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Review Article

NANOCARRIER-MEDIATED CHEMOTHERAPY FOR ORAL SQUAMOUS CELL CARCINOMA: PHARMACOKINETICS, TUMOR TARGETING, AND SAFETY

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ABSTRACT

Oral squamous cell carcinoma often fails chemotherapy because effective intratumoral exposure cannot be sustained without unacceptable systemic toxicity, a mismatch amplified by salivary washout and mucosal barriers in the oral cavity. This narrative review reframes nanocarrier chemotherapy as exposure engineering, defined here as the deliberate design of delivery systems to control the spatial and temporal distribution of drug concentrations across clinically relevant compartments (tumor, regional lymph nodes, and blood), and integrates three co-primary domains: Pharmacokinetics, tumor-targeting with intratumoral coverage, and route-matched safety-by-design. This review emphasizes defining success by compartment-level exposure outcomes, especially tumor and regional lymph-node delivery with minimal systemic peaks, using a transmucosal cisplatin patch paradigm as a translational benchmark. The review also shifts evaluation from accumulation to coverage by prioritizing spatial uniformity metrics that capture underdosed niches. Finally, it extends safety requirements to externally triggered platforms through modality-specific dosimetry and collateral injury surveillance, and proposes a standardization checklist to improve reproducibility and human-forward translation.

Keywords: Nanocarriers, Chemotherapy, Pharmacokinetics, Tumor-targeting, Safety, OSCC.

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) treatment failure is frequently driven by a pharmacologic bottleneck rather than drug potency alone, namely an exposure-to-toxicity mismatch in which systemically delivered agents cannot sustain spatially uniform intratumoral concentrations without crossing dose-limiting toxicity thresholds [1-5]. Heterogeneous perfusion, elevated transport resistance, and microenvironmental barriers such as dense extracellular matrix and acidity create underdosed niches that permit survival under sublethal exposure and foster adaptive resistance programs [6,7]. In the oral cavity, this mismatch is amplified by continuous salivary washout and mucosal barrier constraints that shorten residence time, dilute locally applied agents, and complicate reproducible dosing, particularly when therapy must preserve speech, swallowing, and appearance [8,9]. These anatomic and functional priorities shift the clinical value proposition toward delivery engineering that intensifies lesion-level exposure while limiting systemic peaks and collateral injury.

Accordingly, the scope of this review centers on how nanocarriers and oral-cavity-adapted delivery systems attempt to realign exposure with tolerability through three linked levers: Pharmacokinetic (PK) control, tumor-selective localization and penetration, and safety-by-design. Local or transmucosal strategies illustrate this logic by exploiting anatomical accessibility to achieve high intratumoral and regional lymph-node exposure with minimal blood levels, exemplified by the cisplatin patch paradigm [10]. In parallel, externally triggered modalities such as photodynamic therapy are considered in this review as exposure-gated adjuncts that can preserve form and function in carefully selected early or superficial disease, but demand the same discipline in compartment-level control, namely, field coverage protocol standardization, and modality-specific safety surveillance, which are developed in later sections [6,11-18].

REVIEW AIMS

The narrative synthesis is organized around three coequal questions:
(1) PK: Which nanocarrier design choices reproducibly shift drug exposure toward tumor and nodes while limiting blood exposure. (2) *Tumor targeting*: Which targeting paradigms improve cellular uptake and intratumoral coverage beyond accumulation alone. (3) *Safety*: Which safety-by-design principles and testing endpoints are necessary for route-matched translation.

EVIDENCE-BASED AND SYNTHESIS APPROACH

Literature acquired form the following database: Web of Science, PubMed, Scopus, and Google Scholar. A structured narrative approach adopted that maps evidence across *in vitro* models, animal systems, translational datasets, and human studies, while explicitly separating mechanistic promise from clinically validated benefit. Evidence hierarchy is anchored by human-forward examples and clinical nano-enabled radiotherapy or imaging signals.

PK ENGINEERING

What PK must solve in OSCC

PK is the exposure-control layer that determines whether a potent drug actually reaches OSCC in a sustained and spatially meaningful way [19-22]. In systemic delivery, the core problem is premature loss of bioavailable drug through immune clearance, off-target distribution, and unstable carrier behavior that decouples administered dose from intratumoral exposure [9,23,24]. In local or oral-cavity-adapted delivery, the challenge shifts toward resisting rapid clearance and

maintaining residence long enough to drive penetration and retention inside tumor compartments, while keeping vascular entry low to avoid systemic peaks [8,25]. A clinically relevant PK target in OSCC is also regional lymph-node exposure, because nodal risk is common and locoregional control often depends on whether the drug reaches draining nodes at pharmacologically active levels without systemic toxicity escalation [10,26-28].

Design levers that reshape exposure

Exposure engineering begins with controlling the physicochemical variables that set circulation time, extravasation probability, and intracellular availability [29-31]. Across OSCC nanoplatforms, consistent levers include tight size distribution, surface charge tuning, stealth chemistry such as polyethylene glycol functionalization, protein-corona behavior, and stability against premature leakage, with release kinetics designed to activate under tumor-relevant triggers rather than in blood [6,32-35]. These features are not cosmetic. Small shifts in charge or surface chemistry can reprogram opsonization and macrophage uptake, reshaping both half-life and delivered dose fraction at the tumor.

A clear PK-first example is macrophage-membrane camouflage combined with a pH-responsive drug linkage. Yang *et al*. [36] reported a circulation half-life of 9.26 h versus 1.94 h using a RAW264.7 macrophage-membrane-coated construct to reduce immune uptake and extend systemic exposure, reporting a markedly prolonged circulation half-life of 9.26 h compared with 1.94 h for a free-drug surrogate, alongside reduced macrophage uptake and greater tumor accumulation. The same system increased drug release under acidic conditions, aligning liberation with the tumor microenvironment rather than the bloodstream, which is the essential logic of exposure-biased release [36]. Related biomimetic strategies also report prolonged blood retention, supporting the general principle that immune-evasive shells can function as PK multipliers when coating quality and stability are reproducible [37-39].

Local exposure intensification in OSCC can be even more decisive when anatomy allows direct access. PRV111 is a self-adhesive topical transmucosal cisplatin patch that incorporates cisplatin-loaded chitosan particles and is designed to favor mucosal penetration while constraining vascular entry through particle-size and formulation logic [10,40-43]. This design translated into a high tumor-concentrating, systemically sparing PK profile, with cisplatin enriched in tumor tissue (mean 336.8 μg/g) and regional lymph nodes (mean 110 μg/g) while maintaining minimal blood exposure (mean maximum concentration, Cmax, 0.24 μM) [10]. That pattern is the practical definition of PK success for locally accessible OSCC: high intralesional and nodal exposure, low systemic peak, and sufficient dwell time to drive cytotoxic effect [44]. Reviews of locoregional systems reinforce that mucoadhesion, depot behavior, and controlled release are the main strategies to resist washout and prolong effective residence in the oral cavity [8,9,25,45].

Stimulus-responsive designs further refine exposure by coupling release to acidity, redox stress, enzymes, or external inputs such as near-infrared (NIR) irradiation, effectively converting tumor context into a release gate [6,9,46]. For instance, a fibroblast activation protein (FAP)-targeted platform showed substantially higher doxorubicin release at pH 5.5 than at pH 7.4, with additional thermal acceleration under External inputs such as NIR exposure, illustrating how microenvironmental and external triggers can jointly sharpen local drug availability over time [46].

PK reporting framework

Minimum PK reporting in OSCC nanocarrier studies should move beyond single-endpoint tumor volume and document exposure in the compartments that matter [47]. At a minimum, report tumor-to-blood exposure ratios, Cmax, area under the curve, and half-life when systemic delivery is used, plus lymph-node exposure whenever assessed, because nodal delivery is often clinically consequential [10,26]. Release validation should be performed under tumor-relevant conditions and explicitly linked to formulation stability in physiological media, because uncontrolled leakage makes PK claims uninterpretable [6,32]. Where feasible, PK shifts should be connected to a pharmacodynamic endpoint that reflects mechanism, such as apoptosis signaling, immune infiltration changes, or other biologically proximal readouts, rather than relying on tumor size alone [10,48].

TUMOR TARGETING AND INTRATUMORAL COVERAGE

Targeting taxonomy for OSCC nanocarriers

Passive targeting is usually the entry layer rather than the solution. Enhanced permeability and retention (EPR) can increase lesion exposure when vascular leakiness and lymphatic drainage patterns permit, yet OSCC frequently presents with spatially uneven perfusion, high interstitial resistance, and matrix-dense regions that blunt both extravasation and subsequent movement away from vessels [49-52]. As a result, passive accumulation alone often produces a perivascular enrichment pattern without reliable access to invasive fronts or hypoxic niches, which is why several reviews frame EPR as context-dependent and insufficient as a standalone strategy in oral tumors [6,32,53,54].

Active targeting adds a receptor-recognition layer through ligand, antibody, peptide, or aptamer functionalization. In OSCC, the practical value is not simply higher uptake, but a higher probability of engaging tumor cell subpopulations that are otherwise underdosed when distribution is governed mainly by transport physics [55-57]. Active targeting is most defensible when receptor overexpression is documented in the intended model, receptor accessibility is preserved *in vivo*, and internalization or retention improves payload delivery beyond what a long-circulating carrier can achieve [6,58-60].

Dual targeting is an explicit response to intratumoral heterogeneity. A common design logic couples microenvironment sensing, such as acidity-triggered behavior, with receptor binding so that recognition and uptake are preferentially expressed where tumor biology makes drug release most desirable [61-63]. This dual logic is repeatedly highlighted as a route to improve specificity and functional uptake in heterogeneous oral lesions rather than relying on a single biomarker whose expression may be patchy [6,58].

Biomimetic targeting leverages cell-membrane cloaking to reduce immune clearance and, in some designs, enable homotypic uptake. Cancer cell membrane coating can promote self-recognition and retention within OSCC tissue while supporting longer circulation, and macrophage membrane camouflage can simultaneously reduce phagocytic uptake and enhance lesion localization through inflammation-homing behaviors [36,64-66]. These systems shift targeting from a single receptor axis toward a multi-antigen surface phenotype, which is attractive in OSCC but demands rigorous validation of what fraction of the tumor is actually reached.

Stromal targeting treats the tumor scaffold as the gating barrier. FAP-directed delivery is a representative approach, aiming to engage cancer-associated fibroblast-rich regions, weaken stromal impedance to transport, and enable chemo photothermal synergy through spatially localized heating and release [46,67,68]. In OSCC, this category is particularly relevant because stromal architecture can be the dominant determinant of whether a nanoparticle that has arrived can actually distribute.

Receptor and ligand selection framework

A receptor-guided personalization layer can be built from the OSCC receptor landscape consolidated by Cao and colleagues, with recurrent targets including epidermal growth factor receptor (EGFR), cluster of differentiation 44 (CD44), integrins, urokinase-type plasminogen activator receptor (uPAR), programmed death-ligand 1 (PD-L1), mesenchymal epithelial transition factor (c-Met), gastrin-releasing peptide receptor (GRPR), podoplanin (PDPN), transferrin receptor 1 (TfR1), and secreted protein acidic and rich in cysteine (SPARC) [58,69]. A receptor-guided targeting strategy is only as credible as its patient-

level expression prevalence and spatial accessibility. To make this clear, it is summarized the reported expression rates in human OSCC tissue, recognizing that prevalence estimates vary with antibody clone, scoring system, and positivity threshold. Clinically mature or widely human-validated targets in OSCC include EGFR, CD44 (including CD44v6), PD-L1, c-Met, PDPN, and stromal-access targets such as uPAR and integrin αvβ6, each supported by multiple human-tissue datasets with high observed positivity rates in many cohorts [70-72]. By contrast, TfR1 and GRPR are best treated as emerging translational candidates: both have human-cancer evidence and OSCC-relevant signals, but the field still lacks the same density of standardized OSCC-only prevalence mapping and harmonized cutoffs seen for EGFR, PD-L1, or c-Met. Accordingly, these receptors are retained as plausible access points but are presented with a tighter evidentiary boundary and a recommendation for confirmatory mapping in patient-derived specimens before escalation to "lead target" status [73,74] (Table 1).

Ligand choice must then align with the biology of the receptor and the delivery route. Peptides offer compact size and potentially better penetration than bulky antibodies, illustrated by HN-1-guided delivery that improved tumor targeting and penetration in OSCC models [84]. Antibodies can provide high affinity and specificity but may increase steric bulk and alter transport, particularly in matrix-dense regions. Aptamers can add specificity with tunable chemistry, yet require stability assurance in saliva-rich or enzyme-active oral environments [85-87].

Critically, receptor expression in OSCC is spatially heterogeneous, so "more uptake" is not an adequate endpoint. Targeting success should be judged using penetration depth and spatial distribution patterns across tumor compartments, including invasive edges and stromal barriers, not by bulk fluorescence or whole-tumor mean concentration alone [58].

Coverage, not just accumulation

Intratumoral coverage is the practical bridge between "nanoparticles reached the tumor" and "tumor regions received lethal exposure." Several barriers create a recurrent failure mode: carriers accumulate near vessels, release is incomplete or poorly timed, and drug exposure collapses with distance into hypoxic, acidic, or stromal-dense zones [32]. Therefore, evaluation should elevate metrics that approximate coverage.

Key coverage proxies include intratumoral diffusion profiles, perivascular concentration gradients as a function of vessel distance, stromal impedance readouts that quantify how matrix and fibroblast-rich regions restrict movement, and cell-level internalization heterogeneity that reveals whether only a minority of cells are loaded. These can be operationalized through spatial mapping of labeled carriers and payloads, distance-to-vessel analyses, and dispersion statistics that report how uniformly exposure is distributed rather than only how high the peak is.

Coverage thinking also clarifies why microenvironment-aware modalities matter. For example, photodynamic therapy (PDT) efficacy depends on oxygen availability, so distribution into hypoxic regions may not translate into phototoxicity unless oxygen constraints are addressed, reinforcing that spatial biology can dominate apparent targeting gains [23]. Finally, locally intensified systems illustrate a different coverage strategy: rather than relying on systemic transport, they raise intratumoral exposure while minimizing blood levels, as shown by a transmucosal cisplatin patch approach that achieved high tumor tissue concentrations with minimal systemic exposure, reframing coverage as a controllable, route-engineered outcome [10].

SAFETY AND BIOCOMPATIBILITY AS A CO-PRIMARY DOMAIN

Safety-by-design principles

Safety in OSCC nanomedicine should be treated as a design constraint that is specified early, quantified repeatedly, and defended across each iteration of formulation and scale-up. Across contemporary OSCC platforms, the most defensible safety gains arise when biodegradability and controllable clearance are engineered alongside tight control of size distribution, surface chemistry, and impurity burden, because

Table 1: Human OSCC receptor expression prevalence and validation maturity

Receptor	Human OSCC tissue prevalence (representative)	Human validation status	Key notes on scoring/cutoff
EGFR [71,75]	~56–93% positive across cohorts	Strong (human OSCC)	Thresholds vary; some report any membranous staining versus proportion-based cutoffs.
CD44/CD44v6 [76,77]	CD44 immunopositivity can approach 100% in OSCC cohorts; CD44v6 reported~94%	Strong (human OSCC)	Often high baseline epithelial expression; interpret alongside spatial pattern (invasive front, buds).
Integrins (αvβ6 emphasized) and uPAR [70]	Integrin αvβ6~97% expression rate in OSCC primary tumors	Strong (human OSCC)	Integrin family is broad; αvβ6 has particularly high OSCC tissue positivity in IHC mapping studies. Tumor versus adjacent epithelium contrast and compartment localization matter for targeting feasibility.
PD-L1 [78]	~88% CPS≥1 (OSCC cohort reported)	Strong (human OSCC)	Assay and score (CPS vs. TPS) materially change prevalence; report method explicitly.
c-Met [79,80]	~64–83% positive depending on cutoff	Strong (human OSCC)	Many studies use proportion thresholds (e.g. ≥50% stained cells) which shift positivity rates.
PDPN (podoplanin) [81]	~94–100% positive reported	Strong (human OSCC)	Often enriched at invasive front/budding; useful for coverage-aware targeting logic.
TfR1 (TFRC/CD71) [73]	"High TFRC" subgroup about 34% in one OSCC IHC cohort (classification-based)	Moderate (human OSCC, emerging)	Evidence exists, but prevalence depends on classification scheme; needs harmonized cutoffs across cohorts.
SPARC [82]	Tumor-cell SPARC reported~89% positive (moderate/high) in one OSCC series	Moderate to strong (human OSCC)	Stromal versus tumor-cell signal can differ; specify compartment assessed.
GRPR [83]	72.5% positivity reported in SCC cohort spanning head-neck and esophagus; OSCC tissue shows elevated GRPR versus normal in OSCC-targeting work	Moderate (human SCC; OSCC-specific mapping still limited)	Include with a "candidate" label unless OSCC-only prevalence mapping is added/expanded.

OSCC: Oral squamous cell carcinoma, EGFR: Epidermal growth factor receptor, CD44: Cluster of differentiation 44, integrins, uPAR: Urokinase-type plasminogen activator receptor, PD-L1: Programmed death-ligand 1, c-Met: Mesenchymal epithelial transition factor, GRPR: Gastrin-releasing peptide receptor, PDPN: Podoplanin, TfR1: Transferrin receptor 1, SPARC: Secreted protein acidic and rich in cysteine

small shifts in corona formation, residual solvents, endotoxin, or surface charge can reprogram immune recognition and alter biodistribution. Reviews consistently highlight that translation is often limited less by potency than by uncertainty in long-term biocompatibility, clearance kinetics, and reproducibility, particularly for inorganic or multifunctional constructs where persistence and tissue deposition remain plausible risks [32,88,89]. Biomimetic coatings illustrate both opportunity and obligation: macrophage membrane camouflage and cancer cell membrane cloaking can reduce immune uptake, prolong circulation, and improve tumor enrichment, but they also introduce added requirements for membrane source standardization, batch level immunologic predictability, and validation of hemocompatibility and organ safety markers [36,37,90,91].

Route-matched safety evaluation

Route-matched safety evaluation should be treated as non-negotiable, because the relevant risks differ sharply between local oral cavity systems and systemic constructs. For local delivery, the primary safety domain is mucosal and functional tolerance. Evaluation should prioritize mucosal irritation, ulceration risk, pain burden, dysphagia, local inflammatory signals, wound healing trajectories, and regional lymph node effects, because local systems may deliberately enrich tumor and nodal compartments while minimizing blood exposure. This logic is clinically illustrated by transmucosal cisplatin patch delivery that achieved high tumor and lymph node cisplatin with minimal systemic levels and no dose-limiting toxicities, while still requiring careful documentation of local adverse effects and mucosal tolerability [10,92-95].

For systemic systems, safety assessment should extend beyond generic cytotoxicity and include hemolysis, complement and immune activation risk, hepatic and renal injury markers, and biodistribution-linked persistence, with explicit attention to payload-specific liabilities such as cardiotoxicity proxies for anthracycline-loaded constructs. Biomimetic and targeted doxorubicin nanocarriers in OSCC models have reported low hemolysis and favorable liver and kidney marker profiles, supporting feasibility, yet these signals should be paired with longer horizon immune monitoring and deposition surveillance when non-degradable components or inorganic cores are used [32,36,37].

Energy-triggered platforms require an additional modality-specific safety layer because spatial control can still produce collateral injury if dosimetry is not standardized. In PDT, inflammatory spillover and depth-limited effects should be tracked alongside conventional toxicity, with standardized reporting of photosensitizer parameters, light wavelength, fluence, irradiance, oxygen dependence, and surveillance for local inflammation and recurrence risk [96-99]. In photothermal or chemo photothermal systems, photothermal collateral injury should be quantified using reproducible thermal and light exposure reporting, including temperature mapping, exposure duration, and tissue-level thermal dose descriptors, because efficacy-linked hyperthermia can overlap with thresholds for vascular and mucosal injury [37,100].

CROSS-CUTTING MODULES THAT INTEGRATE THE THREE PILLARS

Oral cavity-adapted delivery engineering

Oral cavity delivery succeeds or fails on residence time. Saliva washout, chewing, and rapid mucosal turnover can erase otherwise strong PK and targeting. Platform choice, therefore, becomes a first-order design variable that links exposure engineering to safety by minimizing systemic spillover while sustaining locoregional concentration [8,25,101-104]. Self-adhesive patches and mucoadhesive films prioritize prolonged mucosal contact and directional transport, making them suited for anatomically accessible lesions where repeated placement is feasible. Hydrogels add a second layer of control by functioning as depots that buffer burst release and can conform to irregular surfaces, while nanoemulsions and lipid-based buccal systems emphasize spreading, mucosal penetration, and high loading of lipophilic agents, often coupled with mucoadhesive excipients to slow clearance [8,33]. Intratumoral injections remain the most direct route to bypass epithelial barriers and stromal transport resistance, but their exposure advantage depends on local retention and lymphatic distribution rather than rapid vascular escape [25]. Within this module, PRV111 represents the clearest clinical demonstration of oral cavity-adapted exposure engineering: a transmucosal patch that concentrates cisplatin in tumor tissue and regional nodes with minimal blood exposure, achieving rapid tumor reduction without dose-limiting toxicity signals in early-stage clinical testing [10,105].

Stimuli-responsive and externally triggered release

Stimuli-responsive release converts microenvironment heterogeneity into selectivity, aligning tumor exposure with systemic safety. pH-responsive systems exploit acidic tumor compartments to accelerate payload liberation, while redox-responsive designs use elevated glutathione or reactive species gradients to unmask drugs intracellularly, improving functional targeting beyond mere accumulation [7,106,107]. Enzyme-responsive carriers leverage protease-rich tumor niches for site-biased degradation, and hypoxia-coupled strategies attempt to synchronize activation with low-oxygen regions that are often therapy-resistant. These endogenous triggers can be layered with biomimicry to extend circulation and reduce immune capture, preserving PK advantage while still permitting local activation, as shown by macrophage-membrane camouflage combined with acid-amplified drug release [36,108]. External triggers then add spatial control. Light-triggered systems, including PDT-adjacent constructs, allow on-demand activation within the illuminated field and create a controllable boundary between tumor and healthy mucosa, but outcomes depend on the photosensitizer, light delivery, and oxygen availability. Depth-extension innovations such as NIR excitation and photochemical internalization, a light-activated strategy that uses photosensitizer-mediated endosomal membrane disruption to promote endosomal escape and cytosolic release of internalized therapeutics, can expand treatable volume while also improving intracellular delivery [100].

Multimodal integration to overcome resistance and microenvironment barriers

Combination logic should be formalized around complementary constraints rather than additive toxicity. Chemo plus PDT couples cytotoxic exposure with a reactive oxygen species-driven kill mechanism that can remodel cytokine signaling and potentially prime immune activity, yet recurrence signals and inflammatory spillover argue for structured surveillance and careful protocol standardization [23,108-110]. Chemo plus photothermal therapy leverages heat-enhanced permeability, perfusion shifts, and thermally accelerated release, often producing sharper spatial confinement than chemo alone. Biomimetic chemo-photothermal platforms illustrate this synergy by combining membrane-mediated targeting with NIR heating to intensify tumor control while maintaining favorable biosafety signals in model systems [37]. Dual-targeted graphene oxide designs further show how NIR activation can be paired with pH-responsive release to amplify tumor-selective doxorubicin delivery [37,46]. Chemo plus radiotherapy emphasizes radiosensitization and nano-enabled integration with integration with intensity-modulated radiotherapy in human-forward evidence, aligning local control with tolerability in patients who cannot receive standard systemic intensification [26]. Chemo plus immunomodulation reframes microenvironment remodeling as targeting-adjacent, aiming to reduce stromal shielding and immune escape while improving penetration and response durability [6].

Resistance biology, cancer stem cells (CSCs), and microenvironment constraints

Delivery failure is not neutral; uneven exposure can select for persistence. CSC-enriched fractions and niche-driven plasticity support survival under sublethal dosing, contributing to relapse and metastatic competence [111-114]. This module, therefore, links resistance biology to transport barriers and maps nanocarrier countermeasures to specific failure points. Improved penetration and spatial uniformity address

underdosed niches, while subcellular targeting and stimulus-responsive release increase the probability that internalized drug reaches lethal compartments rather than being expelled or detoxified [7]. Multi-agent co-delivery further targets pathway redundancy by synchronizing intracellular availability of synergistic payloads, including chemo plus sensitizers or chemo plus nucleic acids, which can dampen efflux, restore apoptosis signaling, or suppress invasion programs [115]. In practice, the most credible resistance-facing designs will be those that jointly optimize residence, penetration, and controllable activation, because CSC biology and microenvironment constraints are inseparable from exposure geometry in real OSCC lesions [6,111].

TRANSLATION AND STANDARDIZATION

Clinical translation status and evidence hierarchy

Across OSCC, the evidence base for nanocarrier-enabled chemotherapy still concentrates in mechanistic and formulation studies, followed by *in vitro* cytotoxicity and uptake experiments, then small-animal efficacy and biodistribution work, with comparatively sparse progression into well-powered human trials [88,92]. This hierarchy matters because many platforms demonstrate improved tumor inhibition in xenografts, yet the field still lacks robust long-term randomized datasets that connect physicochemical design choices to durable clinical benefit, recurrence control, and functional outcomes [6,7,9].

PRV111 functions as a practical translational anchor for local chemotherapy intensification because it operationalizes a clinically compatible concept: high intratumoral cisplatin exposure with minimal systemic peaks, supported by concordant preclinical models and an early human neoadjuvant signal with favorable tolerability [10]. In parallel, near-term feasibility is also being shaped by nano-enabled diagnostics and radio-enhancement signals. Human datasets on lymphotropic ultrasmall superparamagnetic iron oxide contrast for nodal characterization and early clinical experience with hafnium oxide nanoparticles as radio enhancers help define where nanotechnology can integrate with standard staging and radiotherapy workflows in oral cavity carcinoma [26]. At the same time, the human PRV111 dataset should be read as proof of mechanism rather than proof of durable clinical benefit. The reported experience is constrained by a small sample size, a single-arm design without a comparator, and short follow-up, which limits inference on durability, recurrence, and functional outcomes [26]. Response heterogeneity is also expected in early translational studies, and not all treated patients achieve objective regression, with some best categorized as stable disease rather than response. For this review, PRV111 therefore serves primarily as a human-forward demonstration of compartment-level exposure realignment rather than a definitive efficacy benchmark [10].

Externally triggered platforms further illustrate the evidence gradient. PDT shows encouraging short-term control in carefully selected early or superficial OSCC, yet recurrence and protocol heterogeneity highlight why standardized dosimetry, surveillance structure, and higher-quality long-term trials remain prerequisites for durable translation [6].

Standardization checklist for future OSCC nanocarrier studies

Characterization and release control

Report size distribution and polydispersity index with method transparency, plus stability in relevant biofluids to anticipate corona-driven drift in behavior [7]. Define surface chemistry, ligand density where applicable, payload loading, encapsulation efficiency, and batch-to-batch reproducibility, then map release kinetics under tumor-relevant triggers such as acidic pH, redox, or enzyme conditions [9].

PK and exposure-linked pharmacodynamics

Quantify tumor-to-blood exposure ratios, time-resolved biodistribution, and if clinically relevant, regional lymph-node exposure rather than tumor-only readouts [10,26]. Exposure metrics should be linked to mechanistically relevant pharmacodynamic endpoints that reflect the intended biological action, rather than relying on tumor volume alone [7].

Targeting validation and intratumoral coverage

Document receptor expression mapping in the tested model, then include competitive inhibition or blocking controls to confirm specificity beyond uptake claims [58]. Measure penetration depth and spatial uniformity inside tumors, and add stromal-barrier assessment when extracellular matrix or fibroblast-rich architecture is a known constraint [9].

Safety package aligned to route and materials

Use route-matched endpoints, including hemolysis screening for systemic systems, organ markers plus histology, and long-term clearance or deposition when inorganic components are used [36]. Add an immunotoxicity screen scaled to the platform risk profile, especially for biomimetic or multifunctional constructs where immune recognition can shift with modest surface changes [7,36].

Model relevance and reproducibility

Prefer orthotopic models when feasible, and report microenvironment realism such as acidity, hypoxia, and stromal density because these variables condition penetration and trigger performance [10]. Ensure reporting supports replication, including dosing schedule, administration technique, and clear inclusion of negative or neutral findings to reduce publication bias [88,92].

Trigger reporting for photo-activated and thermal platforms

Standardize light or thermal dosimetry reporting for PDT and photothermal therapy (PTT), including wavelength, irradiance, exposure duration, spot size, depth constraints, and oxygenation considerations that directly condition efficacy and collateral injury [100]. Where photosensitizer delivery is carrier-mediated, report dark toxicity, phototoxic window, and trigger-coupled release behavior to separate carrier benefit from irradiation effects [6,96].

FUTURE DIRECTIONS

The translational pathway for OSCC nanocarrier chemotherapy should move from platform novelty to decision-led personalization, beginning with biomarker-stratified targeting that couples receptor mapping with microenvironment signals such as hypoxia to select ligands, triggers, and coverage endpoints that reflect heterogeneity rather than mean uptake alone [7,58]. Because oral anatomy enables exposure control that systemic dosing rarely achieves, near-term priority should be oral-cavity-adapted engineering that resists salivary washout, prolongs residence, and documents tumor and nodal exposure with minimal blood peaks, using clinically anchored paradigms such as transmucosal cisplatin patch delivery as a benchmark for what actionable PK success looks like [8,10,25]. Next, multimodal regimens should be protocol-standardized rather than opportunistic, with harmonized scheduling, dosimetry, and recurrence-focused follow-up for combinations such as chemotherapy with photodynamic therapy or photothermal triggers, so that outcomes can be compared across studies and advanced into higher-quality long-term trials [23,100]. Across all steps, safety-by-design must function as the gating constraint, requiring degradability and controllable clearance, impurity control, and route-matched immunologic and organ-safety surveillance before escalation in complexity or clinical ambition [32,36].

CONCLUSION

This narrative review contributes a delivery-first framework that treats OSCC management as an exposure engineering problem rather than a platform catalogue. The central novelty is the explicit integration of PK, tumor targeting, and safety as co-primary and co-dependent design domains, with success defined by compartment-level exposure outcomes, not by bulk tumor uptake or xenograft shrinkage alone. In particular, this review elevates locally accessible, oral-cavity-adapted systems as a near-term translational advantage because they can intensify intratumoral and regional lymph-node drug levels while suppressing systemic peaks, using a transmucosal cisplatin patch

paradigm as a practical benchmark for clinically meaningful PK realignment. A second new contribution is the shift from accumulation to coverage, recommending spatial uniformity, distance-to-vessel gradients, and stromal impedance as decision metrics that better reflect OSCC heterogeneity and underdosed niches. Third, route-matched safety is non-negotiable and extends safety-by-design into modality-specific reporting for externally triggered platforms, aligning photodynamic and photothermal systems with standardized dosimetry and collateral injury surveillance. Finally, the proposed standardization checklist operationalizes these principles into a reproducible reporting scaffold intended to accelerate human-forward, comparable, and safety-credible translation across the field.

AUTHORS' CONTRIBUTIONS

Fareedi Mukram Ali: Conceptualization, literature search, writing original draft. Ahmed Mostafa: Conceptualization, writing original draft, critical revision. Nouf Odabi: Literature search, data curation. Razan Mohammed Gadri: Literature search, data curation. Mohamed Shaalan Elnewihi Allam: Evidence synthesis, writing review, and editing. Mohammad A. Alsaleh: Evidence synthesis, supervision, writing review, and editing. All authors have read and approved the final manuscript.

CONFLICTS OF INTEREST

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