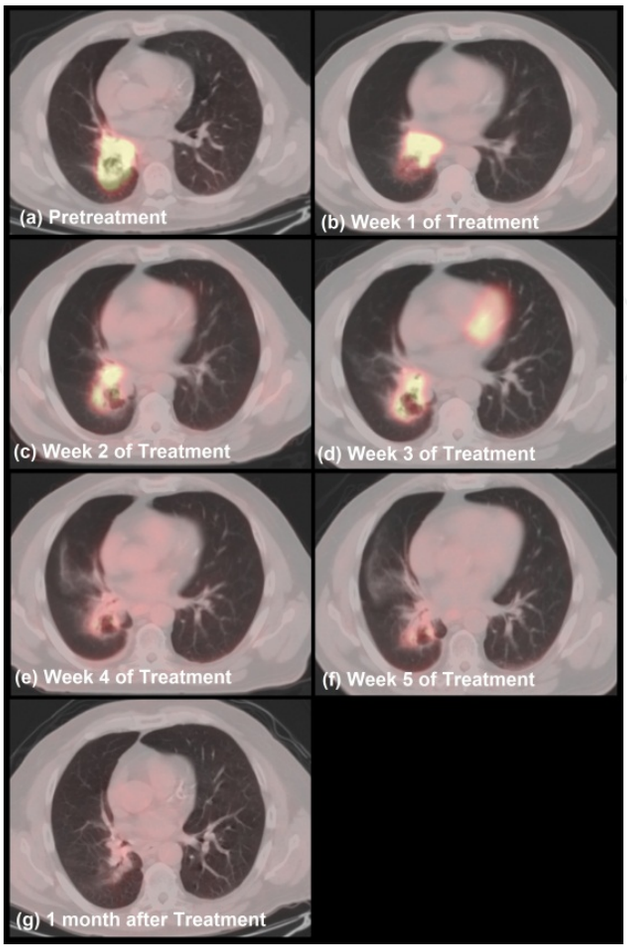
Table 9. On-treatment SUV kinetics of locally-advanced NSCLC treated with concurrent chemoradiation

PET shows prognostic potential in this disease site from prior to treatment to early in treatment, to later in follow-up. It further holds potential for adjusting management (e.g. discontinuing ineffective chemotherapy, potentially modifying radiation therapy during treatment, and predicting delayed local failure for potential earlier biopsy/intervention). We await further prospective PET data and clinical trials to best define the role of PET in assessment of treatment in NSCLC.

5. Future directions

As PET is used for staging and radiotherapy prior to treatment for a number of organ sites, PET further has potential for restaging and replanning radiotherapy during the course of therapy. Beyond mid-treatment prognostication, this facilitates potential treatment modification. For radiotherapy re-planning, potential changes are include modification of target volumes based on anatomic changes from treatment, modification of boost volumes, and potentially adjustment of prescription dose based on response (e.g. higher dose for poor responders vs. less dose for good responders). Such investigations are currently ongoing in clinical protocols.

In treatment of locally-advanced head and neck squamous cell carcinomas, our institution has initiated a prospective, non-randomized trial evaluating the utility of such an adaptive approach focusing on target volume adaptation. Patients receiving 70 Gy IMRT in 35 daily fractions (7 week duration) with concurrent cisplatin or cetuximab are eligible. ^{18}FDG-PET-CT is utilized for treatment planning. Repeat PET-CTs and diagnostic CTs are obtained after



1.5 Gy twice daily with concurrent Taxotere. He had a complete metabolic response to treatment evident at first follow-up PET 1-month after treatment. SUV values (early → delayed): (a) Pre: 29.4 → 36.9; (b) Week 1: 17.8 → 23.6; (c) Week 2: 13.3 → 16.0; (d) Week 3: 15.7 → 17.0; (e) Week 4: 4.6 → 5.8; (f) Week 5: 4.2 → 5.3; (g) 1 month follow-up: 2.0 → 2.2

Figure 3. This is a 68-year-old male who presented with dyspnea and hemoptysis. Workup revealed a stage IIIB (T4, N2, M0) squamous cell carcinoma of the right lower lobe, 7cm in size invading the mediastinum. He received hyperfractionated intensity-modulated radiotherapy, 66 Gy in 1.5 Gy fractions twice daily.

fractions 10 and 22 for the purpose of treatment adaptation. Three different treatment plans will be created, one for fractions 1-12 (based on pre-treatment PET-CT), one for fractions 13-24 (based on PET-CT after fraction 10), and one for fractions 25-35 (based on PET-CT after fraction 22). Such an adaptive approach may help decrease dose delivered to normal tissue as tumors decrease in size during treatment, potentially decreasing toxicity. On this protocol, patients also obtain weekly PET-CTs for assessment of treatment response, though prescription dose is not modified in this study.

For non-small cell lung cancer, investigators have further used on-treatment PET to facilitate PET-adaptive replanning, with PET-adaptive dose escalation incorporated into a currently-enrolling Radition Therapy Oncology Group (RTOG) Protocol, RTOG 1106 [195,196]. All

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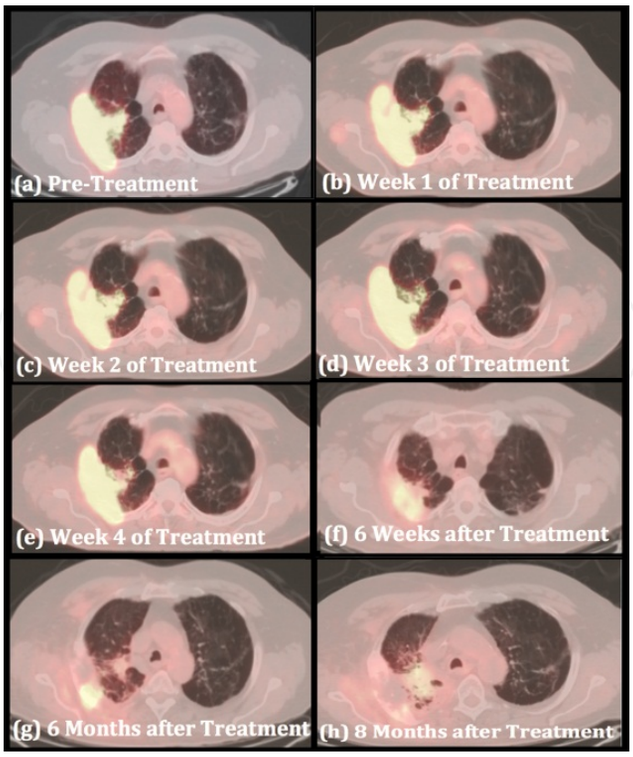

SUV values (early → delayed): (a) Pre: 23.4 → 28.7; (b) Week 1: 14.8 → 16.0; (c) Week 2: 11.0 → 12.7; (d) Week 3: 11.0 → 12.8; (e) Week 4: 12.1 → 15.; (f) 6-week FU: 6.5 → 8.; (g) 6-month FU: 12.5 → 15.7; (h) 8-month FU: 4.9 → 6.3

Figure 4. This is a 66-year-old male who presented with right shoulder pain. Workup revealed a clinical stage IIIA (T3 N1 M0) squamous cell carcinoma of the right upper lobe of the lobe with chest wall invasion causing destruction of ribs 2-4. He received hyperfractionated intensity-modulated radiotherapy 72Gy, 1.5 Gy twice daily, with concurrent and maintenance taxotere for 4 months. SUV nadir occurred at 6 weeks with evident local progression at 6 months.

patients on this protocol will have ^{18}FDG-PET; however, a subset are planned to also have ^{18}F-MISO-PET at staging.

As such radiotracers beyond ^{18}F-FDG show particular promise, further results of clinical trials implementing these are awaited.

6. Conclusion

Over the past 20 years, the body of data assessing treatment response with PET has grown significant. Assessing treatment response with PET can yield highly prognostic information. Such information, however, may have no end-effect on management. As clinicians, many of our PET-based decisions are based on retrospective and prospective data without comparison of management options based on PET results. Such results are significantly hypothesis-generating. The high negative predictive value of PET in various organ sites may increase comfort of clinicians when considering omitting potentially unnecessary interventions (e.g. neck dissection after complete metabolic response of locally-advanced head and neck cancer

to chemoradiation, esophagectomy after complete metabolic response to chemoradiotion, or consolidative radiotherapy after complete metabolic response in Hodgkin lymphoma). High-level evidence to justify such treatment-adapting decisions based on PET are currently lacking, thus we caution application of such data as justification for modifying standard of care. We strongly encourage PET-adaptive management under the guise of clinical trials at this time, as the role of PET in oncology continues to best be defined.

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