7 Conventional Radiological Techniques and PET-CT in Treatment Response Evaluation in Post-Radiotherapy Setting

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7.1 Introduction

In most Western countries, radiotherapy forms part of 40% of oncology treatment pathways and is the mainstay of 19% of curative treatment [1]. Intensity-modulated radiotherapy has become the standard of care for multiple malignancies by virtue of the ability to deliver highly conformal doses while minimizing damage to adjacent tissues [2].

Accurate response assessment informs future treatment decisions and in some situations guides the need for potentially curative surgical salvage. Early recognition of treatment success or failure can, therefore, impact on patient survival. Traditionally, this assessment relied upon anatomical measurement of disease, such as CT evaluation using Response Evaluation Criteria in Solid Tumors (RECIST). However, such measurements are of inherently limited value following radiotherapy, as residual masses/tissue abnormalities are common posttreatment and do not necessarily infer the presence of viable clonogenic tumor cells. For example, in head and neck cancer, residual lymph node masses are well recognized following radiotherapy and, particularly with human papillomavirus-related disease, can continue to regress many months following completion of treatment [3]. Anatomic imaging assessments performed with CT or MR imaging are usually less capable of depicting small residual disease deposits. In addition, because surgery, chemotherapy, and radiotherapy produce edema, hyperemia, scarring, and loss of facial planes, differentiation of residual or recurrent disease from posttherapy changes using conventional imaging techniques including CT and MRI is particularly challenging. Moreover, novel therapeutic agents may be cytostatic instead of cytoreductive in which case treatment response may not be reflected in a decrease in tumor size [4].

The challenge of determining the presence or absence of viable tumor within residual masses following radiotherapy provides a powerful rationale for the incorporation of functional imaging into response assessment protocols.

PET/CT employs radioactive tracers to assess molecular characteristics of tissues. Malignancies have distinctive molecular profiles, which differ compared with surrounding normal tissue and may, therefore, be exploited by PET/CT imaging with appropriate tracers [4].

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PET/CT in radiotherapy response assessment is useful for several reasons. Firstly, molecular response to radiotherapy may precede anatomical response, and PET/CT may allow a more accurate assessment at an earlier stage than standard cross-sectional imaging. Secondly, use of specific tracers allows a more reliable discrimination of tumor from treatment-related inflammation or fibrosis. Thirdly, tumors respond heterogeneously during radiotherapy [5]. Although this may not be apparent on anatomical imaging, by using an appropriate molecular biomarker, which changes at an early stage and correlates with response, this variability may be demonstrated with PET/CT and the treatment adapted accordingly [4].

PET/CT has potential utility at different stages of radiotherapy response. Firstly, a growing area of research focuses on employing PET/CT during radiotherapy; this can facilitate an adaptive individualized approach to treatment with potential for escalation or de-escalation strategies depending on the quality/speed of on-treatment response or switching of treatment approach, for example, to surgery in the event of an absent early response to radiotherapy. Secondly, imaging can be used after radiotherapy to stratify patients who are responding and conversely identify nonresponders and discriminate this from treatment effects, allowing for early aggressive treatment of persistent or progressive disease [4].

7.2 Functional Imaging for Disease Response Assessment to Radiotherapy

The use of functional MR imaging techniques to assess biomarkers of early response has also been proposed. The use of apparent diffusion coefficient (ADC) values from diffusion-weighted MR imaging has been reported to result in a lower false-positive rate for both primary and nodal disease response than the use of uptake at ^{18}F-labeled Fluorodeoxyglucose (FDG) PET [6].

Overall, functional imaging appears to be a promising addition to clinical examination and anatomic imaging for assessing the response of head and neck squamous cell carcinoma (SCC) tumors to radiation therapy. This is particularly true in the clinical scenario of residual masses, where anatomic imaging techniques are inaccurate. The use of FDG PET/CT is now supported by considerable data [7]. A role also may be established for other PET- and MR imaging-based techniques.

7.2.1 Functional, Metabolic PET Imaging

Various PET tracers are available for imaging cellular processes such as metabolism, proliferation, hypoxia, and cell membrane synthesis. PET tracers, along with advances in understanding of molecular cancer biology, can help individualize therapeutic approaches.

7.2.1.1 Glucose Metabolism

The use of FDG PET/CT to demonstrate altered cellular glucose metabolism is the most widely used application of molecular imaging. Complementary anatomical and functional information facilitates an accurate noninvasive assessment of surrogate biomarkers of disease activity. FDG PET has an emerging role as a response assessment tool in treatment response to radiotherapy. FDG PET/CT is a useful modality for assessing treatment response because it is able to evaluate the metabolic activity as a marker of tumor cell viability, overcoming the known limitations of morphologic imaging modalities.

FDG PET/CT is recommended by the NCCN guidelines for therapy assessment after chemoradiotherapy (CRT) or radiotherapy (RT). For example, in patients with head and neck SCCs, the pooled sensitivity, specificity, positive predictive value, and negative predictive value of PET/CT for assessing disease response were 87.7%, 87.8%, 75.7%, and 94.3%, according to the results of two meta-analyses [7, 8]. PET had a higher diagnostic accuracy if performed more than 12 weeks after the completion of treatment. The high negative predictive value of a finding of complete metabolic response can be used to guide management decisions. In a study of FDG PET-based response assessment performed by Porceddu et al. [9], 41 patients with PET-negative residual nodal masses were observed

without subsequent nodal failure. Therefore, a complete metabolic response at PET can be used to avoid unnecessary surgery to residual masses.

7.2.1.2 Tumor Hypoxia

Hypoxia is an established indicator of poor prognosis for patients with different cancers [10]. It leads to radiation resistance in tumor cells by preventing irreversible damage to cell deoxyribonucleic acid (DNA) by free radicals induced by ionizing radiation; oxygen is needed for the production of free radicals. Cell DNA, thus, undergoes repair and tumor cells survive [11]. The critical partial pressure of oxygen (pO_2) threshold, below which solid tumors show resistance to radiation therapy, is approximately 10–15 mmHg [10]. The amount of radiation needed to achieve cell kill in hypoxic conditions is three times that needed in normoxic conditions [6]. There is limited evidence of improved treatment outcomes with a reduction in hypoxia [12], which can be achieved by adding oxygen-mimicking agents to radiation therapy or by giving radiation therapy along with an oxygen-enhanced gas mixture such as carbogen (a mixture consisting of 95% oxygen and 5% carbon dioxide) [10].

Tumor hypoxia can be assessed by a number of invasive techniques, including polarographic oxygen electrodes and immunohistochemical staining of pathologic specimens to allow detection of hypoxia-specific markers. In addition, there are a number of PET tracers available that allow noninvasive visualization of hypoxia. At present, there is no consensus on which hypoxia-specific agent is most effective for PET; each of these agents has its advantages and disadvantages and may be better suited for evaluating some tumor types than others.

FMISO is the most extensively investigated PET imaging agent and has been used for the assessment of head and neck SCCs [13–16]. Studies have shown that uptake of FMISO is not necessarily correlated with uptake of FDG [15, 16] and, thus, that the two agents represent different tumor properties. However, high uptake of FMISO before radiation therapy can be predictive of local-regional treatment failure, and thus indicative of a poor prognosis. However, further work is needed to investigate the normal variation in FMISO uptake and tumor oxygenation kinetics before therapy, as well as changes in the hypoxic subvolume during therapy, before FMISO imaging can be clinically used to guide hypoxia-mediated intensity modulated radiation therapy (IMRT) [17, 18].

^{18}F-fluoroazomycin arabinoside (FAZA) is a hypoxia-specific PET agent that clears the blood more rapidly than FMISO and, as a result, produces a higher target-to-background signal ratio [19]. Fluorine ^{18}F-erythronitroimidazole (FETNIM) is theoretically a more potent indicator of hypoxia than FMISO, owing to its greater hydrophilia and better pharmacokinetics [20]. FAZA and FETNIM both appear to be promising hypoxia-specific radiotracers, but further studies of these agents are needed, especially in direct comparison with FMISO.

Radioactive copper-labeled diacetyl-bis-(N4-methylthiosemicarbazone) (ATSM) is a different type of hypoxia-specific PET tracer. ATSM is a neutral lipophilic compound that can permeate cell membranes. In hypoxic conditions, ATSM molecules are reduced and negatively charged, causing the agent to accumulate selectively in hypoxic cells while it washes out rapidly from normoxic cells. ATSM clearance through the blood leads to a high tumor-to-background signal ratio on PET images [21]. Pilot studies of the effectiveness of ATSM for evaluating different tumors showed a significant difference in the uptake of this tracer between patients with residual or recurrent tumor and those without residual or recurrent tumor; by contrast, there was no significant difference in FDG uptake between the two patient groups [22]. The disparity in uptake between the two tracers suggests that ATSM may be more useful for predicting early tumor response to chemoradiation therapy.

7.2.1.3 Tumor Cell Proliferation

Radiation therapy and chemotherapy can lead to a rapid decrease in the rate of cellular proliferation in responding tumors, a change that usually precedes a decrease in tumor size [23]. By contrast, accelerated tumor cell repopulation is an important indicator of underlying radiation resistance and, hence, treatment failure [11]. Imaging

strategies for identifying tumor cell repopulation as part of the early response assessment and for delineating areas of high cell turnover as targets for dose escalation are, therefore, desirable.

^{18}F-labeled FLT PET is the functional imaging technique most widely used to assess cellular proliferation [24]. FLT, unlike FDG, is taken up only by actively dividing cells, not by surrounding inflammatory cells, and thus allows specific detection of cellular division. Changes in the intensity of FLT uptake can be used to monitor cellular response to treatment even before there are visible changes in tumor volume [11, 25].

Promising results have been reported from studies in which FLT was used to assess early disease response to therapy in patients with head and neck SCCs, with good reproducibility of SUV measurements and changes in uptake preceding changes in tumor volume [25–27]. The ability to delineate areas of high cellular proliferation means that dose escalation to these areas is technically feasible [25].

However, definitive histologic validation for this use of FLT is lacking. Linecker et al. found no correlation between FLT uptake and the Ki-67 index, an endogenous marker of cellular proliferation in a study of 19 patients with head and neck SCCs [28]. FLT does not allow reliable differentiation between benignity and malignancy of abnormal cervical lymph nodes because its uptake by the germinal centers of reactive lymph nodes leads to a low positive predictive value [29]. Further research will be needed before a role may be established for FLT in early treatment response assessment and adaptive radiation therapy planning.

7.2.1.4 Apoptosis

Apoptosis, also known as programmed cell death, is an important mechanism by which chemotherapy and radiation therapy regimens induce tumor cell death. Radiation resistance and subsequent treatment failure may result from mutations that lead to deregulated cellular proliferation and suppression of apoptotic mechanisms [30]. Noninvasive imaging of apoptosis, therefore, has the potential to allow early monitoring of response to therapy. The use of technetium 99m (^{99m}Tc)–labeled annexin V, a protein that binds to a major phospholipid constituent of cell membranes, has been investigated for imaging apoptosis in various malignancies, including head and neck SCCs [31].

The difficulty of radiolabeling annexin V with fluorine 18 has led to the development of other apoptosis-specific PET tracers. ^{18}F-labeled compound 2-[5-fluoro-pentyl]-2-methyl-malonic acid (ML-10) is one of a set of novel small-molecule probes designed to allow visualization of the unique complex of apoptosis-related cellular alterations [32]. This compound, the first apoptosis-specific PET tracer to undergo clinical testing, produced promising results in several small clinical trials in patients with acute ischemic stroke or metastases to the brain after whole-brain radiation therapy, in whom it allowed early detection of response to treatment [32]. ML-10 is also useful for differentiating between apoptotic and necrotic cells.

7.2.1.5 Amino Acid Transport and Protein Synthesis

Carbon 11 (^{11}C)-labeled methionine (MET) is a PET tracer used to image amino acid transport and accelerated protein synthesis in malignant tissue [33]. MET allows effective visualization of different cancers but not differentiation of the histologic grade [34]. Lindholm et al. showed a good correlation between FDG and MET, with similar sensitivities and specificities for tumor detection [35].

A study evaluating early treatment response in patients with head and neck SCCs showed a greater decline in uptake at tumor sites with histology-confirmed complete response in comparison with sites of residual tumor tissue after radiation therapy [36]. In another study performed in patients with head and neck SCCs, an early decrease in MET uptake was reported to correlate with an end-of-treatment tumor volume reduction seen at MR imaging, a finding that suggested that MET could be used for early treatment adaptation [37]. By contrast, Nuutinen et al. observed a substantial early decline in MET uptake after radiation therapy in 15 patients with head and neck SCCs but found that the rate of

decrease in tracer uptake was comparable between patients with disease recurrence and those with preserved local control [38]. At present, there is no clear role for the use of MET in the imaging of head and neck cancers.

^{18}F-labeled fluoroethyltyrosine (FET) is another amino acid analog that is taken up by tumor cells through amino acid transport systems [39]. High diagnostic accuracies have been achieved with the use of FET in patients with brain tumors, but the tracer has lower sensitivities (64%–75%) in comparison with FDG (89%–95%) in the evaluation of head and neck SCCs [40–42]. Although its specificity (90%–100%) is higher than that of FDG (50%–79%), the consensus is that FET is not a suitable replacement for FDG in the initial assessment of different malignancies, owing to its poorer sensitivity. It may, however, have a role in helping differentiate between residual tumor tissue and inflammatory tissue after therapy.

7.2.1.6 Cell Membrane Synthesis

Choline is a ubiquitous substance that is incorporated into phospholipids, which are the major constituent of cell membrane synthesis [43]. Up until now, there is a paucity of data on the use of radiolabeled-choline in malignancies and response to treatment. In an initial feasibility study on 45 patients, C-labeled choline was found to be as effective as FDG for detecting malignant head and neck tumors at PET [44]. However, the usefulness of this tracer for assessing posttreatment response requires further evaluation; in one study, choline PET/CT was not found to be superior to FDG PET/CT for the detection of recurrent disease [45].

7.2.1.7 Epidermal Growth Factor Receptor Status

The status of epidermal growth factor receptor (EGFR) is an important tumor microenvironment factor, and blockade of EGFR by cetuximab increases the effectiveness of radiation therapy [46]. EGFR activation causes tumor cell proliferation, apoptosis, and production of hypoxia-related proteins, all of which can cause resistance to chemotherapy and radiation therapy [47]. Because PET can be used to assess both EGFR status and cetuximab uptake, this imaging modality may be useful for treatment selection and treatment response assessment [48].

7.2.2 Functional MR Imaging Techniques

Advanced MR imaging techniques such as dynamic contrast-enhanced imaging, diffusion-weighted imaging, blood oxygenation level–dependent (BOLD) imaging, and spectroscopy hold the promise of providing functional information about disease [49]. These techniques can be used for planning, monitoring, and assessing the results of radiation therapy in patients with head and neck SCCs [50].

7.2.2.1 Dynamic Contrast-Enhanced MR Imaging

Dynamic contrast-enhanced MR imaging is a noninvasive technique that helps characterize the microvasculature, thereby providing markers specific to perfusion, permeability of blood vessels, and the volume of extracellular space. Abnormal microvessels seen at dynamic contrast-enhanced MR imaging themselves may be a marker of hypoxia: Tumor angiogenesis is associated with chaotic vessel formation and incompetent arteriovenous shunts, which lead to less effective perfusion and a more hypoxic environment than exists in normal tissues [51].

The identification of hypoxic tumors allows hypoxia-modifying therapy, treatment escalation, or even primary surgery [52]. Newbold et al. demonstrated a statistically significant correlation between various dynamic contrast-enhanced MR imaging parameters, particularly K_{trans} (which represents the permeability of blood vessels) and pimonidazole staining (an exogenous marker for hypoxia) [53]. The appearance of head and neck SCCs at dynamic contrast-enhanced MR imaging, for example, has been used to successfully predict treatment response to chemoradiation therapy in the tumors [54].

7.2.2.2 Diffusion-Weighted MR Imaging

Diffusion-weighted MR imaging is a noninvasive imaging technique that facilitates tissue characterization on the basis of the molecular motion of water molecules. Diffusion is quantified by using the ADC, which is inversely correlated with cellularity and is a potential biomarker for apoptosis [55]. The increased density of cells within malignant lymph nodes reduces their ADC at diffusion-weighted MR imaging. Studies have shown that diffusion-weighted MR imaging can be useful for differentiating small malignant lymph nodes from nonmalignant ones [56, 57].

In a study on 33 patients with head and neck SCCs, change in ADC was used as a marker of tumor response 1 week after the commencement of chemoradiation therapy [58]. Change in tumor ADC after 1 week of treatment had a high sensitivity and specificity for identifying patients who would have a partial or complete response to treatment. Dirix et al. evaluated the usefulness of diffusion-weighted MR imaging for radiation therapy planning and found that patients with local-regional recurrence had lower ADC values within the tumor after 4 weeks of radiation therapy [59]. This finding suggests that diffusion-weighted imaging would be useful for identifying patients who might benefit from adaptive escalation of the radiation dose.

7.2.2.3 BOLD Imaging

BOLD imaging, also known as intrinsic susceptibility-weighted MR imaging, is a functional imaging technique that is primarily used to evaluate brain activity triggered by exercise or other external stimuli. In recent years, it also has been used as a hypoxia-specific imaging technique.

Contrast at BOLD imaging depends on the quantity of paramagnetic deoxyhemoglobin within red blood cells, which generates an MR signal based on the transverse relaxation rate (i.e., R2*) [60]. This imaging technique was used to assess reoxygenation of tumors while patients breathed oxygen-enriched gas (i.e., carbogen) [61]. In another study, a heterogeneous response in different tumors during carbogen breathing at BOLD MR imaging permitted the identification of patients who would be likely to benefit from carbogen-induced sensitization to radiation [62]. Hypoxic tumors with high blood flow have a high R2* and are more likely to respond to carbogen for radiation sensitization. Conversely, in small animal studies, hypoxic tumors with low blood volumes were found to have low R2* values and to be less likely to respond to carbogen [63].

7.2.2.4 MR Spectroscopy

MR spectroscopy allows noninvasive molecular imaging of cellular metabolism. Both phosphorus 31 MR spectroscopy and proton (hydrogen 1) MR spectroscopy have been studied extensively. An early study of proton MR spectroscopy performed by Mukherji et al. demonstrated a qualitatively consistent pattern between in vitro and in vivo metabolic profiles of different carcinomas [64]. Increased choline-to-creatine ratios and consistently narrow lipid resonances were noted in spectral waveforms from in vitro and in vivo MR spectroscopy. The technique is potentially useful for differentiating tumors from benign abnormalities, and the choline-to-creatine ratio may be useful in monitoring for response to treatment. In addition, MR spectroscopy can be used to identify certain amino acids in tumors that are not detected in normal tissues, findings that may have prognostic implications, and may lead to changes in therapy [65]. However, Le et al. investigated the usefulness of in vivo lactate resonances at MR spectroscopy for assessing cervical lymph nodes in patients with stage IV head and neck SCCs and reported that these measurements do not correlate with either tumor pO_2 or treatment outcome [66].

7.2.3 Functional Imaging with Perfusion CT

Perfusion CT, or dynamic contrast-enhanced CT, relies on the passage of iodinated contrast material through a region of interest to produce changes in attenuation, which may be used as markers of microvascular blood flow [67]. A kinetic model analysis of these changes in attenu-

ation allows the derivation of several physiologic parameters, including blood flow (BF) or perfusion, blood volume (BV), mean transit time (MTT), and permeability.

CT perfusion has been studied in cancer patients for the diagnosis and characterization of disease and the prognostication and evaluation of its response to treatment. The development of new blood vessels (i.e., neoangiogenesis), an adaptive response to hypoxia within the tumor, is an indirect marker that is depicted on perfusion CT images as an increase in tumor perfusion, BV, MTT, permeability, or a combination thereof. Gandhi et al. showed that BF, BV, and permeability were all increased, whereas MTT was reduced, in tumors compared with surrounding normal structures [68]. In another study, tumors that did not respond to CRT were found to have had significantly lower baseline BF and BV values [69]. In a larger study, in which tumor response to chemoradiation therapy was assessed over 4 years of follow-up, findings were similar, with significantly lower baseline BF and permeability in patients with local-regional treatment failure [70]. The results of these studies support the hypothesis that tumors with low perfusion have greater levels of hypoxia and, therefore, exhibit more resistance to treatment.

7.2.4 Emerging Integrated Hybrid Imaging Techniques

7.2.4.1 Integrated PET/CT Perfusion Imaging

The combined use of PET and CT to determine the relationship between the metabolic status of tumors and their perfusion shows promise [71–73]. Further understanding of the multitude of hypoxia-driven adaptive responses and their relations to tumor perfusion and aerobic and anaerobic glycolysis is required before more extensive clinical application of this technique can be considered.

7.2.4.2 Integrated PET-MR Imaging

Responding to the global success of PET/CT, commercial scanner manufacturers brought the first integrated PET-MR imaging systems to market in 2011. This newly developed technology offers potential advantages over PET/CT, including reduced radiation exposure, superior soft-tissue contrast resolution, and the ability to acquire functional PET and MR imaging data simultaneously, and thus facilitates a spatially and temporally correlated multiparametric analysis of PET and MR functional biomarkers. Although this technology remains in its infancy, early clinical experience has shown that it may have great promise [74].

7.3 Assessment of Treatment Response After Radiotherapy

There is great interest in surrogate metrics for survival after investigational cancer treatments, such as response rate, time to tumor progression, or progression-free survival [75]. Changes in tumor size after treatment are often, but not invariably, related to duration of survival. A variety of approaches to measuring response rate have been developed, beginning with the original reports by Moertel on physical examination in 1976 and continuing to the subsequent World Health Organization (WHO) criteria (1979) and RECIST 1.1 (2009) [76–78]. Response rate typically refers to how often a tumor shrinks anatomically and has been defined in several ways. Not uncommonly, complete response, partial response, stable disease, and progressive disease are defined as in the WHO and RECIST criteria (Tables 7.1 and 7.2) [78].

Response rates must be viewed with some caution when one is trying to predict outcomes in newer cancer therapies that may be more cytostatic than cytocidal. With such newer treatments, lack of progression may be associated with a good improvement in outcome, even in the absence of major shrinkage of tumors as evidenced by partial response or complete response [80]. To determine lack of progression by changes in tumor size requires regular and systematic assessments of tumor burden. The newer PET metrics may be more informative [81].

Table 7.1 Comparison of WHO response criteria and RECIST

Characteristic	WHO	RECIST	RECIST v1.1
Measurability of lesion at baseline	1. Measurable, bidimensional[a] (product of LD and greatest perpendicular diameter)	1. Measurable, unidimensional (LD only: Size with conventional techniques ≥20 mm, with spiral CT ≥10 mm)	1. Measurable, unidimensional (LD only: Size with conventional techniques ≥20 mm, with spiral CT ≥10 mm; nodes: Target short axis ± 15 mm, nontarget 10–15 mm nodes, normal <10 mm)
	2. Nonmeasurable/evaluable (e.g., lymphangitic pulmonary metastases, abdominal masses)	2. Nonmeasurable: All other lesions, including small lesions; evaluable is not recommended	2. Nonmeasurable: All other lesions, including small lesions; evaluable is not recommended
Objective response	1. Measurable disease (change in sum of products of the LD and greatest perpendicular diameters, no maximal number of lesions specified): CR, disappearance of all known disease, confirmed at ≥4 weeks; PR, ≥50% decrease from baseline, confirmed at ≥4 weeks; PD, ≥25% increase of one or more lesions or appearance of new lesions; NC, neither PR nor PD criteria met	1. Target lesions (change in sum of LD, maximum of five per organ up to ten total [more than one organ]): CR, disappearance of all target lesions, confirmed at ≥4 weeks; PR, ≥30% decrease from baseline, confirmed at 4 weeks; PD, ≥20% increase over smallest sum observed or appearance of new lesions; SD, neither PR nor PD criteria met	1. Target lesions (change in sum of LDs, maximum of two per organ up to five total [more than one organ]): CR, disappearance of all target lesions, confirmed at ≥4 weeks; PR, ≥30% decrease from baseline, confirmed at 4 weeks; PD, ≥20% increase over smallest sum observed and overall 5 mm net increase or appearance of new lesions; SD, neither PR nor PD criteria met
	2. Nonmeasurable disease: CR, disappearance of all known disease, confirmed at ≥4 weeks; PR, estimated decrease of ≥50%, confirmed at 4 weeks; PD, estimated increase of ≥25% in existent lesions or new lesions; NC, neither PR nor PD criteria met	2. Nontarget lesions: CR, disappearance of all nontarget lesions and normalization of tumor markers, confirmed at ≥4 weeks; PD, unequivocal progression of nontarget lesions or appearance of new lesions; non-PD, persistence of one or more nontarget lesions or tumor markers above normal limits	2. Nontarget lesions: CR, disappearance of all nontarget lesions and normalization of tumor markers, confirmed at ≥4 weeks; PD, unequivocal progression of nontarget lesions or appearance of new lesions; non-PD: Persistence of one or more nontarget lesions or tumor markers above normal limits; PD must be "unequivocal" in nontarget lesions (e.g., 75% increase in volume); PD can also be new "positive PET" scan with confirmed anatomic progression. Stably positive PET is not PD if it corresponds to anatomic non-PD
Overall response	1. Best response is recorded in measurable disease	1. Best response is recorded in measurable disease from treatment start to disease progression or recurrence	1. Best response is recorded in measurable disease from treatment start to disease progression or recurrence

Table 7.1 (continued)

Characteristic	WHO	RECIST	RECIST v1.1
	2. NC in nonmeasurable lesions will reduce CR in measurable lesions to overall PR	2. Non-PD in nontarget lesions will reduce CR in target lesions to overall PR	2. Non-PD in nontarget lesions will reduce CR in target lesions to overall PR
	3. NC in nonmeasurable lesions will not reduce PR in measurable lesions	3. Non-PD in nontarget lesions will not reduce PR in target lesions	3. Non-PD in nontarget lesions will not reduce PR in target lesions
		4. Unequivocal new lesions are PD, regardless of response in target and nontarget lesions	4. Unequivocal new lesions are PD, regardless of response in target and nontarget lesions
Duration of response	1. CR: From date CR criteria are first met to date PD is first noted	1. Overall CR: From date CR criteria are first met to date recurrent disease is first noted	1. Overall CR: From date CR criteria are first met to date recurrent disease is first noted
	2. Overall response: From date of treatment start to date PD is first noted	2. Overall response: From date CR or PR criteria are first met (whichever status came first) to date recurrent disease is first noted	2. Overall response: From date CR or PR criteria are first met (whichever status came first) to date recurrent disease is first noted
	3. In patients who achieve only PR, only period of overall response should be recorded	3. SD: From date of treatment start to date PD is first noted	3. SD: From date of treatment start to date PD is first noted

LD longest diameter, *CR* complete response, *PR* partial response, *PD* progressive disease, *SD* stable disease, *NC* no change

[a]Lesions that can be measured only unidimensionally are considered measurable (e.g., mediastinal adenopathy or malignant hepatomegaly)

Table 7.2 Time point response: patients with target (±nontarget) disease (RECIST 1.1) [79]

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR complete response, *PR* partial response, *SD* stable disease, *NE* not evaluable, *PD* progressive disease

Surrogate end points for survival should provide earlier, hopefully correct, answers about the efficacy of treatment and should allow better decisions on whether a drug should be advanced from early phase I to phase II or III trials. Until now, for drug development and regulatory approval purposes, indices of efficacy of treatment of solid tumors have been based solely on systematic assessments of tumor size, including the WHO, RECIST, and International Workshop Criteria (IWC) for lymphoma. However, for many years, there has been evidence that nuclear medicine imaging techniques could provide unique, biologically relevant, and prognostically important information unavailable through anatomic imaging [82].

Quantitative FDG PET/CT was introduced for the early sequential monitoring of tumor response of breast cancer in 1993 [83]. Since then, there

has been growing interest in using FDG PET/CT to quickly assess whether a tumor is—or is not—responding to therapy [83]. In the initial report, women with newly diagnosed breast cancer had a rapid and significant decline in standardized uptake value (SUV), influx rate for FDG determined by Patlak analysis and estimated phosphorylation rate of FDG to FDG-6 phosphate within 8 days of the start of effective treatment. These parameters continued to decline with each progressive treatment in the responding patients, antedating changes in tumor size. By contrast, the nonresponding patients did not have a significant decline in their SUV. Since that report, there have been many others in a wide range of tumors [84, 85]. Abundant data now exist that PET is a useful tool for response assessment in a variety of diseases, at the end of treatment, at mid treatment, and when performed soon after treatment is initiated. Quantitative nonanatomic imaging approaches can be used as a biomarker of cancer response to predict or assess the efficacy of treatments [86–88]. PET with FDG appears, thus, to be one of the most powerful biomarkers introduced to date for clinical trials and for individual patients.

7.3.1 Anatomic Response Criteria (WHO, RECIST)

7.3.1.1 WHO Criteria

The proposed WHO methods included determining the product of the bidimensional measurement of tumors (i.e., greatest perpendicular dimensions), summing these dimensions over all tumors, and then categorizing changes in these summed products as follows: complete response—tumor has disappeared for at least 4 weeks; partial response—50% or greater reduction in sum of tumor size products from baseline confirmed at 4 weeks; no change—neither partial response nor complete response nor progressive disease; and progressive disease—at least a 25% increase in tumor size in one or more lesions, with no complete response, partial response, or stable disease documented before increase in size, or development of new tumor sites [82].

The WHO criteria is not explicit on such factors as how many tumor foci should be measured, how small a lesion could be measured, and how progression should be defined. Thus, despite efforts at standardization, the WHO criteria do not fully standardize response assessment. The WHO criteria are still in use in some trials and are the criteria used to define clinical response rates in many trials from the past two decades—which are important reference studies. Although not as commonly used at present, familiarity with the WHO response criteria is essential for comparison with more recent studies using RECIST, especially as relates to the issue of when tumors progress (Table 7.1) [82].

7.3.1.2 RECIST v1.1

The RECIST group, which included representatives from, among others, the EORTC, the National Cancer Institute (NCI), the National Cancer Research Network, and industry reported response criteria for solid tumors, RECIST v1.1 [79].

RECIST v1.1 requires that:

- A maximum of five target lesions, with a maximum of two per organ with a longest diameter of at least 10 mm.
- In lymph nodes, the short axis rather than the long axis should be measured, with normal nodes measuring <10 mm, nontarget nodes ≥10 mm but <15 mm and target nodes ≥15 mm.
- Osteolytic lesions with a soft tissue component and cystic tumors may serve as target lesions (Table 7.1).

Additionally, within RECIST v1.1, there are guidelines for reporting findings of lesions that are too small to measure and for measuring lesions that appear to have fragmented or coalesced at follow-up imaging [78].

The RECIST categories for response include (Table 7.2):

- Complete response (CR)—disappearance of all tumor foci for at least 4 weeks.
- Partial response (PR)—a decline of at least 30% in tumor diameters for at least 4 weeks.
- Stable disease (SD)—neither partial response nor progressive disease.
- Progressive disease (PD)—at least a 20% increase in the sum of all tumor diameters from the lowest tumor size. Additionally, an augmentation of the criteria defining progressive disease or target lesions was introduced in RECIST v1.1 to not only include a ≥20% increase in the sum of the longest diameter (SLD) from the nadir, but also a ≥5 mm absolute increase in the SLD.

PD of nontarget lesions can only be applied if the increase in nontarget lesions is representative of change in overall tumor burden. RECIST v1.1 has the inclusion of PET findings among the indicators of disease response [78].

Thus, essential elements within structured reports in oncologic imaging could include: (1) the identification with appropriate terminology of target lesion (their localization, size [two dimensions for primary lesions and for nodal disease if for lymphoma, long axis for metastases, and short axis for nodal disease for solid tumors]), (2) nonmeasurable and (3) new disease.

Although these anatomic criteria may appear to be arcane, the RECIST 1.1 criteria are used in virtually every clinical trial of new solid tumor therapeutics, as response is essentially always measured. Further, regulatory agencies have accepted RECIST as the de facto standard in response assessment for clinical trials in many countries. Familiarity with the implications of trials in which response is measured using the WHO, RECIST, and RECIST v1.1 criteria is essential, as they are not identical and do not produce identical results. Inclusion of the RECIST information in the reports will minimize errors in response allocation and, thus potential patient harm, while at the same time can be helpful for minimizing secondary reviews of examinations should patients subsequently enter into clinical trials [78].

7.3.1.3 Limitations of Anatomic Response Criteria

There is increasing awareness that anatomical approaches based on measurements of tumor size such as RECIST have significant limitations including the presence of tumors that cannot be measured, poor measurement reproducibility and mass lesions of unknown activity that persist following therapy, reducing intrinsically continuous data on tumor size, and tumor response to a series of four bins in response. Faced with these limitations, more sophisticated measurements (including tumor volume and lesion regression rates) have been applied to the evaluation of tumor response to therapy. Other more recent approaches make use of CT density (Hounsfield units) measurements for the evaluation of gastrointestinal stromal tumors or contrast enhancement patterns after vascular interventional therapies in hepatic lesions (European Association for the Study of the Liver) [76–79].

7.3.2 Metabolic Response Criteria

7.3.2.1 Qualitative Assessment

PET scans for diagnosis and primary staging, response assessment, and restaging in clinical practice are typically interpreted using qualitative methods in which the distribution and intensity of tracer uptake in potential tumor foci are compared with tracer uptake in normal structures such as blood pool, muscle, brain, and liver.

The IWC + PET criteria developed through the efforts of Juweid and Cheson dichotomizes PET results into positive and negative relative to the intensity of tracer uptake, as compared with the blood pool or nearby normal structures (Tables 7.3 and 7.4).

Such a dichotomous reporting has been introduced in clinical reporting in lymphoma, including response to radiotherapy, and proposed in evaluation of gastrointestinal and lung tumors after chemoradiation therapy.

Table 7.3 Response definitions for clinical trials: lymphoma response [89]

Response	Definition	Nodal masses	Spleen, liver	Bone marrow
CR	Disappearance of all evidence of disease	(a) FDG–avid or PET-positive before therapy must be PET-negative after therapy; mass of any size is permitted if PET is negative; (b) variably FDG–avid or PET-negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate has cleared on repeated biopsy; if indeterminate by morphology, immunohistochemistry should be negative for CR
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to six largest dominant masses; no increase in size of other nodes;(a) FDG–avid or PET-positive before 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 before therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG–avid or PET-positive before 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 new lesions >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of previously identified node >1 cm in short axis; lesions PET-positive if FDG–avid lymphoma or PET-positive before therapy	>50% increase from nadir in SPD of any previous lesions	New or recurrent involvement

CR complete remission, *PR* partial remission, *SPD* sum of product of diameters, *SD* stable disease, *PD* progressive disease

7.3.2.2 Quantitative Assessment (PERCIST v1.0)

PET Response Criteria in Solid Tumors (PERCIST 1.0) were introduced in 2009 as guidelines for systematic and structured assessment of response to therapy with PET in patients with cancer, with suggested application in clinical trials, and, potentially, in the clinical practice of PET reporting. PERCIST v1.0 describes in detail methods for controlling the quality of PET imaging conditions to ensure the comparability of PET images from different time points and to allow quantitative expression of the changes in PET measurements and assessment of the overall response according to PET results. PERCIST has been referenced widely, and authors of several articles have reported that the metrics described in PERCIST 1.0 are associated with clinical outcomes after therapy in patients with several different types of cancer, including small-cell lung cancer, colorectal cancer, non-Hodgkin lymphoma, esophageal cancer, and the Ewing sarcoma family of tumors [82].

Table 7.4 Comparison of qualitative PET response criteria and IWC + PET [89–91]

Characteristic	Hicks criteria	IWC + PET (lymphoma)
Measurability of lesion at baseline	1. FDG–avid	1. DG–avid tumor; baseline PET scan is desirable
	2. Standardized display with normalization to liver	2. Variably FDG–avid tumor; FDG baseline PET scan is required
		3. Follow-up PET at least 3 weeks after last chemotherapy session or at least 8–12 weeks after last radiation therapy session
Objective response	Complete metabolic response: FDG–avid lesions revert to background of normal tissues in which they are located	Complete response in FDG–avid tumors: No focal or diffuse increased FDG uptake over background in location consistent with tumor, regardless of CT abnormality; new lung nodules in lymphoma patient, without history of lung involvement (regardless of FDG avidity), are not considered lymphoma; increased focal or multifocal marrow uptake is not considered tumor unless biopsy is done
	Partial metabolic response: "Significant reduction in SUV in tumors"	Noncomplete response: Diffuse or focal uptake exceeding mediastinal blood pool if >2 cm in size; in nodes <2 cm diameter, uptake of FDG greater than background is positive; lesions >1.5 cm in size in liver or spleen, with uptake equal to or greater than spleen, are considered tumor
	SMD: "No visible change in metabolic activity of tumors"	Partial remission: See Table 7.2
	Progressive metabolic disease: "Increase in intensity or extent of tumor metabolic activity or new sites"	Progressive disease: See Table 7.2

7.4 Current Uses of FDG PET/CT in Treatment Response Following Radiation Therapy

7.4.1 Head and Neck Cancer

Head and neck cancer has an annual incidence of 550,000 worldwide [92]. Chemoradiotherapy (CRT) is the standard of care for locally advanced HNSCC for both unresectable disease and to achieve organ preservation [93]. The avoidance of unnecessary post-CRT neck dissection in complete responders depends on accurate posttreatment response assessment. Conventional imaging is hampered by treatment-related anatomical distortion and residual masses as well as the possibility of small occult deposits.

FDG PET/CT has an established role in post-CRT assessment in locally advanced HNSCC. Posttreatment FDG PET/CT has an NPV up to 99% for nodal disease (when performed at 4 months) [94], benefit over conventional assessment (anatomical imaging and clinical examination) [95], and a high probability of long-term regional control (2.3% regional failure rate at 36 months) [96]. A recent randomized controlled trial, the UK PET-NECK study, demonstrated that PET/CT surveillance had equivalent survival outcome at lower overall cost, when compared with routine neck dissection for N2/3 nodal disease post-CRT for advanced nodal disease [97]. In this study, PET/CT took place 12 weeks following CRT. In line with this, a prior meta-analysis had shown that diagnostic accuracy was improved when response assessment was performed more than 12 weeks posttreatment [7]. Some groups have adopted a policy of response assessment at least 4 months posttreatment [94, 98]. The clinical management of equivocal results remains problematic [94, 97, 99]. The majority of published data relate to the use of response assessment PET/CT following CRT for

oropharyngeal carcinoma; the test characteristics of PET/CT for other head and neck tumor sites and following the use of radiotherapy alone remain less clear. Future work includes the incorporation of standardized qualitative interpretative response assessment criteria, for example, Hopkins criteria [100], which may help stratify management and the use of FDG PET/CT during radiotherapy to optimize the therapeutic ratio [101].

7.4.2 Esophageal Carcinoma

Neoadjuvant CRT is a standard of care for locally advanced disease, but responders and nonresponders have a significantly differing prognosis [102]. Use of interim post-CRT FDG PET/CT prior to surgery can help guide appropriate further management, specifically by identifying interim metastatic disease (which may occur in up to 17%) preventing futile surgery [103, 104].

The added benefit of surgery for those with complete metabolic response (CMR) is less well defined. A substantial minority (20–30%) of patients with resectable disease have a complete pathologic response (CPR) to CRT [105]. Multiple groups have described the correlation between CMR on post-CRT FDG PET/CT, CPR and survival benefit [106]. Monjazeb et al. [107] suggested patients with CMR may be spared surgery. Cervino et al. [108] described a 91% 18-month disease-free survival for patients with a negative FDG PET/CT, who did not undergo surgery post-neoadjuvant treatment. However, the reported data are heterogeneous, for example, Elliot et al. [109] found that CMR on post-CRT FDG PET/CT and CPR did not correlate. This may partly relate to study timing, as radiation-induced esophagitis can mimic residual active disease and limit the utility of interim and posttreatment PET/CT. Many advocate surgery for even complete responders post-CRT and consider the role of FDG PET/CT to be guiding biopsy and highlighting patients requiring escalation of treatment [110].

7.4.3 Rectal Carcinoma

Neoadjuvant CRT prior to resection is the standard of care for locally advanced rectal cancer (LARC). Early evidence of treatment response can alter surgical management, and accurate restaging is critical.

MRI is the mainstay of radiological staging of rectal cancer but has limited value in response assessment following CRT [111]. International guidelines do not yet reflect a role for FDG PET/CT in the post-CRT restaging of LARC. However, several small studies have indicated a correlation between metabolic and pathologic response and demonstrated a superior NPV (up to 95.5%) of FDG PET/CT for CPR compared with MRI in LARC restaging [112–114]. Furthermore, a recent systematic review combining results of over 1500 patients found a high-pooled accuracy for early PET restaging post-CRT for LARC [115].

The role of PET/CT should not be overstated. Two systematic reviews of post-CRT FDG PET/CT suggest the main role for functional imaging was in identification of nonresponders rather than selection for organ-sparing strategies [115, 116]. However, post-CRT FDG PET/CT has a role in early outcome prediction with markers for metabolic response correlating with overall survival and disease-free survival [117].

7.4.4 Brain Tumors

Following radiotherapy for brain tumors, radiation necrosis can occur and mimic tumor progression or recurrence on conventional imaging.

FDG PET/CT has an established role in differentiating radiation necrosis from tumor progression. Stereotactic radiotherapy can result in apparent expansion and increased enhancement of treated lesions. FDG PET has a reported sensitivity of 75% and specificity of 81% for distinguishing radiation necrosis from recurrent tumor at sites of radiosurgery [118].

Distinction of radiation necrosis from residual tumor after fractionated radiotherapy can be problematic. The two often coexist, radiation

necrosis may be hypermetabolic, and local seizure activity may falsely increase uptake [119]. Increased uptake relative to contralateral grey matter has been demonstrated to have 68% accuracy in the diagnosis of recurrent tumor [120].

The role of FDG PET/CT postradiotherapy is largely problem-solving and biopsy guidance in combination with MRI and other advanced imaging techniques. However, owing to the suboptimal sensitivity and specificity of FDG-PET, other PET tracers may have superior accuracy [121]. Fluorine-18 fluoro-ethyl-tyrosine is an amino acid analog with improved tumor-to-background contrast compared with FDG and higher sensitivity for detection of recurrent glioma [122]. Fluoro-ethyl-tyrosine does not require an on-site cyclotron, and cost-effectiveness has been reported in diagnostic and recurrent indications [123], although not yet specifically for postradiosurgery indications.

7.4.5 Cervical Carcinoma

Cervical cancer is the third most common malignancy worldwide [124]. Locally advanced disease is treated with CRT (typically external beam radiotherapy plus cisplatin with subsequent intrauterine brachytherapy), but 20–40% of patients suffer disease persistence or recurrence [125]. Preexisting methods of assessment such as International Federation of Gynaecology and Obstetrics stage do not reliably predict early treatment response or outcome [126]. Hence, the development of noninvasive surrogate biomarkers to predict poor treatment response and facilitate treatment escalation is of clinical pertinence. Opportunities to use PET/CT for this purpose may exist both during and after completion of treatment.

Evidence suggests that early treatment (prebrachytherapy) FDG PET/CT may be used to delineate metabolically active disease, allowing treatment field adaptation [127]. Furthermore, CMR predicts end of treatment response; Kidd et al. [128] found that maximum standardized uptake values (SUV_{max}) and FDG heterogeneity at 4 weeks during treatment correlated with 3-month posttreatment PET response. Yoon et al. [129] reported that in patients with FDG-avid pelvic nodal disease, failure to achieve nodal CMR correlated with a markedly reduced disease-free survival (71% with CMR vs. 18%; $p < 0.001$). While such use remains experimental, this may represent a method to flag those in need of treatment escalation.

A number of trials have demonstrated that FDG PET/CT at 3 months post-CRT predicts prognosis. Persistent abnormal or new FDG activity post-CRT represented the most important predictor of disease-related death by 5 years in one study [130]. However, posttherapy PET biomarkers remain of uncertain value in assessing long-term treatment success; one study suggested that delta $SUV_{max} > 60\%$ predicted disease-free survival, and [127] another study reported a limited NPV with 21% of patients with CMR on posttreatment FDG PET/CT, developing disease recurrence during the median 28-month follow-up [131], with tumor size and stage acting as predictors for recurrent disease. Furthermore, a systematic review suggests that although more accurate than MRI, PET/CT is less cost-effective in posttreatment surveillance [132] than standard follow-up. Therefore, while PET/CT offers promise in posttreatment assessment of cervical cancer, its potential to add value to the treatment pathway remains to be fully realized.

7.4.6 Lung Carcinoma

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related mortality [133]. FDG PET/CT is well established as a cost-effective staging tool prior to radical treatment. CRT is the standard treatment in locally advanced disease, but locoregional treatment failure rates are 15–40%, and treatment escalation can cause morbidity [134]. Anatomical imaging response assessment post-CRT does not correlate well with histopathological response, and distinction of posttreatment fibrosis from residual tumor is problematic. Therefore, the use of noninvasive surrogate biomarkers to flag nonresponders early in treatment is crucial.

Studies suggest that surrogate PET biomarkers such as total lesion glycolysis [135] and SUV_{max} [136] may predict treatment response during CRT. However, the applicability of metabolic markers in predicting long-term outcomes post-CRT in NSCLC remains unclear. One study suggested that FDG PET poststereotactic radiotherapy did not reliably predict long-term outcome [137]. More recently, Ding et al. [138] found that metabolic tumor volume (MTV) at FDG PET/CT post-CRT was predictive of recurrence-free survival post-CRT at 2 years.

Surgical resection post-CRT is a potential curative treatment option for selected patients with Stage IIIA NSCLC, and the high NPV of FDG PET/CT may aid interim treatment decisions post-CRT. Kim et al. [139] demonstrated improved disease-free survival and overall survival in patients who demonstrated CMR.

FDG PET/CT may also have a role in adaptive radiotherapy planning in NSCLC, with changes in MTV [140] and gross tumor volume [138] being used to adapt treatment. The use of FDG PET/CT to distinguish tumor recurrence from fibrosis has been reported to guide posttreatment problem-solving [141] but can be challenging.

7.4.7 Hepato-Pancreatico-Biliary Tumors, Particularly Pancreatic Carcinoma and Liver Metastases (Postselective Internal Radiotherapy Treatment)

CRT is a standard of care for locally advanced pancreatic cancer. However, local relapse rates are high (42–68%) and distant recurrence is common [142].

FDG PET/CT performed 12 weeks post-CRT demonstrated that increased delta SUV_{max} predicts overall survival and progression-free survival. The use of FDG PET/CT during CRT is limited by the inflammation caused by bile duct occlusion. Allowing for this, in the future, integration of PET/CT as a response assessment tool may help define futility owing to interim distant metastatic disease and allow adaptation of the therapy field and selection for aggressive treatment [143].

Selective internal radiotherapy treatment is an important palliative treatment for unresectable metastatic liver disease. Early assessment of treatment response can help guide further treatment [144]. FDG PET/CT can provide an earlier and more accurate assessment of response to ^{90}Y-microsphere therapy than CT imaging alone [145]. MTV and total lesion glycolysis are reported to be the best predictors of survival in colorectal metastatic disease [146]. However, recent evidence suggests that diffusion-weighted MRI may be the superior modality with an NPV of 92% vs. 56% for FDG PET/CT [147], and further investigation is required for clarification.

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