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Hydrogels for osteosarcoma treatment: Bioprinting strategies and local tumor eradication–bone regeneration

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Abstract

Osteosarcoma remains a clinically challenging primary bone malignancy because effective postoperative treatment must both eradicate residual tumor cells and restore function after tumor resection. Hydrogel-based platforms have emerged as versatile local therapeutic systems because of their injectability, tunable physicochemical properties, cavity-conforming capacity, high local retention, and ability to integrate antitumor and osteoregenerative functions. This review summarizes recent advances and design principles in hydrogel-based osteosarcoma treatment and bioprinting Strategies, with emphasis on local tumor eradication–bone regeneration. The reviewed platforms include architecturally programmed 3D-printed hydrogel and scaffold–hydrogel hybrid constructs, postoperative locoregional depots, tumor-microenvironment-responsive hydrogels, chemoimmunotherapeutic and sonodynamic systems, photothermally actuated theragenerative platforms, and externally regulated magnetic and piezoelectric depots. Particular attention is given to the complementary clinical roles of injectable hydrogels and patient-specific printed constructs. Hydrogels are thus evolving from passive drug reservoirs into programmable biomaterial systems capable of spatiotemporal treatment control, immune–stromal modulation, molecularly targeted delivery, and functional reconstruction. Key translational barriers include the limited relevance of current preclinical models, normal-tissue safety of field-regulated therapies, degradation and long-term biocompatibility of multifunctional materials, sterilization, quality assurance, regulatory classification, manufacturability, and integration into surgical workflows. Overall, the most clinically realistic direction is a staged and adaptable platform that provides early local tumor control while progressively supporting bone regeneration and structural reconstruction.

Keywords: Bioprinting; Hydrogel; Osteosarcoma; Tumor Microenvironment; Bone regeneration

1. Introduction

Osteosarcoma is the most common primary malignant bone tumor and predominantly affects children, adolescents, and young adults[1]. Despite progress in multimodal management, the disease remains clinically challenging because of its aggressive local behavior, early metastatic potential, and persistent risk of relapse[2]. Current standard treatment still relies on a combination of surgery and multi-agent chemotherapy[3]. While this strategy has substantially improved outcomes for patients with localized disease, prognosis remains markedly worse in patients who present with metastasis or later develop recurrent disease[4]. At diagnosis, approximately 15%–20% of patients already have evidence of metastases, most commonly in the lungs, underscoring the urgent need for more precise and biologically effective therapeutic strategies[5]. A central difficulty in osteosarcoma treatment is that tumor control and skeletal reconstruction must often be achieved simultaneously[6]. Wide resection is essential for local control, but it frequently leaves behind irregular bone defects, compromised mechanical integrity, and a postoperative niche that may still harbor microscopic residual disease[7]. Systemic chemotherapy can suppress disseminated tumor cells. However, its efficacy is constrained by dose-limiting toxicity, limited drug accumulation within the tumor-bearing bone microenvironment, and the inability to address the local regenerative demands created by surgery[8]. The clinical problem is not simply how to kill osteosarcoma cells, but how to eradicate residual malignant cells while restoring the biological and structural function of bone. Hydrogel-based biomaterials have emerged as particularly attractive candidates for addressing this dual challenge[9]. Owing to their high water content, tissue-like architecture, injectability or implantability, tunable porosity, and capacity to encapsulate a broad range of therapeutic cargos, hydrogels can function simultaneously as local drug depots, defect-filling matrices, and bioactive microenvironmental regulators[10,11]. Compared with systemic administration, local hydrogel delivery can maintain higher drug concentrations at the target site, reduce systemic exposure, and enable spatiotemporally controlled release of chemotherapeutics, nucleic acids, ions, proteins, or catalytic nanomaterials[12,13]. At the same time, hydrogel platforms can be engineered to support osteogenesis, modulate immune or stromal responses, and interface with scaffolds or external stimuli, making them especially well suited to the postoperative osteosarcoma setting[14-16]. Importantly, hydrogels have evolved beyond the early concept of being as passive carriers for local chemotherapy. Recent studies have increasingly exhibited hydrogels as programmable therapeutic systems, which are capable of matching treatment function to pathological context and healing stage[17]. Therefore, hydrogels may integrate local tumor eradication, tumor microenvironment reprogramming, and bone regeneration within a single biomaterial logic[18].

Bioprinting may further extend the utility of hydrogel systems by enabling controlled spatial organization of cells, drugs, inorganic particles, and structural components within patient-specific constructs[19]. In contrast to conventional injectable hydrogels, bioprinted

platforms can generate predefined pore architectures, cargo gradients, core–shell structures, and region-specific mechanical properties[20]. These capabilities are relevant to osteosarcoma reconstruction, where the tumor-facing region may require early and intensive antitumor activity, whereas areas adjacent to viable host bone may require a more permissive osteogenic environment. Nevertheless, this design rationale also introduces important safety considerations. Osteogenic, angiogenic, and immunomodulatory signals that support bone healing could potentially influence residual tumor cells or the postoperative tumor microenvironment if delivered without adequate spatial or temporal control. Therefore, postoperative osteosarcoma hydrogels should not be regarded simply as bone-regenerative materials loaded with anticancer agents. They should be designed as staged and compartmentalized therapeutic systems that prioritize local tumor control while subsequently supporting tissue repair. In this review, relevant studies were identified through searches of major databases, including PubMed, Web of Science, and Google Scholar, using combinations of keywords related to osteosarcoma, postoperative recurrence, bone defect repair, hydrogels, local drug delivery, antitumor therapy, bone regeneration, and bioprinting. Priority was given to representative, high-quality, and recent studies. We summarized recent progress in hydrogel-based postoperative osteosarcoma treatment and bioprinting strategies, with particular emphasis on local tumor eradication and bone regeneration (**Figure 1**). We reviewed architecturally programmed 3D-printed hydrogel constructs. We discussed the major antitumor mechanisms incorporated into hydrogel platforms, including chemotherapy, photothermal therapy, photodynamic therapy, chemodynamic therapy, immunomodulation, and bioactive ion-mediated approaches. We further examine hydrogel composition, controlled-release behavior, spatial and temporal programming, and the emerging role of bioprinting in constructing multifunctional postoperative implants. Finally, we highlight key translational challenges, including oncologic safety, the balance between antitumor and regenerative functions, mechanical competence, degradation control, manufacturing reproducibility, and clinical applicability.

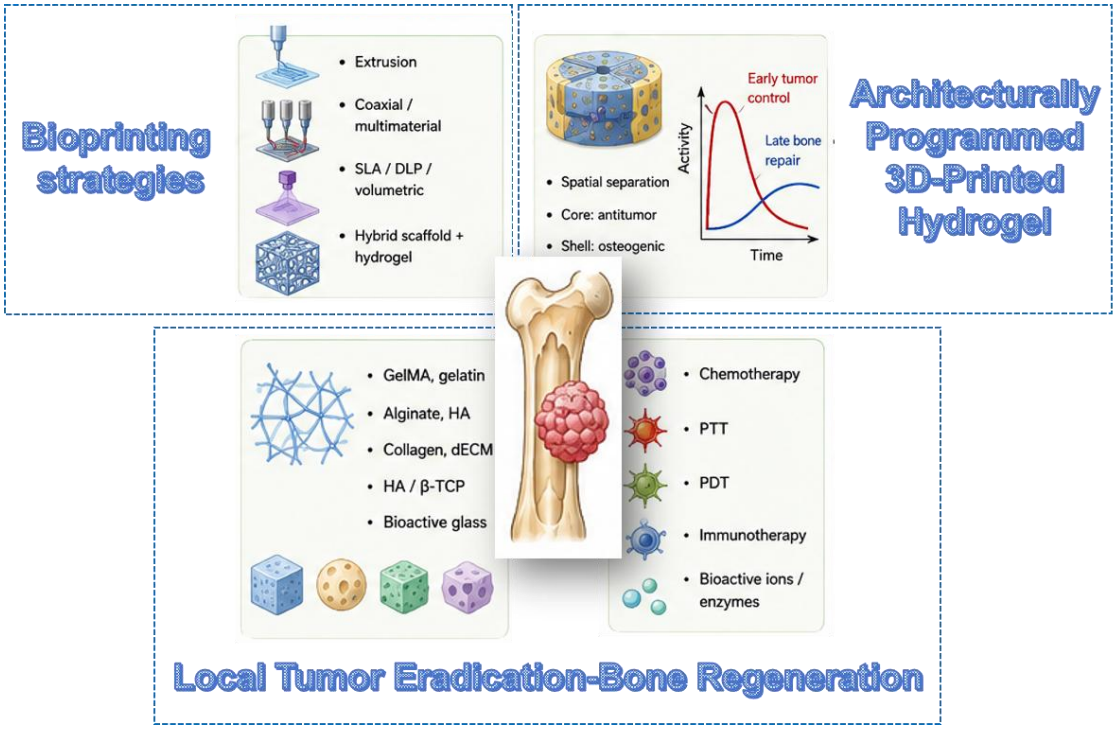

Figure 1. Hydrogels for Osteosarcoma Treatment: Bioprinting Strategies and Local Tumor Eradication–Bone Regeneration.

2. Bioprinting Strategies for hydrogel-based osteosarcoma treatment

Bioprinting offers a route to convert hydrogel-based osteosarcoma treatment from a bulk implant into a spatially programmed construct that simultaneously addresses postoperative residual disease and segmental bone loss[21]. Importantly, most osteosarcoma studies reporting combined tumor ablation and bone repair have used 3D-printed acellular ceramic, polymer, or metal-based scaffolds rather than fully cell-laden bioprinted implants. These reports should therefore be interpreted as strong design precedents for future bioprinted systems, rather than as clinical validation of cell-containing constructs. The central objective is to integrate a transient antitumor function with a regenerative microenvironment while preserving construct fidelity, implantation feasibility, and mechanical competence.

2.1 Bioprinting approaches for osteosarcoma reconstruction

A bioink for osteosarcoma reconstruction must satisfy competing requirements before, during, and after printing[22]. Before printing, the formulation requires sufficient viscosity, shear-thinning behavior, yield stress, and structural recovery to permit continuous filament formation without nozzle clogging or collapse. During deposition, printing pressure, nozzle diameter, shear exposure, and temperature must be controlled to preserve cell viability and therapeutic-cargo integrity. After printing, the construct must rapidly stabilize through an appropriate crosslinking mechanism while maintaining cytocompatibility, degradability, nutrient transport, and osteogenic potential[23]. These requirements are interdependent. Raising polymer concentration or ceramic loading may improve shape fidelity and stiffness but can

increase extrusion stress and compromise cell survival. For osteosarcoma applications, bioinks should ideally combine an ECM-mimetic hydrogel phase, such as gelatin methacryloyl, gelatin, alginate, hyaluronic acid, collagen, or decellularized matrix components, with osteoconductive additives including hydroxyapatite, β-tricalcium phosphate, bioactive glass, or silicate-based particles[24]. The hydrogel phase supports cell encapsulation and localized drug incorporation, whereas the inorganic phase can improve mechanical behavior, mineralization, and osteogenic signaling. However, nanoparticle incorporation must be optimized carefully because it can alter rheology, light penetration during photocuring, degradation kinetics, and drug release. Therapeutic-cargo compatibility is particularly important in this setting. Cytotoxic drugs, photothermal agents, catalytic nanoparticles, immune modulators, and osteogenic molecules may each alter gelation behavior or adversely affect encapsulated progenitor cells. A rational strategy is therefore to separate these functions spatially or temporally rather than co-localizing them indiscriminately. For example, an antitumor compartment can be designed for early, localized release or externally triggered activation, followed by conversion of the remaining construct into a regenerative matrix. This principle is illustrated by a core–shell scaffold in which doxorubicin-loaded gelatin formed the core, while a β-TCP/$SrCuSi_4O_{10}$ shell provided photothermal activity, bioactive-ion release, and an osteogenic framework after degradation of the drug-containing core.

Extrusion bioprinting is currently the most practical approach for osteosarcoma reconstruction because it accommodates viscous, particle-containing, cell-laden hydrogels and permits deposition of large, anatomically relevant constructs[25]. Multimaterial and coaxial extrusion strategies further enable the spatial organization of distinct bioinks or cell populations into separate compartments, providing a potential approach for constructing heterogeneous tissue and tumor models[26]. Its main limitations are relatively modest resolution and potential cell damage from nozzle-induced shear stress. Light-based approaches, including stereolithography, digital light processing, and volumetric bioprinting, provide superior resolution and may be valuable for fabricating fine channels, defect-conforming interfaces, and highly regular porous architectures. These methods require photocrosslinkable formulations and careful control of light attenuation, photoinitiator concentration, and thermal or photochemical damage to cells and drugs. Volumetric bioprinting is especially attractive for rapid fabrication of complex living constructs, although its application to load-bearing osteosarcoma defects remains preliminary[19]. Multi-material printing should be prioritized where the resection cavity contains heterogeneous functional demands. Side-by-side, layered, and core–shell deposition can generate tumor-facing therapeutic regions, osteogenic regions adjacent to viable host bone, and vascularization-supporting channels. In particular, coaxial core–shell printing provides a direct means of isolating an anticancer cargo from a cell-laden or mineralized outer phase. For defects exposed to substantial mechanical load, scaffold–hydrogel hybrid fabrication may offer the most realistic route. A patient-specific porous

thermoplastic, metallic, or bioceramic lattice can provide immediate structural support, while a hydrogel phase supplies cells, drugs, growth factors, and a permissive regenerative niche. This division of labor is important because high-temperature thermoplastic printing is generally incompatible with direct cell deposition, whereas hydrogel-only constructs may not provide sufficient early mechanical stability in large load-bearing defects.

2.2 Printed architectures for spatial separation of antitumor and osteogenic functions

Spatial segregation should be treated as a core design principle rather than a secondary formulation feature. One strategy is a core–shell architecture in which the core provides controlled chemotherapy, ferroptosis induction, photothermal conversion, or immunomodulation, while the outer shell provides osteoconductive mineral content and mechanical integrity. Zhang et al. designed a doxorubicin-loaded gelatin core within a β-TCP/$SrCuSi_4O_{10}$ shell. Near-infrared-II irradiation activated photothermal therapy and triggered on-demand drug release, while subsequent gelatin loss generated channels that supported tissue ingrowth and the shell released Sr, Cu, and Si ions associated with vascularized bone regeneration[27]. Alternatively, a tumor-facing peripheral zone can be enriched with antitumor agents, whereas the defect interior may contain osteogenic cells, mineral particles, angiogenic cues, or controlled BMP-2 delivery. This architecture may reduce direct exposure of regenerative cells to cytotoxic drugs. A printed gelatin–sodium alginate–CuO hydrogel could suppress postoperative tumor recurrence through glutathione-depletion-mediated ferroptosis and photothermia-enhanced chemodynamic therapy, supporting the feasibility of hydrogel-based local antitumor platforms. Temporal programming is equally important. Ideally, the construct should provide an early high-intensity antitumor phase, followed by a lower-inflammatory osteogenic phase. A multifunctional titanium scaffold carrying doxorubicin- and immune-checkpoint-inhibitor-loaded nanomaterials has similarly shown preclinical osteosarcoma control together with bone-regeneration bioactivity, reinforcing the rationale for staged therapeutic–regenerative constructs.

2.3 Bioprinted constructs versus injectable hydrogels

Patient-specific bioprinting can integrate preoperative CT and MRI with image segmentation, virtual surgical planning, computer-aided design, and manufacture of defect-matched constructs. In osteosarcoma surgery, CT/MRI-derived 3D models and patient-specific cutting guides have already been used to improve resection planning and allograft reconstruction. 3D-printed guiding templates supported precise tumor resection and allograft implantation, with reduced operative time, blood loss, and radiation exposure in their clinical series. A future workflow could proceed from preoperative imaging-based tumor mapping to virtual resection, design of a patient-matched lattice or hydrogel construct, and sterile fabrication before surgery. Intraoperative scanning and direct printing may be useful when the final defect differs from the planned geometry because of margin modification or unexpected tissue loss. Proof-of-concept work in non-oncologic bone and osteochondral defects has

shown that 3D scanning, Boolean defect modeling, and rapid in situ hydrogel printing can generate close geometric matches. This approach remains experimental for osteosarcoma and would require stringent validation of sterility, manufacturing speed, oncologic safety, mechanical fixation, and regulatory compliance.

Injectable hydrogels remain advantageous for narrow, irregular, deep, or difficult-to-access defects because they can conform to complex cavities with minimally invasive delivery. They are also attractive when intraoperative defect geometry is uncertain. However, injectable systems provide limited control over internal pore architecture, spatial distribution of multiple cargos, and early load-bearing capacity. By contrast, bioprinted constructs enable predefined pore networks, drug gradients, internal channels, and defect-matched external geometry. These advantages are particularly relevant for osteosarcoma cavities requiring simultaneous local recurrence control and organized osseous regeneration. Their limitations include longer manufacturing workflows, more demanding sterilization and quality-control requirements, potential mismatch between planned and actual surgical defects, and insufficient mechanical strength for some segmental or weight-bearing reconstructions. Therefore, a hybrid strategy may be most appropriate for large or mechanically demanding postoperative defects: a patient-specific printed lattice can provide fixation and load transfer, while an injectable or bioprinted hydrogel fills residual gaps and delivers local antitumor and osteogenic factors. Overall, bioprinting should not be viewed simply as a more elaborate route to fabricate hydrogels. Its major value lies in the ability to spatially and temporally program tumor eradication, regenerative signaling, mechanical support, and defect-specific geometry within a single therapeutic platform. The translational priority is to establish whether these multifunctional constructs can maintain local tumor control without compromising cell viability, bone formation, mechanical safety, or clinical workflow feasibility.

3. Architecturally Programmed 3D-Printed Hydrogel for Osteosarcoma Therapy

Three-dimensional printing introduces a distinct advantage to osteosarcoma hydrogel therapy[28]. It allows the biomaterial to be designed not only as a chemical carrier, but as a geometrically and architecturally programmable implant[29]. This matters in osteosarcoma because the postoperative defect is rarely uniform. The resection cavity may require structural support, controlled macroporosity, and spatial segregation of therapeutics that cannot be stably co-formulated in a homogeneous hydrogel[30]. Thus, while injectable systems are attractive for minimally invasive filling, 3D-printed hydrogels offer an alternative route for shape-matched implantation, compartmentalized release, and structure-function coupling in the resection bed[31]. This logic is exemplified by the sandwich-structured 3D-printed hydrogel scaffold reported for multimodal postoperative osteosarcoma therapy. In this system, copper hexacyanoferrate nanoparticles (CuHCF) and mitoxantrone (MTO) are incorporated into distinct compartments using in situ stacked 3D printing (**Figure 2**)[32]. The sandwich architecture is not merely a manufacturing detail. It is the mechanism by which physicochemical incompatibility between therapeutic components is reduced while enabling

sequential and sustained release after implantation. The scaffold combines Fenton-like chemodynamic activity, DNA-damaging chemotherapy, and near-infrared-enhanced photothermal therapy, and significantly inhibits recurrence in a mouse osteosarcoma resection model. 3D printing can maintain spatial order among multiple agents whose therapeutic roles, release kinetics, and stability requirements differ sharply. The significance of 3D-printed hydrogels in osteosarcoma lies less in printing per se than in programmable heterogeneity[33]. Postoperative bone-tumor defects are intrinsically heterogeneous environments with distinct peripheral, central, and osseous interfaces. A printed scaffold can localize one function to the residual-tumor margin, the defect core, and the osteogenic interface[34]. This is a major conceptual advantage over isotropic injectable depots. At the same time, translation will require better reconciliation of print fidelity, mechanical competence, implantability in irregular defects, and biological remodeling[35]. Many current printed systems are elegant as prototypes, but their clinical value will depend on whether they can be produced reproducibly, sterilized without loss of function, and implanted without compromising intimate tissue contact at the resection boundary.

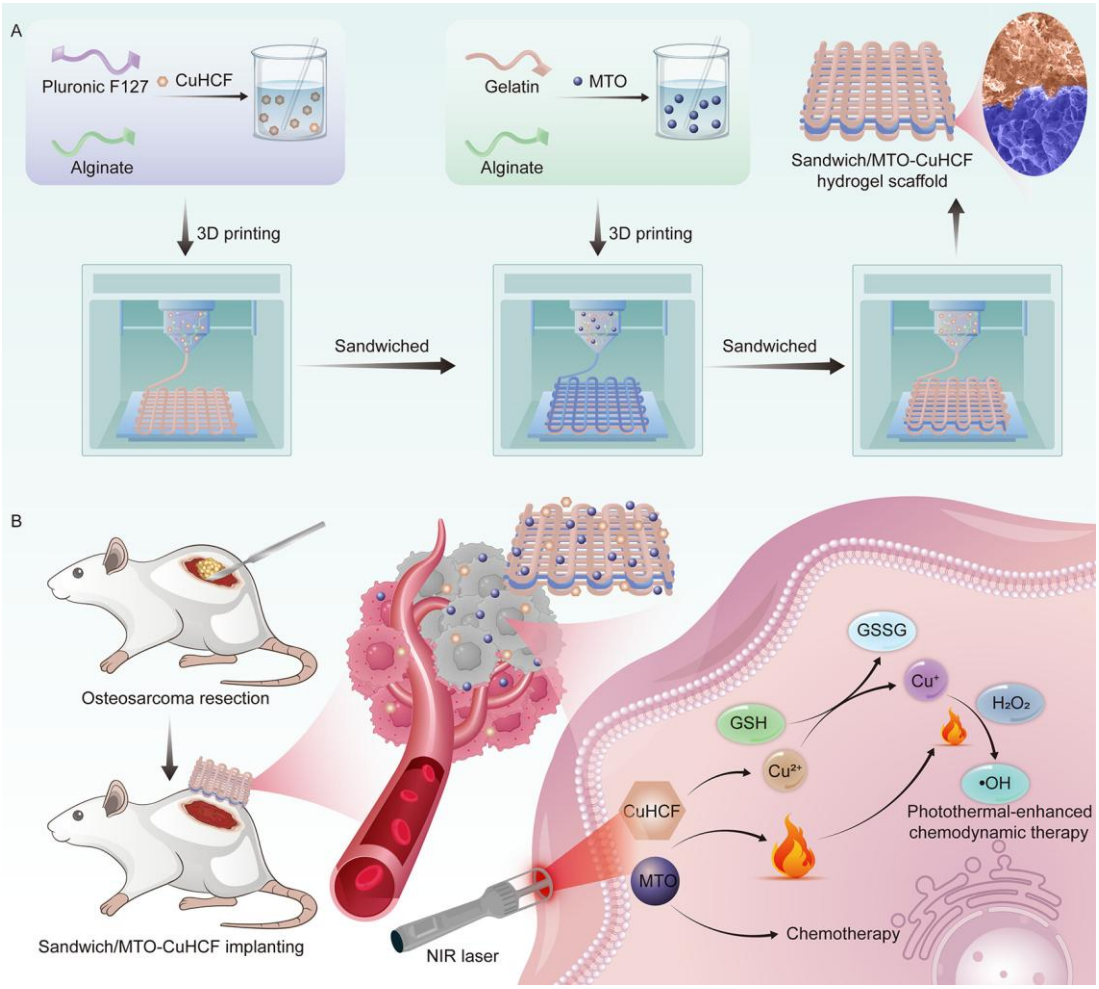

Figure 2. Schematic Illustration of Sandwich/MTO-CuHCF Hydrogel Scaffold for Preventing Postoperative Osteosarcoma Recurrencea. (A) Preparation process of the sandwich/MTO-CuHCF

hydrogel scaffold. (B) Implantation of sandwich/MTO-CuHCF hydrogel scaffold at the osteosarcoma resection site and the underlying therapeutic mechanism for inhibiting postoperative osteosarcoma recurrence. Reprinted with permission from Su et al.[32] Copyright © 2025 ACS.

A mechanistically important extension of this architectural logic is provided by the simvastatin/hydrogel-loaded 3D-printed titanium alloy scaffold reported by Jing et al[36]. Rather than treating the printed scaffold and the hydrogel as interchangeable components, this study assigns them clearly differentiated roles. The porous Ti6Al4V scaffold supplies the mechanical framework and defect-matching architecture required for reconstruction, whereas the thermosensitive PLGA-PEG-PLGA hydrogel serves as the local drug reservoir for simvastatin. This division of labor is conceptually significant because it shows that in osteosarcoma reconstruction, 3D printing is not limited to shaping a biomaterial carrier; it can be used to create a structurally competent implant whose internal space is secondarily functionalized by a hydrogel-mediated therapeutic phase. In this sense, the hydrogel does not replace the scaffold but converts it from a passive implant into an active postoperative therapeutic construct. The choice of simvastatin is also noteworthy. Unlike conventional cytotoxic payloads, simvastatin is a pleiotropic small molecule with both osteogenic and antitumor potential, making it especially suitable for postoperative osteosarcoma defects where regeneration and recurrence control must be pursued simultaneously. In the rabbit condyle defect model, the resulting Sim-3DTi scaffold enhanced osteogenesis, bone ingrowth, and osseointegration relative to the unloaded printed titanium scaffold, with increased BMP-2 expression. In parallel, the scaffold showed clear anti-osteosarcoma activity in vivo, reducing tumor volume by 59%–77% in a nude mouse model without evident organic damage. These findings matter because they demonstrate that a 3D-printed implant can be designed not only to fill space and bear load, but also to locally deliver a multifunctional drug in a way that preserves biosafety while addressing both major postoperative tasks. The significance of 3D-printed hydrogels in osteosarcoma is not confined to printable soft matrices. Equally important are hybrid constructs in which a rigid printed implant provides architectural and mechanical fidelity, while the hydrogel supplies temporal control over local drug presentation. Such systems are especially attractive for load-bearing bone defects, where purely injectable depots may lack structural competence and purely metallic implants may lack biological instruction. From this perspective, the future of 3D-printed hydrogel therapy may lie less in choosing between scaffold and hydrogel than in designing increasingly precise scaffold–hydrogel partnerships that integrate mechanics, release kinetics, and tumor biology within the same postoperative platform[37]. The design trend moves from passive postoperative filling to programmable local systems that combine site retention, temporally staged tumor control, TME rewriting, and defect-oriented bone reconstruction as summarized in **Table 1.**

Table 1 Postoperative local hydrogels, TME-responsive hydrogels, and 3D-printed hydrogel/scaffold systems for osteosarcoma treatment.

Article	Classification	Material design	Key therapeutic cargo	Main antitumor logic	Bone reconstruction logic	Comparative takeaway	Reference
Chu et al., *Biomaterials* (2025)	Postoperative local hydrogel	Bioactive nanocomposite hydrogel based on HA-BP and self-assembled Mg-BP nanoparticles	Mg^{2+}, anti-PD-L1 antibody, vismodegib	Combines immune checkpoint blockade with Hedgehog-pathway inhibition and enhanced $CD8^+$ T-cell activity	Sustained Mg^{2+} release creates a pro-osteogenic niche and upregulates ALP, COL1, RUNX2, and BGLAP	An example of a postoperative osteoimmunotherapeutic depot rather than a simple chemotherapy reservoir	38
Zhang et al., *Nano Letters* (2025)	Postoperative local hydrogel	Injectable hydrogel incorporating nHAP-stabilized Pickering emulsions	Local delivery of a RANKL inhibitor within an nHAP-containing emulsion–hydrogel system	Induces apoptosis and inhibits migration of osteosarcoma cells; suppresses local tumor growth	nHAP provides an osteoconductive mineral phase and supports new bone formation in a skull-defect model	Highlights emulsion-based compartmentalization plus mineral osteoconduction as a route to dual antitumor/regenerative therapy	39
Zhou et al., *ACS Appl. Mater. Interfaces* (2025)	Postoperative local hydrogel	Bone-adhesive peptide hydrogel (GelA-CDDP)	Cisplatin	Sustained local cisplatin release with strong retention at the resection margin; recurrence suppression in an orthotopic setting	Bone affinity is the main design strength; explicit osteogenesis is less central than depot retention	Important because bone adhesion functions as a pharmacological retention strategy, not just a mechanical feature	40
Zhou et al., *ACS Appl. Mater.*	Postoperative local hydrogel	ZIF-8-modified catechol-chitosan hydrogel with RNA-DOX@ZIF-8 nanocomplexes	Doxorubicin + PD-L1 siRNA	Local chemo-immunogene therapy; improves immune-cell	In a femoral defect setting, the coated scaffold promoted bone regeneration in parallel with	Extends postoperative design toward a chemo-immunogene-regenerative format and shows	41

Article	Classification	Material design	Key therapeutic cargo	Main antitumor logic	Bone reconstruction logic	Comparative takeaway	Reference
Interfaces (2025)				infiltration and enhances $CD8^+$ T-cell killing	recurrence control	how MOF-enabled nucleic acid delivery can be localized	
Zhang et al., *Biomaterials* (2025)	Postoperative local hydrogel	Injectable, adhesive, in situ cross-linkable MgO_2-potentiated hydrogel using MgO_2 nanoparticles and dopamine-conjugated gelatin	MgO_2-derived H_2O_2 / Mg^{2+}; paired with photothermal triggering	Early H_2O_2 release synergizes with photothermal therapy to suppress residual tumor cells and recurrence	Later sustained Mg^{2+} release promotes osteogenesis; the depot also offers hemostatic and cavity-adaptive benefits	A clear example of temporally programmed postsurgical therapy: first antitumor amplification, then osteogenesis	[42]
Ma et al., *Bioactive Materials* (2025)	TME-responsive hydrogel	Injectable TME-responsive nanocomposite hydrogel for a molecularly defined subgroup	NHWD-870 + IL11Rα-targeted liposomes containing cisplatin-loaded MnO_2	MYC degradation, macrophage repolarization, GSH-responsive Mn^{2+}/ROS generation, ICD induction, dendritic-cell maturation	Bone regeneration is not the primary endpoint; the emphasis is TME rewriting and metastasis suppression	Distinct because it is built around MYC-amplified osteosarcoma, making it pathology-guided rather than merely stimulus-responsive	[43]
Lin et al., *Advanced Functional Materials* (2025)	TME-responsive hydrogel	Self-adaptive RPSH dual-network hydrogel (PAAm/SA/HA) loaded with RRx-001/ICG@diselenide nanoparticles	RRx-001, ICG, diselenide nanoparticle module	Early anti-inflammatory niche correction via HA/NF-κB modulation, followed by ROS/selenium-mediated multimodal tumor	Long-term regulation of the osteogenic–osteoclastic balance supports reconstruction; reported BV/TV was ~59% at 8 weeks	Exemplifies cascade microenvironment correction: stabilize the niche, debulk tumor, then reconstruct bone	[44]

Article	Classification	Material design	Key therapeutic cargo	Main antitumor logic	Bone reconstruction logic	Comparative takeaway	Reference
				inhibition			
Xie et al., *Small* (2025)	TME-responsive hydrogel	3D-printed scaffold combined with UV-crosslinked GelMA/SA/borax hydrogel carrying cRGD-modified Cu–Cys–PEG nanoparticles	Copper-containing nanoparticles for CDT/cuproptosis-oriented therapy	Acidic TME triggers hydrogel disintegration; released nanoparticles deplete GSH, convert Cu^{2+} to Cu^{+}, and drive Fenton-like ROS plus cuproptosis	After the early tumor-killing phase, the printed scaffold provides structural support and a reparative microenvironment	Important for showing that TME responsiveness can impose a sequential therapy program rather than just trigger release	45
Su et al., *ACS Appl. Mater. Interfaces* (2025)	3D-printed hydrogel	Sandwich-structured 3D-printed hydrogel scaffold with compartmentalized loading	Copper hexacyanoferrate nanoparticles + mitoxantrone	Fenton-like chemodynamic therapy + chemotherapy + NIR-enhanced photothermal therapy	The key design strength is architectural compartmentalization; direct regenerative signaling is less emphasized than recurrence control	Demonstrates how 3D printing enables programmable heterogeneity and spatial separation of incompatible therapeutic modules	32
Jing et al., *Bioactive Materials* (2024)	3D-printed hydrogel	Porous 3D-printed Ti6Al4V scaffold secondarily functionalized with thermosensitive PLGA-PEG-PLGA hydrogel	Simvastatin	Local simvastatin delivery suppresses osteosarcoma through TF/NOX2-associated ferroptosis	Strong osteogenic performance, bone ingrowth, osseointegration, and BMP-2 upregulation in a load-bearing defect context	A strong hybrid example in which the rigid scaffold provides mechanics and the hydrogel provides temporal drug control	36

4. Local Tumor Eradication-Bone Regeneration

4.1 Postoperative Locoregional Hydrogel Depots for Osteosarcoma Treatment

Postoperative local hydrogels are emerging as one of the most rational formats for osteosarcoma management[46]. They directly address the two most stubborn postsurgical problems, microscopic residual disease and large, and irregular bone defects[47]. In contrast to systemic delivery, injectable or implantable hydrogels can conform to the resection cavity, maintain a high local drug concentration, reduce systemic exposure, and simultaneously provide a provisional matrix for tissue repair[48,49]. Recent osteosarcoma drug delivery and hydrogel-assisted treatment have therefore converged on the idea that local biomaterial depots are especially attractive for the postsurgical setting, where tumor eradication and bone regeneration must occur in the same anatomical space but on partially different timescales (**Figure 3**)[50]. A representative example is the bioactive nanocomposite hydrogel reported by Chu et al., which was specifically designed for postsurgical osteosarcoma with high hedgehog activity, residual tumor burden, and major bone loss (**Figure 4**)[38]. This system co-delivers Mg^{2+}, anti-PD-L1 antibody, and the hedgehog inhibitor vismodegib, thereby integrating immune checkpoint blockade, pathway-targeted therapy, and osteogenic stimulation in a single depot. Mechanistically, the platform is notable because it does not treat “tumor control” and “bone repair” as parallel but disconnected goals. Instead, it couples enhanced $CD8^+$ T-cell activity and tumor growth suppression with a sustained Mg^{2+}-mediated pro-osteogenic microenvironment, leading to upregulation of osteogenic markers such as ALP, COL1, RUNX2, and BGLAP *in vivo*. This study is important not simply because it combines agents, but because it exemplifies a postoperative osteoimmunotherapeutic hydrogel rather than a conventional chemotherapy reservoir.

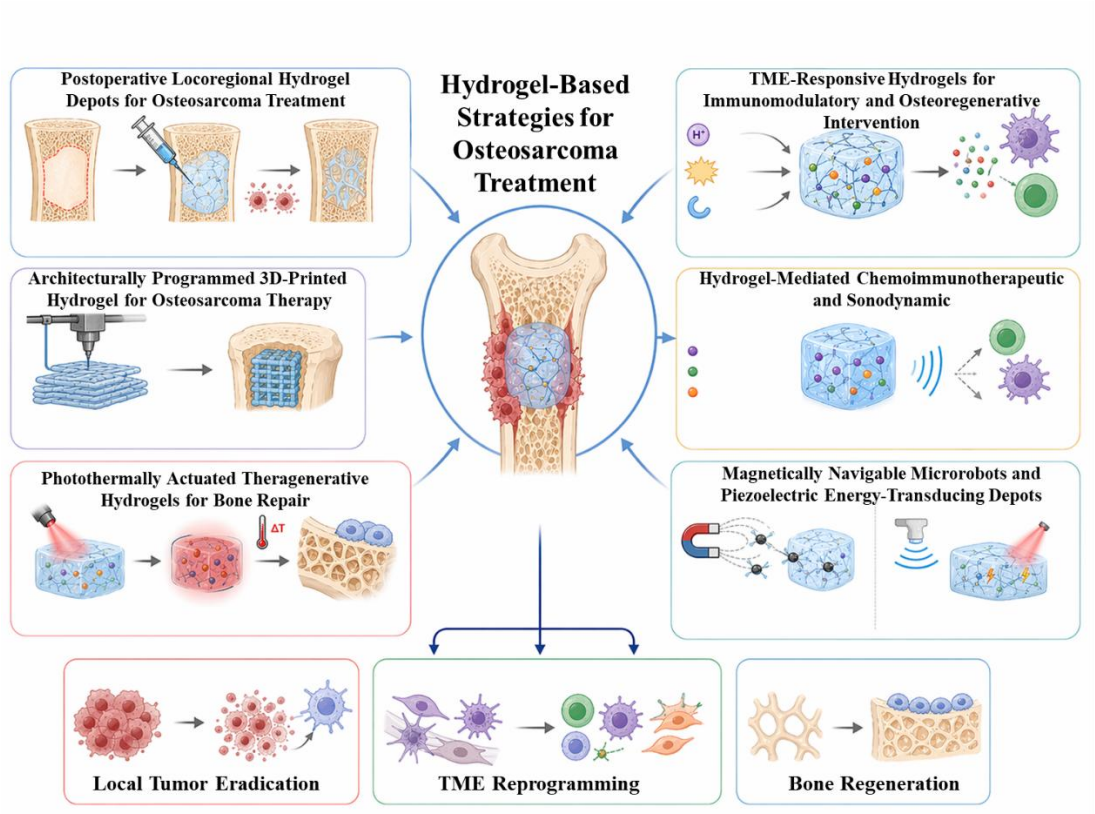

Figure 3. Hydrogel-Based Strategies for Osteosarcoma Treatment: Orchestrating Local Tumor Eradication, Tumor Microenvironment Reprogramming, and Bone Regeneration

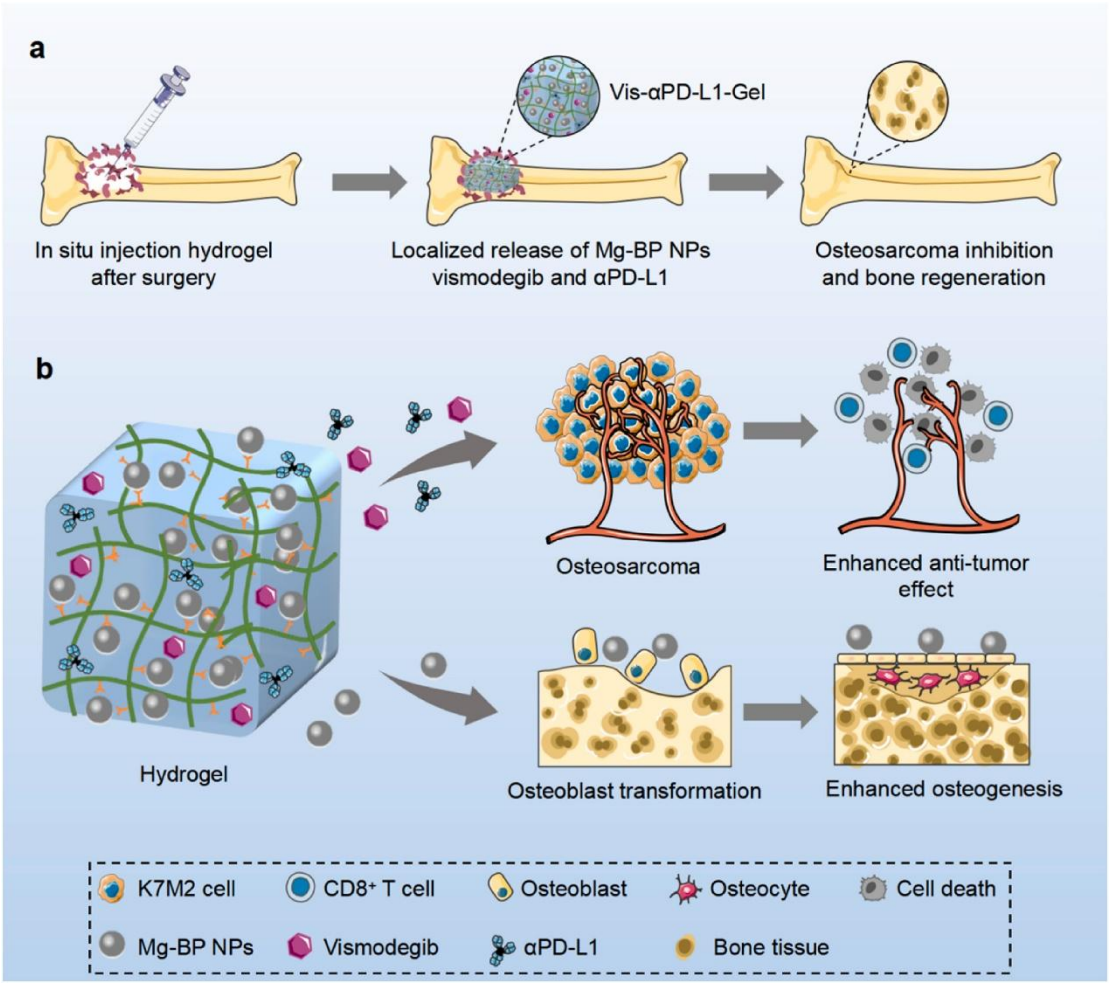

Figure 4. Schematic illustration of bioactive nanocomposite hydrogel for enhanced bone tumor immunotherapy and bone regeneration. a The nanocomposite hydrogel is fabricated using bisphosphonate-modified hyaluronic acid (HA-BP) and self-assembled magnesium (Mg)-bisphosphonate (BP) nanoparticles (Mg-BP NPs). b The αPD-L1 and vismodegib released from the hydrogel directly block PD-L1 in the tumor microenvironment. Reprinted with permission from Chu et al. [38] Copyright © 2025 Elsevier.

Recent studies have further broadened this postoperative design logic. A nanohydroxyapatite-stabilized Pickering-emulsion-incorporated hydrogel was developed to prevent postoperative osteosarcoma recurrence while promoting bone repair, underscoring the growing interest in using emulsion-based compartmentalization together with osteoconductive mineral phases to unify antitumor function and skeletal reconstruction[39]. Zhou et al. reported a bone-adhesive peptide hydrogel loaded with cisplatin for postoperative osteosarcoma treatment[40]. This GelA-CDDP platform combines strong hydroxyapatite affinity, good biocompatibility, and sustained cisplatin release over 7 days, and that it significantly inhibited postoperative recurrence in an orthotopic model. Conceptually, this work is important because bone adhesion is not merely a mechanical convenience. It is a pharmacological design principle that can improve depot retention at the resection margin,

where local relapse is most likely to arise. Taken together, postoperative local hydrogels are moving from passive cavity fillers toward multifunctional, site-retentive, biologically instructive depots. The systems no longer rely on a single cytotoxic payload, but instead integrate local immune activation, pathway inhibition, osteoconduction, or bone-adhesive retention. Studies further sharpen this postoperative paradigm by showing that local hydrogels can be engineered not only for dual antitumor/regenerative function, but also for more precise control over how these functions are staged and retained at the surgical site. In maxillofacial osteosarcoma, Zhou et al. developed a ZIF-8-modified multifunctional hydrogel (Gel@RDZ) in which doxorubicin and PD-L1 siRNA were co-loaded into a stable RNA-DOX@ZIF-8 nanocomplex and then incorporated into a catechol-modified chitosan matrix[41]. The resulting construct showed high drug-loading capacity, favorable viscoelasticity, and strong scaffold adhesion, properties that are especially relevant in craniofacial postoperative settings where defect geometry is complex and local retention is difficult to maintain. Importantly, this was not simply another local chemotherapy depot. In a rat femoral defect model, the Gel@RDZ-coated scaffold improved bone regeneration, while in a murine osteosarcoma recurrence model it increased immune-cell infiltration, reduced tumor recurrence, and enhanced the tumor-killing activity of $CD8^+$ T cells. Conceptually, this study is significant because it extends the logic of postoperative local hydrogel design toward a chemo-immunogene-regenerative format, and it also illustrates how metal-organic-framework-enabled nucleic acid delivery may help bring gene-silencing strategies into clinically relevant postsurgical osteosarcoma treatment.

A complementary but mechanistically distinct advance was reported by Zhang et al. in their injectable and adhesive MgO_2-potentiated hydrogel (MOG hydrogel) for postsurgical osteosarcoma[42]. This platform uses MgO2 nanoparticles and dopamine-conjugated gelatin to create an in situ cross-linkable depot in which MgO_2 serves as a multifunctional active component rather than a passive additive. The optimized 10MOG formulation exhibited gel stability, injectability, shape adaptability, tissue adhesion, and rapid hemostatic performance, all of which are highly desirable for irregular resection cavities. More importantly, the system was designed around sequential function: early H_2O_2 release synergized with photothermal therapy to suppress residual tumor cells and prevent recurrence, whereas the subsequent sustained release of Mg^{2+} promoted bone regeneration. This study is particularly important at the design-principle level because it frames postoperative hydrogel therapy as a temporally programmed process rather than a simple co-delivery problem. In other words, the hydrogel is intended to behave first as a surgical sealant and local antitumor amplifier, and only later as an osteogenic microenvironment, which is arguably closer to the real biological sequence of postoperative osteosarcoma management. Taken together, these studies indicate that postoperative local hydrogels are evolving toward programmable, site-retentive therapeutic ecosystems rather than passive drug reservoirs. The field is moving beyond the earlier "kill

tumor plus fill defect" paradigm toward systems that integrate local adhesion, immunoregulation, gene silencing, externally augmentable tumor therapy, hemostasis, and osteoinductive ion signaling within a single material platform[51]. For osteosarcoma specifically, this shift is important because postoperative success depends not only on eliminating residual malignant cells, but also on matching therapeutic sequence to wound healing sequence[52]. The most persuasive next-generation hydrogels may be those that are explicitly designed to change roles over time, guiding the transition toward bone regeneration and functional reconstruction.

4.2 Tumor-Microenvironment-Responsive Hydrogels for Immunomodulatory and Osteoregenerative Intervention

If postoperative local hydrogels define the anatomical logic of osteosarcoma treatment, then tumor-microenvironment-responsive hydrogels define its biological logic[53]. Osteosarcoma lesions are not simply masses of proliferating malignant cells. They are dynamic niches characterized by aberrant redox balance, high glutathione levels, immune suppression, inflammatory dysregulation, and oncogene-specific dependencies in some subtypes. Accordingly, the advanced hydrogel systems are no longer designed merely to persist at the tumor site, but to sense and exploit pathological microenvironmental cues[54]. They are designed to trigger drug release, amplify tumor-selective toxicity, and reprogram local immunity[55,56]. This shift aligns with broader osteosarcoma drug-delivery trends that increasingly prioritize responsive release and microenvironment-directed therapy over constitutive payload leakage. A particularly strong example is the TME-responsive nanocomposite hydrogel developed for MYC-amplified osteosarcoma (**Figure 5**)[43]. This work is notable because it does not frame osteosarcoma as a single disease entity, but instead builds a hydrogel around a molecularly defined high-risk subgroup. The platform co-delivers the MYC inhibitor NHWD-870 and IL11Rα-targeted liposomes containing cisplatin-loaded MnO_2, thereby combining oncogene suppression, targeted chemotherapy, chemodynamic activity, and immune remodeling. Mechanistically, NHWD-870 degrades MYC and downregulates CCL2 and IL13, favoring macrophage repolarization toward an M1-like phenotype, while the MnO_2/cisplatin module reacts with intratumoral GSH to generate Mn^{2+} and reactive oxygen species, inducing immunogenic cell death and dendritic-cell maturation. The key conceptual advance is that the hydrogel is not only responsive to the TME, but actively rewrites it. MYC signaling and ICD are co-regulated so that immune infiltration, T-cell activity, and suppression of lung metastasis are enhanced *in vivo*. In other words, responsiveness becomes a means of immune conversion, not just of drug release.

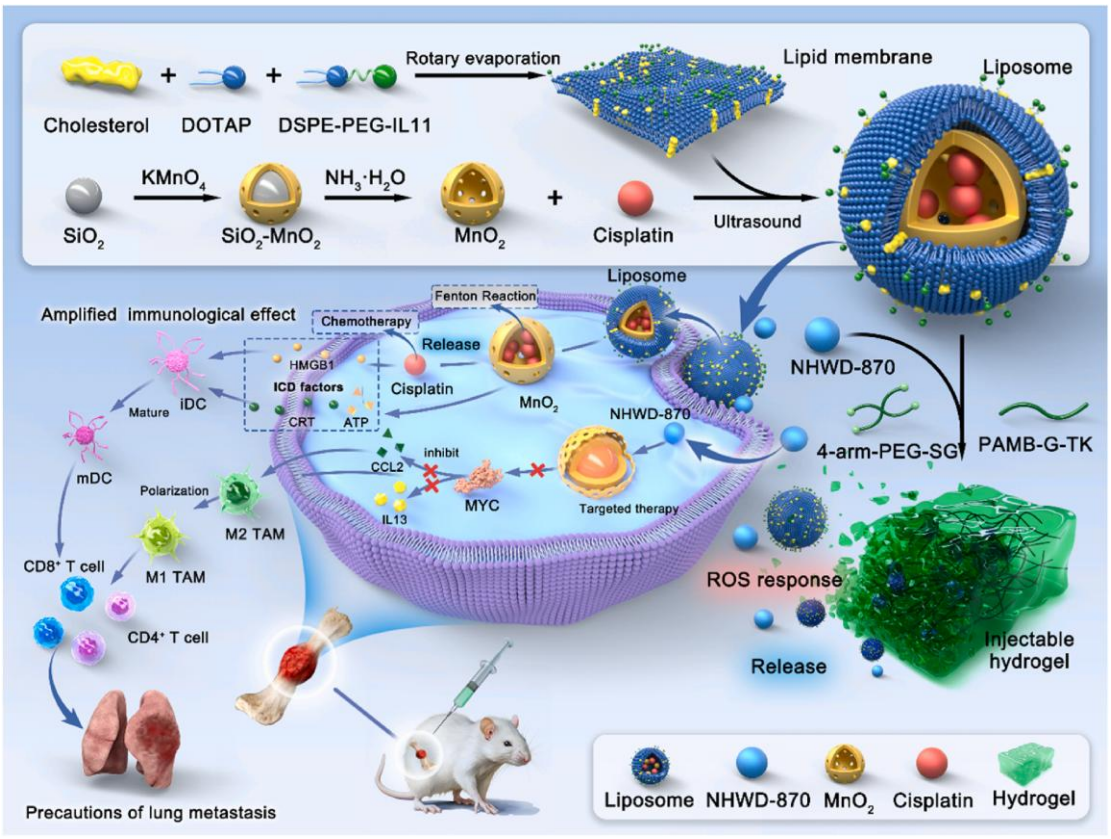

Figure 5. An injectable TME-responsive nanocomposite hydrogel loaded with an effective MYC inhibitor and IL11Rα-targeted liposomes containing cisplatin-loaded MnO2 (Cis/Mn@Lipo-IL11) was developed, establishing a targeted chemotherapy-chemodynamic therapy-immunotherapy triple-combination therapy to treat MYC-amplified osteosarcoma. Reprinted with permission from Ma et al. [43] Copyright © 2025 KeAi.

An equally instructive but biologically distinct strategy is provided by the self-adaptive RPSH hydrogel reported by Lin et al[44]. This system integrates RRx-001/ICG@diselenide nanoparticles into a PAAm/SA/HA dual-network matrix and is built around a cascade sequence of microenvironmental corrections. The early phase is dominated by high-molecular-weight hyaluronic acid, which suppresses NF-κB signaling and promotes macrophage polarization toward the M2 phenotype, thereby dampening the inflammatory milieu after osteosarcoma resection. Subsequently, the dual-responsive nanoparticle module supports multimodal antitumor therapy through increased reactive oxygen species and bioactive selenium species, while long-term regulation of the osteogenic–osteoclastic balance promotes bone reconstruction. The reported tumor growth inhibition at 3 weeks and substantial new-bone formation with a BV/TV of ~59% at 8 weeks are important. This study embody a key principle for postoperative biomaterials as the local niche should first be stabilized, then debulked, and finally reconstructed. Another illustrative example is the TME-responsive hydrogel/scaffold platform reported by Xie et al., which further advances the idea

that osteosarcoma biomaterials should not merely respond to the tumor microenvironment, but should use that responsiveness to impose a therapeutic sequence[45]. In this study, a UV-crosslinked hydrogel composed of GelMA, sodium alginate, and borax was injected into a 3D-printed PLA scaffold and used to carry cRGD-modified Cu–Cys–PEG nanoparticles. The design is notable because the hydrogel is positioned not only as a release vehicle, but also as a buffer interface between scaffold and host bone, reducing local abrasion while enabling tumor-targeted nanoparticle delivery. Mechanistically, the early acidic tumor microenvironment promotes hydrogel disintegration and release of the copper-containing nanoparticles, which deplete intracellular glutathione, convert Cu^{2+} to Cu^{+}, and drive a Fenton-like reaction with enhanced reactive oxygen species generation. In the context of this study, chemodynamic stress is coupled with cuproptosis-oriented tumor killing, thereby creating a distinctly TME-amplified antitumor phase rather than constitutive cytotoxic leakage. These TME-responsive studies suggest that the field is evolving from "smart release" toward pathology-guided local therapy[57]. This is an important distinction. A hydrogel that responds only to pH or redox conditions remains fundamentally a materials solution[58]. By contrast, a hydrogel that is designed around MYC amplification, macrophage polarization, ICD induction, or osteoimmune rebalancing begins to function as a localized systems therapy.

4.3 Hydrogel-Mediated Chemoimmunotherapeutic and Sonodynamic Reprogramming of the Osteosarcoma Immune–Stromal Niche

Chemoimmunotherapeutic and sonodynamic hydrogels further extend the function of local osteosarcoma depots from responsive release toward active remodeling of the immune–stromal barrier[59]. This is an important conceptual step. In osteosarcoma, weak immunotherapy is often not simply a failure of immune activation per se, but a failure to overcome physical and biochemical exclusion mechanisms within the tumor niche[60]. Dense extracellular matrix, cancer-associated fibroblast (CAF) activation, poor T-cell infiltration, and insufficient immunogenic cell death can jointly blunt the efficacy of otherwise rational antitumor agents[61]. Accordingly, the most instructive recent hydrogel systems in this category do not merely combine therapies[62]. They sequence stromal rewiring, tumor-cell killing, and immune amplification so that each stage improves the conditions for the next.

A representative example is the sequential nanocomposite hydrogel reported by Wang et al., which was explicitly designed to overcome the CAF-rich, T-cell-excluding stroma of osteosarcoma (**Figure 6**)[63]. This injectable carboxymethyl chitosan/tetrabasic polyethylene glycol hydrogel co-delivers a Nox4 inhibitor and liposomal doxorubicin, but the key innovation lies in its release logic rather than in simple co-encapsulation. The Nox4 inhibitor is released earlier to suppress CAF activation, reduce collagen-rich stromal barriers, and alleviate T-cell exclusion, whereas liposomal doxorubicin is released subsequently to induce immunogenic cell death. In other words, stromal normalization is used to create immunological access before cytotoxic immune priming is intensified. The biological consequences are important. In stroma-rich osteosarcoma models, this strategy increased

tumor T-cell infiltration, improved antitumor immunity, and became even more effective when combined with PD-1 blockade in an orthotopic model. Conceptually, this work is notable because it reframes chemoimmunotherapy augmentation as a problem of microenvironmental sequencing rather than simple drug synergy.

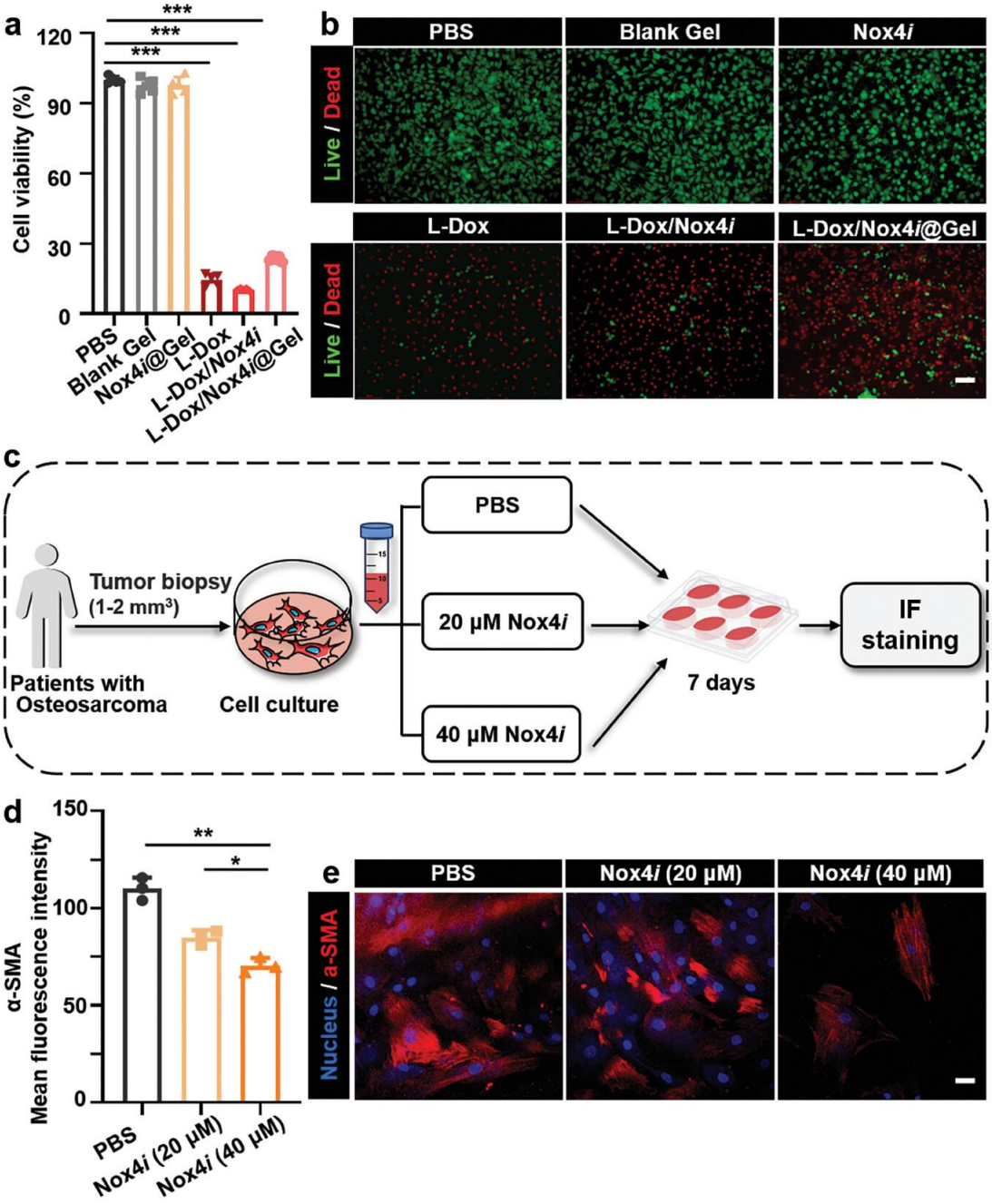

Figure 6. Assessment of cancer cell killing and CAF deactivation using L-Dox/Nox4i@Gel treatment. a) Cytotoxicity assessment for Blank Gel, Nox4i, L-Dox, L-Dox/Nox4i and L-Dox/Nox4i@Gel in K7M2 cells. b) Different formulations were co-incubated with K7M2 cells for 24 h followed by live/dead staining. Scale bar: 200 μm. c) Scheme of extraction and tissue culture of human CAFs by crawl-out method. d) The semi-quantitative analysis of α-SMA content in primary CAFs received Nox4i treatment at 20 and 40 μm for 7 days. *$p < 0.05$; **$p < 0.01$. e) The representative α-SMA immunofluorescence staining in (d). Scale bar: 20 μm. Reprinted with permission from Wang et al. [63]

A closely related but mechanistically distinct strategy was described by Lin et al. in a hydrogel delivering both the nano-sonosensitizer PCN-224@MnO2@HA and the antifibrotic agent SIS3[64]. This study is especially relevant because it addresses two major limitations of sonodynamic therapy (SDT) in osteosarcoma at the same time: insufficient reactive oxygen species generation in a hypoxic, glutathione-rich microenvironment, and poor immune-cell infiltration caused by CAF-driven extracellular matrix deposition. Here, the MnO2-containing sonosensitizer improves SDT by catalyzing oxygen generation from endogenous hydrogen peroxide while depleting intracellular glutathione, thereby amplifying ROS production under ultrasound. At the same time, SIS3 blocks TGF-β/SMAD3 signaling to reprogram CAFs, reduce collagen deposition, and open the stromal barrier to immune infiltration. The importance of this platform is therefore not limited to stronger SDT. Rather, it shows that energy-based local therapy becomes substantially more effective when antifibrotic microenvironment correction is built into the same depot. The reported 50% reduction in collagen deposition and 76% inhibition of tumor growth support the view that SDT should not be considered an isolated physical modality, but part of a broader stromal-immunological intervention.

An even more immunologically refined direction is illustrated by the functionalized photoimmune hydrogel microspheres reported by Luo et al[65]. This CP-MOF@gel system incorporates core-shell nanoparticles with an amorphous ZIF-8 shell carrying the photosensitizer Cypate and a PD-L1-targeting PROTAC molecule, ppd, and then packages them into hydrogel microspheres through microfluidic and photocuring processes. Mechanistically, the platform is notable because it divides local therapy into an "inside-out" sequence. After sustained release from the microspheres, part of the nanoparticle population is internalized by tumor cells, where irradiation-driven photothermal and ROS effects trigger caspase-1/GSDMD-dependent pyroptosis and thereby activate antitumor immunity from within the tumor cells. Meanwhile, extracellular nanoparticles promote precise PD-L1 degradation through the PROTAC component, relieving immune suppression at the tumor interface and enhancing T-cell-mediated killing. This study is important because it moves beyond conventional checkpoint blockade toward localized checkpoint-protein degradation, while also coupling that degradation to photoimmune induction and prolonged tumor retention. In conceptual terms, it suggests that hydrogel-based immunotherapy for osteosarcoma may increasingly rely not on systemic antibody logic, but on spatially organized local immune editing. Taken together, these studies indicate that chemoimmunotherapy- and SDT-oriented hydrogels are shifting from combination platforms to locally programmed immune-engineering systems. The strongest examples no longer treat chemotherapy, SDT, photoimmunotherapy, and stromal remodeling as parallel modules. Instead, they use hydrogels to determine treatment order. First loosen or reprogram the fibrotic and

immunosuppressive niche, then induce immunogenic or inflammatory tumor-cell death, and finally sustain T-cell-accessible immune pressure through checkpoint inhibition or even checkpoint-protein degradation. For osteosarcoma, where dense stroma and poor immune infiltration remain central barriers, this design logic may be more important than the identity of any single payload[66]. Thus, effective local hydrogels should not merely deliver antitumor agents into the tumor microenvironment, but should restructure that microenvironment so that subsequent therapies can actually work.

4.4. Photothermally Actuated Theragenerative Hydrogels for Bone Repair

Among the various osteosarcoma-oriented hydrogel strategies, photothermal hydrogels remain especially attractive because they are well aligned with the postsurgical clinical scenario[67]. After bulk tumor resection, what remains is not usually a large tumor mass but a limited burden of microscopic residual cells dispersed along the surgical margin. In that setting, local photothermal therapy (PTT) can function as a margin-sterilization modality, while the hydrogel simultaneously serves as a depot, adhesive, or regenerative matrix. However, the field has matured substantially beyond early "heat-generating scaffolds." Recent work increasingly favors mild or controllable PTT, integration with redox-based modalities, and deliberate coupling of photothermal function with osteogenesis. The design objective is no longer maximal heating, but therapeutically efficient thermal dosing without sacrificing repair biology. A clear example is the nano-bio-coordination dynamic hydrogel reported by Wu et al (**Figure 7**)[68]. This system uses CuS_2 nanoparticles, thiolated osteogenic peptide, and thiolated gelatin connected through reversible coordination chemistry, yielding a material with injectability, self-healing, controlled degradability, and photothermal capability. Under NIR irradiation, the CuS_2 phase ablates residual osteosarcoma cells, while the sustained release of osteogenic peptide and trace copper ions supports osteogenic differentiation and bone repair. Importantly, this work illustrates a broader design principle in current photothermal hydrogels. Dynamic bonding is not only useful for injectability and self-healing, but also for matching degradation to the postoperative repair sequence. The result is a platform in which tumor ablation and tissue regeneration are materially intertwined.

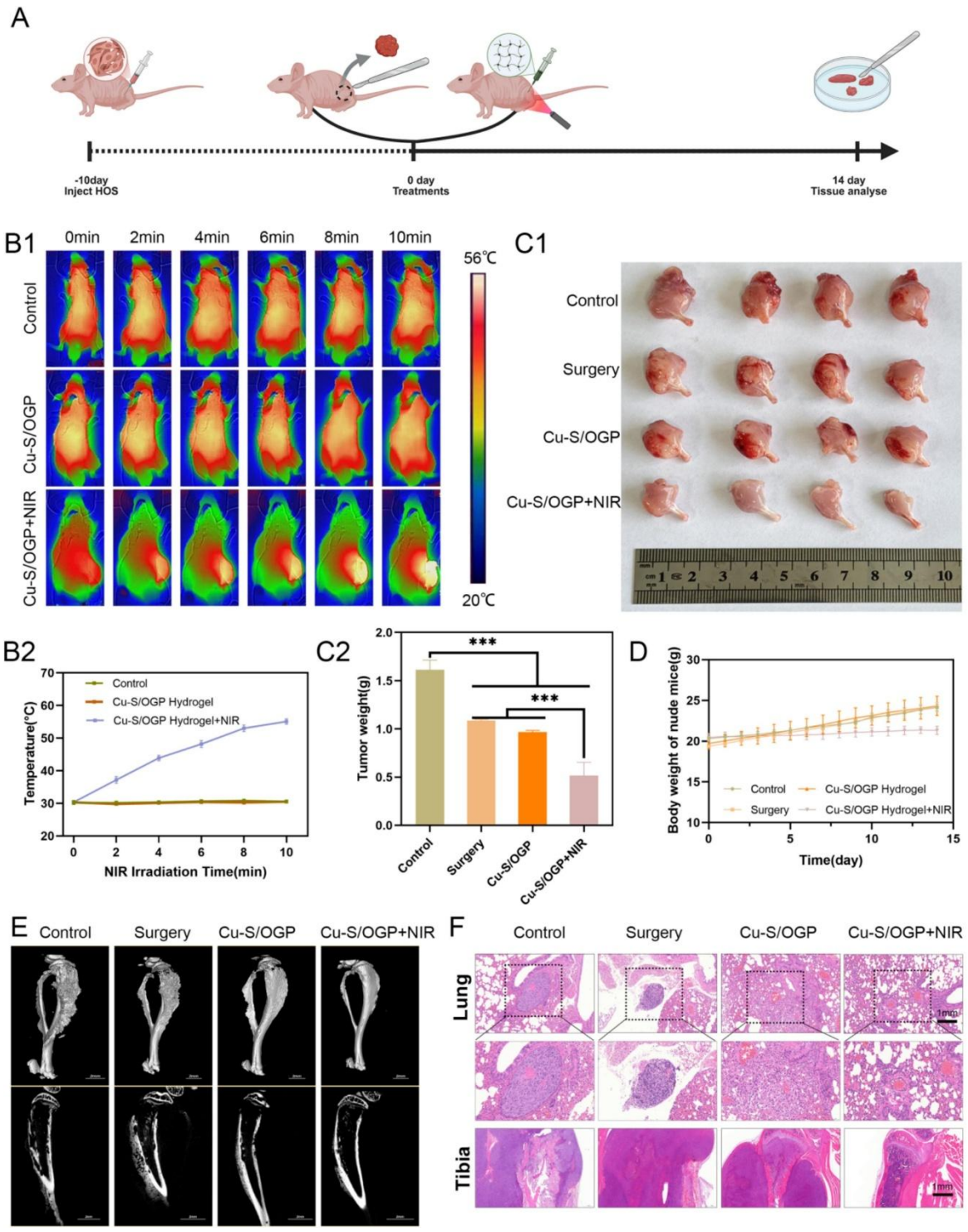

Figure 7. *In vivo* antitumor evaluation of photothermal hydrogel. (A) Schematic of the postoperative treatment. (B1) Infrared thermography and (B2) temperature–time profiles of the tumor region (n = 3). (C1) Gross images of excised tumors. (C2) tumor weights on day 14 (n = 3). *P < 0.05, **P < 0.01, ***P < 0.001 by Turkey's test. (D) Body-weight trajectories (n = 3). (E) Micro-CT images of tibial lesions after 14 days of treatment. (F) H&E staining of lung and tibia at day 14. Reprinted with permission from Wu et al. [68] Copyright © 2025 Elsevier.

The emphasis on mild PTT is particularly well represented by the SOH1(CP)1 injectable hydrogel developed by Yao et al[69]. This dual-ion-doped organic–inorganic system combines sericin-based hydrogel chemistry with Se/Mg co-doped HAp nanorods and polydopamine-coated CaO_2 nanospheres. Rather than relying on aggressive thermal ablation alone, the platform couples a mild photothermal effect with ion release and selenium-associated antitumor activity. Available summaries indicate that the system achieved 100% tumor inhibition after 18 days while supporting complete bone repair at 12 weeks, underscoring the value of temporally staged "antitumor first, regeneration next" design. Conceptually, this study is important because it argues that the most useful temperature in osteosarcoma therapy may not be the highest one, but the one that best balances tumoricidal efficiency with preservation of an osteogenic microenvironment. Chen et al. extended this line of thought with a theragenerative injectable bone-adhesive hydrogel based on silk fibroin and silk sericin, further functionalized through catechol-inspired chemistry and Cu^{2+}/tannic-acid-mediated crosslinking[70]. This system is notable for three reasons. First, it explicitly targets minimally invasive application through injectability and self-healing. Second, it addresses the often-overlooked issue of bone/tissue adhesion, which is essential for maintaining therapeutic contact at the defect surface. Third, it frames PTT not as a standalone modality, but as one component of a larger "theragenerative" strategy in which strong local adhesion, osteogenic potential, and photothermal ablation are co-optimized. This is particularly relevant for osteosarcoma, where surgical margins are difficult to sterilize and the defect environment is mechanically dynamic.

The field is also moving toward photothermal-plus designs, in which heat acts as a sensitizer for additional cytotoxic mechanisms. The GelMA-nHA/$FePS_3$ hydrogel exemplifies this trend. In that platform, $FePS_3$ nanosheets provide photothermal, photodynamic, and chemodynamic functions, while also driving ferroptosis through Fe-mediated glutathione depletion and GPX4 inactivation (**Figure 8**)[71]. Simultaneously, continuous release of phosphorus and calcium supports biomineralization and osteogenic differentiation. This multimodal design is significant because it reduces dependence on heat alone and exploits the oxidative vulnerabilities of osteosarcoma cells, thereby widening the therapeutic window for local treatment. In effect, the hydrogel becomes an integrated catalytic microreactor rather than a passive light absorber. Overall, photothermal hydrogels in osteosarcoma are undergoing a clear conceptual transition from simple hyperthermic depots to precision local platforms that combine thermal, catalytic, adhesive, and regenerative functions. The critical challenge going forward is not whether PTT can kill osteosarcoma cells, but whether clinically relevant light delivery can achieve reproducible thermal dosimetry in deep or irregular defects without damaging surrounding bone marrow, vasculature, and osteoprogenitor populations. Future studies should therefore place greater emphasis on thermal field mapping in orthotopic defects, bone-specific safety thresholds, and laser-compatible surgical workflows, especially if these systems are to move beyond proof-of-

concept implantation studies.

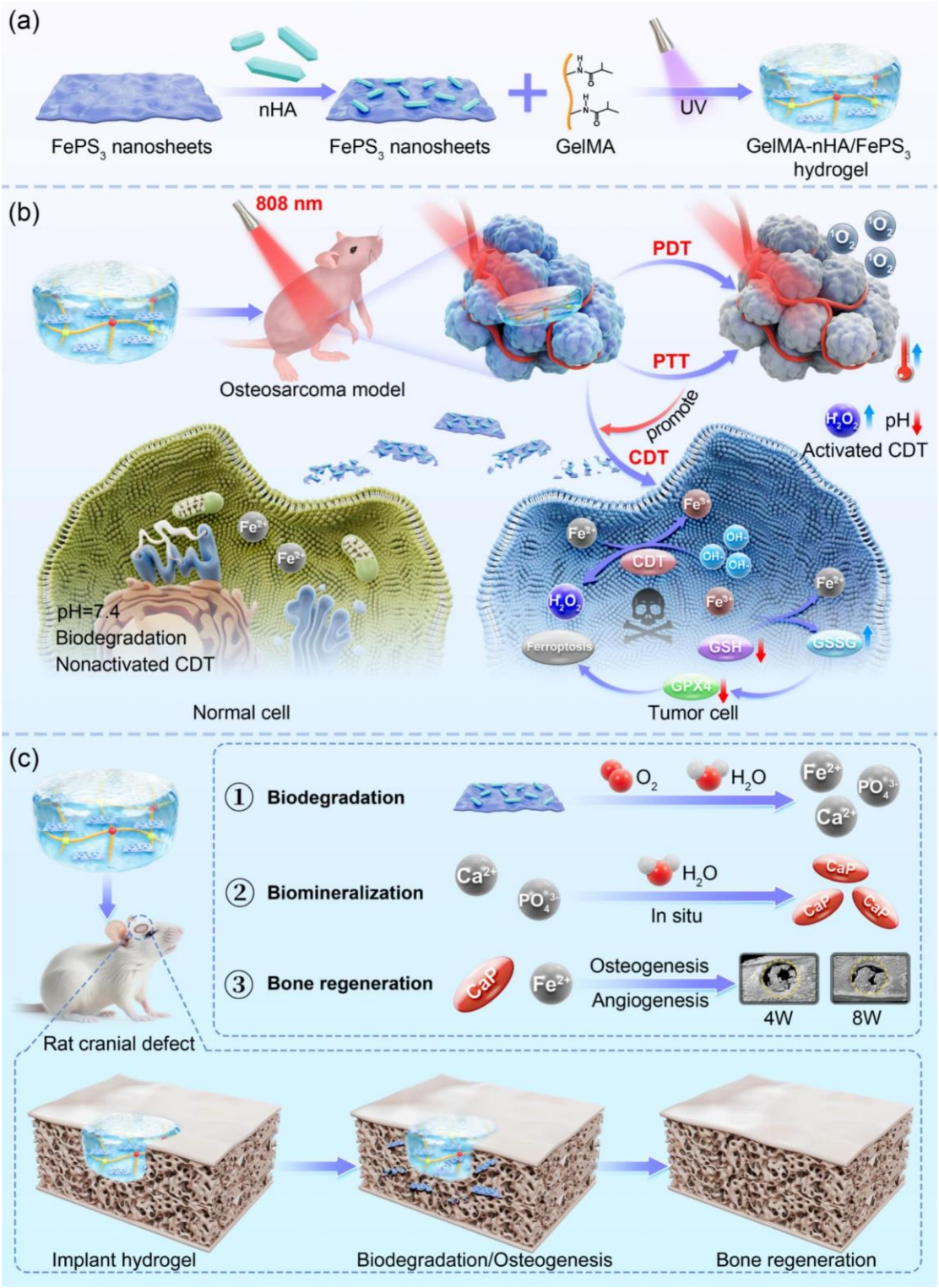

Figure 8. Schematic illustration of the GelMA-nHA/FePS3 multifunctional nanocomposite hydrogel as an "all in one" therapeutic platform for eradicating osteosarcoma and repairing bone defects. Reprinted with permission from Ye et al. [71] Copyright © 2025 Elsevier.

4.5. Externally Field-Regulated Hydrogel Systems: Magnetically Navigable Microrobots and Piezoelectric Energy-Transducing Depots for Osteosarcoma Control

Magnetically driven hydrogel systems represent a more exploratory but conceptually intriguing branch of targeted osteosarcoma therapy. Unlike stationary local depots, these systems seek to convert hydrogels into mobile, externally navigable carriers, typically in the form of gelatin-based microrobots fabricated by droplet microfluidics and loaded with magnetic particles and anticancer agents. The appeal of this approach is obvious. If microrobots can be guided with sufficient precision, they could in principle navigate to residual disease foci, release drugs locally, and improve intralesional targeting beyond what passive diffusion allows. In osteosarcoma, where drug resistance and irregular tumor geometry complicate treatment, such external control is highly attractive. Researchers used magnetically driven hydrogel microrobots to promote osteosarcoma chemotherapy through a synthetic lethality strategy, loading the carriers with doxorubicin and Ro-3306 and demonstrating directional motion, sustained release, and cytotoxicity *in vitro* under both 2D and 3D culture conditions[72]. Another study used a similar microrobotic architecture to enhance the efficacy of anlotinib in resistant osteosarcoma by co-delivering the MET inhibitor SCR1481B1[73]. The microrobots showed controllable motion under external magnetic fields, a peak speed of 3.5 μm/s, and effective drug release, again with strong in vitro killing of osteosarcoma cells under 2D and 3D culture conditions. Together, these studies establish the technical feasibility of using hydrogel microrobots as magnetically guided targeted delivery systems for osteosarcoma. At the same time, this category remains clearly pre-translational. The present studies are still dominated by proof-of-principle demonstrations of motion control and *in vitro* tumor killing, rather than convincing evidence in orthotopic postoperative models. That distinction matters. Navigation in a culture dish or simplified chamber is fundamentally different from navigation in a postoperative bone cavity filled with blood, fibrin, necrotic debris, uneven mineral surfaces, and rapidly changing interstitial forces. Moreover, clinical translation remains mostly unexplored at present.

A conceptually distinct extension of this field-driven logic is provided by piezoelectric hydrogel systems, which do not rely on external guidance to move the carrier, but instead use externally applied physical energy to activate therapeutic function after the material is already retained at the tumor site. In this sense, piezoelectric hydrogels differ fundamentally from magnetically navigated microrobots. The goal is not locomotion, but spatiotemporally controlled energy conversion. A particularly instructive example is the injectable biopolymer hydrogel reported by Xiao et al., which integrates ultrasmall Bi/$SrTiO_3$ nanoheterojunctions into a local hydrogel depot for combined anti-osteosarcoma therapy and bone regeneration (**Figure 9**)[74]. The Bi/$SrTiO_3$ nanoheterostructure couples the piezoelectric effect of $SrTiO_3$ with the surface plasmon resonance of bismuth, thereby promoting fast charge separation and markedly improving reactive oxygen species generation under combined near-infrared

irradiation and ultrasound. This study is important because it shows that "field-driven" hydrogel therapy need not mean physical transport of the carrier. Instead, the hydrogel can remain as a local depot while external stimuli dynamically switch on catalytic tumor killing. *In vivo*, the Bi/$SrTiO_3$-integrated hydrogel showed strong antitumor performance in both patient-derived xenograft and tibial osteosarcoma models, with reported tumor suppression rates of 98.6% and 67.6%, respectively, under the combined action of NIR and ultrasound. Mechanistically, this platform is therefore best understood not as a conventional photodynamic hydrogel, but as a piezo-photocatalytic local system in which ultrasound and light cooperate to amplify ROS-mediated tumor destruction beyond what traditional photosensitizers can typically achieve. Equally important, this platform preserves the dual-function logic that is especially valuable in osteosarcoma treatment. The injectable hydrogel had good filling and retention within the bone-defect region and could support bone repair by delivering piezoelectrically mediated electrical cues under mild ultrasound exposure. The osteogenic effect was linked to activation of the PI3K/AKT pathway, reinforcing the idea that piezoelectric hydrogels can serve not only as antitumor actuators but also as regenerative bioelectrical microenvironments. Conceptually, this work broadens the scope of field-driven osteosarcoma hydrogels beyond magnetic guidance alone.

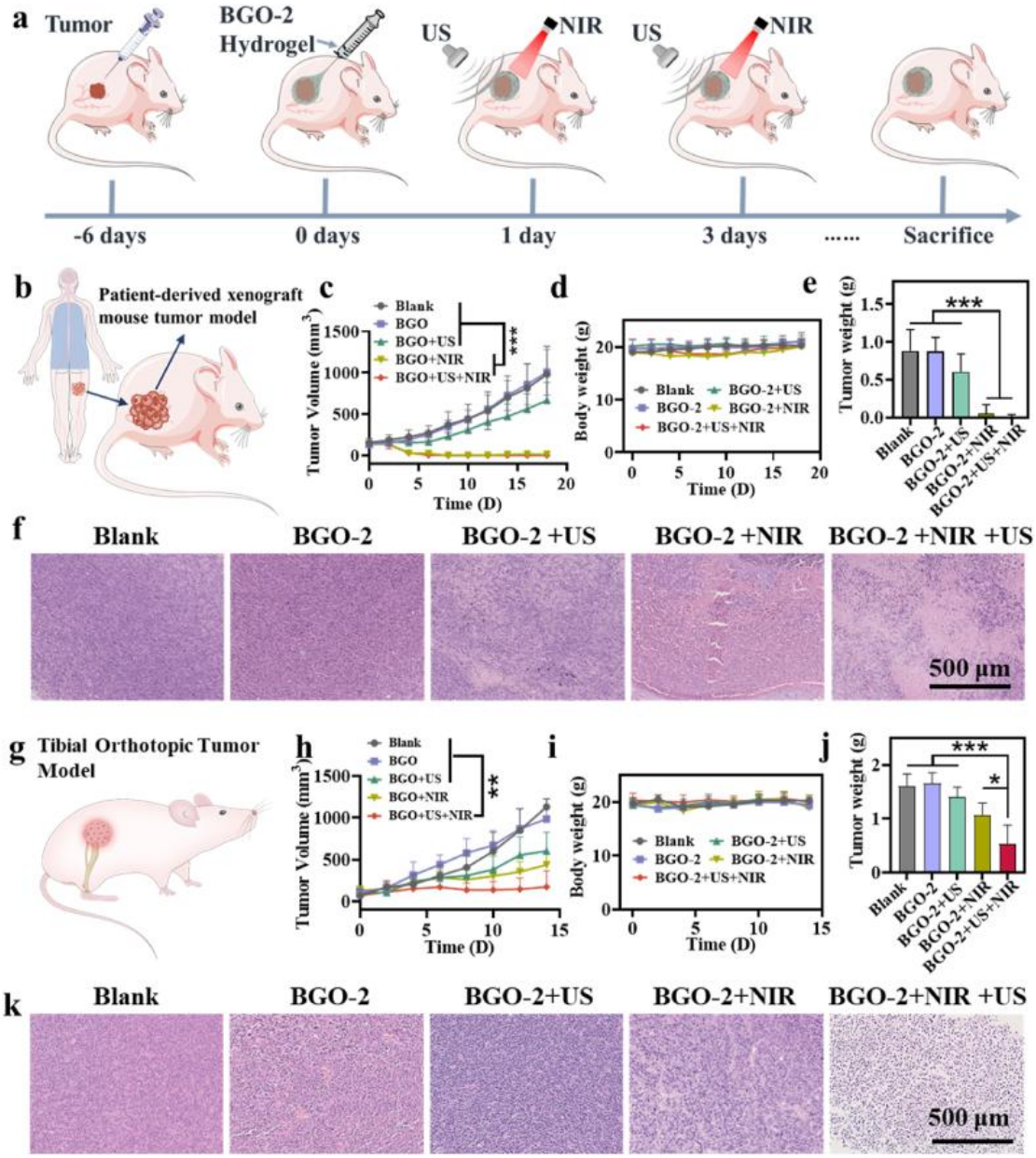

Figure 9. *In vivo* osteosarcoma therapy of different tumor models using BGO-2 hydrogels. (a) Schematic illustration of piezo-augmented photodynamic therapy in vivo. (b) Schema of the PDX tumor model in mice. (c) average tumor growth curves of the PDX tumor model mice (n = 3). (d) Time dependent body weights of the PDX tumor model mice (n = 3). (e) Average tumor weight of the PDX tumor model (n = 3). (f) Microscopy images of H&E stained PDX tumor slices. (g) Schematic of the tibia osteosarcoma model in mice. (h) Average tumor growth curves of the tibia osteosarcoma model mice (n = 3). (i) Time dependent body weights of the tibia osteosarcoma model mice (n = 3). (j) Average tumor weight of the tibia osteosarcoma model mice (n = 3). (k) Microscopy images of H&E stained tibia osteosarcoma slices. *p < 0.05, **p < 0.01, ***p < 0.001. Reprinted with permission from Xiao et al. [74] Copyright © 2024 KeAi.

Future externally controlled systems may diverge into at least two distinct classes, navigable carriers that improve targeting through motion, and stationary but stimulus-activatable depots that improve therapy through on-demand energy transduction. For osteosarcoma, the latter strategy may be especially attractive in the postoperative setting, where precise cavity retention is often more realistic than long-range intrabody navigation. Hydrogel design evolves from local drug depots into externally regulated or microenvironment-reprogramming therapeutic systems. The dominant trend is no longer simple payload combination, but functional sequencing: stromal normalization before immune activation, mild or multimodal photothermal catalysis instead of heat alone, and externally controlled magnetic or piezoelectric activation for more precise spatial or temporal control as summarized in **Table 2**.

Table 2. Chemoimmunotherapy/sonodynamic, photothermal, and magnetically/piezoelectric field-driven hydrogel-based strategies for osteosarcoma treatment.

Article	Classification	Material design	Key cargo	Main therapeutic mechanism	Bone-regeneration role	Main model	Comparative significance	Reference
Wang et al., *Adv Mater* (2024)	Chemoimmunotherapy and SDT	Injectable sequential nanocomposite hydrogel based on carboxymethyl chitosan / PEG network	Nox4 inhibitor + liposomal doxorubicin	Early CAF reprogramming and stromal loosening, followed by ICD-inducing chemotherapy; improves T-cell infiltration and synergizes with PD-1 blockade	Bone repair not the primary focus	Stroma-rich osteosarcoma models, including orthotopic setting	A representative microenvironment-sequencing platform: stromal normalization first, immune-competent killing second	63
Lin et al., *Bioact Mater* (2026)	Chemoimmunotherapy and SDT	Hydrogel co-delivering antifibrotic drug and nano-sonosensitizer	SIS3 + PCN-224@MnO2@HA	Antifibrotic reprogramming via TGF-β/SMAD3 inhibition plus MnO2-enhanced SDT through O2 generation and GSH depletion	Bone regeneration not central	In vivo osteosarcoma treatment with reported collagen reduction and tumor inhibition	Shows that SDT works better when stromal fibrosis is corrected simultaneously	64
Luo et al., *Adv Healthc*	Chemoimmunotherapy and SDT	Functionalized photoimmune hydrogel	Cypate + PD-L1-targeting PROTAC	"Inside-out" photoimmunotherapy:	Bone repair not emphasized	Local osteosarcoma immunotherapy proof-	Advances from checkpoint	65

Article	Classification	Material design	Key cargo	Main therapeutic mechanism	Bone-regeneration role	Main model	Comparative significance	Reference
Mater (2026)		microspheres fabricated via microfluidics/photocuring	(ppd) in CP-MOF nanoparticles	intracellular pyroptosis plus extracellular PD-L1 degradation		of-concept	blockade to localized checkpoint-protein degradation	
Wu et al., *Materials & Design* (2025)	Photothermal hydrogel	Nano-bio-coordination dynamic injectable hydrogel	CuS2 nanoparticles + thiolated osteogenic peptide + thiolated gelatin	NIR-triggered photothermal ablation of residual tumor cells	Sustained release of osteogenic peptide and trace Cu ions supports osteogenesis	In vivo postoperative antitumor and tibial repair evaluation	Illustrates dynamic-bonded PTT hydrogel where degradation, ablation, and repair are materially integrated	[68]
Yao et al., *Adv Funct Mater* (2024)	Photothermal hydrogel	Injectable sericin-based dual-ion-doped organic–inorganic hydrogel	Se/Mg co-doped HAp nanorods + PDA-coated CaO2 nanospheres	Mild PTT combined with selenium-associated antitumor activity and ion release	Strong regenerative outcome with complete bone repair reported	In vivo osteosarcoma-related bone defect model	A strong example of mild photothermal therapy designed to	[69]

Article	Classification	Material design	Key cargo	Main therapeutic mechanism	Bone-regeneration role	Main model	Comparative significance	Reference
					at later time points		preserve an osteogenic microenvironment	
Chen et al., *Biomater Sci* (2025)	Photothermal hydrogel	Theragenerative injectable bone-adhesive hydrogel based on silk fibroin/sericin and catechol-inspired chemistry	Photothermal component integrated into adhesive silk-based matrix	Local PTT plus strong tissue/bone adhesion and minimally invasive delivery	Explicitly designed for simultaneous bone repair	Injectable / adhesive theragenerative platform	Important because it treats bone adhesion as essential for stable photothermal treatment at defect surfaces	[70]
Ye et al., *Chem Eng J* (2025)	Photothermal hydrogel	GelMA-nHA multifunctional nanocomposite hydrogel	FePS3 nanosheets	Combined PTT, PDT, CDT, and ferroptosis via Fe-mediated GSH depletion and GPX4 inactivation	Continuous Ca/P release supports biomineralization and osteogenesis	Multifunctional in vivo osteosarcoma/bone repair platform	Represents a shift from simple heating to an “all-in-one catalytic microreactor”	[71]

Article	Classification	Material design	Key cargo	Main therapeutic mechanism	Bone-regeneration role	Main model	Comparative significance	Reference
Tao et al., *Front Chem* (2024)	Magnetically/piezoelectric field driven hydrogel	Magnetic gelatin-based hydrogel microrobots fabricated by droplet microfluidics	Doxorubicin + Ro-3306 + magnetic particles	External magnetic guidance for targeted delivery; synthetic lethality-based chemotherapy	No bone-regenerative function reported	In vitro 2D/3D osteosarcoma models	Establishes feasibility of magnetically guided hydrogel microrobots for targeted osteosarcoma chemotherapy	[72]
Wang et al., *Front Bioeng Biotechnol* (2024)	Magnetically/piezoelectric field driven hydrogel	Magnetically driven hydrogel microrobots	Anlotinib + MET inhibitor SCR1481B1 + magnetic particles	Magnetically controlled motion with co-delivery to overcome anlotinib resistance	No regenerative function reported	In vitro 2D/3D resistant osteosarcoma models	Extends microrobot logic toward drug-resistance reversal rather than only passive drug delivery	[73]
Xiao et al., *Bioact Mater*	Magnetically/piezoelectric field driven hydrogel	Injectable biopolymer hydrogel integrating Bi/SrTiO3	Bi/SrTiO3 piezo-photocatalytic nanoheterojunctions	NIR + ultrasound trigger enhanced charge separation and ROS generation for	Promotes osteogenesis via bioelectrical	PDX and tibial osteosarcoma models	Distinct from magnetic systems because	[74]

Article	Classification	Material design	Key cargo	Main therapeutic mechanism	Bone-regeneration role	Main model	Comparative significance	Reference
(2024)		nanoheterojunctions		piezo-photocatalytic tumor killing	cues and PI3K/AKT activation		it uses stationary, stimulus-activatable energy transduction rather than locomotion	

5. Challenges and future perspectives

Despite the rapid progress of hydrogel-based osteosarcoma therapy, several barriers still limit clinical translation. First, many current platforms remain validated primarily in simplified *in vitro* systems or small-animal models, whereas the real postoperative osteosarcoma cavity is mechanically unstable, blood-filled, immunologically dynamic, and spatially irregular. This gap means that future studies should place greater emphasis on clinically relevant orthotopic, postresection, and load-bearing models, together with standardized preclinical evaluation of implantation strategy, device performance, safety, and outcome measures. Second, the field still faces a difficult materials-engineering balance between therapeutic complexity and translational practicality. Multifunctional hydrogels are increasingly expected to combine controlled release, immune modulation, tumor ablation, and bone regeneration, but greater complexity often creates new problems in reproducibility, material characterization, large-scale production, sterilization, and regulatory approval[75]. These issues are not peripheral. They are central determinants of whether a promising laboratory construct can become a clinically usable product. Third, more attention is needed to treatment precision *in vivo*. For stimulus-responsive systems, including ultrasound-, magnetic-, or light-activated hydrogels, clinical success will depend on reliable control of field strength, penetration depth, spatial selectivity, and treatment timing in irregular bone defects[76]. At the same time, antitumor efficacy must be balanced against preservation of osteoprogenitor cells, marrow function, angiogenesis, and long-term osseointegration. Future hydrogel design should therefore move toward quantitatively programmable systems whose degradation, cargo release, and bioactivity are aligned with the sequential biology of osteosarcoma surgery, immune remodeling, and bone healing. Looking ahead, the most promising direction is likely not simply "more multifunctionality," but better integration of material design with clinical workflow. Hydrogel platforms that are surgically compatible, manufacturable, sterilizable, mechanically appropriate, and testable in rigorous translational models will be more valuable than highly elaborate systems that remain difficult to reproduce. In this sense, the future of the field lies in converting hydrogels from elegant proof-of-concept biomaterials into robust postoperative therapeutic systems that can coordinate local tumor control, tumor microenvironment reprogramming, and functional bone regeneration in a clinically actionable manner.

5.1. Sterilization, quality assurance, and regulatory considerations

Sterilization should be considered an integral design constraint rather than a downstream manufacturing step for hydrogel-based osteosarcoma platforms. Terminal sterilization methods, including gamma irradiation, electron-beam irradiation, and ethylene oxide treatment, may alter hydrogel network structure, crosslinking density, swelling behavior, degradation, mechanical properties, drug-release kinetics, and the activity of incorporated nanoparticles or therapeutic cargos. These effects may be particularly relevant for multifunctional systems containing chemotherapeutics, proteins, nucleic acids, photothermal

agents, catalytic nanomaterials, or bioactive ions. Therefore, sterilization compatibility should be evaluated together with post-sterilization rheology, mechanical performance, cargo stability, release behavior, cytocompatibility, and antitumor and osteogenic activity. For cell-laden bioprinted constructs or systems containing highly labile biological cargos, aseptic processing may be more appropriate than terminal sterilization. However, this strategy requires strict control of raw materials, printing conditions, crosslinking procedures, packaging, storage, and batch-to-batch reproducibility. In particular, patient-specific constructs may create additional manufacturing challenges because individualized geometry and limited production scale can complicate conventional quality-control and sterility-assurance procedures. Regulatory classification will depend on the composition, primary mode of action, and intended clinical use of each platform. A printed scaffold designed primarily to restore structural function may be evaluated as a medical device, whereas a hydrogel that delivers chemotherapeutic drugs, biologics, nucleic acids, or active nanomaterials may be considered a drug–device combination product. Cell-laden bioprinted constructs may require further evaluation as advanced combination products because of their biological and regenerative functions. Consequently, product classification, sterility assurance, manufacturing reproducibility, release specifications, storage stability, and surgical workflow compatibility should be incorporated early in platform development. These considerations are essential for converting multifunctional hydrogel systems from laboratory prototypes into clinically translatable postoperative osteosarcoma therapies.

5.2. Scaling from murine studies to large-animal models

Most hydrogel-based osteosarcoma platforms have been evaluated in murine models, which remain valuable for screening local tumor control, release behavior, immune responses, and preliminary biosafety. However, these systems have important limitations for postoperative reconstruction. Murine models cannot adequately reproduce the defect dimensions, mechanical loading, fixation requirements, marrow environment, surgical workflow, and long-term osseointegration relevant to large human osteosarcoma defects. This limitation is particularly important for bioprinted constructs and scaffold–hydrogel hybrids intended for segmental or weight-bearing reconstruction. Accordingly, translational development should follow a stepwise model-selection strategy. After proof-of-concept validation in murine orthotopic or postresection models, promising platforms should be evaluated in larger animals according to their intended clinical function. Rabbit models can provide an intermediate stage for assessing critical-sized defects, implant fixation, bone ingrowth, degradation, and osseointegration. Canine models may provide additional relevance for osteosarcoma biology and postoperative treatment because spontaneous canine osteosarcoma shares several clinical and biological features with the human disease. Porcine models may be particularly useful for evaluating patient-specific implants, surgical handling, load transfer, construct–bone integration, and the feasibility of reconstructing defects at a clinically relevant anatomical scale. Large-animal studies should evaluate more than

radiographic bone formation or short-term tumor suppression. Essential endpoints include local recurrence, metastatic progression, implant stability, mechanical performance under physiological loading, degradation kinetics, host immune response, marrow safety, long-term osseointegration, and functional recovery. In addition, studies should assess whether treatment delivery, external stimulation, fixation, and construct placement remain feasible within a realistic surgical workflow. Such validation is necessary to determine whether hydrogel-based systems can preserve local antitumor efficacy while providing safe and durable reconstruction of load-bearing postoperative defects.

5.3. Safety considerations for field-regulated hydrogel systems and oncological safety

Field-regulated hydrogel systems, including magnetic, piezoelectric, ultrasound-responsive, and photothermal platforms, offer attractive spatiotemporal control for postoperative osteosarcoma therapy. However, external-field activation is not intrinsically tumor-specific. In the postoperative bone cavity, the hydrogel is surrounded by marrow, cortical bone, periosteal tissue, vasculature, nerves, immune cells, and regenerating osteogenic cells. Therefore, the same physical stimulus used to activate tumor killing may also affect adjacent normal tissues. For magnetic hydrogel microrobots, key risks include incomplete localization, unintended migration, off-target drug deposition, persistent magnetic-particle retention, and difficulty controlling movement in a complex postoperative cavity containing blood, fibrin, necrotic debris, irregular mineral surfaces, and changing interstitial forces. These issues are particularly important because current magnetic microrobot studies remain largely proof-of-concept and have not yet fully demonstrated safe navigation, retention, clearance, and antitumor efficacy in clinically relevant postresection bone defects. For piezoelectric and ultrasound-activated hydrogels, potential safety concerns include nonselective reactive oxygen species generation, local heating, acoustic cavitation, mechanical disruption of fragile regenerating tissue, and unintended effects on marrow cells, vascular endothelium, and osteoprogenitor cells. Although bioelectrical stimulation may support osteogenesis under controlled conditions, excessive or poorly localized stimulation could disturb the balance among tumor killing, inflammation resolution, angiogenesis, and bone remodeling. For photothermal hydrogels, thermal dose control is essential. Excessive heating or heterogeneous heat distribution may damage surrounding bone marrow, periosteal vasculature, osteoprogenitor cells, peripheral nerves, or newly forming bone. Mild photothermal therapy may be more compatible with tissue repair than high-temperature ablation, but its safety depends on precise control of irradiation intensity, exposure duration, penetration depth, heat dissipation, and local material distribution. Future studies should therefore evaluate field-regulated systems using safety endpoints that extend beyond tumor suppression and gross body-weight monitoring. An important challenge in the design of osteosarcoma-related regenerative constructs is the potential conflict between bone regeneration and oncological safety. Bioactive factors that enhance osteogenesis, angiogenesis, or immune-mediated tissue repair may also affect residual tumor cells or the

postoperative tumor microenvironment. Activation of growth-factor, vascular, or immunoregulatory pathways may support osseous regeneration while simultaneously promoting tumor-cell survival, vascularization, invasion, immune escape, or therapeutic resistance. Importantly, pro-regenerative signaling is not necessarily oncologically neutral. In osteosarcoma models, BMP-2 has shown context-dependent effects and may promote residual tumor growth, motility, and invasion[77]. Kendal et al. further found that BMP-2 increased local tumor growth in some osteosarcoma cell-line and murine models, although the effect differed among cell lines[78]. The authors therefore warned that BMP-2 could stimulate microscopic residual disease in susceptible tumors. Therefore, regenerative performance alone is insufficient to establish the suitability of a bioprinted construct for post-resection osteosarcoma repair. The effects of each bioactive component on residual osteosarcoma cells should be evaluated directly, preferably in tumor–bone co-culture systems, residual-disease models, and orthotopic models assessing local recurrence and pulmonary metastasis.

5.4. Degradation products and long-term biocompatibility

Long-term biocompatibility is a critical but insufficiently investigated issue for multifunctional osteosarcoma hydrogels. In postoperative reconstruction, degradation is not simply the disappearance of the hydrogel matrix. It determines the duration of local mechanical support, therapeutic retention, tissue infiltration, and exposure of the surrounding bone microenvironment to released drugs, ions, nanoparticles, and polymer fragments. Degradation that is too rapid may cause premature loss of local tumor control or structural support, whereas persistent materials or poorly cleared residues may impair bone remodeling, provoke chronic inflammation, or interfere with osseointegration. Future studies should therefore evaluate degradation kinetics together with the fate of all active components rather than assessing hydrogel mass loss alone. Relevant analyses should include changes in swelling, mechanical integrity, crosslink density, drug-release behavior, ion or nanoparticle release, and degradation under physiologically relevant inflammatory, acidic, and enzyme-rich conditions. In vivo studies should further assess local tissue responses, marrow function, osteogenesis, angiogenesis, osteoclast activity, chronic inflammation, systemic biodistribution, clearance pathways, and histological changes in major organs over extended follow-up periods. For materials intended for load-bearing reconstruction, evaluation should extend to long-term osseointegration, mechanical stability, bone remodeling, and functional recovery. Large-animal studies may be particularly important for determining whether degradation products remain confined to the defect site or redistribute during prolonged remodeling. Ultimately, clinically translatable hydrogel systems should be designed with predictable degradation profiles, controllable release of active components, and demonstrable clearance or long-term tolerance of all material residues.

6. Conclusion

Hydrogel-based platforms offer a promising approach to postoperative osteosarcoma management because they can potentially combine local tumor control with defect-directed

bone repair. Among the emerging strategies, spatially and temporally programmed hydrogels, multimodal local therapeutic systems, and bioprinted or scaffold–hydrogel hybrid constructs appear particularly valuable. These platforms may enable early delivery of antitumor agents within the tumor-facing region, followed by a more permissive regenerative phase that supports bone formation, vascular integration, and restoration of mechanical function. However, the central challenge is not merely to combine anticancer and osteogenic components within one material. Postoperative osteosarcoma reconstruction requires a careful balance between tumor eradication and regeneration. Signals that promote osteogenesis, angiogenesis, immune activation, cell recruitment, or matrix remodeling may have complex effects in a residual tumor-associated microenvironment. Therefore, future systems should prioritize oncologic safety through controlled local retention, staged release, spatial compartmentalization, and rigorous assessment of residual tumor-cell behavior, local recurrence, and metastatic potential. Most current studies remain preclinical and are commonly evaluated in simplified animal models that may not adequately reproduce the surgical margins, residual disease burden, immune environment, mechanical loading, and metastatic risk encountered in clinical osteosarcoma. Translation will require standardized and clinically relevant postoperative models, long-term biosafety assessment, predictable degradation and release kinetics, sufficient mechanical competence for load-bearing defects, reproducible manufacturing, sterilization compatibility, and feasible integration into surgical workflows. Overall, the most realistic clinical direction may be an integrated and staged construct in which local antitumor therapy is delivered during the early postoperative period, while regenerative and structural functions are progressively activated after adequate tumor control. Addressing these biological, engineering, and regulatory requirements will determine whether hydrogel-based systems can progress from promising experimental platforms to clinically useful strategies for function-preserving osteosarcoma reconstruction.

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Conflict of interest

The authors declare no conflicts of interest related to this work.

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