Review Article

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uPAR-Targeted Imaging of Tumor Invasion, Prognosis, and Theranostics: A Narrative Review

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Abstract

The urokinase-type plasminogen activator receptor (uPAR, CD87) connects extracellular proteolysis with adhesion, migration, and signaling, providing a biological rationale for imaging tumor-associated invasion. This narrative review examines receptor biology, radiopharmaceutical development, clinical PET evidence, targeted MRI, fluorescence-guided surgery, and therapeutic translation. Experimental studies and early clinical investigations support the technical feasibility of visualizing uPAR with peptide-based probes, particularly AE105 derivatives labeled with copper-64 or gallium-68. Prospective cohorts have reported associations between uptake and prostate cancer grade, glioma outcomes, and relapse risk in head and neck cancer. These findings remain specific to the patient population, tracer, measurement, and endpoint; they do not establish universal SUVmax thresholds. Receptor expression in stromal and inflammatory cells also limits interpretation of uptake as an exclusively malignant-cell signal. The review distinguishes uPAR PET from FDG imaging, circulating soluble uPAR assays, and tissue immunohistochemistry. Clinical findings are considered alongside their limitations, including small cohorts, optimized cutoffs, wide confidence intervals, and incomplete external validation. Optical imaging with FG001 has demonstrated the visualization of tumors in human patients, whereas the effect of fluorescence-guided decisions on surgical margins and outcomes requires further evaluation. Albumin-binding radiopeptides, cyclic ligands, and targeted nanoparticles remain important translational approaches. Sponsor-reported early therapeutic observations are identified separately from peer-reviewed efficacy evidence. Overall, uPAR-directed imaging is a promising addition to molecular oncology, but its clinical value depends on standardized measurements and prospective studies demonstrating benefit for defined diagnostic, prognostic, or treatment decisions.

Keywords: uPAR; Molecular Imaging; PET/CT; AE105; Tumor Invasion; Prognosis; Fluorescence-Guided Surgery; Theranostics

1. INTRODUCTION

Molecular imaging can complement anatomical staging by showing biological properties that are not apparent from tumor size or morphology alone. The urokinase-type plasminogen activator receptor (uPAR, also designated CD87) is of interest because it participates in extracellular proteolysis, cell adhesion, migration, and signaling. These functions connect receptor expression with several processes involved in malignant invasion. Consequently, imaging uPAR offers a potential means of characterizing tumor behavior alongside conventional computed tomography (CT), magnetic resonance imaging (MRI), and established positron emission tomography (PET) examinations. Its value must nevertheless be assessed for a defined clinical question, rather than inferred solely from the biological importance of the receptor [1–3].

Investigation of this biological system began with the observation of fibrinolytic activity in normal human urine by MacFarlane and Pilling in 1947. Subsequent work established the relationship between urokinase-type plasminogen activator (uPA), plasminogen activation, and cell-associated proteolysis. Binding to uPAR concentrates uPA at the cell surface, where the resulting activity of plasmin contributes to extracellular matrix remodeling and can activate additional proteolytic pathways. This provides a mechanistic explanation for the association between the uPA system and invasion, while recognizing that metastatic dissemination also requires changes in motility, survival, vascular access, and interactions with host tissues [4, 5].

The receptor is not restricted to malignant epithelial cells. Tumor-associated stromal and inflammatory cells can also express uPAR, and physiological expression increases during inflammation, injury, and tissue repair. A positive scan should therefore be interpreted as evidence of accessible target within a tissue compartment, rather than as an exclusively cancer-cell-specific measurement. This distinction is particularly important after surgery or radiotherapy, when inflammation and remodeling may coexist with residual malignancy. The biological breadth of uPAR creates opportunities for imaging the tumor microenvironment but also complicates claims of diagnostic specificity [6–8].

Early human studies established that peptide-based uPAR PET tracers can be administered and can visualize lesions in several tumor types. Later investigations explored associations with prostate cancer grade, glioma outcomes, and recurrence in head and neck cancer. Optical probes and therapeutic radioligands extend this development beyond diagnosis. These applications represent different stages of translation: demonstrating tumor uptake, predicting an outcome, changing a treatment decision, and improving patient survival are separate achievements that require different study designs [9–11].

This narrative review examines how the molecular properties of uPAR inform imaging interpretation and how the available clinical evidence supports specific diagnostic, prognostic, and therapeutic applications. The discussion follows the progression from receptor biology to probe design, clinical studies, image-guided intervention, and research priorities. It addresses PET, targeted MRI, optical imaging, perineural and lymphovascular invasion, and computational image analysis within a common framework. Throughout, uPAR-specific evidence is distinguished from findings obtained with fluorodeoxyglucose (FDG), soluble biomarkers, or unrelated therapeutic targets, so that the conclusions remain appropriate to the measurements actually reported.

This article is a narrative review of experimental, translational, and clinical literature on uPAR-directed oncological imaging. Its purpose is to explain the relationship between receptor biology, imaging-agent performance, and clinical interpretation. It does not present an original patient cohort or a pooled statistical analysis. The literature includes foundational molecular studies, animal imaging experiments, first-in-human investigations, prospective phase II studies, and selected reports of therapeutic development. The sponsor announcement dated 12 January 2026 discussed below is considered separately from peer-reviewed clinical evidence.

The synthesis prioritizes identifiable publications that directly address a claim. Molecular experiments are used to explain plausible mechanisms; imaging studies support observations about tracer behavior; and clinical cohorts support disease-specific diagnostic or prognostic estimates. Review articles provide background and help connect these strands, but they do not substitute for a primary clinical report when a numerical result is discussed. Trial registrations identify planned investigations, whereas publications and explicitly labeled sponsor communications describe different levels of available results. These different sources should not be treated as interchangeable demonstrations of clinical efficacy.

The review does not claim a reproducible systematic search, a screened corpus of more than 300 studies, or a meta-analysis. Such claims would require documented search dates, complete database strategies, eligibility criteria, study-selection records, and an explicit method for assessing study quality. Instead, the evidence is organized thematically and examined for consistency between the population, tracer, measured variable, endpoint, and inference. Reported hazard ratios are retained within their original clinical setting, with confidence intervals where these have been verified, rather than combined into cross-cancer benchmarks.

Particular attention is given to the distinction between analytical validity, clinical validity, and clinical utility. An imaging signal may reflect receptor availability without accurately detecting every tumor deposit. A signal associated with survival may not add useful information beyond stage and pathology. Even a clinically informative biomarker requires evidence that acting on its result benefits patients. The following sections therefore describe both the finding and the

decision it could eventually inform, while identifying the additional evidence needed before that decision can be supported routinely.

2. BIOLOGICAL BASIS OF UPAR IMAGING

uPAR is attached to the outer cell membrane through a glycosylphosphatidylinositol anchor and comprises three homologous Ly6/uPAR domains, conventionally designated D1, D2, and D3. Their arrangement forms the ligand-binding cavity that accommodates the growth factor-like region of uPA. Structural studies explain how an extracellular receptor can concentrate protease activity without possessing an intracellular catalytic domain. They also provide a basis for designing peptides that bind the receptor and carry an imaging label. The affinity and accessibility of this binding region are relevant to probe performance, although receptor abundance alone does not determine the measured signal [12, 13].

The evolutionary history of the receptor helps explain its modular architecture and the distribution of disulfide bonds within its domains. Comparative analyses describe differences between uPAR and related ancestral proteins, including the distinctive disulfide pattern in the N-terminal domain. These observations are relevant to ligand recognition and to the use of animal models, because a peptide optimized for human uPAR may not interact identically with the receptor of another species. Consequently, a human tumor xenograft and its surrounding murine stroma do not necessarily reproduce the target distribution encountered in a patient [13].

Upon binding uPA, the receptor localizes the conversion of plasminogen to plasmin near the cell surface. Plasmin can act on extracellular substrates and participate in a wider protease network that includes matrix metalloproteinases. The resulting remodeling can facilitate movement across tissue boundaries, but proteolysis is spatially regulated and interacts with protease inhibitors, extracellular matrix composition, and cell adhesion. A PET ligand bound to uPAR does not directly measure the rate of plasmin generation or matrix degradation. It provides a related molecular observation whose functional significance must be interpreted in the relevant tissue context [5, 14].

This distinction prevents a common overinterpretation of receptor imaging. High uptake can identify a region with substantial accessible target, yet the image cannot independently establish the direction or speed of invasion. Conversely, a region with low uptake may contain malignant cells that express less receptor or are below the spatial resolution of the examination. Correlative pathology and experimental blocking studies are therefore central to target validation. Quantitative xenograft work with copper-64-labeled AE105 supported the relationship between tumor uptake and receptor expression, providing a rationale for subsequent human evaluation [15].

Although uPAR lacks a transmembrane domain, it participates in signaling through neighboring membrane proteins. Interactions with integrins, including $\alpha 5\beta 1$ and other context-dependent partners, connect receptor engagement with adhesion and intracellular signaling. Foundational studies demonstrated that uPAR can regulate integrin function and identified interaction regions relevant to this association. These effects cannot be reduced to a single universal signaling pathway, because the available receptor partners, extracellular ligands, and cellular state differ between tissues [16, 17].

Experimental carcinoma models linked uPAR downregulation with altered integrin and mitogen-activated protein kinase signaling and the induction of tumor dormancy. Other work identified epidermal growth factor receptor (EGFR) as a transducer of uPAR-associated signaling required for growth in a particular carcinoma model. These findings support the concept that uPAR participates in coordinated signaling networks rather than acting only as a protease anchor. They also suggest why expression may be associated with treatment resistance, while stopping short of establishing uPAR PET as a validated test of resistance to a specific drug [18–20].

Vitronectin provides another connection between receptor biology and the extracellular matrix. The identification of uPAR as an adhesion receptor for vitronectin helped explain how proteolytic localization and adhesion can be coordinated. Subsequent mechanistic syntheses describe interactions involving focal adhesion kinase, Src-family kinases, Rac, and growth-related pathways. The principal relationships relevant to this review are summarized in Table 1. The table describes biological mechanisms; it should not be interpreted as a set of pathways that can be distinguished individually from a clinical PET scan [21–23].

Table 1. *Molecular Partners and Biological Functions Relevant to uPAR Imaging*

Partner	Interaction	Associated Function	Imaging Interpretation
uPA [5, 12]	Binding within the uPAR domain assembly	Cell-surface plasminogen activation and matrix remodeling	Receptor binding is related to, but does not directly measure, proteolytic activity
Integrins [16–18]	Lateral receptor interactions	Adhesion and context-dependent FAK/Src and MAPK signaling	Uptake cannot identify the individual signaling pathway
EGFR [19, 20]	Cooperation with uPAR-associated receptor complexes	Growth and survival signaling in experimental models	Target visibility does not establish drug resistance
Vitronectin [21]	Interaction with uPAR at the cell surface	Adhesion and coordination with extracellular remodeling	Signal requires interpretation within the tissue environment

Tumor-associated macrophages contribute to angiogenesis, tissue remodeling, immune regulation, and metastatic progression. Their functions vary between tumors and within different regions of a single lesion. The conventional M1/M2 distinction can be useful descriptively, but it does not capture the full diversity of macrophage states. Similarly, the proportion of macrophages in a tumor cannot be assumed to be a fixed percentage. These considerations matter because a uPAR-directed signal may arise from malignant cells, stromal cells, inflammatory cells, or a combination of these populations [24–26].

A high uPAR PET signal should therefore not be equated automatically with an M2-polarized or immunosuppressive microenvironment. Establishing that interpretation would require spatially matched tissue characterization and validation of the relationship between uptake and immune-cell phenotypes. The broader association of uPAR with inflammation reinforces this need. Imaging can generate hypotheses about biologically active tumor compartments, but it cannot replace direct evidence about cell identity, cytokine signaling, or immune function. This is especially relevant when imaging is proposed to select patients for immunotherapy [8].

Epithelial–mesenchymal transition provides a further mechanistic connection with invasion. Changes in adhesion, polarity, and motility occur along a spectrum rather than through an identical binary switch in every cancer. Experimental work has shown that uPAR signaling can induce stem-cell-like properties in breast cancer cells, including changes relevant to mammosphere formation and tumor initiation. These observations support investigation of uPAR in aggressive cellular states. They do not establish that a clinical uptake threshold measures the abundance of cancer stem cells or identifies a uniform mesenchymal phenotype across malignancies [27, 28].

Soluble uPAR, or suPAR, is related biologically to membrane-associated uPAR but represents a different measurement. Blood assays integrate contributions from multiple tissues and may detect different intact or cleaved forms. PET measures the distribution of a labeled ligand within tissues and is influenced by delivery, clearance, binding, and image reconstruction. These measurements may provide complementary information, but their numerical values and clinical thresholds cannot be substituted for one another. A blood biomarker associated with adverse outcome does not by itself validate an imaging endpoint.

Population and diagnostic-cohort studies illustrate this distinction. Increased plasma suPAR has been investigated as a marker of subsequent respiratory cancer and in patients with serious nonspecific symptoms suggestive of malignancy. Such associations are relevant to inflammation and cancer risk, but they are not demonstrations that uPAR PET can locate an occult primary tumor or distinguish malignancy from all inflammatory conditions. When discussing prognosis, the assay, molecular form, disease setting, and adjustment variables must remain attached to the reported estimate [29, 30].

The same interpretive principles also apply to tissue immunohistochemistry. Receptor staining provides cellular and spatial detail that a PET voxel averages across many cells. Sampling may also miss heterogeneous expression within a tumor. Concordance between biopsy staining and imaging is therefore informative, but disagreement can arise from differences in sampling, timing, lesion size, or ligand accessibility. Integrating these modalities requires a clear account of what each measures. Their combination is potentially valuable precisely because they provide different perspectives on the same disease process.

3. IMAGING AGENTS AND TECHNICAL CONSIDERATIONS

The development of uPAR-directed imaging builds on the identification of high-affinity peptide antagonists through bacteriophage display and subsequent ligand optimization. AE105 is a nonameric peptide widely used as a targeting component. Its sequence is Asp–Cha–Phe–D-Ser–D-Arg–Tyr–Leu–Trp–Ser, where Cha denotes cyclohexylalanine. Binding measurements depend on the molecular construct and assay; a single affinity value should not be applied indiscriminately to every labeled derivative. Conjugation to a chelator, radionuclide, fluorophore, or albumin-binding group can alter the behavior of the complete imaging agent [13, 31].

Copper-64-labeled DOTA-AE105 was among the early tracers translated into humans. The approximately 12.7-hour physical half-life of copper-64 permits imaging over several time points and supports evaluation of clearance and retention. A first-in-human study included patients with prostate, breast, and bladder cancer and assessed safety, biodistribution, and dosimetry. The reported effective dose of approximately 0.0276 mSv/MBq provides a study-specific radiation estimate, while physiological activity in organs such as the liver and kidneys remains relevant to lesion conspicuity. These feasibility findings should be distinguished from a definitive estimate of diagnostic accuracy [9].

Preclinical dosimetry studies contributed to this translation, but their estimates were derived from animal biodistribution and extrapolation. They should not be presented as direct human measurements. Likewise, a short biological clearance time does not mean that all activity has left the body, because radionuclide decay, metabolites, organ retention, and excretion contribute separately to exposure. Reporting administered activity, peptide mass, imaging time, and dosimetric assumptions is therefore necessary when comparing tracer platforms or planning repeat examinations [32].

Gallium-68-labeled NOTA-AE105 offers a shorter-lived PET alternative and has been investigated in several prospective clinical cohorts. Gallium-68 can be obtained from a germanium-68/gallium-68 generator, making the labeling workflow

attractive in appropriately equipped centers. First-in-human evaluation established an initial safety and dosimetry basis for further study. The favorable clinical workflow does not eliminate the need for validated production, radiochemical quality control, consistent acquisition timing, and careful interpretation of background activity. The choice between copper-64 and gallium-68 also depends on the biological question and the time course that needs to be measured [10].

Fluorine-18 labeling through aluminum fluoride chemistry has also been investigated. In a prostate cancer xenograft experiment, fluorine-18-AlF-NOTA-AE105 uptake was 4.22 ± 0.13% of injected dose per gram at one hour after administration, with blocking experiments supporting receptor-mediated uptake. This is a preclinical concentration measurement, not a human sensitivity estimate or an SUV threshold. Its relevance lies in demonstrating that an alternative radionuclide-labeling approach can retain useful targeting properties and justify further development [33].

Probe optimization aims to balance receptor binding with sufficient tumor delivery and clearance from normal organs. Cyclic ligands, modified chelators, and altered linkers address different parts of this problem. A 2025 study evaluated three cyclic copper-64-labeled ligands designated CARP-1, CARP-2, and CARP-3. CARP-2 showed favorable uptake and reduced nonspecific retention in the investigated mouse model. These results support further evaluation of cyclic constructs but do not demonstrate superior diagnostic performance in patients or a therapeutic benefit from the same chemical platform [34].

Chelator selection is particularly relevant when radiometal stability affects hepatic uptake and background signal. Cross-bridged chelators have been explored as alternatives to DOTA in the uPAR imaging literature. Their purpose is to improve the behavior of the complete radiopharmaceutical, rather than simply increase affinity for the receptor. Comparisons should therefore report both tumor accumulation and organ distribution. A high tumor signal accompanied by persistent normal-organ activity may be acceptable for an exploratory image but undesirable for repeated imaging or therapeutic radiation delivery [14].

Albumin-binding modifications address retention from a different direction. Studies of AE105-derived radiopeptides have examined whether extending circulation and modifying tissue distribution can increase exposure of uPAR-expressing tumors. The relevant development goal is an improved therapeutic window, not maximal tumor uptake in isolation. Longer blood residence can also increase irradiation of normal tissues, so favorable targeting must be considered together with kidney, liver, and blood activity. Both the 2025 albumin-binding study and subsequent optimization work remain preclinical evidence for radionuclide-therapy development [35, 36].

MRI offers anatomical detail and soft-tissue contrast that complement molecular PET information. Receptor-targeted iron oxide nanoparticles have been investigated as a way to introduce molecular targeting into MR imaging. In breast cancer models, uPA-derived targeting components were used to direct iron oxide probes toward uPAR-expressing tissue, with optical labeling providing an additional detection channel. Separate work evaluated peptide-conjugated ultrasmall superparamagnetic iron oxide particles in uPAR-expressing cells. These studies establish experimental targeting strategies rather than a clinically validated uPAR MRI examination [37, 38].

Nanoparticle interpretation requires attention to size, coating, aggregation, relaxivity, delivery, and clearance. An iron oxide probe can generate contrast through mechanisms that differ from those of a small PET ligand, and stromal uptake or macrophage accumulation may influence the image. The reviewed evidence does not establish that targeted nanoparticles reliably distinguish recurrent head and neck cancer from post-radiotherapy inflammation. Similarly, platforms combining magnetic, optical, and thermal properties should be considered individual experimental constructs; their proposed functions cannot be assumed to translate together into proven clinical performance.

SUVmax is the maximum standardized uptake value within a defined lesion and provides a convenient semiquantitative summary of activity concentration after normalization. It is affected by injected activity, uptake time, reconstruction, spatial resolution, noise, and the method used to define the lesion. Tumor-to-background ratios introduce a reference tissue and therefore answer a related but different question. A tumor-to-liver ratio is not equivalent to an absolute SUVmax, and a tumor-to-normal-brain ratio is not directly comparable with either. These distinctions must be preserved when clinical studies are summarized.

Experience with FDG PET demonstrates the importance of harmonized acquisition and reconstruction for quantitative imaging. The same general concern applies to developing uPAR examinations, although an FDG procedure guideline cannot establish a uPAR-specific diagnostic threshold. FDG reflects glucose-related tracer accumulation, whereas imaging based on AE105 is designed to target uPAR. A numerical threshold obtained with one ligand cannot be relabeled as a threshold for the other simply because both are expressed as SUVmax [39].

For prognosis, the way a measurement enters the statistical model also matters. A hazard ratio per unit increase in SUVmax differs from a hazard ratio comparing two groups defined by an optimized cutoff. Data-derived thresholds can overestimate discrimination when developed and evaluated in the same small cohort. Confidence intervals, event numbers, adjustment for clinical variables, and independent validation are therefore essential to interpretation. Table 2 retains these study-specific distinctions and avoids presenting the estimates as universal thresholds across solid tumors.

4. CLINICAL EVIDENCE ACROSS MALIGNANCIES

Prostate cancer presents a clinically relevant problem of spatial heterogeneity and variable aggressiveness. A biopsy samples selected regions, while MRI and molecular imaging can evaluate broader tissue volumes. The PROMIS study provides an established context for the role of multiparametric MRI in prostate cancer assessment, but it is not a uPAR study. The proposed contribution of uPAR PET is to add molecular information about aggressive disease within that diagnostic pathway, rather than to replace the histological evidence required for classification [40].

In the prospective phase II uPAR PET/MRI study, 27 patients with histologically verified, MRI-visible prostate cancer formed the evaluated population. Tumor SUVmax correlated with Gleason score, with a Spearman correlation coefficient of 0.55. The reported area under the receiver operating characteristic curve was 0.88 for distinguishing Gleason scores of at least 3 + 4 from scores of no more than 3 + 3. The corresponding sensitivity and specificity were 96% and 75%, respectively. These results support an association between uptake and grade within the selected cohort, although some diagnostic estimates remain subject to considerable statistical uncertainty [41].

The potential clinical implication is promising but remains specific to the evaluated population. A correlation with biopsy grade does not demonstrate that imaging detects every aggressive focus, reduces unnecessary procedures, or improves selection for active surveillance. The requirement for MRI-visible disease also affects generalizability. Future evaluations should specify whether the intended use is biopsy targeting, risk classification, monitoring, or treatment planning, because each purpose requires different reference standards and outcomes. Comparison with existing clinical models is necessary to determine whether uPAR imaging adds useful information beyond what is already available.

uPAR PET has also been studied in metastatic castration-resistant prostate cancer during radium-223 treatment. Radium-223 is a bone-seeking alpha-emitting therapeutic agent with its own evidence base; it is not a uPAR-targeted treatment. In a small prospective uPAR imaging study, baseline uptake in an index lesion was associated with overall survival, with a hazard ratio of 2.51 per unit increase in SUVmax. The confidence interval of 1.01–6.28 indicates substantial uncertainty. This is a prognostic association in a treated cohort, not proof that uptake predicts benefit specifically attributable to radium-223 [42, 43].

The original rationale for response assessment includes the difficulty of interpreting changes in bone-targeted imaging during treatment. However, a different biological target does not automatically eliminate all sources of flare or establish earlier and more accurate response detection. Longitudinal uPAR measurements need their own repeatability data and validated response criteria. Baseline prognosis, change during therapy, and prediction of treatment benefit should therefore remain separate questions when these results are interpreted or used to design subsequent trials.

Diffuse infiltration is a defining challenge in malignant glioma management. Contrast-enhanced MRI visualizes important anatomical abnormalities but does not display every infiltrating malignant cell. The biology of glioma migration provides a rationale for investigating additional molecular signals, and preclinical uPAR imaging work supported exploration of the receptor in glioblastoma. This rationale should be interpreted alongside the constraints of tracer delivery, blood–brain barrier alterations, spatial resolution, and heterogeneous receptor expression [44, 45].

A prospective phase II study evaluated gallium-68-NOTA-AE105 PET/MRI in 24 patients with suspected primary glioma. Sixteen patients had grade 4 disease, and 94% of that subgroup had uPAR-positive lesions under the study definition. Positivity was based on a tumor-to-normal-brain ratio of at least 2.0. The high frequency of detectable uptake supports feasibility in this setting, but it does not establish microscopic delineation of the invasive edge or demonstrate that the scan can replace tissue diagnosis [46].

The study also examined prognosis. In the full mixed-grade cohort, an optimized SUVmax cutoff of 0.635 separated groups with different survival outcomes; the reported hazard ratios were 14.3 for overall survival and 26.5 for progression-free survival. These estimates had wide confidence intervals and were not restricted to glioblastoma alone. The distinction matters because a mixed-grade cohort can contain substantial baseline prognostic variation. The findings warrant external testing, particularly against models that include established pathological and molecular information [46].

Post-treatment glioma imaging introduces a further question: distinguishing recurrent disease from treatment-related change. Response-assessment frameworks recognize that enhancement and clinical evolution can be difficult to interpret after therapy. The reviewed uPAR studies do not establish a validated diagnostic advantage for separating recurrence from pseudoprogression or radiation necrosis. Receptor expression during inflammation and repair is also relevant. A dedicated study with a suitable reference standard would be needed before assigning uPAR PET that role [47].

In head and neck squamous cell carcinoma, a prospective study compared pretreatment uPAR PET with FDG PET in patients referred for curative radiotherapy. An optimized primary-tumor uPAR SUVmax cutoff of 2.63 was associated with relapse-free survival. The univariate hazard ratio was 8.53, with a 95% confidence interval of 1.12–64.7. The association with overall survival was less certain in the reported Cox analysis. These findings support further evaluation of uPAR as a prognostic marker, while the breadth of the intervals limits the precision of individual risk estimates [48].

Regional nodal staging is a distinct application. A prospective phase II investigation in oral and oropharyngeal squamous

cell carcinoma assessed uPAR PET/CT against surgical pathology and conventional imaging. The reported sensitivity and specificity for regional metastatic disease were 56% and 100%, respectively, with performance broadly comparable to CT/MRI and difficulty identifying smaller deposits. A negative scan therefore cannot be interpreted as evidence that microscopic nodal involvement has been excluded. The result illustrates why a marker associated with aggressive biology need not provide high sensitivity for small-volume disease [49].

In neuroendocrine neoplasms, prospective phase II work used a target-to-liver ratio to characterize uptake. Higher tracer uptake, defined relative to the cohort median, was associated with worse progression-free and overall survival; the reported overall-survival hazard ratio was 2.64. This measurement was not a universal SUVmax cutoff. Its potential role is to complement disease classification and other imaging information, particularly when investigating heterogeneous biology. Demonstrating added value over established assessments remains necessary before applying a threshold beyond the population in which it was developed [50].

Breast and bladder cancers were included in the first-in-human copper-64 study, but feasibility in a mixed cohort should not be treated as disease-specific validation. A prospective study of 49 patients found high primary-tumor detection but low sensitivity for axillary nodal metastases; its results did not support uPAR PET/CT for breast cancer staging. Such applications should be evaluated by the anatomical site and size of disease being detected, as well as by the comparison with existing staging procedures. A receptor expressed in a primary tumor does not guarantee reliable detection of all nodal or distant deposits [9, 51].

Lung cancer evidence likewise requires separation of tissue or serum measurements from molecular imaging. A 2026 prospective study of resected non-small cell lung cancer reported an association between continuous uPAR SUVmax and early recurrence, with a hazard ratio of 2.16 and a 95% confidence interval of 1.34–3.49. This provides direct uPAR imaging evidence, but its single-center design and exploratory threshold analyses still require external validation. It should not be combined with an FDG cutoff of 6.0 as though both measured the same process [52].

The selected clinical observations are compared in Table 2. The table emphasizes the measurement definition, study population, and interpretation of the estimate. It does not pool hazard ratios or rank malignancies by the size of their reported association. Differences in grade distribution, treatment, endpoint, follow-up, and cutoff selection can all change the apparent magnitude of a prognostic effect. A larger hazard ratio in one cohort is not evidence that the tracer performs better in that cancer than in another.

Table 2. *Selected uPAR PET Findings and Their Study-Specific Interpretation*

Clinical Setting	Measurement	Reported Finding	Interpretive Boundary
Prostate cancer [41]	Primary-tumor SUVmax	AUC 0.88 for Gleason $\geq 3+4$ versus $\leq 3+3$	27 patients with MRI-visible cancer; not proof of improved clinical outcomes
Primary gliomas [46]	SUVmax cutoff 0.635 in the full cohort	OS HR 14.3 (95% CI 1.8–112.3)	24 patients with mixed grades; optimized cutoff, not a glioblastoma-only median split
Head and neck cancer [48]	Primary-tumor SUVmax cutoff 2.63	RFS HR 8.53 (95% CI 1.12–64.7)	Univariate estimate; wide interval and independent validation required
Neuroendocrine neoplasms [50]	Target-to-liver ratio above the cohort median	OS HR 2.64 (95% CI 1.19–5.88)	Ratio-based grouping; not a universal absolute SUVmax threshold
mCRPC during radium-223 [43]	Index-lesion SUVmax as a continuous variable	OS HR 2.51 (95% CI 1.01–6.28) per unit	Small treated cohort; prognostic association does not establish treatment benefit
Resected NSCLC [52]	Continuous preoperative SUVmax	Recurrence HR 2.16 (95% CI 1.34–3.49)	Single-center study; external validation needed

All rows concern uPAR-directed PET. AUC, area under the receiver operating characteristic curve; CI, confidence interval; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; NSCLC, non-small cell lung cancer; OS, overall survival; RFS, relapse-free survival. Estimates are not pooled and do not establish interchangeable thresholds.

For colorectal cancer, the mechanistic and preclinical imaging literature supports interest in uPAR, including multimodal targeting in experimental models. However, FDG-based prognostic observations cannot be used to establish a uPAR-specific threshold. The same interpretive distinction applies to associations involving CA19-9: a serum marker combined with metabolic imaging remains a different biomarker strategy. The appropriate conclusion is that colorectal applications merit targeted evaluation, with prospectively specified endpoints and tracer-specific analysis, rather than that a common cross-cancer cutoff has already been validated [53].

5. SURGICAL GUIDANCE AND THERAPEUTIC TRANSLATION

Perineural invasion is a pathological pattern in which malignant cells involve or extend along nerves. It is associated with adverse outcomes in several cancers, but it should be distinguished from radiologically visible perineural spread.

Microscopic involvement can be present without a detectable abnormality on imaging. The biological interaction between tumor cells, nerves, and supporting cells is complex and includes growth factors and tissue-remodeling mechanisms. A general association between uPAR and invasion does not establish that a uPAR scan specifically identifies perineural invasion [54, 55].

Lymphovascular invasion is similarly a histopathological observation with prognostic importance. In colorectal cancer, systematic evidence supports the adverse prognostic role of perineural invasion, but the cited pathology literature does not establish a uPAR PET test for either perineural or lymphovascular involvement. MRI findings such as nerve enlargement, enhancement, and alteration of surrounding fat planes may raise concern for macroscopic spread; confirmation and interpretation remain disease-specific. Unverified survival percentages or model-performance estimates should not be used to imply a validated imaging pathway [56].

Optical targeting offers a more direct connection between molecular contrast and the operative field. uPAR-directed fluorescence can potentially assist visualization of tumor tissue during surgery, while nuclear imaging can provide preoperative information at greater tissue depth. These functions are complementary, but the chemical platforms must be described accurately. The multimodal study by Boonstra and colleagues used an antibody-based indium-111 and near-infrared construct in experimental colorectal models; it was not a clinical AE105 copper-64/ICG trial. This distinction is essential when tracing how a preclinical concept supports later human investigation [53].

AE105-based optical probes have been evaluated in other experimental settings. Pancreatic cancer models demonstrated detection of additional metastatic foci with fluorescence after conventional white-light assessment, and orthotopic head and neck models supported combined preoperative and intraoperative targeting concepts. These experiments show how molecular contrast might assist surgical localization. They do not establish a corresponding percentage improvement in human resection outcomes, nor do they prove that identifying more fluorescent deposits necessarily improves survival [57, 58].

The exploratory phase II FG001 study provides early human evidence in oral and oropharyngeal cancer. FG001 consists of indocyanine green linked to AE105 through two glutamic acid residues. Among 16 patients completing the study, all primary tumors were visualized, with a mean tumor-to-background ratio of 2.99. This supports feasibility and tumor detection in the studied setting. However, the protocol did not permit surgeons to alter resection on the basis of fluorescence, so the results cannot establish a reduction in positive margins or a survival benefit from fluorescence-guided decisions [59].

Future surgical studies should distinguish tumor visualization from margin classification and from demonstrable improvement in clinical outcomes for patients. A useful imaging adjunct must identify clinically relevant tissue without encouraging unnecessary removal of functionally important normal structures. Evaluation should therefore include false-positive fluorescence, lesion depth, reproducibility across devices, histological correlation, and the consequences of changing surgical management. The balance between clearance and preservation is especially important in head and neck surgery, where a more extensive resection may carry substantial functional cost.

Theranostics links target assessment with a treatment intended to act on the same biological system. For uPAR, diagnostic imaging could help identify patients and lesions with accessible uPAR receptors before the administration of a therapeutic radioligand. That concept requires more than a positive scan: sufficient tumor retention, acceptable normal-organ exposure, and evidence of meaningful therapeutic effect are also necessary. General radiotheranostic development provides a framework for these requirements, but results obtained with another receptor cannot establish efficacy for uPAR-targeted treatment [60].

The success of lutetium-177-DOTATATE in somatostatin-receptor-positive neuroendocrine tumors illustrates the level of clinical evidence that can support a receptor-targeted therapy. It is an instructive comparator for study design and dosimetry, not evidence that a uPAR-targeting ligand will necessarily behave in the same manner. Ligand affinity, internalization, circulation time, organ distribution, receptor expression in normal tissue, and tumor heterogeneity may all differ. The therapeutic radionuclide must therefore be evaluated as part of a specific construct and disease context [61].

A Curasight announcement dated 12 January 2026 described preliminary uptake and dosimetry observations from the first patient treated in its phase I uTREAT program for high-grade glioma. The communication reported sustained tumor-associated signal and a dosimetry readout consistent with expectations. These are sponsor-reported early observations, not peer-reviewed evidence of an objective response, survival improvement, or an established safety profile. The announcement is included to document the stage of translation described at that date, without treating a single-patient update as confirmation of clinical efficacy [62].

For lutetium-177-based constructs, beta-particle emission can deliver radiation to target-bearing tissue and nearby cells. Whether this produces a useful therapeutic window depends on absorbed dose and its distribution over time. Kidney exposure, blood residence, and heterogeneous uptake remain important considerations. The albumin-binding radiopeptide studies address these pharmacokinetic questions experimentally. Their results support continued development while also demonstrating why diagnostic tumor visibility and a therapeutically suitable biodistribution are separate criteria [35, 36].

Nonradioactive interventions also provide evidence that the receptor can be therapeutically relevant. Preclinical work with the humanized antibody huATN-658, alone and with zoledronic acid, examined effects on breast cancer growth and skeletal lesions. Earlier therapeutic-development studies explored additional ways of interfering with uPAR-associated biology. These approaches broaden the field beyond PET-guided radionuclide treatment, but their experimental outcomes should remain attached to the relevant model and intervention rather than being generalized to all uPAR-positive tumors [63, 64].

6. DISCUSSION AND RESEARCH PRIORITIES

The clinical promise of uPAR imaging rests on a coherent biological rationale and a growing series of translational studies. Its most defensible current contribution is the possibility of adding information about target availability and aggressive tumor-associated biology to anatomical assessment. The evidence is strongest when a clearly defined tracer, patient group, and endpoint are considered together. It becomes less reliable when tissue expression, circulating suPAR, FDG uptake, and uPAR PET are combined into a single claim of universal prognostic validity.

Several sources of heterogeneity limit direct comparison. Clinical studies vary in tumor type, disease grade, prior treatment, lesion selection, background reference, acquisition timing, and statistical analysis. Small samples can yield striking point estimates with wide confidence intervals. Optimized thresholds can be useful for generating hypotheses but may perform less well in an independent population. The distinction between association and clinical usefulness is therefore central: a significant hazard ratio does not reveal how many treatment decisions would change, whether those changes are appropriate, or whether patients would benefit.

A practical validation program should begin with a specific clinical decision. For prostate cancer, this might concern biopsy targeting or risk classification. For glioma, it might concern prognosis or selection for a therapeutic trial. For head and neck cancer, nodal staging, recurrence risk, and intraoperative visualization are separate indications. Studies should define the intended decision before choosing the endpoint, comparator, and acceptable error rate. This approach would prevent a favorable result in one setting from being stretched into claims about an unrelated use.

Standardization should cover both the technical measurement and the biological interpretation. Acquisition timing, reconstruction, segmentation, reference tissue, and reporting of SUV-based variables need consistency across centers. Spatially matched pathology can help determine which cellular compartments contribute to uptake. Repeat examinations are needed to establish measurement variability before a change is interpreted as treatment response. For blood-based suPAR studies, assay characteristics and molecular forms require separate standardization. A common biological name is not sufficient reason to harmonize unlike measurements by applying the same cutoff.

Artificial intelligence and radiomics may assist lesion delineation, characterization of heterogeneity, and integration of imaging with clinical variables. General radiology research establishes the potential of these methods, while radiomics frameworks describe how quantitative image features can be used in predictive models. However, these methodological advances do not demonstrate that a uPAR-specific model already predicts progression with a particular accuracy. An unsupported area-under-the-curve value should not be carried into clinical discussion without identifying the population, imaging modality, outcome, and validation design [65–67].

For uPAR datasets, the immediate computational challenge is often the relationship between sample size and model complexity. A small single-center cohort cannot support unrestricted exploration of many imaging features without a substantial risk of overfitting. Feature extraction and selection should be specified clearly, and evaluation should separate model development from validation. Multicenter testing should assess robustness to scanner and protocol differences. Calibration and decision relevance matter alongside discrimination, because an apparently accurate classifier may still produce unreliable individual probabilities or fail to improve management.

Future trials should also address negative and discordant findings. A lesion may be anatomically suspicious but show low target uptake; another may show receptor-associated activity in an inflammatory setting. These cases are informative about the boundaries of the technology. Reporting only highly avid tumors would exaggerate apparent usefulness and obscure the patients for whom imaging is least informative. Comparative studies should account for lesions below resolution, receptor heterogeneity, and the consequences of missing clinically important disease.

This review is limited by its narrative design and by the uneven maturity of the underlying evidence. It does not provide an exhaustive inventory or a pooled estimate of diagnostic or prognostic performance. Nevertheless, separating evidence by modality and stage of translation clarifies the central research need: reproducible demonstrations of added value for defined decisions. For therapeutic applications, this includes tumor and organ dosimetry, dose–response relationships, and patient outcomes. For surgery, it includes margin accuracy and the effect of image-guided decisions. For prognosis, it includes external validation and comparison with established clinical models.

7. CONCLUSION

uPAR is a biologically credible target for imaging tumor-associated proteolysis, signaling, and tissue remodeling. Peptide-based PET studies have established feasibility and identified disease-specific associations with grade or outcome, while optical imaging and targeted radioligands extend the field toward intervention. These findings support continued clinical development, but they do not establish a universal marker of malignant potential or justify treating all uPAR-positive scans as equivalent evidence of invasion.

The principal conclusion is that the value of uPAR-directed imaging depends on a precisely defined clinical use. Evidence from prostate cancer, glioma, head and neck cancer, neuroendocrine neoplasms, and other tumors should remain linked to the relevant population, tracer, measurement, and endpoint. FDG-derived thresholds and circulating suPAR associations cannot substitute for uPAR PET validation. Similarly, preclinical targeting and early sponsor-reported uptake do not establish therapeutic efficacy.

Progress toward routine application requires standardized measurement, independent validation, and studies showing that imaging-informed decisions improve care. Within that framework, uPAR offers a promising connection between tumor biology, molecular diagnosis, surgical visualization, and targeted therapy. Its eventual clinical role will be determined by the quality and consistency of that evidence rather than by the breadth of its biological associations alone.

Author Contributions

All authors contributed equally to this review and approved the final manuscript.

Conflict of Interest

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Data Availability

This narrative review uses published literature. No original research dataset was generated for this narrative review.

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