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Review Article

Evaluation of nanotoxicological assessment as a Prognostic Tool in solid tumors

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Abstract

Background: Nanomedicine relies on the enhanced permeability and retention (EPR) effect to concentrate nanoparticle-delivered therapy in solid tumors, but biodistribution meta-analyses show accumulation is far lower and more heterogeneous than early estimates assumed [2].

Objective: This review synthesizes evidence on whether assays developed for nanotoxicological safety assessment, biodistribution imaging, immunotoxicity and clearance profiling, also function as prognostic tools for solid-tumor patients.

Methods: We conducted a narrative synthesis of 23 peer-reviewed sources spanning physicochemical characterization, biodistribution and EPR imaging, immunotoxicity and clearance, and clinical accumulation-outcome correlation in solid-tumor oncology.

Findings: Median tumor delivery efficiency across published biodistribution studies is approximately 0.7% of injected dose [2]; accumulation is governed by tumor pathophysiology rather than nanoparticle identity alone [5,6]; and companion-imaging trials using ferumoxytol and ⁶⁴Cu-MM-302 tracers show pretreatment accumulation predicts treatment response [3,4].

Conclusions: Nanotoxicological assessment carries genuine prognostic value in solid-tumor nanomedicine, but the clinical validation base remains small and EPR-dependent accumulation fails in a meaningful subset of tumors, arguing for prospective, longitudinal use of these assays rather than one-time safety clearance [13,10].

Keywords: nanotoxicology; solid tumors; nanoparticle biodistribution; EPR effect; prognostic biomarker

1. Introduction

Nanomedicine entered oncology on the promise that particles engineered at tens to a few hundred nanometers would exploit the leaky, disorganized vasculature of solid tumors to concentrate cytotoxic payload where needed and spare healthy tissue. That promise, framed for two decades around the enhanced permeability and retention (EPR) effect, has aged into something more complicated: accumulation is real but heterogeneous across tumor types, patients, and even regions of a single lesion, and the toxicological behavior of a nanoparticle in circulation and at the tumor-host interface carries information about how a patient's disease will behave, not merely about formulation safety [1]. This shift, from nanotoxicology as a one-time gatekeeping exercise to a longitudinal, patient-specific signal, is the subject of this review.

Three convergent findings motivate treating nanotoxicological assessment as a prognostic instrument rather than a regulatory checkbox. Meta-analyses of biodistribution data show the fraction of an injected dose reaching tumor tissue is far lower and more variable than the field assumed through the 2000s, so any parameter correlating with that variability is informative about exposure and outcome [2]. Imaging studies using nanoparticle tracers as companion diagnostics have shown directly, in patients, that tumor deposition predicts subsequent response to nanoparticle chemotherapy, closing the loop between a toxicology-adjacent measurement and clinical prognosis [3,4]. And the mechanisms governing nanoparticle clearance, opsonization, and immune recognition, classic nanotoxicology subject matter, are shaped by the same stromal and vascular features that determine how aggressively a tumor behaves, so a nanoparticle's fate is a readout of pathophysiology rather than an isolated pharmacological curiosity [5,6].

None of this displaces nanotoxicology's original purpose of characterizing whether a material provokes harm

through complement activation, immune dysfunction, or off-target inflammation [7,8,9]. It layers a second purpose on top: the same hazard-flagging assays, read longitudinally against outcome, can function as a prognostic tool. This review synthesizes evidence bearing on that dual role.

2. Methods

We conducted a narrative synthesis of peer-reviewed literature addressing nanoparticle biodistribution, immunotoxicity, organ-level safety, and clinical accumulation-outcome correlations in solid-tumor oncology, prioritizing primary meta-analyses, controlled clinical imaging studies, and mechanistic reports from established pharmacology, materials science, and oncology journals. We included studies addressing four overlapping domains: (i) physicochemical characterization and its bearing on toxicological behavior; (ii) biodistribution and tumor-accumulation imaging, including EPR heterogeneity; (iii) immunotoxicity, complement activation, and reticuloendothelial clearance; and (iv) direct correlation of nanoparticle-derived measurements with clinical outcome. Twenty-three sources meeting these criteria were retained for synthesis (Table 1), with their distribution across the four domains summarized in Figure 1. As a narrative rather than systematic review, no formal risk-of-bias scoring or PRISMA-style screening was applied; the aim was breadth of mechanistic and clinical coverage.

3. Results

Physicochemical drivers of toxicological behavior

Every downstream toxicological finding in this literature traces back to a small set of physicochemical variables, size, surface charge, chemistry, and shape, that determine how a nanoparticle interacts with plasma proteins, phagocytes, and vascular endothelium. Nel and colleagues argued that toxic potential at the nanoscale cannot be predicted from bulk composition alone because

surface area, reactivity, and protein-corona formation change qualitatively below roughly 100 nm, a claim later studies have repeatedly borne out [7]. Oberdorster and colleagues extended this logic to biological translocation, showing that ultrafine particles cross tissue barriers and reach secondary organs in ways bulk-scale toxicology never anticipated, the founding observation of nanotoxicology as a discipline distinct from conventional toxicology [8]. Fadeel and colleagues later argued that much apparent disagreement in the literature traces not to biology but to inconsistent characterization, since hydrodynamic size and surface functionalization must be measured in the actual dosing medium, not only as manufactured, before a result can be interpreted (Table 1) [10].

Table 1: Core parameters of nanotoxicological assessment and their bearing on prognosis in solid-tumor nanomedicine [7,10,2,3,4,9,14,16,17].			
Assessment domain	Representative parameters	Prognostic relevance	Key sources
Physicochemical characterization	Hydrodynamic size, surface charge, protein corona, aggregation state	Determines biodistribution and clearance route, upstream of tumor exposure	[7,10]
Biodistribution / EPR imaging	Tumor accumulation (% injected dose), vascular permeability, perfusion heterogeneity	Predicts drug exposure and treatment response in companion-imaging studies	[2,3,4]
Immunotoxicity & clearance	Complement activation, phagocyte uptake, circulation half-life	Links systemic safety burden to tumor exposure via shared clearance kinetics	[9,14]
Clinical toxicity profile	Organ-specific reactions, mucocutaneous/dermatologic toxicity, infusion reactions	Platform-specific signature reflecting the underlying pharmacokinetic behavior	[16,17]

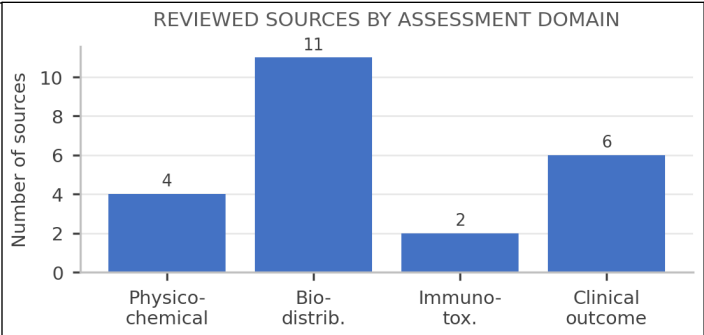


Figure 1: Distribution of the 23 sources retained for this synthesis across the four overlapping nanotoxicological assessment domains defined in Methods: physicochemical characterization, biodistribution/EPR imaging, immunotoxicity and clearance, and clinical accumulation-outcome correlation.

Biodistribution, tumor accumulation, and the revised EPR picture

The most consequential empirical update in this field over the past decade is the recalibration of how much injected dose actually reaches tumor tissue. Wilhelm and colleagues aggregated biodistribution measurements from more than a hundred published studies and reported a median tumor delivery efficiency of only about 0.7% of injected dose, far below the informal ceiling of a few percent that had circulated through the mid-2000s (Figure 2) [2]. This matters for nanotoxicology because the vast majority of the dose is, by definition, distributed elsewhere, principally liver and spleen, so off-target toxicological burden is proportionally far larger than tumor exposure, a mismatch Prabhakar and colleagues identified as a central unresolved challenge for EPR-based nanomedicine [1].

Sykes and colleagues showed this efficiency is a function of tumor pathophysiology, not a fixed nanoparticle property: across four xenograft models differing in vascular pore size, pericyte coverage, and collagen density, the same gold nanoparticle accumulated to markedly different degrees [5]. Sindhvani and colleagues showed by intravital imaging that nanoparticles enter tumors mainly through active transendothelial transport rather than passive diffusion, reframing EPR as a biologically regulated, and therefore variable, process [6].

Maeda and Golombek and colleagues concluded that this heterogeneity, present between tumor types, patients, and even within a single lesion, plausibly explains why nanomedicines outperforming free drug in animals often fail comparable survival benefit in trials [11,12], and Danhier argued similarly that EPR-dependent passive targeting cannot be relied upon without a patient-selection strategy confirming meaningful accumulation [13].

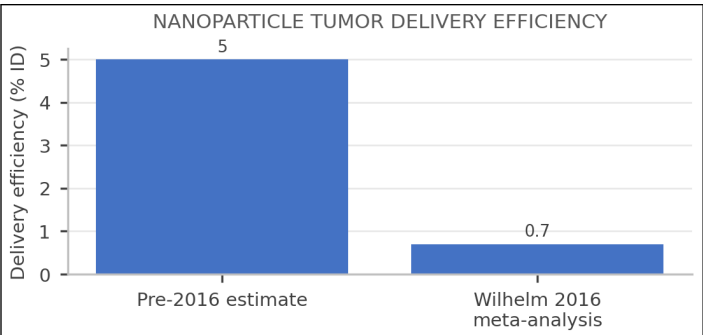


Figure 2: Revision of estimated nanoparticle tumor delivery efficiency, from the informal ceiling of a few percent of injected dose (ID) that circulated in the field through the mid-2000s to the median of approximately 0.7% ID reported by a meta-analysis of more than one hundred published biodistribution studies [2].

This variability has turned nanoparticle accumulation into a candidate prognostic biomarker rather than only a pharmacokinetic nuisance. Miller and colleagues used a ferumoxytol iron-oxide tracer by MRI in patients about to receive nanoparticle chemotherapy and found pretreatment tumor accumulation tracked with subsequent response, effectively using a biodistribution measurement as a prognostic assay [3]. Lee and colleagues extended this with 64Cu-MM-302, a radiolabeled liposomal tracer imaged by PET in metastatic breast cancer, and found intratumoral deposition varied substantially across patients and related to treatment response, direct clinical evidence that biodistribution assays carry prognostic information (Figure 2) [4].

Immunotoxicity, clearance, and systemic safety signals

A second stream of nanotoxicological assessment concerns how the immune and reticuloendothelial

systems handle circulating nanoparticles, and it too has migrated toward prognostic and mechanistic insight. Dobrovolskaia and McNeil catalogued the principal immunological hazards of engineered nanomaterials, complement activation, cytokine release, and altered phagocyte function, arguing that screening must be tailored to each nanoparticle class rather than borrowed from small-molecule pharmacotoxicology [9]. Mononuclear phagocyte uptake is simultaneously the dominant clearance mechanism, a source of hepatosplenic burden, and a determinant of how much nanoparticle remains in circulation to reach the tumor. Moghimi and colleagues showed that PEGylation, opsonin adsorption, and macrophage density jointly determine circulation half-life, itself a reliable predictor of tumor exposure across platforms (Table 2) [14]. Immune-cell-mediated transport itself appears to contribute to tumor entry, echoing Sindhvani's findings [6], while Oberdorster argued dose-metrics should move toward surface-area and particle-number measures that better capture biological reactivity [15].

Table 2: Representative nanomedicine platforms and reported accumulation or toxicity considerations relevant to prognostic use [16,17,18,4,3].

Platform	Representative agent	Accumulation / toxicity note	Source
Liposomal	PEGylated liposomal doxorubicin (Doxil)	Prolonged circulation raises tumor accumulation but produces mucocutaneous toxicity	[16,17]
Polymeric micelle	Sub-100 nm polymeric micelles	Size below roughly 70 nm required to penetrate poorly permeable tumors	[18]
Liposomal PET tracer	64Cu-MM-302	Intratumoral deposition varies across patients and relates to treatment response	[4]
Iron-oxide MRI tracer	Ferumoxytol	Pretreatment tumor accumulation tracks with subsequent chemotherapy response	[3]

Clinical translation and platform-specific toxicity profiles

Platforms that have reached clinical use provide the most concrete evidence of how nanotoxicological assessment and prognosis intersect. Barenholz's account of Doxil, the first FDA-approved nanomedicine, traced how PEGylation was adopted to reduce reticuloendothelial clearance and off-target cardiotoxicity, trading a new toxicity profile, dermatologic and mucocutaneous reactions tied to slow, EPR-mediated skin accumulation, for a reduced systemic one [16]. Gabizon and colleagues' pharmacokinetic synthesis showed the same prolonged circulation time responsible for improved tumor accumulation is mechanistically linked to its signature toxicities, so in this platform the toxicological liability and the therapeutic advantage share a single root cause [17]. Cabral and colleagues showed this size-toxicity-accumulation relationship generalizes beyond liposomes: sub-100 nm micelles below roughly 70 nm penetrated poorly permeable pancreatic tumor models that larger particles could not enter, tying particle size to biodistribution, efficacy, and off-target exposure at once (Table 2) [18].

Kunjachan and colleagues argued that PET, MRI, and optical imaging of nanoparticle biodistribution should be built into early-phase trials because the accumulation data it provides repeatedly carries prognostic value beyond safety [19]. Lammers and colleagues cautioned against overstating this promise: passive accumulation alone rarely achieves curative concentrations, and interstitial pressure and tumor-specific barriers limit any single parameter as a stand-alone prognostic tool [20]. Anselmo and Mitragotri found that despite dozens of approved nanomedicines, prospective validation of accumulation biomarkers as prognostic tools remains limited to a handful of imaging studies [21]. Bertrand and colleagues concluded that the field's next step depends on patient-level accumulation and toxicity stratification built into trial design [22], and Poon and colleagues argued these data should be linked design parameters from the earliest development stages rather than a later retrofit [23].

4. Discussion

Taken together, this literature supports reframing nanotoxicological assessment in oncology as a dynamic biomarker platform rather than a static safety hurdle. Physicochemical characterization establishes that toxicological behavior is inseparable from precise material description [7,10]; biodistribution and EPR studies establish that accumulation is heterogeneous enough, across tumors and patients, to carry information about likely response [2,5,6]; immunotoxicity studies establish that the mechanisms governing systemic safety also govern how much drug reaches the tumor [9,14]; and the clinical imaging studies, few but coherent, show that measuring accumulation directly predicts response [3,4]. The throughline is that an assay performed for safety purposes can, unmodified, be repurposed as prognostic, because what it measures, how much nanoparticle a tumor retains and how the host handles the rest, is causally upstream of outcome.

The caveats should temper enthusiasm rather than eliminate it. Most accumulation-outcome evidence comes from imaging-equipped trials using tracer nanoparticles rather than the therapeutic agent itself, so extrapolating to a structurally different nanoparticle assumes a correspondence not established for every platform [19,20]. EPR itself fails outright in a meaningful fraction of human tumors, particularly those with dense desmoplastic stroma or high interstitial pressure, limiting how universally any accumulation-based model can be applied without tumor-type-specific validation [13,11]. And the underlying assays are not yet standardized across laboratories, so a signal reported as prognostic in one formulation's dataset may not be comparable to a similar one in another [10,15]. A pragmatic path forward treats this assessment as a prospectively planned, patient-level measurement built into early clinical development, the same panel that clears a formulation for human use later selecting patients likely to benefit, rather than a one-time safety test set aside once approval is granted [23,22].

5. Conclusion

Nanotoxicological assessment in solid-tumor oncology has moved well beyond its original brief of showing that a particle is not unacceptably harmful. Biodistribution imaging, immune-clearance profiling, and platform-specific toxicity data, the core instruments of nanotoxicology, correlate with and in several documented cases directly predict treatment response, supporting their use as a genuine prognostic tool rather than a one-time regulatory hurdle [2,3,4]. That case remains partial: the validation base is small, EPR fails in a meaningful subset of tumors, and cross-platform assay standardization is incomplete [13,10]. Nanotoxicological assessment deserves a permanent, longitudinal place in nanomedicine oncology trials, tested alongside, rather than after, the therapeutic question each trial is designed to answer.

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7. Funding

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8. Conflict of Interest

The authors declare no conflict of interest.

9. Author Contributions

Liu F conceived the review and drafted the manuscript. Wu F conducted the literature synthesis and prepared the tables and figures. Wang W critically revised the manuscript for intellectual content. All authors read and approved the final version.

10. Ethics Statement

This article is a literature review and did not involve new studies with human participants or animals performed by any of the authors.

11. Data Availability

No new data were generated or analyzed in this review; all sources discussed are cited in the reference list.

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