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REVIEW

# The Role of Nuclear Medicine in Predicting Treatment Response to Immunotherapy and Targeted Therapy in Hepatocellular Carcinoma: A Narrative Review

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**Objective:** Targeted and immunotherapy offer new treatment options for patients with advanced hepatocellular carcinoma (HCC); however, the proportion of patients who benefit from these therapies remains limited. Moreover, these treatments can involve complications and add financial burdens to patients, underscoring the need to identify those who are likely to benefit. As an advanced molecular imaging technique, nuclear medicine has the potential to predict treatment efficacy in targeted and immunotherapy, though its predictive accuracy remains uncertain. This narrative review aims to summarize existing research on nuclear medicine applications in this area, providing clinicians with new perspectives.

**Materials and Methods:** We conducted a literature review across multiple medical databases, including PubMed, Embase, Cochrane Library, Web of Science, and Scopus. Relevant studies were identified, organized, and summarized to present findings in the field.

**Results:** The findings indicate that metrics such as maximum standardized uptake value (SUVmax) and metabolic tumor volume (MTV) correlate with the efficacy of targeted and immunotherapy. Additionally, emerging nuclear medicine techniques have shown promise in predicting PD-L1 expression.

**Conclusion:** Nuclear medicine holds potential for identifying patients who are likely to benefit from targeted and immunotherapy. However, further refinements are necessary to optimize its predictive capabilities.

**Keywords:** nuclear medicine, hepatocellular carcinoma, immunotherapy, targeted therapy, FDG PET/CT

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## Introduction

Cancer treatment has rapidly evolved with the introduction of immunotherapy and targeted therapy, especially for advanced-stage malignancies like hepatocellular carcinoma (HCC). Immunotherapy, particularly immune checkpoint inhibitors (ICIs), has gained prominence by enhancing the body's natural immune response to recognize and destroy cancer cells. ICIs such as anti-programmed cell death protein 1 (PD-1) and anti-programmed death-ligand 1 (PD-L1) antibodies block inhibitory pathways in T-cells, thereby restoring antitumor immunity. Agents like nivolumab and pembrolizumab have shown efficacy in various cancers, including melanoma and non-small cell lung cancer,[1–3] and are now being investigated for their benefits in HCC.[4]

Targeted therapies, on the other hand, aim to disrupt specific molecular pathways crucial for tumor growth and survival. In HCC, tyrosine kinase inhibitors (TKIs) such as sorafenib and lenvatinib, and anti-vascular endothelial growth factor (VEGF) agents like bevacizumab, have demonstrated effectiveness in inhibiting angiogenesis and cellular proliferation. Combining targeted therapies with ICIs has become an attractive strategy, as these agents can potentially enhance the tumor's immunogenicity, thereby improving the response to immunotherapy combined target therapy.[5]

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## Challenges in Treatment Response Prediction

Despite the advancements in immunotherapy and targeted treatments, predicting treatment response remains a significant challenge.[6] The efficacy of ICIs is often limited to a subset of patients, with many experiencing resistance or incomplete responses. Traditional biomarkers such as PD-L1 expression and tumor mutational burden (TMB) have been explored for predicting responses to ICIs. However, their utility is limited by tumor heterogeneity, dynamic expression changes over time, and variations in assay methods across clinical settings. For instance, PD-L1 expression in HCC may not consistently correlate with treatment outcomes due to variability in expression within the tumor microenvironment and across different lesions[5].[7] This inconsistency highlights the need for non-invasive, real-time monitoring tools that can provide a comprehensive view of tumor biology and therapeutic response, addressing biomarker heterogeneity through whole-body metabolic imaging.[1,6] Advanced imaging modalities, particularly molecular imaging techniques, have emerged as promising candidates to fulfill this need.[1]

## Role of Nuclear Medicine in Oncology

Nuclear medicine plays a pivotal role in modern oncology by providing unique insights into tumor biology through advanced imaging techniques such as positron emission tomography/computed tomography (PET/CT) and PET/magnetic resonance imaging (MRI). These modalities not only offer anatomical details but also evaluate metabolic and functional aspects of tumors using radiotracers like fluorodeoxyglucose (FDG). For instance, FDG-PET/CT is particularly effective in detecting changes in tumor metabolism, which can indicate early treatment responses before any morphological changes are visible on conventional imaging techniques. This is especially important in monitoring therapies such as chemotherapy or immunotherapy, where metabolic alterations often precede anatomical changes.[1,8,9] Moreover, early changes in FDG uptake on PET/CT scans have been linked to better clinical outcomes and overall survival, especially in patients undergoing combined therapy. While traditional criteria like RECIST may not fully capture treatment effects, especially in cases of pseudoprogression or atypical response patterns seen with immune checkpoint inhibitors, PET-based criteria such as PERCIMT or iPERCIST have been developed to better assess metabolic responses and adapt therapeutic strategies accordingly.[10,11]

The concept of theranostics, which combines diagnostic imaging and targeted radiotherapy, has further expanded the utility of nuclear medicine.[12] In theranostics, radiolabeled agents are used for both imaging and delivering therapeutic radiation to cancer cells. This approach allows for the visualization of target expression (eg, PD-L1) and the subsequent administration of radionuclide therapy, providing a personalized treatment strategy. Theranostics has shown promise in managing neuroendocrine tumors and prostate cancer,[13] and its application is now being explored in HCC.[14]

By integrating molecular imaging with conventional therapies, nuclear medicine has the potential to improve patient selection for ICIs or targeted therapy and to monitor treatment efficacy more accurately. This dual diagnostic and therapeutic capability makes it a valuable tool in the era of precision oncology.

## HCC Pathobiology and Imaging Challenges

HCC exhibits variable FDG avidity due to glucose-6-phosphatase (G6Pase) activity: well-differentiated tumors are FDG-low, while poorly differentiated are FDG-avid, complicating prediction vs other cancers.[15] Historical tracers like [11C]-acetate/choline address this, but immune-specific tracers (eg, granzyme B) offer superiority by targeting TME dynamics.[16]

## Novelty and Scope of This Review

While prior reviews have summarized nuclear medicine in oncology (eg, Aide et al, 2019;[1] Iravani and Hicks, 2020[9]), this narrative review provides an updated, HCC-focused synthesis of post-2020 evidence on predictive biomarkers like MTV and novel tracers, integrated with AI and practical barriers, offering fresh perspectives for clinical translation not covered in earlier works (eg, Iravani et al, 2021;[17] Aide et al, 2020[11]). This narrative review focuses on the predictive/prognostic value of nuclear medicine biomarkers for ICI ± anti-VEGF therapy in HCC, with primary endpoints including ORR, MPR/pCR, PFS, and OS, and secondary endpoints like PD-L1 expression and immune infiltration.

# Mechanisms of Immunotherapy and Targeted Therapy in HCC

## Immune Checkpoint Inhibitors (ICIs)

ICIs target pathways like PD-1/PD-L1 and CTLA-4 to restore T-cell activity. Anti-PD-1/PD-L1 agents (eg, nivolumab, atezolizumab) block tumor immune evasion, while anti-CTLA-4 (eg, ipilimumab) enhances T-cell proliferation.[1,5] In HCC, these show response rates of 15–20% as monotherapy, improving to 30–40% in combinations.[18] Response heterogeneity remains a challenge, with ICIs yielding 15–20% ORR in HCC due to variable TME immunosuppression.[18]

## Targeted Therapy Mechanisms

Targeted therapies focus on inhibiting specific molecular pathways that drive tumor growth and progression. In HCC, several signaling pathways are commonly dysregulated, including the VEGF, RAF/MEK/ERK, and PI3K/AKT/mTOR pathways. The agents sorafenib and lenvatinib have been approved as first-line treatments for advanced HCC due to their ability to target multiple kinases involved in tumor cell proliferation and angiogenesis.[19]

### Sorafenib

As a multi-kinase inhibitor, sorafenib targets the RAF kinase in the MAPK/ERK signaling pathway, which is involved in cell division and survival, as well as VEGFR and PDGFR, which are key regulators of angiogenesis. By inhibiting these pathways, sorafenib reduces tumor growth and blood vessel formation, thereby limiting nutrient supply to the tumor.[20]

### Lenvatinib

Lenvatinib also acts as a multi-kinase inhibitor but has a broader range of targets, including VEGFR, FGFR, PDGFR, and the RET receptor tyrosine kinases. It is particularly effective in reducing angiogenesis and tumor invasion by inhibiting both VEGF and FGF signaling pathways, which are essential for tumor vascularization. This inhibition not only restricts tumor growth but may also alter the tumor microenvironment, potentially making it more susceptible to immune attack.[21,22]

## Combination Therapies

Combining immunotherapy with targeted therapies represents a promising approach to overcoming resistance mechanisms and enhancing therapeutic efficacy.[23] The rationale for combination strategies lies in the complementary mechanisms of action: while ICIs restore immune function and enable T cells to recognize and attack cancer cells, targeted therapies directly inhibit tumor cell proliferation and disrupt the supportive tumor microenvironment.[24]

## Rationale for Combination

Targeted agents, such as sorafenib or lenvatinib, can potentially increase the immunogenicity of the tumor by modulating the immune microenvironment. For instance, the inhibition of VEGF not only reduces angiogenesis but can also normalize the tumor vasculature, improving the infiltration of immune cells, such as cytotoxic T lymphocytes, into the tumor.[25,26] Additionally, some targeted therapies may induce immunogenic cell death, which releases tumor antigens and promotes an adaptive immune response, further enhancing the effects of ICIs.

## Clinical Examples

The combination of atezolizumab (an anti-PD-L1 antibody) and bevacizumab (an anti-VEGF agent) has shown improved survival outcomes in patients with advanced HCC compared to sorafenib alone, as demonstrated in the IMbrave150 trial.[27] This combination takes advantage of bevacizumab's ability to modulate the tumor vasculature and enhance immune cell infiltration while atezolizumab reactivates T-cell function. Such strategies exemplify the synergistic potential of integrating immunotherapy and targeted therapy for better clinical outcomes.

Understanding the mechanisms underlying ICIs, targeted therapies, and their combination is crucial for developing effective treatment strategies for HCC. Continued research into optimizing these therapies and identifying predictive biomarkers will be essential for personalizing treatment and improving patient outcomes.

# Molecular Imaging in Predicting Treatment Response

## FDG PET/CT in Immunotherapy Evaluation

Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) is a widely used molecular imaging technique in oncology that assesses metabolic activity in tumors by measuring glucose uptake. Its role in immunotherapy evaluation lies in the ability to detect metabolic changes associated with immune responses, such as T-cell activation and tumor inflammation, which can manifest as increased FDG uptake.[1,8,9] These metabolic changes often occur earlier than structural changes, making FDG PET/CT valuable for assessing early treatment responses to immune checkpoint inhibitors (ICIs). FDG changes serve as predictive indicators as they reflect underlying biological processes in the tumor microenvironment, particularly changes in cellular metabolism associated with an immune response. Increased glucose uptake seen on FDG PET/CT may indicate active immune cell infiltration, as immune cells like activated T-cells have higher metabolic demands and thus consume more glucose. By identifying these metabolic shifts early, FDG PET/CT can provide an early indication of treatment efficacy, helping to differentiate between responders and non-responders before conventional imaging shows anatomical changes. This early metabolic insight allows for timely adjustments to treatment plans, potentially improving outcomes by allowing more personalized therapeutic approaches.[11,28,29]

Recent studies have highlighted the utility of FDG PET/CT in predicting treatment responses in HCC patients undergoing combination therapy with Lenvatinib and PD-1 inhibitors. Metabolic parameters such as the maximum standardized uptake value (SUVmax) and the tumor-to-normal liver standardized uptake value ratio (TLR) were found to correlate with major pathological response (MPR). High baseline TLR values and significant reductions in TLR after treatment were associated with better treatment outcomes, including prolonged progression-free survival (PFS) and overall survival (OS). These findings suggest that FDG PET/CT can serve as a valuable biomarker for preoperative evaluation and prognosis prediction in HCC patients, especially when assessing the effectiveness of conversion therapy.[9,30] The predictive power of FDG PET/CT in this context arises from its ability to capture metabolic alterations that reflect tumor aggressiveness and responsiveness to therapy. Higher baseline SUVmax and TLR values typically indicate more active tumor metabolism, which can correlate with greater tumor burden and aggressiveness. However, reductions in these values following treatment may signal an effective tumor response to the combination therapy, as metabolic activity decreases in responsive tumors. By monitoring these shifts, FDG PET/CT provides insight into the metabolic state of the tumor over time, helping to evaluate the effectiveness of therapy early in the treatment course. This enables clinicians to make data-informed adjustments to therapy, enhancing personalized treatment approaches for better patient outcomes[30,31].[32]

Additionally, MTV has emerged as a significant predictor of overall survival in HCC patients receiving combination therapy. Higher MTV values ($\geq$39.65 cm$^3$) were associated with poorer prognosis, while a combination of MTV, ECOG performance status, Child-Pugh classification, and the presence of bone metastases allowed for better stratification of patients into different risk groups. These findings suggest that FDG PET/CT metabolic parameters, especially MTV, can serve as valuable biomarkers for evaluating prognosis and guiding treatment decisions in HCC patients undergoing immunotherapy and targeted therapy.[31] The significance of MTV as a predictor lies in its ability to reflect the overall metabolic burden of the tumor, which correlates with tumor aggressiveness and the extent of disease. Higher MTV values indicate a larger volume of metabolically active tumor tissue, which can signal advanced disease and a greater likelihood of resistance to therapy. By incorporating MTV alongside clinical factors such as ECOG performance status, liver function (Child-Pugh classification), and bone metastasis presence, clinicians can achieve a more comprehensive risk assessment. This multimodal approach allows for precise prognostication and more personalized treatment planning, tailoring interventions according to the predicted disease trajectory and improving overall patient management[31,33] (see Table 1 for a summary of HCC cohorts evaluating FDG metrics for ICI ± TKI).

## Correlation with PD-L1 Expression and Immune Infiltration

Higher FDG uptake metrics—such as standardized uptake value maximum (SUVmax) and metabolic tumor volume (MTV)—correlate with PD-L1 expression and tumor-infiltrating lymphocytes, enabling non-invasive patient stratification

**Table 1** HCC Cohorts Evaluating FDG Metrics for ICI ± TKI

| Study | Metric/Cutoff | Outcome | HR/AUC | Validation |
|---|---|---|---|---|
| Wang et al, 2023[22] | TLR >2.5 (baseline); ΔTLR >30% | MPR, PFS/OS | HR 2.8; AUC 0.82 | Internal |
| Wang et al, 2023[23] | MTV ≥39.65 cm³ | OS | HR 3.1; AUC 0.75 | None |
| Wang et al, 2022[25] | TLR >3.0 | Pathological response | AUC 0.78 | External |

for ICIs (eg, high TLR predicts MPR and guides conversion therapy decisions)[30] t ADDIN EN.CITE a, and hepatocellular carcinoma (HCC), where higher SUVmax is linked to immune cell infiltration (eg, CD8+ T cells, M2 macrophages) and aggressive features like poor differentiation or portal vein thrombosis.[1,34,35] Recent studies have indicated that pretreatment metabolic parameters measured by 18F-FDG PET/CT, such as the tumor-to-normal liver standardized uptake value ratio (TLR), are valuable in predicting treatment response in HCC patients undergoing combination therapy with PD-1 inhibitors and lenvatinib. Higher TLR values have been associated with a better pathological treatment response, suggesting that metabolic imaging can help identify patients more likely to benefit from combined therapies. This correlation between higher SUV metrics and favorable responses may be attributed to increased immune cell activity within the tumor microenvironment, serving as a predictive biomarker for immunotherapy outcomes in HCC and other cancers, such as colorectal liver metastases (CRLM).[9,35,36]

Further research has introduced innovative approaches to understanding the role of PD-L1 in immunotherapy. One study utilized lysosome-targeting chimeras (LYTACs) for targeted protein degradation to selectively degrade PD-L1 on tumor cells while leaving host immune cells unaffected. PET imaging with a PD-L1-specific tracer (89Zr-αPD-L1/Fab) demonstrated that the degradation of tumor cell PD-L1 did not significantly impact the efficacy of anti-PD-1 therapy, whereas the presence of PD-L1 on host cells played a crucial role in the treatment response. This finding highlights the differential impact of PD-L1 expression on various cell types within the tumor microenvironment, suggesting that host PD-L1 is a more relevant target for predicting and enhancing the efficacy of immunotherapy. The combination of targeted protein degradation and PET imaging provides a novel strategy to non-invasively assess PD-L1 expression and its functional role in immunotherapy. These insights could improve patient selection and optimize immunotherapy approaches in HCC and other cancers.[37]

## Novel PET Radiotracers for Immunotherapy Prediction

While FDG PET/CT is useful for assessing metabolic activity, it is not specific for immune-related changes, as FDG uptake can also reflect non-immune processes, such as increased glycolysis in aggressive tumors. To overcome this limitation, novel PET radiotracers have been developed to target specific immune markers, providing more precise information about the tumor microenvironment.[9,28]

## Radiotracers Targeting PD-L1 and CD8+ T Cells

New PET tracers, such as [89Zr]Zr-DFO-anti-PD-L1 and [64Cu]Cu-DOTA-CD8, are designed to bind to PD-L1 or CD8+ T cells, respectively. 89Zr with chelating agent added can specifically bind to PD-L1 at the tumor site, and the nuclear signal value is 4–6 times that of the surrounding tissue.[38] These tracers can provide insights into the distribution and density of immune checkpoints or effector T cells within the tumor. Imaging with these tracers enables the non-invasive assessment of immune cell activity and checkpoint expression, potentially predicting response to ICIs. For example, [89Zr]Zr-DFO-anti-PD-L1 has shown promise in assessing the expression of PD-L1 in real-time, allowing for dynamic evaluation of changes in the immune landscape during therapy.[39,40]

Recent studies demonstrated that [89Zr]Zr-DFO-anti-PD-L1 can quantitatively assess PD-L1 expression levels in vivo, offering precise, non-invasive evaluation of immune checkpoint expression. In xenograft and syngeneic tumor models, this tracer successfully distinguished varying PD-L1 expression levels among tumors and detected therapy-induced changes, such as PD-L1 upregulation after radiotherapy. This capability allows for real-time monitoring of PD-L1 dynamics, potentially predicting responses to PD-L1-targeted therapies and guiding personalized treatment decisions.[41]

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**Table 2** Emerging Immune Tracers

| Tracer | Target | Modality | Timing | Population | Endpoint | HCC-Specific Evidence | Limitations |
|---|---|---|---|---|---|---|---|
| 89Zr-DFO-REGN3504[29] | PD-L1 | PET | Preclinical | Tumors/normal tissues | PD-L1 expression | Sensitive detection in HCC models | Limited clinical data |
| 89Zr-Atezolizumab[31] | PD-L1 | PET | Preclinical/ clinical | Renal cell carcinoma (tumorgrafts) | PD-L1 in vivo | Potential for HCC; correlates with response | Heterogeneity in uptake |
| Site-labeled PD-L1 Ab[32] | PD-L1 | PET | Preclinical | Xenograft/syngeneic models | Quantitative PD-L1 | HCC applicability inferred; high specificity | Animal models only |
| Granzyme B PET[34] | Granzyme B | PET | Preclinical | HCC | ICI response stratification | Stratifies responders in HCC | Early stage; limited validation |

Similarly, [99mTc]-NM-01, a SPECT-based radiotracer, has been developed to target PD-L1 with high specificity. Preclinical studies demonstrated that [99mTc]-NM-01 effectively binds to PD-L1 and can non-invasively image PD-L1-positive tumors with high tumor-to-background contrast. This tracer provides an additional option for assessing PD-L1 expression without interfering with therapeutic antibodies, making it suitable for monitoring changes during immunotherapy[42] (see Table 2 for emerging immune tracers).

## Radiotracers Targeting Granzyme B for Monitoring Immune Activation

Recent studies have introduced novel radiotracers that target granzyme B, a serine protease released by activated immune cells such as cytotoxic T lymphocytes and natural killer (NK) cells. One promising example is [18F]AlF-mNOTA-GZP, a PET tracer designed to bind to granzyme B, allowing for the assessment of immune cell activity directly within the tumor microenvironment. In preclinical models of hepatocellular carcinoma (HCC), this tracer demonstrated its ability to differentiate between tumors that responded to immune checkpoint inhibitors and those that did not. The increased uptake of [18F]AlF-mNOTA-GZP in responsive tumors was correlated with higher levels of granzyme B-positive NK cells, suggesting that this tracer could serve as a valuable biomarker for predicting the effectiveness of immunotherapy in HCC. Such radiotracers provide a more specific assessment of immune-related processes compared to FDG, potentially enhancing the precision of treatment response evaluation.[16]

## Limitations of FDG PET/CT

One significant limitation of FDG PET/CT in immunotherapy monitoring is the occurrence of pseudoprogression and hyperprogression.[11,28] Pseudoprogression refers to an apparent increase in tumor size or metabolic activity due to immune cell infiltration, which can mimic disease progression on imaging but is later followed by tumor regression. Hyperprogression, on the other hand, is characterized by an accelerated tumor growth rate after initiating immunotherapy. These phenomena can complicate the interpretation of PET/CT scans, highlighting the need for specific radiotracers that can distinguish between true progression and immune-related changes.[8,11,28]

## PET/MRI and Multimodal Imaging

Combining PET with magnetic resonance imaging (MRI) provides an advanced multimodal imaging approach that integrates the functional information from PET with the high-resolution anatomical and soft tissue contrast from MRI. This combination is particularly advantageous in characterizing complex tumors like HCC, which exhibit significant heterogeneity.[43]

## Advantages of PET/MRI in HCC

PET/MRI can offer superior lesion characterization by providing both metabolic information and detailed anatomical images, which can improve the accuracy of staging and detection of liver lesions. For example, the addition of diffusion-weighted imaging (DWI) from MRI can help assess tumor cellularity and distinguish viable tumor tissue from necrosis. In HCC, PET/MRI has been used to identify molecular subtypes of the disease and predict features such as microvascular invasion, which is critical for prognosis and treatment planning.[44]

**Table 3** PET/MRI Parameters Associated with Response to ICI/Anti-VEGF

| Parameter | Association | Outcome | Evidence | Limitations |
|---|---|---|---|---|
| ADC (DWI) | Higher ADC post-treatment | Response (vascular normalization) | Correlates with CK19 status in HCC[36] | Small cohorts |
| Ktrans (perfusion) | Decreased Ktrans | Anti-VEGF efficacy | Multimodal changes after VEGF/ICI[37] | Preclinical focus |

Recent studies have further demonstrated the utility of integrating PET and MRI with additional quantitative imaging biomarkers. For instance, parameters such as apparent diffusion coefficient (ADC), Ktrans (a parameter reflecting vascular permeability), and lactate-to-choline ratio (Lac/Cho) can provide valuable information about tumor characteristics. These parameters have shown to correlate with changes in the tumor microenvironment induced by treatments, such as vascular endothelial growth factor (VEGF) inhibitors and immune checkpoint inhibitors (ICIs)[45] (see Table 3 for PET/MRI parameters associated with response to ICI/anti-VEGF).

## Integration of Functional and Anatomical Data

By combining metabolic activity, anatomical structure, and potentially molecular information (eg, radiomics), PET/MRI allows for a more comprehensive evaluation of the tumor's biological behavior. This multimodal approach can improve treatment decision-making by providing insights into the tumor's response to therapies, including both ICIs and targeted treatments.[44] Molecular imaging techniques such as F ADDIN EN.CITE g the response to cancer immunotherapy and targeted treatments. These techniques not only facilitate early response assessment but also help overcome challenges associated with traditional biomarkers, paving the way for more personalized treatment strategies.

# Radiomics and Artificial Intelligence in Nuclear Medicine

## Radiomics in PET Imaging

Radiomics refers to the extraction and analysis of a large number of quantitative features from medical imaging, which can reveal patterns not discernible to the naked eye. In PET imaging, radiomics involves analyzing features such as texture, shape, and intensity distributions within the tumor region to provide insights into tumor biology and behavior.[46,47]

### Quantitative Feature Extraction and Clinical Applications

Texture analysis from PET images can quantify tumor heterogeneity by evaluating variations in voxel intensities. This approach has been shown to predict important clinical outcomes, such as microvascular invasion (MVI) in hepatocellular carcinoma (HCC), which is associated with higher recurrence rates and poorer prognosis. Additionally, radiomic features can be used to predict overall survival, disease-free survival, and response to therapies.[46,47] For example, radiomic signatures derived from FDG PET/CT have been correlated with treatment outcomes in patients undergoing immunotherapy, providing a potential tool for early response assessment.[47,48]

### Advances in Predictive Modeling for Immunotherapy and Targeted Therapies

Recent studies have demonstrated the utility of radiomics in developing predictive models for response to immune checkpoint inhibitors (ICIs) or targeted therapies such as anti-VEGF agents. Radiomics-based models can integrate various imaging features to generate a risk score or treatment response likelihood, aiding in patient stratification. For instance, texture features that reflect intratumoral metabolic activity can indicate the degree of immune cell infiltration, which is an important predictor of response to ICIs. In HCC, radiomics has also been applied to predict the suitability of transarterial chemoembolization (TACE) and assess tumor characteristics such as necrosis and angiogenesis, which are relevant for targeted treatments.[46,49]

### Artificial Intelligence (AI) and Machine Learning (ML) Models

Artificial intelligence (AI), particularly machine learning (ML), has emerged as a powerful tool in nuclear medicine for analyzing complex imaging data. The integration of AI in imaging workflows allows for the development of predictive models that can analyze large datasets and uncover patterns related to treatment response, disease progression, and survival (as shown in Figure 1).[50,51]

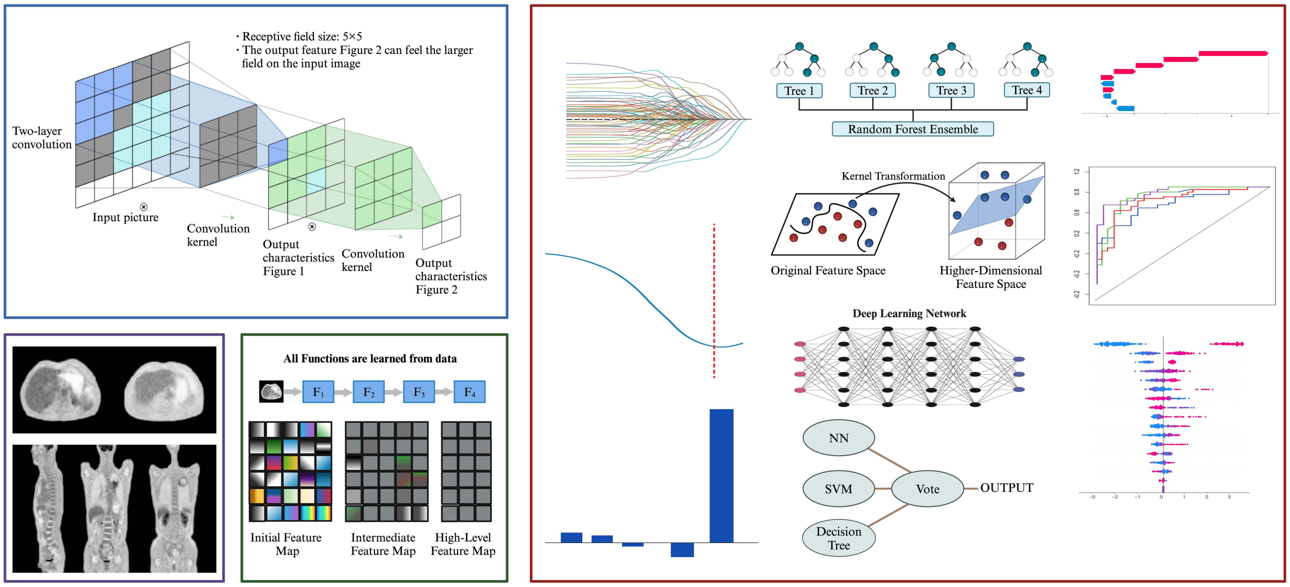

**Figure 1** General workflow of nuclear medicine radiomics. Data is extracted from imaging, followed by data processing and construction of a predictive model. Green arrows indicate the sequential flow of steps (eg, from data extraction to processing); cross symbols denote potential decision points or exclusions during model validation.

## AI in Predicting Response to Combination Therapies

Machine learning algorithms can analyze multidimensional imaging data to identify features that correlate with treatment outcomes, making it possible to predict responses to combination therapies such as ICIs with anti-VEGF agents. In HCC, combining radiomics features with clinical data has shown promise in predicting responses to immunotherapy plus anti-angiogenic treatments, as these combination strategies target both the immune system and the tumor vasculature. AI-driven models can automatically identify relevant features from imaging data that are associated with therapeutic outcomes, thus aiding in personalized treatment planning. Although research combining machine learning and nuclear medicine radiomics in HCC immunotherapy or targeted therapy remains limited, recent studies have explored machine learning with nuclear radiomics to predict the tumor immune microenvironment in lung cancer, demonstrating the potential of this approach for immune profiling and personalized therapy decisions.[47,50]

## Integrating Imaging Data with Clinical and Molecular Features

The integration of AI and radiomics allows for a comprehensive approach to precision medicine by combining imaging features with molecular and clinical data. For instance, ML models can incorporate radiomic signatures from PET images with genomic data (eg, gene expression profiles or mutational status) to improve the accuracy of predicting treatment responses.[46,49] These integrated models have the potential to optimize patient selection for immunotherapy or targeted therapy and to guide adaptive treatment strategies based on real-time imaging assessments.[50,51]

## Challenges and Barriers in Radiomics and AI

Despite their promise, radiomics and AI in nuclear medicine face practical and economic barriers, including data standardization issues, overfitting in ML models, high computational requirements, limited accessibility in low-resource settings, and the need for large, diverse datasets for validation.[52,53] Solutions may involve international collaborations for data sharing, development of standardized protocols (eg, IBSI guidelines), and cost-effective cloud-based AI tools to enhance clinical translation.[51,52]

Radiomics and AI are transforming the field of nuclear medicine by enabling the development of advanced predictive models that integrate diverse data sources. These approaches hold great potential for improving personalized cancer treatment by providing non-invasive biomarkers for treatment response and prognostic evaluation.

## Theranostics in Nuclear Medicine

Theranostics combines diagnostic imaging and radionuclide therapy in one approach, allowing personalized treatment by using radionuclides that provide both therapeutic and diagnostic functions. For instance, ^177Lu is widely used for its dual ability to target tumors with beta radiation for therapy and gamma rays for imaging. In HCC, theranostic agents targeting specific markers, like glypican-3, enable imaging to assess tumor uptake and subsequently deliver precise, localized treatment. This approach offers a promising complement to traditional therapies, especially in advanced cancer stages, by integrating treatment and monitoring in a single modality.[12,54,55] Copper-64 has been widely adopted for theranostic applications due to its dual properties: they emit beta particles for therapeutic purposes and gamma rays for diagnostic imaging.[14]

## Future Directions and Challenges

### Need for Standardized Imaging Criteria

The increasing use of molecular imaging in immunotherapy and targeted therapy has highlighted the need for standardized imaging criteria to assess treatment response effectively. Unlike traditional response criteria (eg, RECIST) that primarily focus on tumor size, new approaches must account for changes in tumor metabolism and immune activity, which are critical in the context of immunotherapy.[28,56]

### Consensus on Imaging Biomarkers and Response Criteria

There is a growing recognition of the need for unified response criteria tailored for immunotherapy, such as PERCIMT (PET Response Criteria for Immunotherapy) and iPERCIST (Immune PET Response Criteria in Solid Tumors).[29] These criteria incorporate metabolic changes in the tumor, such as variations in FDG uptake, which reflect immune activity rather than simple tumor shrinkage. The adoption of these criteria could improve the accuracy of treatment monitoring by distinguishing between true progression and phenomena such as pseudoprogression, where increased FDG uptake is due to immune cell infiltration rather than tumor growth. Establishing a consensus on which biomarkers and criteria should be used across different clinical settings would enhance the reliability and reproducibility of imaging results in clinical trials and routine practice.[11,56,57]

### Integrating Multimodal Data for Predictive Modeling

The future of cancer treatment lies in precision medicine, which integrates various data types to make more informed treatment decisions. Multimodal data, which include imaging features, genomic profiles, and clinical information, can offer a comprehensive understanding of tumor biology and treatment response.

### Importance of Combining Imaging, Genomics, and Clinical Data

Integrating data from multiple modalities allows for the development of more accurate predictive models. For instance, radiomic features extracted from PET/CT images can be combined with genomic data, such as tumor mutational burden or gene expression profiles, to predict response to immune checkpoint inhibitors (ICIs) or targeted therapies. These comprehensive models can identify patients who are more likely to benefit from specific treatments, allowing for personalized therapy selection. Additionally, incorporating clinical data, such as patient demographics and laboratory test results, can further refine these predictive models, increasing their utility in real-world settings.[37,47]

### Comparative Positioning

Nuclear medicine biomarkers, such as SUVmax and MTV from FDG PET/CT, offer incremental value over traditional predictors like serum AFP (which has limited sensitivity and specificity) or circulating tumor DNA (ctDNA, which requires invasive sampling and may not capture spatial heterogeneity). By providing whole-body, real-time functional insights into tumor metabolism and immune activity, nuclear imaging addresses limitations of these alternatives, enabling better patient stratification and monitoring.[56,58] Realistic clinical pathways include baseline PET/CT for initial risk

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assessment, followed by interim scans to detect early response or resistance, guiding therapy adjustments (eg, switching from TKI to ICI combinations).[30,31,57]

## Novel PET Imaging Approaches

Recent advancements in PET imaging for cancer immunotherapy include novel strategies aimed at improving the specificity and effectiveness of monitoring immune responses. Three main approaches are being explored: direct ex vivo labeling, indirect in vivo labeling via PET reporter genes, and direct in vivo labeling of endogenous immune cell pathways.[59] Direct ex vivo labeling involves tagging immune cells with radioactive probes before reinfusion, though it is limited by probe dilution. Indirect in vivo labeling with PET reporter genes enables long-term monitoring of genetically modified immune cells but presents challenges with potential toxicity and engineering complexity. Finally, direct in vivo labeling targets specific metabolic pathways of immune cells, such as using tracers like 18F-FAC, which can better distinguish immune activity from tumor metabolism compared to traditional 18F-FDG. These methods offer new avenues for enhancing the precision of immunotherapy monitoring and guiding treatment adjustments.[8,56]

## Prospective Clinical Trials

While retrospective studies have demonstrated the potential of imaging biomarkers and radiomics in predicting treatment outcomes, large-scale, prospective clinical trials are needed to validate these findings and establish their clinical utility[56].[57]

## Need for Validation Through Prospective Trials

Prospective trials are essential for confirming the predictive value of imaging biomarkers and radiomics-based models across diverse patient populations and treatment settings. These trials can provide robust evidence on the role of advanced imaging techniques, such as FDG PET/CT, PET/MRI, and novel radiotracers, in guiding therapeutic decisions and monitoring treatment response. Furthermore, prospective studies can help standardize imaging protocols and optimize the use of AI-based algorithms in clinical practice, thereby improving the generalizability of predictive models. The results of such trials would also inform guidelines on how to integrate molecular imaging into standard cancer care.[37,57]

## Practical and Economic Barriers

Translating nuclear medicine advancements into routine HCC care faces significant practical and economic barriers, including high costs of PET/CT scans ($2000-5000 USD per scan), limited accessibility in low- and middle-income countries (where HCC prevalence is high but cyclotron facilities are scarce), infrastructure requirements (eg, radiotracer production and specialized equipment), variable reimbursement policies, and the need for clinician training in interpreting complex imaging data[53].[52,56] Additional challenges include regulatory hurdles for novel tracers and standardization across centers. Potential solutions encompass cost-sharing models, development of portable SPECT alternatives, international training programs (eg, IAEA initiatives), and collaborative research networks to reduce disparities and facilitate global adoption.[52,56,57]

# Conclusion

Nuclear medicine has emerged as a pivotal field in oncology, providing invaluable tools for predicting and guiding cancer treatment, particularly in the realm of immunotherapy and targeted therapy. Advanced molecular imaging techniques such as FDG PET/CT, PET/MRI, and novel theranostic approaches offer unique insights into tumor biology that extend beyond traditional anatomical imaging. These techniques allow for the evaluation of metabolic changes, immune activity, and molecular characteristics of tumors, enabling the early assessment of treatment response and identification of potential therapeutic targets. The use of radiomics and artificial intelligence further enhances the capability of molecular imaging by extracting and analyzing quantitative imaging features that can predict clinical outcomes.

The integration of molecular imaging with radiomics and theranostics represents a significant advancement in personalized medicine, particularly for HCC and other aggressive cancers. This personalized approach not only optimizes therapy selection and dosing but also minimizes unnecessary toxicity and enhances patient outcomes. Moving forward, the clinical adoption of these advanced techniques will require further standardization of imaging criteria and validation through large-scale prospective trials. Addressing these challenges will be crucial for translating the potential of molecular imaging and theranostics into routine clinical practice, ultimately improving the precision and effectiveness of cancer treatments.

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## Disclosure

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