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THE EVOLVING ROLE OF IMAGING IN ONCOLOGY RESPONSE ASSESSMENT: BEYOND RECIST

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ABSTRACT

Background: *The Response Evaluation Criteria in Solid Tumors (RECIST) framework has served as the cornerstone of oncologic response assessment for over two decades. However, the emergence of novel systemic therapies including immune checkpoint inhibitors, targeted molecular agents, and antibodydrug conjugates has exposed fundamental limitations of purely morphologic, sizebased evaluation. This review critically appraises the evolution of imagingbased response assessment in oncology and explores the expanding role of functional imaging, multiparametric magnetic resonance imaging, positron emission tomography/computed tomography beyond fluorodeoxyglucose, radiomics, and artificial intelligence in capturing the biological complexity of tumortreatment interactions.*

Methods: *A comprehensive search of PubMed, MEDLINE, Embase, and Cochrane Library databases was performed (1979–2024) using MeSH terms: 'tumor response assessment,' 'RECIST,' 'iRECIST,' 'PERCIST,' 'radiomics,' 'pseudoprogression,' and 'oncologic imaging.' Randomized controlled trials, phase II/III clinical trials, systematic reviews, metaanalyses, and landmark observational studies were included.*

Results: *RECIST 1.1 retains validity for conventional cytotoxic chemotherapy but inadequately captures response patterns under immunotherapy (pseudoprogression, hyperprogression), targeted therapies (cytostatic responses, tumor cavitation), and locoregional interventions. Disease and modalityspecific criteria (iRECIST, PERCIST, mRECIST, Choi, RANO) provide complementary frameworks. Radiomics and AIbased methods demonstrate promising discriminative accuracy (AUC 0.72–0.88) for response prediction and prognostication, pending external validation. Novel PET tracers, liquid biopsy integration, and theranostic imaging represent frontier technologies redefining the assessment paradigm.*

Conclusions*: No single imaging framework captures the full spectrum of oncologic response in contemporary practice. A precision approach integrating morphologic, metabolic, functional, and molecular imaging with computational analytics is necessary to optimize treatment decisions and clinical trial endpoints. Standardization, prospective validation, and multidisciplinary consensus are prerequisites for clinical implementation.*

Keywords: *RECIST; iRECIST; PERCIST; Pseudoprogression; Radiomics; Immunotherapy response; PET/CT; Multiparametric MRI; Tumor response; Artificial intelligence in oncology*

1. INTRODUCTION

The assessment of tumor response to systemic therapy represents one of the most critical and clinically consequential tasks in oncologic practice. Accurate response evaluation informs individual treatment decisions, guides clinical trial design, and ultimately shapes drug approval pathways. For the past two decades, the Response Evaluation Criteria in Solid Tumors (RECIST) has provided a standardized, reproducible framework for defining tumor response based on anatomic size measurements obtained from crosssectional imaging.

RECIST emerged as an evolution from the World Health Organization (WHO) bidimensional criteria published in 1979, which utilized the product of two perpendicular diameters to quantify tumor burden. The initial RECIST 1.0 guidelines, published in 2000 by Therasse et al. under the auspices of the European Organisation for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada, standardized unidimensional measurement to the longest tumor diameter. RECIST 1.1, published in 2009, introduced further refinements: a reduction in the maximum number of target lesions from 10 to 5, clarification of lymph node pathologic size thresholds, and refined criteria for progressive disease (PD).

Despite its widespread adoption and regulatory acceptance, RECIST was conceived in an era when cytotoxic chemotherapy dominated oncologic practice. The therapeutic landscape has since undergone a fundamental transformation. Immune checkpoint inhibitors (ICIs) targeting PD1/PDL1 and CTLA4, smallmolecule tyrosine kinase inhibitors (TKIs), antibodydrug conjugates (ADCs), bispecific antibodies, and CARTcell therapies now define the standard of care across multiple tumor types. These agents produce biological tumor responses that diverge dramatically from cytotoxic shrinkage patterns including pseudoprogression, hyperprogression, tumor cavitation, and dissociated responses all of which are inadequately captured by sizebased morphologic criteria alone.

Concurrently, remarkable advances in functional and molecular imaging have expanded the toolkit available to oncologic radiologists and nuclear medicine physicians. Integrated positron emission tomography/computed tomography (PET/CT), multiparametric MRI (mpMRI), novel radiotracers targeting tumorspecific molecular pathways, and computational radiomics now provide quantitative insights into tumor biology, vascularity, cellularity, and metabolism that transcend simple measurements of size. These technologies have catalyzed the development of modality and diseasespecific response criteria, including PERCIST for PETbased metabolic assessment, iRECIST for immunotherapy trials, modified RECIST (mRECIST) for hepatocellular carcinoma (HCC), and the Response Assessment in NeuroOncology (RANO) criteria for central nervous system tumors.

This comprehensive review systematically examines the evolution of imagingbased oncologic response assessment from WHO and RECIST through contemporary diseasespecific frameworks and emerging technologies. It critically evaluates the evidence for each approach, identifies gaps and unresolved challenges, and proposes an integrative framework for precision response assessment in the era of modern oncology.

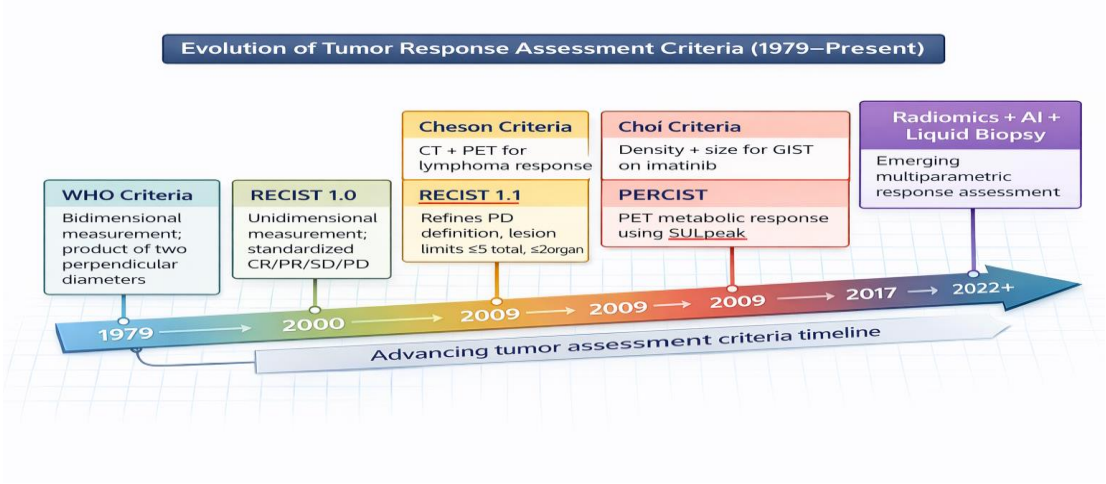

Figure 1. Timeline illustrating the progressive development of response assessment frameworks in oncology, from WHO bidimensional criteria to modern functional and molecular imaging paradigms.

2. THE RECIST FRAMEWORK: PRINCIPLES, STRENGTHS, AND LIMITATIONS

2.1 Principles of RECIST 1.1

RECIST 1.1 defines four response categories for solid tumor assessment: Complete Response (CR), indicating disappearance of all target lesions with normalization of tumor markers; Partial Response (PR), representing a ≥30% decrease in the sum of longest diameters (SLD) of target lesions from baseline; Stable Disease (SD), defined as neither sufficient shrinkage to qualify as PR nor sufficient increase to qualify as PD; and Progressive Disease (PD), defined as a ≥20% increase in SLD from nadir or the appearance of any new lesion. Target lesions are limited to a maximum of five (two per organ), are selected based on size and measurability, and must be followed at consistent imaging time points using standardized protocols.

RECIST 1.1 stipulates specific technical requirements: CT slice thickness ≤5 mm, minimum target lesion size ≥10 mm in longest diameter (≥15 mm for lymph nodes in short axis), and reproducible imaging conditions between assessment time points. MRI is acceptable for certain anatomic sites, particularly the liver, pelvis, and central nervous system. Bone lesions are considered nonmeasurable, and pleural effusions, pericardial effusions, and lymphangitic carcinomatosis are classified as nontarget lesions.

2.2 Strengths of RECIST 1.1

The enduring utility of RECIST 1.1 derives from several intrinsic strengths. First, it provides a simple, reproducible, and objective method for tumor measurement that can be consistently applied across institutions and imaging platforms with acceptable interreader agreement (intraclass correlation coefficient typically 0.85–0.95 for target lesions). Second, RECIST endpoints particularly objective response rate (ORR) and progressionfree survival (PFS) have demonstrated statistically significant correlations with overall survival in numerous cytotoxic chemotherapy trials, providing regulatory agencies with established surrogate endpoints for drug approval. Third, the framework is applicable across virtually all solid tumor histologies, facilitating crossstudy comparisons and metaanalyses. Fourth, its simplicity requiring only a ruler and crosssectional imaging enables broad implementation without specialized infrastructure or expertise.

2.3 Limitations and Paradigm Shifts Challenging RECIST

The limitations of RECIST have become increasingly apparent as novel therapies have entered clinical practice. Perhaps the most consequential limitation is RECIST's inability to distinguish pseudoprogression a transient increase in tumor size or the appearance of new lesions driven by inflammatory immune infiltration from true

disease progression under ICI therapy. Pseudoprogression occurs in approximately 4–10% of patients receiving PD1/PDL1 inhibitors and up to 15% of patients receiving antiCTLA4 therapies. Misclassification of pseudoprogression as true PD under RECIST 1.1 would mandate premature therapy discontinuation, potentially depriving patients of durable longterm benefit from immunotherapy.

Conversely, hyperprogression defined as a ≥2fold increase in tumor growth rate on ICI compared to the pretreatment period, occurring in 10–29% of ICItreated patients depending on the tumor type and definition applied also eludes RECIST detection until radiologically manifest, delaying the recognition of a clinically catastrophic phenomenon. Furthermore, RECIST does not account for cytostatic responses common with molecularly targeted agents, where tumor metabolism is suppressed and clinical benefit is maintained despite unchanged or minimally changed anatomic size. Choi criteria, for example, demonstrated significantly better correlation with clinical outcomes for GIST patients receiving imatinib than RECIST, by incorporating CT density (Hounsfield unit reduction) as a response indicator alongside size.

Additional limitations include RECIST's inability to assess tumor heterogeneity the phenomenon by which individual metastatic deposits may respond discordantly (oligoprogression or dissociated response) within a single patient receiving systemic therapy. This limitation is particularly relevant in the era of targeted therapy where acquired resistance may emerge in a single anatomic compartment while the remainder of measurable disease remains controlled. The framework also does not integrate molecular or functional imaging data, ignores tumor microenvironment dynamics, and provides no prognostic information beyond categorical response classification.

Table 1. ***Comprehensive Comparison of Major Oncologic Response Assessment Criteria: Modality, Tumor Type, Measurement Methodology, and Response Categories***

Criteria	Year	Modality	Tumor Type	Measurement	Response Categories
WHO	1979	CT/Xray	All solid tumors	Bidimensional (product)	CR, PR, NC, PD
RECIST 1.0	2000	CT	Solid tumors	Unidimensional (LD)	CR, PR, SD, PD
RECIST 1.1	2009	CT/MRI	Solid tumors	LD (≤5 lesions)	CR, PR, SD, PD
Cheson (Lymphoma)	2007	CT + PET	Lymphoma	Nodal mass + SUV	CR, CRu, PR, SD, PD
Choi Criteria	2009	CT	GIST	Size + density (HU)	CR, PR, SD, PD
mRECIST	2010	CT/MRI	HCC	Arterial enhancing LD	CR, PR, SD, PD
PERCIST 1.0	2009	FDGPET	Solid tumors	SULpeak (1 cm^3 ROI)	CMR, PMR, SMD, PMD
iRECIST	2017	CT/MRI	Solid tumors (ICI)	LD + new lesions	iCR, iPR, iSD, iUPD, iCPD
RANO	2010	MRI	Brain tumors	Bidimensional (T1+Gd)	CR, PR, SD, PD

Criteria	Year	Modality	Tumor Type	Measurement	Response Categories
RECIST for HER2+	2022	CT + PET	HER2+ breast ca.	LD + SUV hybrid	CR, PR, SD, PD

CR=Complete Response; PR=Partial Response; SD=Stable Disease; PD=Progressive Disease; LD=Longest Diameter; HU=Hounsfield Units; ICI=Immune Checkpoint Inhibitor; HCC=Hepatocellular Carcinoma; GIST=Gastrointestinal Stromal Tumor; CMR=Complete Metabolic Response; PMR=Partial Metabolic Response; SMD=Stable Metabolic Disease; PMD=Progressive Metabolic Disease; iUPD=iRECIST Unconfirmed PD; iCPD=iRECIST Confirmed PD.

3. RESPONSE ASSESSMENT IN THE IMMUNOTHERAPY ERA

3.1 ImmunotherapyRelated Response Patterns

The introduction of immune checkpoint inhibitors has fundamentally altered the relationship between early imaging findings and clinical outcome. Unlike chemotherapy, which produces rapid tumor cell death measurable as prompt dimensional reduction, ICIs engage the host immune system to mount sustained antitumor responses characterized by a temporal delay between treatment initiation and radiologic response. This kinetic difference has necessitated the development of immunotherapyadapted response criteria.

The immunerelated response criteria (irRC) were among the first to address these unique response patterns, introduced by Wolchok et al. in 2009 following observations from ipilimumab trials in melanoma. These criteria incorporated new lesions into total tumor burden calculations rather than classifying them as automatic PD, and required confirmation of progression at a second imaging time point ≥4 weeks apart. Subsequent refinements led to the irRECIST criteria, which maintained unidimensional measurement methodology while retaining the immunemodified framework.

3.2 iRECIST: ImmuneModified RECIST 1.1

iRECIST, formally published by Seymour et al. in 2017, represents the current consensus framework for response assessment in ICI trials. The critical innovation of iRECIST is the introduction of an intermediate response category iUnconfirmed Progressive Disease (iUPD) which replaces the immediate PD classification for cases where new lesions appear or existing lesions increase by ≥20% while the patient remains clinically stable. Confirmation of progression (iCPD) requires a subsequent scan demonstrating further growth (≥5 mm increase in SLD of target lesions, or unequivocal progression of nontarget lesions or new lesions) obtained at least 4–8 weeks after the initial iUPD designation.

This confirmatory framework has been validated retrospectively across multiple tumor types and has demonstrated that approximately 4–5% of patients with an initial iUPD classification ultimately achieve objective response on subsequent imaging (confirmed pseudoprogression). Critically, iRECIST mandates that patients must remain clinically stable without evidence of rapid symptom deterioration, worsening performance status, or laboratory surrogates of disease burden to remain classified as iUPD. Clinically unstable patients should be classified as iCPD regardless of imaging trajectory.

3.3 Hyperprogression: Imaging Characteristics and Clinical Significance

Hyperprogression (HP) represents an extreme manifestation of treatment failure under ICI, characterized not merely by tumor growth but by an accelerated growth kinetic that exceeds baseline tumor growth rates by ≥2fold. Imaging hallmarks of HP include rapid emergence of multiple new metastatic sites, dramatic size enlargement of existing lesions, and clinical deterioration occurring within the first 4–8 weeks of ICI initiation. The reported incidence of HP ranges from 10% to 29% across ICI trials, with higher rates observed in NSCLC, gastric cancer, and head and neck squamous cell carcinoma.

The pathophysiologic mechanisms underlying hyperprogression remain incompletely understood but may involve ICImediated activation of

regulatory Tcells (Tregs), paradoxical stimulation of tumor growth through Fcgamma receptormediated macrophage activation, and preexisting oncogenic amplifications (particularly MDM2, MDM4, EGFR exon 4) associated with HP susceptibility. From an imaging perspective, HP currently lacks a universally accepted radiologic definition, though several quantitative criteria based on growth rate ratio (GRR) and tumor growth kinetics have been proposed and validated in retrospective cohorts.

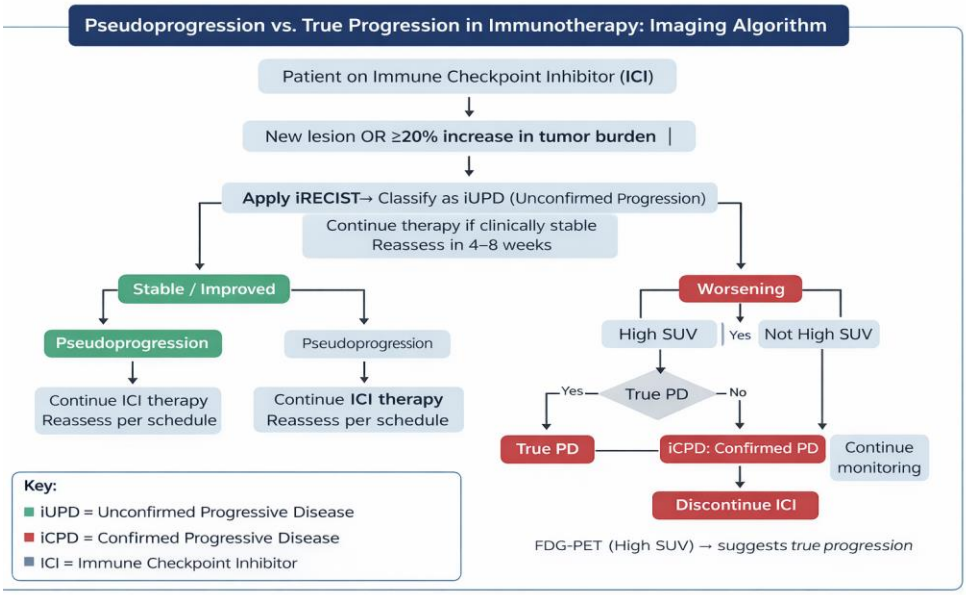

Figure 2. Decision algorithm for differentiating pseudoprogression from true disease progression in patients receiving immune checkpoint inhibitors, incorporating clinical, metabolic, and tissuebased assessment.

Table 2. *Systematic Comparison of RECIST 1.1 and iRECIST Criteria: Key Differences in Terminology, Progression Classification, and Clinical Application for Immune Checkpoint Inhibitor Trials*

Parameter	RECIST 1.1	iRECIST
Response Terminology	CR / PR / SD / PD	iCR / iPR / iSD / iUPD / iCPD
New Lesion Appearance	Immediate PD	iUPD; confirm at next scan (≥4 weeks)
Minimum Lesion Size	≥10 mm (≥15 mm lymph nodes)	Same as RECIST 1.1
Target Lesion Limit	Maximum 5 total (2 per organ)	Same; new lesions tracked separately
Progression Confirmation	Not required (single timepoint)	Required: iUPD → iCPD after repeat scan
Pseudoprogression Handling	Not considered	Formally accommodated (iUPD state)
New Nontarget Lesions	= PD	Classified as iUPD; continue therapy pending confirmation
Clinical Stability Rule	Not applicable	Patient must be clinically stable to remain iUPD

Parameter	RECIST 1.1	iRECIST
Trial Applicability	Universal (all solid tumors)	Specifically designed for ICI monotherapy trials
Key Limitation	Cannot distinguish pseudo from true PD	Delays definitive PD classification; risk of overtreatment

iCR=immune Complete Response; iPR=immune Partial Response; iSD=immune Stable Disease; iUPD=immune Unconfirmed Progressive Disease; iCPD=immune Confirmed Progressive Disease; ICI=Immune Checkpoint Inhibitor.

4. METABOLIC IMAGING: PET/CT AND BEYOND RECIST

4.1 PERCIST: Metabolic Response Assessment with FDGPET/CT

Fluorodeoxyglucose positron emission tomography/computed tomography (FDGPET/CT) provides metabolic information that complements and frequently predates anatomic size changes detectable by CT. The PERCIST (PET Response Criteria in Solid Tumors) framework, proposed by Wahl et al. in 2009, operationalizes FDGPET/CT for response assessment using the standardized uptake value normalized to lean body mass (SULpeak), measured within a fixed 1 cm^3 spherical region of interest placed over the most metabolically active voxel of the most FDGavid target lesion.

PERCIST defines four response categories: Complete Metabolic Response (CMR), indicating the absence of FDG uptake above liver background in all target lesions; Partial Metabolic Response (PMR), representing a ≥30% decrease in SULpeak from baseline; Stable Metabolic Disease (SMD), defined as neither PMR nor PMD criteria met; and Progressive Metabolic Disease (PMD), consisting of a ≥30% increase in SULpeak from nadir or the appearance of new FDGavid lesions. Importantly, a minimum absolute change of 0.8 SUL units is required to qualify as PMR or PMD to avoid misclassification due to measurement noise.

Prospective and retrospective studies across multiple tumor types including NSCLC, esophageal cancer, lymphoma, breast cancer, and colorectal cancer have consistently demonstrated that early metabolic response by PERCIST (typically assessed after 1–2 treatment cycles) predicts pathologic response and survival outcomes more accurately and earlier than RECISTbased anatomic evaluation. In locally advanced esophageal cancer treated with neoadjuvant chemoradiation, for example, a reduction in SUVmax of ≥35% at 2week FDGPET/CT accurately identified histopathologic responders with sensitivity and specificity exceeding 75%.

4.2 Beyond FDG: Novel PET Tracers in Response Assessment

While FDG remains the dominant and most validated PET tracer in clinical oncology, its limitations including physiologic brain uptake precluding CNS lesion assessment, low sensitivity for mucinous tumors, inflammatory artifact during ICI therapy, and inability to distinguish viable hypoxic tumor from necrosis have catalyzed the development of numerous diseasespecific radiotracers. These novel agents target diverse tumor biological processes including proliferation, hypoxia, receptor expression, and amino acid transport, providing complementary or superior metabolic information in specific clinical contexts.

^{68}GaPSMA11 PET/CT has transformed response assessment in prostate cancer, demonstrating markedly superior sensitivity (92–95%) over conventional bone and CT imaging for detecting biochemical recurrence, nodal metastases, and bone metastases. The VISION trial established ^{177}LuPSMA617 theranostic therapy as a survivalprolonging standard of care in metastatic castrationresistant prostate cancer (mCRPC) refractory to enzalutamide/abiraterone, with ^{68}GaPSMA11 PET serving both as a patient selection tool and an early response biomarker through PSMA score quantification. Similarly, ^{68}GaDOTATATE PET/CT provides superior tumortobackground visualization in somatostatin receptorpositive neuroendocrine tumors (NETs), enabling precise response assessment to peptide receptor radionuclide therapy (PRRT) as

demonstrated in the NETTER1 randomized controlled trial.

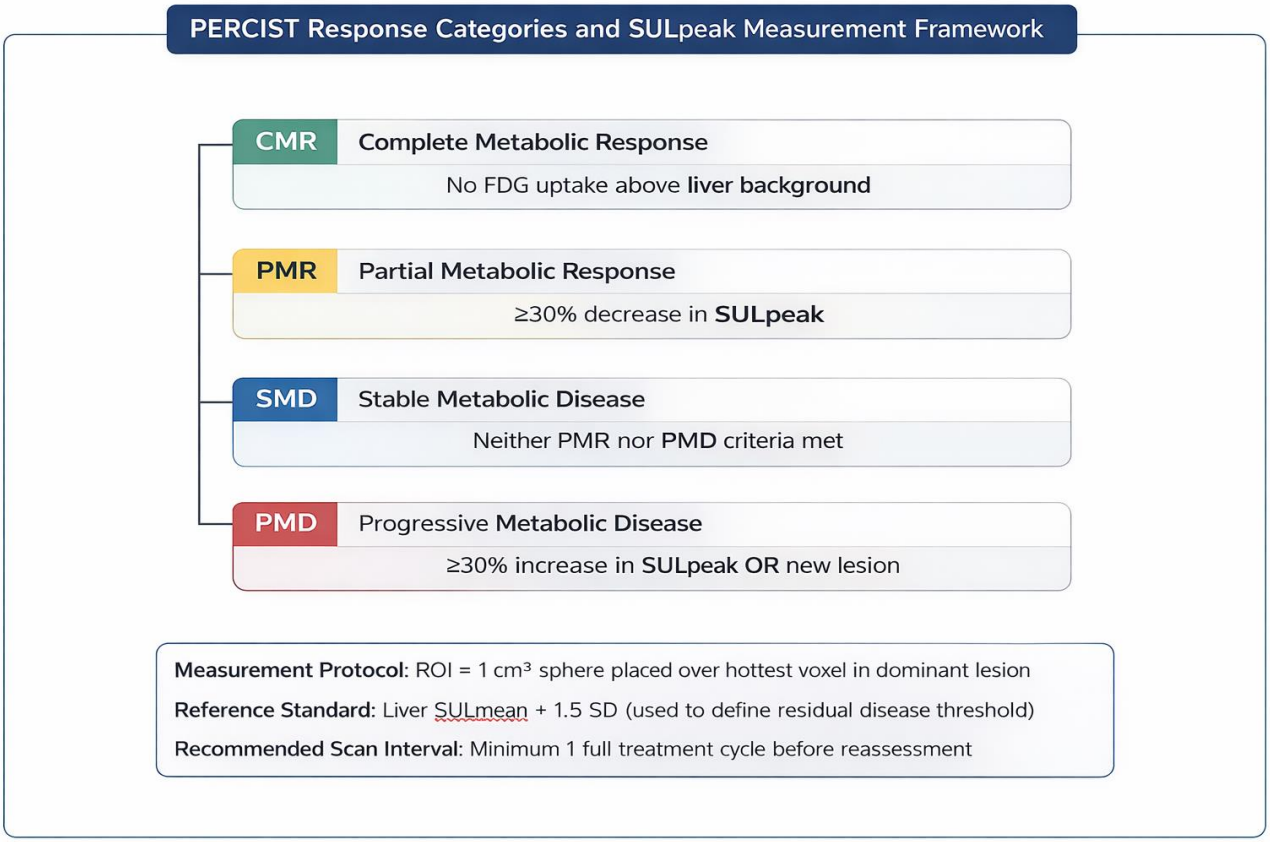

Figure 3. Schematic representation of PERCIST 1.0 metabolic response categories based on FDGPET/CT SULpeak measurements, with practical thresholds for clinical application.

Table 3. ***Novel PET Radiotracers in Oncologic Response Assessment: Biological Targets, Clinical Applications, Key Evidence, and Current Limitations***

PET Tracer	Target Process	Oncologic Application	Key Evidence	Limitations
^{18}FFDG	Glucose metabolism (Warburg effect)	Universal; staging, response, restaging	PERCIST; NCCN endorsed	Brain, lowgrade tumors; posttherapy inflammation
^{18}FFLT	Thymidine kinase 1 (proliferation)	Antiproliferative therapy response	Phase II breast, lung data	Low tumortobackground; no standard criteria
^{18}FFMISO / ^{18}FFAZA	Nitroimidazole (hypoxia)	Radiation therapy planning; hypoxic monitoring	H&N, glioma trials	Poor image quality; complex pharmacokinetics
^{68}GaPSMA	Prostatespecific membrane antigen	Prostate cancer staging & response to ARPI/LuPSMA	VISION, TheraP trials	Limited to PSMAexpressing disease

PET Tracer	Target Process	Oncologic Application	Key Evidence	Limitations
^{68}GaDOTATATE	Somatostatin receptor (SSTR2)	NET: staging, PRRT response assessment	NETTER1 trial	Only SSTR2+ tumors
^{89}ZrTrastuzumab	HER2 receptor expression	HER2+ breast cancer; antibody biodistribution	Phase I/II trials	Radiation dose; availability
^{18}FFDOPA	Amino acid transport	Brain tumor recurrence vs. radiation necrosis	Glioma response	Limited to neurologic tumors

ARPI=Androgen Receptor Pathway Inhibitor; PRRT=Peptide Receptor Radionuclide Therapy; NET=Neuroendocrine Tumor; SSTR=Somatostatin Receptor; H&N=Head and Neck; GBM=Glioblastoma Multiforme; ROI=Region of Interest; SUV=Standardized Uptake Value.

5. MULTIPARAMETRIC MRI IN ONCOLOGIC RESPONSE ASSESSMENT

5.1 DiffusionWeighted Imaging and the Apparent Diffusion Coefficient

Diffusionweighted imaging (DWI) measures the random Brownian motion of water molecules within tissue. In malignant tumors, hypercellularity restricts water diffusion, resulting in reduced apparent diffusion coefficient (ADC) values compared to normal parenchyma. Successful antitumor therapy whether cytotoxic, targeted, or radiosurgical reduces tumor cellularity through cell death and edema, producing measurable increases in ADC that frequently precede detectable changes in tumor size by several weeks. This early ADC response has been prospectively validated as a predictive biomarker for pathologic complete response (pCR) in breast cancer treated with neoadjuvant chemotherapy, hepatocellular carcinoma treated with transcatheter arterial chemoembolization (TACE), and highgrade glioma treated with concurrent chemoradiation.

The RECISTDWI hybrid approach, integrating dimensional measurement with ADC quantification, has demonstrated superior predictive accuracy for pathologic response compared to RECIST alone in several prospective studies. However, ADC quantification remains hampered by significant interscanner variability, scannerfield strength dependency, and the absence of internationally standardized acquisition protocols a challenge being actively addressed by the Quantitative Imaging Biomarkers Alliance (QIBA) DWI profile and the ACRIN 6698 breast DWI trial.

5.2 Dynamic ContrastEnhanced MRI: Vascular Response Assessment

Dynamic contrastenhanced MRI (DCEMRI) quantifies tumor vascularity and vascular permeability through pharmacokinetic modeling of gadolinium contrast agent kinetics. The Ktrans (volume transfer coefficient), which reflects the rate of contrast leakage from the intravascular to the extravascular extracellular space, and ve (fractional extravascular extracellular space volume) are the most widely utilized DCEMRI parameters in oncologic response assessment. Reductions in Ktrans following antiangiogenic therapy (bevacizumab, sorafenib, sunitinib) have been demonstrated within days to weeks of treatment initiation, providing a functional pharmacodynamic biomarker for vascular normalization that correlates with both PFS and OS in glioblastoma, HCC, and renal cell carcinoma.

5.3 MR Spectroscopy and Perfusion Imaging in NeuroOncology

In the central nervous system, the challenge of distinguishing true disease progression from treatmentrelated changes radiation necrosis, pseudoprogression, and antiangiogenic therapyinduced pseudoresponse has driven the adoption of advanced MRI techniques beyond conventional T1gadolinium and T2/FLAIR sequences. Magnetic resonance spectroscopy (MRS)

characterizes tumor metabolites including choline (a membrane turnover marker elevated in highly proliferative tumors), Nacetylaspartate (NAA, a neuronal integrity marker reduced in tumorinfiltrated brain), and creatine (Cr, a metabolic reference standard). An elevated Cho/NAA ratio strongly supports tumor recurrence, whereas a normalized spectroscopic profile is consistent with treatment effect.

Dynamic susceptibility contrast (DSC) MRI, providing relative cerebral blood volume (rCBV) maps, has been validated as a marker of pseudoprogression versus true progression in glioblastoma patients treated with temozolomide and radiation. The RANO Working Group has incorporated advanced MRI recommendations into RANO 2.0 criteria, acknowledging the growing clinical importance of DWI, DSC, DCE, and MRS in routine neurooncologic assessment.

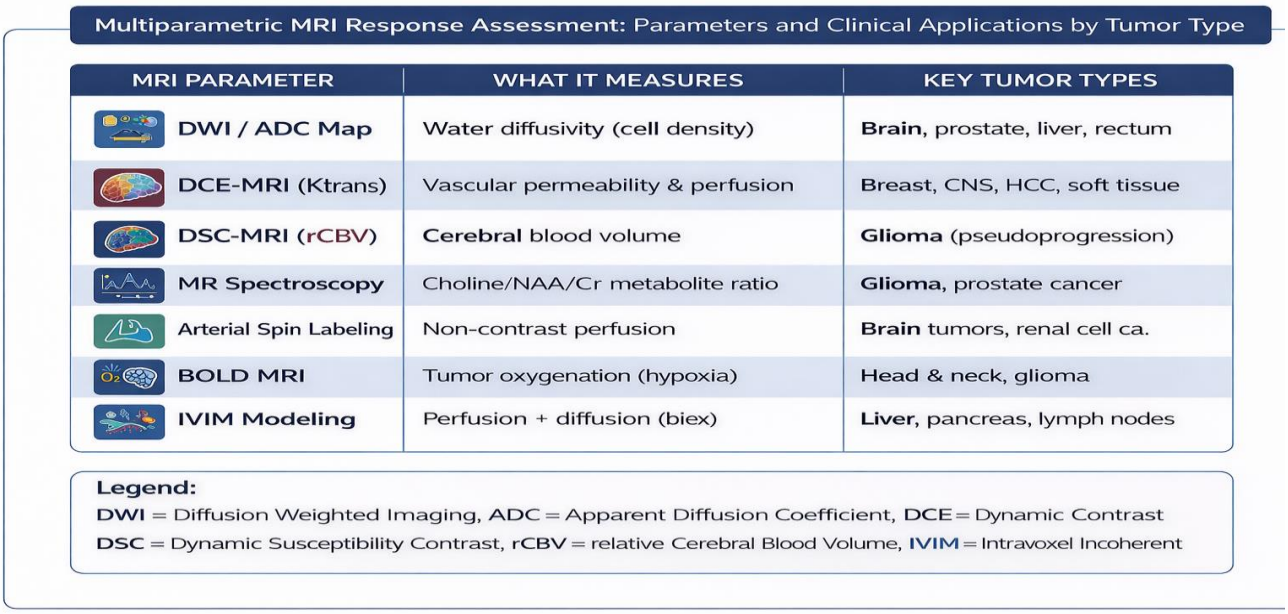

Figure 5. Overview of key multiparametric MRI parameters used in oncologic response assessment, with corresponding tumor types, interpretation targets, and clinical utility across treatment modalities.

6. RADIOMICS AND ARTIFICIAL INTELLIGENCE: QUANTITATIVE IMAGING BIOMARKERS

6.1 Radiomics: Principles and Workflow

Radiomics is the highthroughput extraction of large numbers of quantitative imaging features encompassing firstorder statistics (intensity histogram metrics), shapebased descriptors, and higherorder texture features derived from spatial relationships between voxels (GLCM, GLRLM, GLSZM matrices) from standardofcare medical images, with the goal of uncovering disease characteristics invisible to the human eye. The foundational premise of radiomics is that imaging phenotypes encode underlying tumor biology including genomic, proteomic, and microenvironmental characteristics, enabling noninvasive phenotypic characterization of the whole tumor volume rather than a single biopsy core.

The radiomics workflow encompasses six sequential steps: standardized image acquisition, preprocessing (resampling, noise filtering, intensity normalization), tumor segmentation (manual, semiautomatic, or deep learningbased), feature extraction (typically 100–2,000+ features per image), feature selection and dimensionality reduction (LASSO regularization, elastic net, correlation filtering), and machine learning model development with rigorous internal and external validation. The landmark study by Aerts et al. (2014) in Nature Communications demonstrated that four

quantitative CT radiomic signatures derived from lung and headandneck cancers capturing intratumoral heterogeneity, clonal heterogeneity, and tumor shape were independently prognostic for overall survival and correlated with underlying gene expression patterns.

6.2 DeltaRadiomics for Treatment Response Prediction

Deltaradiomics extends the singletimepoint radiomic analysis to longitudinal changes in imaging features between baseline and early treatment scans, capturing dynamic biological alterations induced by therapy. In several retrospective studies, deltaradiomic features outperformed static baseline features and RECISTbased response categories in predicting durable clinical benefit from ICI. Trebeschi et al. demonstrated that deltaradiomics from CT imaging obtained before and after the first ICI cycle predicted overall survival with an AUC of 0.84 in melanoma and NSCLC patients a performance that substantially exceeded RECISTbased assessment alone and did not require tumor segmentation expertise beyond nodule identification.

Khorrami et al. identified peritumoral texture features on baseline CT that predicted durable benefit from ICI in lung adenocarcinoma (AUC 0.79), providing pretreatment biomarkers for patient stratification. These findings suggest that imagingbased radiomic signatures may serve as complementary or alternative biomarkers to tissuebased predictors such as PDL1 immunohistochemistry and tumor mutational burden (TMB) in the ICI response prediction landscape.

6.3 Deep Learning and Convolutional Neural Networks

The past decade has witnessed the rapid integration of deep learning methodologies particularly convolutional neural networks (CNNs) into radiologic image analysis for oncologic response assessment. Unlike traditional radiomics, which relies on handcrafted features, deep learning models autonomously learn hierarchical feature representations directly from raw imaging data through endtoend supervised training on labeled datasets. Hosny et al. demonstrated that a ResNetbased CNN trained on CT images from NSCLC patients provided prognostication accuracy (AUC 0.74–0.86) competitive with and complementary to clinical staging.

For response prediction, deep learningbased approaches have been applied to predicting pathologic complete response to neoadjuvant chemotherapy in breast cancer from pretreatment MRI, distinguishing pseudoprogression from true progression in glioblastoma from multiparametric MRI, and predicting immunotherapy response in NSCLC from pretreatment CT. Critically, generalizability remains the central challenge: deep learning models trained on singleinstitution datasets frequently exhibit dramatic performance degradation when applied to external cohorts due to scanner heterogeneity, protocol variability, and population shift necessitating multicenter prospective validation as a prerequisite for clinical implementation.

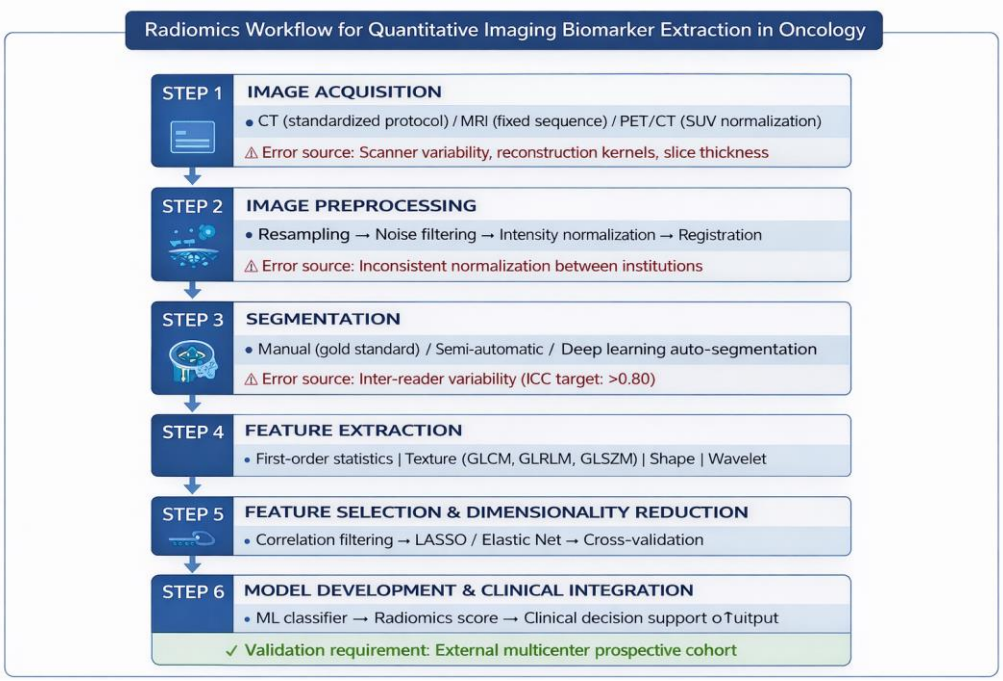

Figure 4. Endtoend radiomics pipeline from image acquisition through machine learning model output, illustrating key steps, potential error sources, and clinical integration points.

Table 4. *Key Radiomics and Artificial Intelligence Studies in Oncologic Response Assessment: Design, Modality, Tumor Type, Outcome, and Discriminative Performance*

Study/Author	Year	Modality	Tumor Type	Outcome	Performance
Aerts et al.	2014	CT	NSCLC / H&N SCC	Survival prediction (4 radiomic signatures)	Cindex 0.65–0.69
Coroller et al.	2015	CT	NSCLC	Distant metastasis prediction preCRT	AUC 0.72
Parmar et al.	2015	CT	NSCLC / H&N	Response prediction (RECIST)	AUC 0.76
Yip & Aerts	2016	PET/CT	NSCLC	Local recurrence after SBRT	AUC 0.80
Hosny et al.	2018	CT	NSCLC	DL survival model (ResNet)	AUC 0.74–0.86
Sun et al.	2018	MRI	GBM	Pseudoprogression vs PD (DWI+DCE)	AUC 0.88
Trebeschi et al.	2019	CT	Melanoma / NSCLC	Immunotherapy response (deltaradiomics)	AUC 0.84

Study/Author	Year	Modality	Tumor Type	Outcome	Performance
Khorrami et al.	2019	CT	NSCLC	Durable benefit from ICI (perilesional texture)	AUC 0.79

NSCLC=NonSmall Cell Lung Cancer; H&N SCC=Head and Neck Squamous Cell Carcinoma; GBM=Glioblastoma Multiforme; CRT=Chemoradiation Therapy; SBRT=Stereotactic Body Radiation Therapy; DL=Deep Learning; AUC=Area Under the Receiver Operating Characteristic Curve; Cindex=Concordance Index; ICI=Immune Checkpoint Inhibitor; DWI=Diffusion Weighted Imaging; DCE=Dynamic Contrast Enhanced MRI.

7. DISEASESPECIFIC AND MODALITYSPECIFIC RESPONSE CRITERIA

7.1 Hepatocellular Carcinoma: mRECIST

Hepatocellular carcinoma (HCC) presents a unique challenge for response assessment because the efficacy of locoregional therapies TACE, ablation, radioembolization and molecularly targeted agents (sorafenib, lenvatinib, atezolizumabbevacizumab) is determined not merely by overall tumor size reduction but by the destruction of viable, arterially enhancing tumor tissue within treated lesions. The modified RECIST (mRECIST) criteria, published by Lencioni and Llovet in 2010, address this by defining measurable target lesions based exclusively on the viable (arterially enhancing) component of HCC nodules, as visualized on the arterial phase of contrastenhanced CT or MRI. A complete response in mRECIST requires complete disappearance of all arterial enhancement in target lesions, while partial response requires ≥30% decrease in viable tumor diameter.

Multiple studies have demonstrated superior correlation between mRECISTdefined response and OS compared to RECIST 1.1, validating the clinical rationale for focusing on viable tumor rather than total lesion dimensions in HCC. The European Association for the Study of the Liver (EASL) response criteria, which assess total necrosis area on contrastenhanced MRI, provide a complementary approach with equivalent or superior OS correlation in some cohorts.

7.2 Gastrointestinal Stromal Tumors: Choi Criteria

GIST exemplifies the cytostatic response paradigm observed with molecularly targeted therapies. Imatinib mesylate (a BCRABL/cKIT/PDGFRA inhibitor) induces rapid cessation of tumor cell proliferation and myxoid degeneration within GIST lesions, frequently resulting in a decrease in CT attenuation (Hounsfield units) and heterogeneity without proportional size reduction sometimes with paradoxical transient size increase due to intratumoral hemorrhage or cystic change. RECIST 1.1, which is sizedependent, dramatically underestimates response rates and timetoresponse for imatinibtreated GIST. Choi criteria requiring a ≥10% decrease in size OR a ≥15% decrease in CT density demonstrated response rates of 97% for GIST on imatinib versus only 7% by RECIST, with superior correlation to PFS and OS.

7.3 Lymphoma: Lugano Classification and LYRIC

Lymphoma response assessment has evolved substantially since the integration of FDGPET/CT into standard staging and response evaluation. The Lugano classification (Cheson et al., 2014) represents the current standard for lymphoma response assessment, defining complete metabolic response (CMR) as Deauville score 1–3 (uptake ≤liver), partial metabolic response (PMR) as Deauville 4–5 with reduced uptake, and progressive metabolic disease (PMD) as Deauville 4–5 with increasing uptake or new lesions. The Deauville fivepoint scale provides a visually intuitive, semiquantitative assessment of residual FDG avidity referenced to mediastinal blood pool and liver.

With the advent of novel immunotherapy approaches for lymphoma including nivolumab, pembrolizumab, and CART cell therapy the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) were developed to parallel

iRECIST principles for the lymphoma context, incorporating indeterminate response (IR) classifications for cases where the radiologic picture is ambiguous due to immunerelated inflammatory changes.

8. LIQUID BIOPSY INTEGRATION WITH IMAGING RESPONSE ASSESSMENT

Liquid biopsy the detection and quantification of tumorderived materials in peripheral blood, including circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), cellfree RNA (cfRNA), and extracellular vesicles represents a transformative complementary technology for oncologic response monitoring. Unlike imaging, which provides spatial and morphologic information about macroscopic tumor deposits, ctDNA analysis captures the genomic landscape of the entire tumor burden with singlenucleotide resolution, enabling detection of emerging resistance mutations, clonal evolution, and minimal residual disease (MRD) below the spatial resolution threshold of any imaging modality.

The integration of ctDNA dynamics with imagingbased response assessment creates a multimodal response monitoring paradigm of superior sensitivity and specificity. In NSCLC, colorectal cancer, and breast cancer, declines in ctDNA allele frequency within the first weeks of therapy initiation predict subsequent radiologic response and OS with greater lead time than RECISTbased assessments. Critically, ctDNA clearance (below assay detection threshold) identifies molecular complete remission with profound prognostic implications even in patients with residual anatomic disease detectable on imaging. Conversely, ctDNA rise preceding radiologic progression (molecular preclinical progression) provides an early warning signal that enables adaptive therapy modification before full radiologic progression.

However, ctDNA monitoring also presents complementary limitations to imaging: it provides no spatial localization of progressing disease, is subject to technical variability (assay sensitivity, tumor shedding rates), and may yield falsenegative results in lowshedding tumor types (primary CNS tumors, MSIhigh tumors). The convergence of quantitative imaging and liquid biopsy into integrated multimodal response assessment platforms represents an active area of translational investigation.

9. EMERGING AND FUTURE TECHNOLOGIES IN ONCOLOGIC RESPONSE ASSESSMENT

9.1 Total Body PET and UltraLow Dose Imaging

The development of total body PET/CT systems (EXPLORER consortium) with axial fields of view of 194–200 cm enables simultaneous visualization of the entire body with dramatically improved sensitivity and count statistics compared to conventional PET. This technology facilitates ultralow radiation dose scanning (suitable for longitudinal monitoring), subcentimeter lesion detection, improved kinetic modeling without arterial blood sampling, and wholebody pharmacokinetic characterization of novel radiotracers. For response assessment, total body PET enables comprehensive evaluation of heterogeneous metastatic disease across all anatomic compartments in a single acquisition, with particular utility for dissociated responses under ICI.

9.2 Spectral PhotonCounting CT

Nextgeneration photoncounting detector CT (PCDCT) provides inherent material decomposition capabilities, improved spatial resolution, and multienergy spectral information without the dose penalties of current dualenergy CT systems. In oncologic response assessment, PCDCT enables quantification of iodine concentration (a surrogate for tumor vascularity and enhancement) with greater precision than conventional CT attenuation, potentially providing CTbased perfusion information applicable to response assessment without the need for dedicated DCEMRI acquisitions. Early clinical data from major academic centers deploying PCDCT systems demonstrate improved lesion conspicuity, superior characterization of necrotic versus viable tumor components, and reduced artifact in patients with metallic implants.

9.3 Theranostic Imaging Platforms

Theranostics the integration of diagnostic imaging and targeted radionuclide therapy within a single molecular platform is emerging as one of the most

dynamic and rapidly evolving frontiers in precision oncology. The foundational principle involves using a diagnostic radiotracer to confirm target expression and wholebody biodistribution, followed by substitution of the diagnostic radionuclide with a therapeutic isotope on the same molecular vector. Response assessment in theranostics is uniquely integrated: posttherapy SPECT/CT or PET imaging using the therapeutic tracer itself (e.g., ^{177}LuPSMA SPECT after ^{177}LuPSMA therapy) provides simultaneous dosimetry verification and response assessment, with target lesion uptake reduction serving as a molecular response indicator.

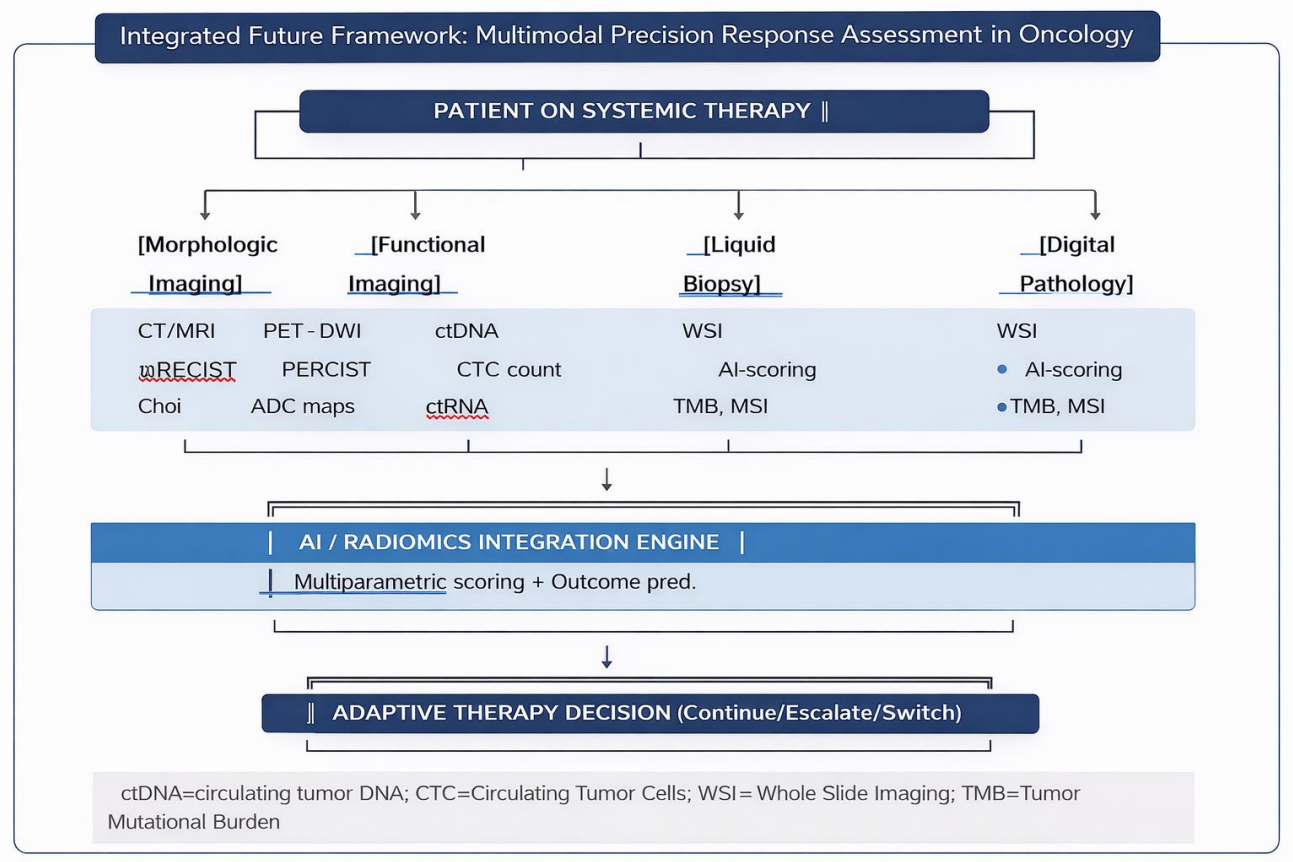

Figure 6. Conceptual framework illustrating the convergence of conventional imaging, functional imaging, liquid biopsy, and artificial intelligence into an integrated precision oncology response assessment ecosystem.

10. CHALLENGES, STANDARDIZATION, AND FUTURE DIRECTIONS

10.1 Interreader Variability and Standardization

Despite efforts to standardize response assessment through published criteria, significant interreader variability persists in clinical and trial practice. Studies evaluating RECIST 1.1 compliance in phase III trials have documented discordant response classifications between institutional and central review in 15–30% of evaluable patients, with implications for both individual treatment decisions and trial outcomes. Sources of variability include inconsistent lesion selection at baseline, failure to follow the same lesions at subsequent time points, inconsistent measurement technique, and ambiguity in distinguishing target from nontarget lesions for certain lesion morphologies (lymph nodes, pleural disease, bone metastases).

For advanced imaging techniques including radiomic analyses and DCEMRI, standardization challenges are considerably greater. Radiomic features demonstrate substantial variability across

scanner manufacturers, acquisition protocols, reconstruction kernels, and segmentation methods with testretest reproducibility (intraclass correlation coefficient) falling below 0.80 for a substantial proportion of commonly extracted features. The Image Biomarker Standardization Initiative (IBSI) has published consensus definitions for radiomic feature computation, and the QIBA has developed profiling documents for DWIADC, DCEMRI, and FDGPET/CT critical steps toward multicenter harmonization.

10.2 Artificial Intelligence: From ProofofConcept to Clinical Deployment

The transition of AIbased imaging biomarkers from research to clinical implementation faces formidable regulatory, technical, and institutional barriers. Regulatory frameworks for AI/MLbased software as a medical device (SaMD) developed by the FDA (AI/MLBased SaMD Action Plan), European Medical Devices Regulation (MDR), and other national agencies require rigorous premarket evaluation including analytical validation, clinical validation against meaningful clinical endpoints, and postmarket surveillance. The concept of locked versus adaptive AI algorithms introduces additional regulatory complexity for continuously learning systems.

Explainability represents another fundamental challenge: stateoftheart deep learning models, despite superior discriminative performance, function as 'black boxes' providing predictions without humaninterpretable rationale a critical limitation in highstakes oncologic decisionmaking. Explainable AI (XAI) methodologies including gradientweighted class activation mapping (GradCAM), SHAP (SHapley Additive exPlanations), and attention mechanisms are being incorporated into oncologic imaging AI systems to improve interpretability and build clinician trust.

10.3 Ethical and Equity Considerations

Advanced imaging technologies for oncologic response assessment are not uniformly accessible across healthcare systems, geographic regions, and patient populations. PET/CT with novel radiotracers, total body PET, PCDCT, mpMRI with advanced sequences, and commercial liquid biopsy platforms are predominantly available in highincome, academically affiliated institutions, creating potential for exacerbating health inequities in cancer outcomes. The development and validation of AI models on datasets predominantly derived from affluent, majoritypopulation patient groups introduces algorithmic bias risks for minority and underserved populations. Prospective clinical trials investigating advanced response assessment methodologies must mandate diverse patient enrollment and incorporate equity analyses as prespecified endpoints.

11. CONCLUSIONS

Oncologic response assessment has undergone a paradigm transformation over the past two decades, driven by the therapeutic revolution in cancer medicine and concurrent advances in imaging science and computational analytics. RECIST 1.1 retains its foundational role in clinical trial design and regulatory drug approval for conventional cytotoxic chemotherapy but is demonstrably insufficient as the sole response assessment framework for immunotherapy, molecularly targeted therapies, and theranostic approaches. The proliferation of diseasespecific and modalityspecific criteria iRECIST, PERCIST, mRECIST, Choi, Lugano, RANO reflects the biological complexity of modern oncologic therapeutics and the diverse imaging technologies available to characterize it.

The future of oncologic response assessment lies not in the replacement of established criteria with a single universal successor but in the thoughtful integration of complementary information streams: anatomic morphology from CT/MRI, metabolic and molecular information from functional PET and multiparametric MRI, quantitative radiomic signatures capturing intratumoral heterogeneity, AIbased pattern recognition, and liquid biopsyderived molecular response indicators. This multimodal precision response assessment framework, underpinned by rigorous standardization, prospective multicenter validation, and multidisciplinary consensus, holds the transformative potential to align imaging endpoints with the biological realities of contemporary cancer treatment ultimately improving patient outcomes through earlier, more accurate treatment adaptation. The imaging community oncologic radiologists, nuclear medicine physicians, medical oncologists,

and clinical trialists must collaborate urgently to achieve this vision. Standardized data sharing infrastructures, federated learning frameworks for multicenter AI development, and prospective adaptive trial designs incorporating advanced imaging biomarkers are the tools through which this transformation will be realized.

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