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Publications 2025

OPEN ACCESS
ONLINE ISSN: 2992-5460
PRINT ISSN: 2992-6041

NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES (NIJRMS)

Volume 7 Issue 1 Page 67-72, 2026

https://doi.org/10.59298/NIJRMS/2026/7.1.6772

Nanotechnology Enhanced Photothermal and Photodynamic Therapies in Obesity-Associated Cancers

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ABSTRACT

Obesity imposes optical, vascular, metabolic, and pharmacokinetic constraints that blunt the performance of photothermal therapy and photodynamic therapy while exacerbating off-target toxicity. Enlarged adipose depots scatter and absorb light differently from lean tissues, abnormal vasculature and extracellular matrix stiffening restrict convection and oxygenation, and dyslipidemia reshapes nanoparticle coronas and mononuclear phagocyte uptake. Nanomaterials overcome these barriers by concentrating energy-absorbing chromophores and photosensitizers in tumors, shifting excitation into near-infrared windows with deeper penetration, converting endogenous metabolites into oxygen for photochemistry, and furnishing real-time imaging to calibrate heat and singlet oxygen generation. Gold, carbon, semiconducting polymer, and upconversion platforms improve photothermal conversion and spatial precision; porphyrin, phthalocyanine, BODIPY, aggregation-induced emission photosensitizer, and metal–organic framework constructs upgrade photodynamic yield in hypoxic and lipid-rich microenvironments. Ligand decoration for endothelial, tumor, and myeloid targets typical of obese tumors, albumin hitchhiking, and stimuli-responsive shells align delivery with pathophysiology. This review evaluates how nanotechnology elevates energy absorption, tumor targeting, and therapeutic precision in high-BMI patients and outlines design, dosing, safety, and translational guardrails that convert optical energy into durable cancer control without collateral metabolic harm.

Keywords: photothermal therapy; photodynamic therapy; obesity-associated cancer; near-infrared nanomaterials; image-guided oncology

INTRODUCTION

Photothermal therapy and photodynamic therapy occupy a unique position in oncology because both use light to localize pharmacology, depositing energy or activating photochemistry in tissue volumes chosen by optics rather than solely by pharmacokinetics[1–4]. In obesity, however, the optical path to tumors is longer and more complex, the microenvironment is hypoxic and fibrotic, and systemic physiology alters the biodistribution, clearance, and immune consequences of treatment[5]. Subcutaneous fat thickness attenuates and scatters incident photons; vascular leakiness coexists with poor perfusion, raising interstitial pressure and limiting nanoparticle convection; macrophage-rich milieus capture opsonized carriers; and insulin resistance, dyslipidemia, and fatty liver disease confound dosing and safety[6]. The very features that link obesity to carcinogenesis leptin-dominant signaling, chronic myeloid inflammation, matrix remodeling, and metabolic rewiring also build a maze for light and for drugs[6, 7].

Nanotechnology reframes these obstacles as design variables. By embedding high–absorption cross-section chromophores into particles with tailored size, shape, and surface chemistry, photothermal agents can convert low radiant exposures into ablative or adjuvant hyperthermia at depth while minimizing epidermal heating[8–11]. By concentrating photosensitizers in tumors and coupling them to oxygen-supplying chemistries, photodynamic agents can harvest light efficiently even in hypoxic pockets. Moving excitation wavelengths from the visible range into near-infrared windows improves penetration and reduces scattering by adipose; in particular, the NIR-II region between one and 1.35 micrometers often yields superior signal-to-background and deeper effective treatment volumes[12, 13]. Stimuli-responsive coatings that dissolve in acidic or protease-rich interstitium restrict active species to diseased tissue; albumin-binding motifs exploit the high flux of albumin

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into inflamed, leaky vasculature; and ligands against integrins on angiogenic endothelium, folate receptor-β and scavenger receptors on tumor-associated macrophages, or tumor-restricted antigens add the deliberate addressability that conventional formulations lack[14–17].
Beyond energy absorption and targeting, nanoplatforms upgrade control and measurement. Photoacoustic and near-infrared fluorescence imaging integrated into the same construct that delivers heat or singlet oxygen permits closed-loop dosimetry; thermal probes and spectroscopic signatures derived from the particles themselves verify that intended thresholds are reached where it matters[18]. Mild, sub-ablative hyperthermia can be scheduled as a preconditioning step that normalizes perfusion and lowers interstitial pressure, increasing delivery of subsequent waves of drugs, biologics, or immune checkpoint inhibitors; photodynamic therapy can be configured to favor immunogenic cell death, turning "cold" obese tumors into antigen-rich, inflamed targets receptive to systemic immunity. The following sections dissect optical and physiologic constraints unique to high-BMI hosts, survey photothermal and photodynamic nanoplatforms that answer those constraints, describe imaging and safety practices for precise dosing, and sketch translational strategies for manufacturing, analytics, and clinical combinations that can make light-driven nanotherapy a reliable component of cancer care in people living with obesity[18].

2 Optical and Physiologic Constraints in Obesity and Their Design Implications

Adipose tissue contains lipid droplets whose refractive index mismatch with cytosol yields high multiple scattering, redistributing photon paths and lowering fluence at depth[5, 19–21]. Hemoglobin absorption declines in the near-infrared, but scattering in fat remains significant in the visible and NIR-I bands; moving to NIR-II often improves penetration and spatial resolution for both therapy and imaging. Thickness and composition are not the only challenges. Vessels in obese tumors are leaky but poorly organized, increasing nanoparticle extravasation yet diminishing homogeneous distribution[22]. Extracellular matrix stiffening elevates interstitial fluid pressure, countering convection and restricting diffusion. Hypoxia emerges from perfusion deficits and high metabolic demand, directly undermining photodynamic efficacy because oxygen is the substrate for singlet oxygen generation. Meanwhile, macrophage and neutrophil density rise, capturing opsonized carriers and amplifying complement activation; dyslipidemia and glycation modify the protein corona that forms on nanoparticles, accelerating hepatic and splenic clearance[19, 19, 23, 24].
Design responses begin with wavelength and cross-section. Photothermal agents tuned to absorb strongly in NIR-II can achieve therapeutic temperatures with less surface heating and lower incident power. Plasmonic nanostructures whose resonance red-shifts with geometry, semiconducting polymer nanoparticles with inherently broad NIR absorption, and doped carbon nanomaterials provide such leverage[25]. For photodynamic therapy, photosensitizers with high intersystem crossing yields at NIR wavelengths and the ability to operate through Type I electron-transfer pathways mitigate oxygen limitations. Oxygen self-supply is achievable by integrating catalase enzymes or manganese dioxide shells that decompose endogenous hydrogen peroxide into oxygen, a metabolite often elevated in inflamed, obese microenvironments. Perfluorocarbon cores serve as oxygen reservoirs[26]. Matrix and perfusion barriers invite sequential strategies: a gentle hyperthermia or enzymatic pretreatment to soften stroma, followed by a curative thermal or photodynamic pulse. Corona control using zwitterionic polymers or poly(2-oxazoline) shields resists dyslipidemia-driven opsonization without invoking anti-PEG immunity that may be more common in metabolic syndrome. Albumin hitchhiking via fatty-acid anchors increases extravasation at inflamed endothelium[26]. Ligands keyed to angiogenic integrins, leptin receptor–positive compartments, or myeloid markers typical of obese tumors sharpen specificity and move effective concentration into otherwise underdosed niches.

3 Photothermal Nanoplatforms Tuned for High-BMI Patients

Photothermal therapy depends on converting absorbed photons into heat with high efficiency and delivering that heat within tumor boundaries. Gold nanorods, nanoshells, and nanostars offer tunable plasmon resonances that can be positioned in NIR-I or NIR-II by adjusting aspect ratio and shell thickness; their photothermal conversion efficiencies are high, and their optical signatures enable concurrent photoacoustic imaging [2, 3, 27]. Surface chemistries that maintain near-neutral zeta potential and dense, non-immunogenic stealth coatings preserve circulation in dyslipidemic plasma. Decorating surfaces with RGD peptides or antibodies to angiogenic endothelium concentrates heat generation at vascular hot spots that feed tumors in obese hosts; alternatively, mannose or folate motifs bias uptake toward tumor-associated macrophages to convert them into intratumoral heaters and, when appropriately programmed, immune adjuvants.
Carbon-based systems such as graphene oxide sheets and carbon nanotubes absorb broadly across NIR and convert energy efficiently, with the added benefit of mechanical robustness and facile loading of adjuvants or checkpoint inhibitors[28]. Semiconducting polymer nanoparticles deliver strong NIR absorption without metal cores, reducing concerns about long-term metal retention in fatty liver. Upconversion nanoparticles paired with NIR excitation produce visible emission that can trigger conventional photosensitizers for combination photothermal–photodynamic therapy, while NIR excitation penetrates adipose more effectively; the upconversion core can be wrapped with a photothermal shell to synchronize modalities.
Precision benefits from thermal modeling that accounts for subcutaneous fat thickness and perfusion heterogeneity. Real-time temperature mapping via photoacoustic thermometry or embedded luminescent

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PRINT ISSN: 2992-6041
nanothermometers prevents epidermal overheating and under-treatment at depth, a risk heightened when adipose attenuates incident fluence[29]. Mild, sub-ablative heating just below cytotoxic thresholds has value beyond sensitization: it transiently normalizes vasculature, lowers interstitial pressure, and increases drug and nanoparticle delivery. In breast and endometrial cancers with adjacent fat pads, interstitial fiber-optic light delivery sidesteps surface attenuation, allowing lower power densities and tighter margins[29]. Across platforms, careful attention to aspect ratio stability under pulse trains, to aggregation in lipid-rich media, and to macrophage uptake kinetics is required to avoid off-target heating in liver and spleen.

4 Photodynamic Nanoplatforms that Overcome Hypoxia and Lipid-Rich Microenvironments

Photodynamic therapy relies on photosensitizers that generate reactive oxygen species upon excitation. In obese tumors, hypoxia and antioxidant buffering limit classic Type II singlet oxygen pathways[12, 26, 30]. Nanoplatforms answer with three strategies. The first is to select or engineer photosensitizers that prefer Type I electron-transfer reactivity, producing superoxide and hydroxyl radicals even when oxygen is scarce; porphyrinoids and BODIPY derivatives tuned for heavy-atom–free intersystem crossing, aggregation-induced emission photosensitizers that brighten upon clustering, and semiconducting oligomers that support charge separation exemplify this approach. The second is to furnish oxygen locally. Manganese dioxide shells react with hydrogen peroxide to generate oxygen and simultaneously consume acidity, improving both photodynamic yield and tissue tolerance; catalase-loaded cores and perfluorocarbon droplets supply oxygen directly[31, 32]. The third is to reform the microenvironment so that oxygen delivery improves before light activation. Mild hyperthermia, hyaluronidase, or transient VEGF pathway inhibition can normalize flow and reduce interstitial pressure, after which photosensitizers are activated.

Metal–organic frameworks integrate high photosensitizer loading with porous architectures that host oxygen or catalase, while also enabling chelation of paramagnetic metals for magnetic resonance imaging[33]. Liposomal indocyanine green and porphyrin–phospholipid vesicles combine clinically familiar components with improved pharmacokinetics and light stability; their bilayers tolerate further functionalization with targeting ligands that recognize endothelial integrins or myeloid receptors enriched by obesity[33]. Upconversion-assisted photodynamic therapy permits activation with NIR light that traverses adipose more effectively, and dual-mode constructs add photothermal capability to ensure cytotoxicity in the most hypoxic pockets. Critically, photodynamic regimens can be tuned toward immunogenic cell death by calibrating fluence and sensitizer concentration; the resulting damage-associated molecular patterns and antigen release synergize with checkpoint blockade, a combination particularly appealing in immunosuppressed, obesity-linked tumors if systemic cytokine surges are avoided through regional activation[33].

***5* Image Guidance, Dosimetry, and Safety for Precise Therapy in High-BMI Hosts**

Light without measurement is guesswork, and obesity amplifies the uncertainty. Nanoplatforms supply their own rulers. Gold and carbon systems provide strong photoacoustic contrast that correlates with local absorber concentration and, through temperature-dependent spectral shifts, with heat deposition[31, 34, 35]. Semiconducting polymer nanoparticles and porphyrinoids emit in the near-infrared, enabling fluorescence mapping of distribution; ratiometric probes diminish dependence on absolute intensity in lipid-rich matrices. Upconversion particles, magnetic iron oxide, and manganese-bearing shells extend imaging to magnetic resonance, offering deep anatomical guidance unaffected by adipose scattering. By integrating these modalities, clinicians can confirm nanoparticle accumulation, plan fiber placement or illumination geometry, and adjust power density to achieve target temperatures or photochemical doses while sparing skin and adipose[35].

Safety frameworks adapt to comorbidities. Complement activation–related pseudoallergy is mitigated by alternative stealth polymers and graded infusion, important in metabolic syndrome where innate immunity is heightened. Hepatic monitoring intensifies when fatty liver disease and splenic sequestration are likely; surface chemistries that minimize macrophage uptake and hydrodynamic sizes in the 70 to 100 nanometer window reduce reticuloendothelial burden without sacrificing tumor penetration[36]. Thermal dose constraints consider lower perfusion in adipose, which reduces heat sink effects and raises burn risk; real-time thermal feedback and conservative ramping protocols reduce complications. For photodynamic therapy, oxygen consumption is balanced against supply by pacing illumination and leveraging self-oxygenating chemistries; pulse trains rather than continuous wave light can sustain ROS generation without collapsing local oxygen. Patient-to-patient variability in subcutaneous fat thickness argues for individualized light modeling from ultrasound or MRI, followed by adaptive power control based on photoacoustic thermometry rather than fixed nomograms[36].

6 Clinical Translation, Combinations, and Dosing Frameworks in Obesity-Associated Cancers

Translation depends on materials that manufacture reproducibly, dose predictably across body compositions, and integrate with standard-of-care. Microfluidic and seed-mediated syntheses yield narrow plasmonic size distributions and stable semiconducting polymers; quality-by-design programs define critical attributes like absorption peak, photothermal conversion[37], photosensitizer loading, ligand density, trigger thresholds and link them to potency assays such as thermal dose–response, singlet oxygen generation in hypoxia, and immune activation readouts. Dosing by lean body mass or allometric scaling outperforms total body weight in predicting exposure; imaging-driven dosimetry further personalizes treatment by verifying intratumoral nanoparticle

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concentration before illumination[37]. In breast and endometrial cancers adjacent to fat pads, interstitial fiber optics or intraoperative illumination reduce surface losses and shorten optical paths, while in hepatocellular and colorectal disease, endoscopic or laparoscopic light delivery positions sources near targets without traversing thick adipose.

Combinations align energy with pharmacology. Sub-ablative photothermal priming improves delivery of cytotoxics, targeted inhibitors, or immunotherapies; photodynamic therapy schedules emphasize immunogenic cell death followed by checkpoint blockade or myeloid reprogramming to counter obesity-driven immune suppression[38, 39]. Metabolic control with GLP-1 or metformin reduces systemic inflammation and may normalize vascular function, broadening therapeutic windows and improving nanoparticle delivery; trials that synchronize nanotherapy with metabolic stabilization will clarify causality[40–42]. Regulatory strategy benefits from choosing excipients and chromophores with clinical precedents and from embedding companion imaging to justify dose selection. Real-world deployment invites BMI-aware eligibility criteria and stratified analysis plans so that efficacy signals in high-BMI cohorts are detected rather than diluted.

CONCLUSION

Obesity complicates light-based oncology by thickening optical paths, starving tissues of oxygen, and diverting nanoparticles into reticuloendothelial sinks, yet it also supplies cues that nanotechnology can read and exploit. By tuning absorption into near-infrared windows, concentrating photothermal and photodynamic potency in tumors through ligand-directed and stimuli-responsive delivery, furnishing oxygen where it is scarce, and instrumenting particles for real-time imaging and dosimetry, nanoplatforms convert variable illumination into precise therapy. When paired with vascular and matrix normalization, metabolic stabilization, and immunotherapy, these materials transform photothermal and photodynamic treatments from opportunistic ablations into programmable, system-aware interventions suitable for people living with obesity. The path forward is disciplined rather than speculative: measure what the light and particles do in each patient, dose by function rather than habit, and adopt manufacturing and safety standards that respect the altered biology of obesity. Under those conditions, energy becomes a selective drug and nanotechnology its most faithful carrier.

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CITE AS: Mwende Wairimu G. (2026). Nanotechnology Enhanced Photothermal and Photodynamic Therapies in Obesity-Associated Cancers. NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES. https://doi.org/10.59298/NIJRMS/2026/7.1.6772

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