

Review

Tissue Resilience in Radiation-Induced Injury: A Hypothesis-Generating Review of Heat Shock Protein 27 in Osteoradionecrosis of the Jaw

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Simple Summary

Osteoradionecrosis of the jaw (ORNJ) is one of the most serious long-term complications of radiotherapy for head and neck cancer. It develops through a complex interaction of reduced blood supply, chronic inflammation, oxidative stress, fibrosis, and impaired bone healing. Despite advances in radiotherapy techniques, ORNJ continues to cause substantial morbidity and negatively affects quality of life. Heat shock protein 27 (HSP27) is a stress-response protein that regulates several biological processes involved in tissue protection, including antioxidant defense, endothelial survival, apoptosis control, fibrosis modulation, immune regulation, and bone remodeling. These functions closely overlap with the key mechanisms implicated in ORNJ pathogenesis. However, no studies have directly investigated the role of HSP27 in ORNJ. This review summarizes current knowledge on ORNJ biology, examines the potential mechanistic links between HSP27 and radiation-induced tissue injury, and highlights future research opportunities. Understanding the role of HSP27 may improve risk stratification, biomarker development, and the design of targeted preventive or therapeutic strategies for ORNJ.

Abstract

Osteoradionecrosis of the jaw (ORNJ) remains one of the most severe late complications of head and neck radiotherapy. Current evidence suggests that ORNJ is a progressive and biologically heterogeneous disorder driven by microvascular injury, chronic hypoxia, oxidative stress, fibro-atrophic remodeling, impaired bone turnover, immune dysregulation, and systemic susceptibility factors. Within this complex pathogenic network, heat shock protein 27 (HSP27) emerges as a biologically plausible but unexplored mediator. HSP27 regulates multiple stress-response pathways, including redox homeostasis, cytoskeletal stabilization, endothelial protection, apoptosis control, fibroblast activation, and osteoblast–osteoclast function, all of which overlap with key mechanisms implicated in ORNJ. However, no studies have directly investigated HSP27 expression, activation, or functional significance in irradiated mandibular tissues or ORNJ-specific cohorts. This review summarizes current knowledge of ORNJ pathobiology, examines potential mechanistic links with HSP27,



Academic Editor: Gabriele Multhoff

Received: 13 June 2026

Revised: 1 July 2026

Accepted: 3 July 2026

Published: 6 July 2026

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and outlines future research priorities involving biomarker development, tissue-level characterization, preclinical modeling, and therapeutic targeting. Integrating HSP27 into ORNJ research may improve understanding of pathogenesis, risk stratification, and the development of novel preventive and therapeutic strategies.

Keywords: osteoradionecrosis; heat-shock proteins; HSP27 heat-shock proteins; head and neck neoplasms/radiotherapy; jaw diseases; cellular stress response

1. Introduction

Osteoradionecrosis of the jaw (ORNJ) remains one of the most debilitating late complications of radiotherapy (RT) for head and neck cancers (HNCs) [1]. Although advances such as intensity-modulated RT (IMRT), adaptive planning, and improved supportive care have reduced high-dose exposure to mandibular structures, ORNJ continues to significantly affect long-term survivors [2,3]. Clinically, it is defined by chronically exposed, non-healing, devitalized bone persisting for at least three months, often accompanied by pain, infection, fistulae, trismus, and pathologic fracture. For many patients, ORNJ represents the most functionally disruptive morbidity of otherwise curative cancer therapy.

1.1. Historical Perspective and Evolving Paradigms

The classical model proposed by Marx—characterized by hypoxia, hypovascularity, and hypocellularity—remains foundational in understanding ORNJ [4]. RT-induced endothelial injury and progressive endarteritis lead to chronic ischemia and diminished healing capacity, predisposing irradiated bone to necrosis after even minor trauma. However, this ischemic framework does not fully explain modern clinical observations. ORNJ may occur many years after RT, sometimes without overt triggers, and patients receiving comparable radiation doses show striking variability in susceptibility [2,5,6]. Such discrepancies indicate that additional biological mechanisms beyond ischemia contribute to disease evolution.

1.2. The Contemporary Fibro-Atrophic Model

Current evidence supports a more integrated fibro-atrophic model in which ORNJ reflects a chronic, dysregulated wound-healing disorder [3]. Ionizing radiation initiates microvascular injury, endothelial apoptosis, impaired nitric oxide signaling, and progressive vessel loss [4]. These changes result in sustained tissue hypoxia and decreased regenerative capacity.

Simultaneously, RT disrupts bone cellular dynamics. Osteocytes—critical mechanosensors—are highly radiosensitive, and their loss limits the bone's ability to initiate remodeling [7]. Osteoblast proliferation, matrix synthesis, and responsiveness to growth factors decline, while osteoclast activity becomes dysregulated [8]. The consequence is a metabolically compromised, structurally fragile bone microenvironment.

Soft tissues undergo parallel injury. Radiation induces fibroblast senescence and drives TGF- β -mediated deposition of dense, disorganized collagen [9]. This fibrotic envelope restricts vascular supply and impairs metabolic exchange, mirroring radiation-induced fibrosis in other organs such as the lung and skin [10].

Chronic inflammation further amplifies this cascade. Periodontal disease, dysbiosis, and mucosal breakdown promote ongoing inflammatory stimulation [11]. Pro-inflammatory mediators such as IL-1 β , TNF- α , and reactive oxygen species (ROS) perpetuate tissue injury, disrupt ECM turnover, and delay healing [12,13]. The convergence of

vascular compromise, fibrotic remodeling, altered bone biology, and persistent inflammation yields the non-healing, progressively destructive lesion characteristic of ORNJ.

1.3. Variability in Clinical Expression and Biological Susceptibility

ORNJ displays broad clinical heterogeneity: some patients maintain stable, superficial lesions for years, whereas others progress rapidly to deep necrosis, fistulae, or fracture. Although radiation dose distribution remains a core predictor of risk, biological susceptibility is increasingly recognized as a key factor. Variations in vascular reserve, immune tone, microbiome composition, nutritional status, and systemic inflammation likely modify disease trajectory. For example, host inflammatory indices such as CARWL may reflect predisposition to exaggerated fibro-inflammatory responses [14]. These inter-individual differences underscore the need for molecular biomarkers that can identify at-risk patients before clinical onset.

1.4. Stress-Response Pathways: A Missing Link in ORNJ Biology?

Despite extensive study of vascular, inflammatory, and fibrotic mechanisms, stress-response pathways—especially the heat shock proteins (HSPs)—have not been adequately explored in ORNJ pathogenesis. HSP27, a small, highly conserved chaperone, is strongly induced by ionizing radiation, oxidative stress, cytokines, and mechanical injury [15]. It regulates many processes central to ORNJ biology: endothelial protection and angiogenic signaling, inhibition of apoptosis, modulation of oxidative stress, fibroblast activation, matrix remodeling, and osteoblast and osteoclast function.

Strikingly, these functions align with the principal domains of ORNJ pathophysiology. Yet no studies have directly evaluated HSP27 expression or activity in osteoradionecrosis tissues, nor its potential as a biomarker of susceptibility. A focused investigation of HSP27 is therefore warranted—not because evidence is established, but because its known biological roles map precisely onto the unresolved mechanistic gaps in ORNJ research. Exploring these intersections may generate new hypotheses, refine pathogenetic models, and ultimately guide the development of predictive biomarkers and therapeutic interventions for this complex, multifactorial complication, providing a rationale for examining HSP27 within the broader framework of radiation-induced cellular stress responses in ORNJ. Because direct studies examining HSP27 in osteoradionecrosis are currently lacking, the following sections emphasize mechanistic parallels between established HSP27 biology and the principal pathogenic domains of ORNJ, thereby outlining a framework for generating testable hypotheses for future investigation.

The unique contribution of this review is not the simple identification of HSP27 as an unexplored molecule in ORNJ, but the development of a mandibular tissue–resilience framework that integrates microvascular injury, oxidative stress, fibro-atrophic remodeling, immune dysregulation, and bone-cell dysfunction with HSP27-regulated stress-response biology. Unlike general HSP27 reviews, this review focuses specifically on how HSP27-related pathways may interact with the distinctive biological constraints of irradiated mandibular tissues. Unlike conventional ORNJ reviews, it shifts attention from established clinical and dosimetric risk factors toward molecular stress-response capacity as a potential determinant of interindividual susceptibility, disease progression, and therapeutic responsiveness.

Recently, we reviewed the broader concept of tissue resilience and stress-response pathways in radiation-induced normal tissue injury [16]. In contrast, the present review focuses specifically on HSP27 in the context of ORNJ, with emphasis on mandibular microenvironmental specificity, the temporal duality of HSP27 signaling, testable mechanistic hypotheses, and translational implications for biomarker development and therapeutic targeting.

Key Points

- Osteoradionecrosis of the jaw (ORNJ) remains a clinically significant complication of head and neck radiotherapy despite advances in modern treatment techniques.
- Radiation dose distribution alone does not fully explain the marked interindividual variability observed in susceptibility to ORNJ.
- Intrinsic cellular stress-response systems play important roles in determining tissue resilience following irradiation.
- Heat shock protein 27 (HSP27) regulates multiple biological pathways implicated in radiation-induced tissue injury, including oxidative stress responses, endothelial integrity, cytoskeletal stability, and fibrotic signaling.
- This review proposes a cellular stress-response resilience model in which HSP27 may modulate the balance between adaptive tissue repair and progression toward osteoradionecrosis.
- Elucidating the role of HSP27 in radiation-induced mandibular injury may enhance mechanistic understanding and support the development of biomarkers and targeted therapeutic strategies.
- Stress-response resilience may represent a broader biological principle influencing susceptibility to diverse radiation-induced tissue injuries

2. Pathophysiology of Osteoradionecrosis of the Jaw: From Radiation Injury to Chronic Tissue Failure

ORNJ results from a multifactorial interplay of radiation-induced tissue injury, dysregulated wound healing, altered bone metabolism, and chronic inflammation. Although early descriptions emphasized hypoxia, hypovascularity, and hypocellularity, contemporary evidence reveals a far more dynamic and self-perpetuating process. Microvascular compromise, fibroblast dysfunction, oxidative stress, immune dysregulation, and systemic susceptibility factors evolve over months to years, ultimately driving progressive and often irreversible mandibular tissue failure [1–6]. To contextualize this multifactorial disease process, Figure 1 provides an integrated visual summary of the contemporary fibro-atrophic model.

Table 1. Core Pathogenic Domains in Osteoradionecrosis of the Jaw (ORNJ) and Mechanistic Intersections with HSP27.

Core Pathogenic Domain in ORNJ	Radiation-Induced Biological Alterations	Established Mediators and Biological Features	Mechanistically Plausible HSP27 Functions Relevant to ORNJ	Representative References
Microvascular injury and chronic hypoxia	Endothelial apoptosis; capillary rarefaction; impaired nitric-oxide signaling; progressive tissue hypoperfusion	Marx “3H” concept (hypoxia–hypovascularity–hypocellularity); endothelial dysfunction; impaired angiogenesis	Preserves endothelial viability; stabilizes actin cytoskeleton; supports nitric-oxide signaling; attenuates oxidative–inflammatory endothelial injury and preserves microvascular integrity	[3–5,17]
Oxidative stress and redox imbalance	Persistent ROS accumulation; mitochondrial dysfunction; depletion of antioxidant defenses	Chronic oxidative injury; inflammatory activation; associations with systemic inflammatory–nutritional indices (CAR/WL, PINI, GINI)	Buffers intracellular ROS; stabilizes mitochondrial function; modulates cellular redox balance; may reduce oxidative–inflammatory stress within irradiated tissues	[8–10,18]
Fibroblast senescence and fibro-atrophic remodeling	Fibroblast senescence; SASP activation; excessive collagen deposition; soft-tissue stiffening	TGF-β1–driven fibrosis; chronic fibro-atrophic remodeling of gingiva, mucosa, and periodontium	Regulates actin cytoskeleton dynamics; modulates TGF-β–dependent myofibroblast activation; influences extracellular matrix remodeling and fibrotic signaling pathways	[9,19]

Table 1. Cont.

Core Pathogenic Domain in ORNJ	Radiation-Induced Biological Alterations	Established Mediators and Biological Features	Mechanistically Plausible HSP27 Functions Relevant to ORNJ	Representative References
Disrupted bone remodeling and osteocellular dysfunction	Osteocyte apoptosis; reduced osteoblast proliferation; altered matrix synthesis; dysregulated osteoclast activity	Impaired bone turnover; microarchitectural deterioration; imbalance between bone formation and resorption	Protects osteoblasts from oxidative injury; regulates osteoclast cytoskeletal organization and resorptive activity; may influence skeletal responses to irradiation	[7,20,21]
Immune-inflammatory dysregulation	Macrophage dysfunction; impaired phagocytosis; persistent low-grade inflammation	Chronic ROS generation; cytokine release (IL-1 β , TNF- α , IL-6); sustained inflammatory signaling loops	Modulates NF- κ B-dependent inflammatory signaling; influences macrophage phenotype and cytokine responses; regulates inflammatory activation thresholds	[22,23]
Oral microbiome disruption and mucosal barrier injury	Radiation-induced dysbiosis; reduced salivary flow; mucosal epithelial injury; increased microbial colonization	Polymicrobial disruption of host-microbiome equilibrium; secondary infections at sites of mandibular vulnerability	May contribute indirectly to epithelial barrier stabilization and mucosal immune regulation, potentially influencing inflammatory tone in irradiated tissues	[11,24]
Host systemic susceptibility	Anemia, malnutrition, systemic inflammation, metabolic comorbidities, vascular fragility	Elevated systemic inflammatory-nutritional indices (CAR/WL, PINI, GINI, SIS) associated with radiation-related toxicities	Functions as a cellular stress-response hub integrating oxidative, inflammatory, and metabolic signals, potentially linking systemic physiological stress to local tissue vulnerability	[14,25]

Abbreviations: CAR/WL, C-reactive protein-to-albumin ratio with weight loss; GINI, Global Immune-Nutrition Index; HSP27, heat shock protein 27; ORNJ, osteoradionecrosis of the jaw; PINI, prognostic inflammatory-nutritional index; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SIS, systemic inflammation score; TGF- β 1, transforming growth factor- β 1.

2.1. Mechanistic Foundations of ORNJ

ORNJ develops through a dynamic, self-perpetuating biological process involving microvascular compromise, fibroblast dysfunction, oxidative stress, and immune dysregulation [1–6]. These mechanisms evolve over months to years and collectively create a biological environment prone to chronic tissue breakdown. Understanding each component clarifies ORNJ biology and provides the foundation for evaluating molecular modulators such as HSP27. The principal pathogenic domains implicated in ORNJ and their mechanistic intersections with HSP27 biology are summarized in Table 1, providing a structured framework that bridges the conceptual overview presented in the graphical abstract with the molecular interactions illustrated in Figure 2.

2.1.1. Microvascular Injury and Endothelial Dysfunction

Endothelial cells are highly radiosensitive. Ionizing radiation induces oxidative stress, DNA damage, and apoptosis, leading to capillary rarefaction and progressive endarteritis obliterans [3,4]. The resulting chronic hypoperfusion impairs osteoblast function, collagen maturation, and progenitor cell recruitment [7]. This microvascular injury is widely regarded as the initiating event that triggers the downstream fibro-atrophic and inflammatory cascades characteristic of ORNJ.

2.1.2. Oxidative Stress and Redox Imbalance

Radiation generates an acute ROS burst followed by chronic oxidative stress driven by mitochondrial dysfunction, cytokine-induced NADPH oxidase activity, and glutathione depletion [8–10]. Persistent redox imbalance promotes lipid peroxidation, protein misfolding, genomic injury, NF- κ B/AP-1 activation, TGF- β 1 stabilization, fibroblast-to-myofibroblast transition, excessive ECM deposition, and premature senescence in endothelial, stromal, and osteogenic cells [9,10]. These processes collectively impair angiogenesis, bone remodeling, and tissue repair. HSP27 is relevant to this context because it regulates responses

to oxidative stress, cytoskeletal stability, mitochondrial integrity, and apoptotic signaling [15,17]. Although direct ORNJ-specific evidence is lacking, dysregulated HSP27 activity may plausibly contribute to maladaptive fibrosis, impaired turnover, and non-healing tissue states.

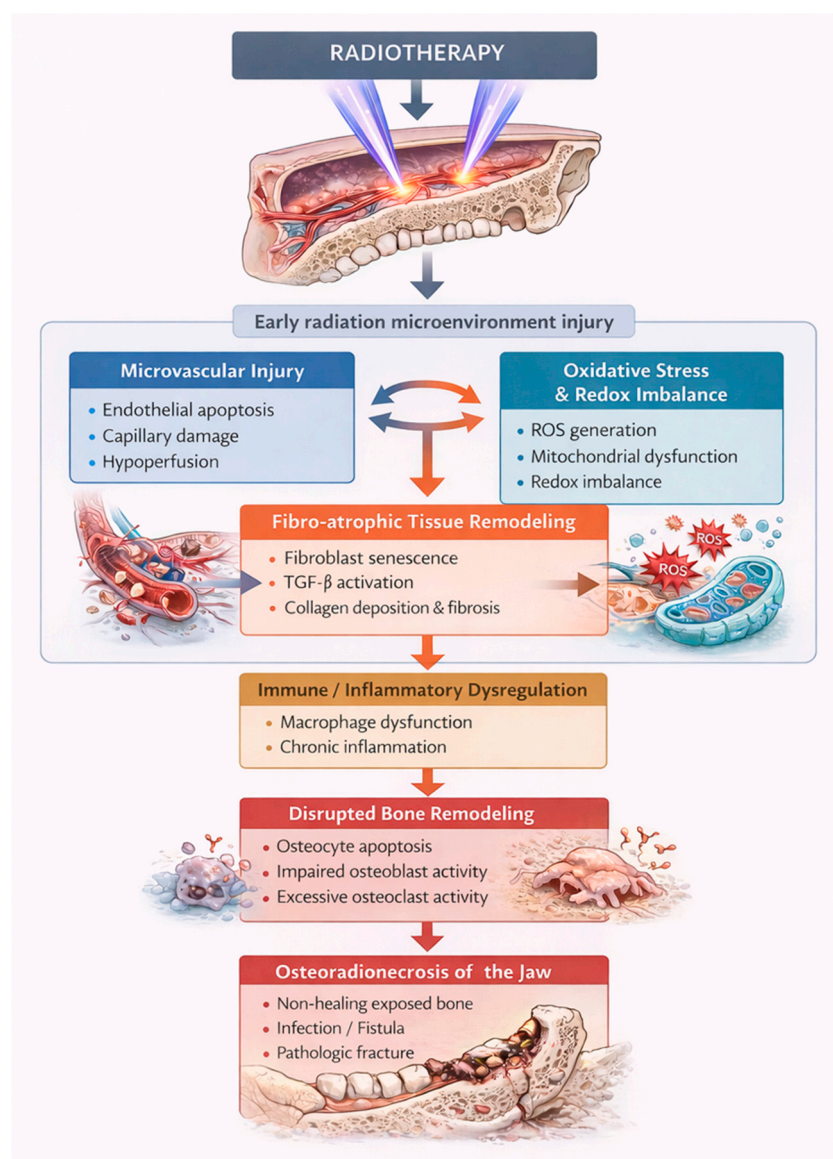


Figure 1. Radiation-induced fibro-atrophic pathogenesis of osteoradionecrosis of the jaw (ORNJ). Note: Radiotherapy initiates endothelial injury and persistent oxidative stress within mandibular tissues, producing progressive microvascular compromise and redox imbalance. These early insults promote fibroblast senescence and transforming growth factor- β (TGF- β)–mediated fibro-atrophic remodeling characterized by collagen deposition and tissue fibrosis. Immune dysregulation and chronic inflammatory signaling further amplify tissue injury and impair normal repair mechanisms. Progressive disruption of osteocyte viability, osteoblast activity, and osteoclast regulation ultimately leads to failure of normal bone remodeling and structural instability of mandibular bone, culminating in osteoradionecrosis. The principal pathogenic domains illustrated correspond to the mechanistic framework summarized in Table 1.

2.1.3. Fibroblast Senescence, TGF- β Activation, and Fibro-Atrophic Progression

A sufficient radiation dose drives fibroblasts toward senescent or parasenescent phenotypes with diminished proliferation, aberrant ECM production, and heightened TGF- β 1 responsiveness [9,19]. These cells exhibit SASP activity, perpetuating matrix disorgani-

zation, ROS production, and cytokine release. The accumulating fibro-atrophic tissue becomes stiff, hypometabolic, and poorly regenerative, leaving the mandible vulnerable to even minor trauma or infection.

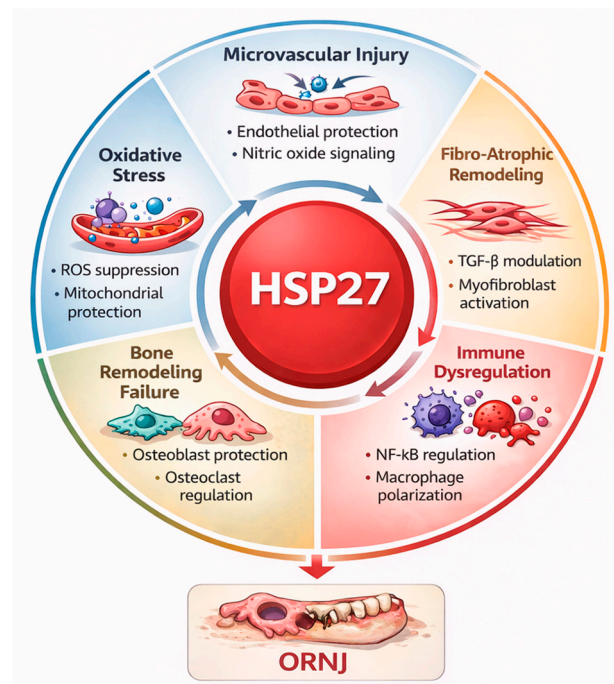


Figure 2. Mechanistic intersections between HSP27 signaling and key pathogenic pathways implicated in osteoradionecrosis of the jaw (ORNJ). **Note:** Heat shock protein 27 (HSP27) is a small stress-response chaperone that regulates multiple cellular processes relevant to radiation-induced tissue injury. Through its roles in cytoskeletal stabilization, redox homeostasis, apoptotic regulation, and inflammatory signaling, HSP27 influences several biological pathways central to ORNJ pathogenesis. These include endothelial survival and nitric oxide signaling within the mandibular microvasculature, suppression of oxidative stress and preservation of mitochondrial integrity, modulation of fibroblast activation and transforming growth factor- β -mediated fibro-atrophic remodeling, regulation of osteoblast and osteoclast function during bone turnover, and control of immune and inflammatory responses through pathways such as NF- κ B signaling and macrophage polarization. The convergence of these mechanisms positions HSP27 as a potential integrative regulator of tissue resilience to radiation-induced injury in mandibular bone and surrounding soft tissues.

HSP27 intersects these pathways by modulating oxidative stress, apoptosis–senescence dynamics, cytoskeletal remodeling, and TGF- β 1-driven myofibroblast persistence. Inhibition of HSP27 reduces fibrosis in preclinical models [19], reinforcing its potential influence on chronic wound-healing trajectories relevant to ORNJ.

2.1.4. Disrupted Bone Remodeling and Cellular Turnover

Radiation disrupts bone homeostasis by inducing osteocyte apoptosis, impairing osteoblast activity, and dysregulating osteoclast function [7,20,21]. These changes reduce mechanotransduction, suppress bone formation, and produce unstable or excessive resorption. Collagen cross-linking abnormalities, altered mineral crystallinity, and microarchitectural degradation further weaken biomechanical strength [19,26,27]. The result is a hypodynamic, brittle skeletal environment that cannot withstand normal loads, predisposing to non-healing necrosis and fracture.

2.1.5. Dysregulated Inflammation and Immune Impairment

Irradiation compromises mucosal integrity, alters the oral microbiome, reduces salivary protection, and increases susceptibility to infection and chronic inflammatory injury [11,28–30]. Persistent mucosal barrier disruption and microbial colonization may sustain low-grade inflammation rather than resolution. Once infection occurs, microbial products can amplify osteoclast activity, bone resorption, and soft-tissue necrosis. This chronic inflammatory loop synergizes with hypoxia and fibrosis to drive the progression of ORNJ.

2.1.6. Integration of Mechanisms

ORNJ reflects the convergence of multiple, mutually reinforcing biological disturbances, including microvascular injury and chronic hypoxia [1–4,7]; oxidative stress and redox imbalance [8–10]; fibroblast senescence with aberrant ECM deposition [9,19]; impaired bone turnover with skeletal microinstability [7,20,21,26,27]; and immune dysfunction accompanied by oral dysbiosis [11,28–30]. These mechanisms form a self-sustaining loop in which hypoxia reinforces fibrosis, inflammation amplifies oxidative stress, senescence limits regenerative capacity, and impaired remodeling prevents structural recovery.

HSP27 operates at many of these mechanistic intersections—supporting endothelial stability [17], buffering oxidative injury [15], regulating apoptosis–senescence dynamics [15–17], amplifying TGF- β 1–driven fibroblast activation [19], and influencing osteoclast–osteoblast cytoskeletal organization [21]. The integrated nature of these roles is illustrated in Figure 2, which summarizes the major molecular domains through which HSP27 may shape ORNJ susceptibility and progression. This conceptual linkage provides the rationale for subsequent sections that explore how HSP27 biology may intersect with clinical phenotype, risk stratification, and disease evolution.

2.2. Clinical Manifestations and Staging of ORNJ

ORNJ presents along a wide clinical spectrum, ranging from small, asymptomatic areas of bone exposure to extensive necrosis accompanied by trismus, infection, fistula formation, and pathologic fractures. These outward manifestations are not isolated findings but the clinical expression of deeper biological derangements—including microvascular failure, progressive fibro-atrophy, immune dysfunction, and collapse of normal skeletal remodeling. The alignment between clinical severity and underlying pathophysiology is well established, and Table 1 summarizes the major clinical features of ORNJ alongside their corresponding biological correlates, providing a structured framework for understanding how diverse presentations arise from shared mechanistic pathways.

Clinical Features

Bone exposure and non-healing wounds: Exposed devitalized bone persisting ≥ 3 months is the hallmark of ORNJ [1,2]. Pain worsens with inflammation or nerve involvement [2,27]. Rough submucosal surfaces may precede overt exposure.

Pain and neuropathic symptoms: Severe nociceptive or neuropathic pain reflects inflammation or medullary extension.

Secondary infections: Reduced vascularity and immune surveillance predispose to infection, which then accelerates osteolysis and soft-tissue necrosis [11,28–30].

Trismus and fibrosis: Fibrotic remodeling of masticatory muscles and TGF- β –mediated collagen accumulation restrict mandibular movement [9,10,19].

Fistula formation: Occurs in advanced disease with structural breakdown [1,2].

Pathologic fractures. Represent end-stage biomechanical failure from cumulative osteocyte loss, disrupted remodeling, and matrix degradation [7,20,21,26,27].

Radiographic Features

CT reveals cortical erosion, sequestra, trabecular loss, and mixed lytic–sclerotic patterns. MRI identifies marrow changes (T1 hypointensity; T2/STIR hyperintensity) and soft-tissue involvement. Bone scintigraphy and PET provide metabolic information. Together, these modalities define the extent of disease, differentiate ORNJ from recurrence, and support treatment planning [22].

Staging Systems

Several staging systems have been proposed to characterize disease extent and guide management. The Notani classification is based on the anatomical extent of disease relative to the inferior alveolar canal [31]. The Lyons system emphasizes symptoms and clinical complications [2], whereas IMRT-era classifications, such as the Tsai system, incorporate dosimetric considerations and contemporary radiation treatment patterns [26]. In addition, the AAOMS staging system, originally developed for medication-related osteonecrosis of the jaw, is occasionally extrapolated to ORNJ for descriptive purposes [32].

Clinical Implications

Disease stage predicts prognosis and informs treatment intensity. Early-stage disease may respond to conservative management, whereas advanced disease often requires segmental mandibulectomy. Clinical severity reflects the cumulative effects of hypoxia, fibrosis, inflammation, and skeletal injury. These biological domains overlap substantially with the regulatory functions of HSP27, highlighting the potential value of staging systems for future biomarker and mechanistic investigations.

2.3. Risk Factors for ORNJ

ORNJ arises from the interplay of radiation-induced tissue injury with patient-, treatment-, microbial-, and systemic-level vulnerabilities. Although radiation dose distribution remains the most important determinant of risk, accumulating clinical evidence indicates that multiple host and environmental factors influence both susceptibility and disease progression. These determinants include RT dose–volume characteristics, dental and periodontal health, local trauma, systemic comorbidities, nutritional status, and inflammatory burden. The principal clinical, dosimetric, and host-related determinants associated with ORNJ development are summarized in Table 2.

Table 2. Clinical, Dosimetric, and Host Determinants of Osteoradionecrosis of the Jaw and Their Mechanistic Links to ORNJ Pathobiology.

Domain	Specific Risk Factor	Clinical/Biological Rationale	Mechanistic Domains Involved (See Table 1)	Representative References
Radiotherapy dose–volume parameters	High mandibular dose (>60–70 Gy); elevated V60/V70; focal dose hotspots	High radiation dose directly damages mandibular microvasculature and osteocytes, promoting hypoxia, oxidative stress, and impaired tissue repair	Microvascular injury; oxidative stress; disrupted bone remodeling	[3,5,7,33]
Radiotherapy technique and modality	Conventional RT vs. IMRT/VMAT vs. proton therapy	Conformal techniques reduce dose to uninvolved mandible, but high-dose subvolumes can still initiate radiation injury cascades	Microvascular injury; oxidative stress	[3,33,34]
Re-irradiation or postoperative RT	Second radiation course or adjuvant radiotherapy following surgery	Cumulative endothelial, stromal, and osteocellular injury increases susceptibility to fibro-atrophic tissue remodeling	Microvascular injury; fibro-atrophic remodeling; bone remodeling failure	[33,34]
Tumor location and treatment field geometry	Oral cavity or oropharyngeal tumors adjacent to mandible	Determines mandibular dose exposure and likelihood of periosteal or periodontal injury	Microvascular injury; bone remodeling disruption	[3,35,36]

Table 2. Cont.

Domain	Specific Risk Factor	Clinical/Biological Rationale	Mechanistic Domains Involved (See Table 1)	Representative References
Baseline dental disease	Periodontal disease, poor dentition, chronic infection	Chronic inflammation and microbial colonization impair mucosal integrity and bone healing capacity	Immune–inflammatory dysregulation; microbiome disruption	[2,11,37]
Dental extraction and invasive oral procedures	Post-RT extractions or traumatic dental procedures	Hypovascular irradiated bone has reduced regenerative capacity, predisposing to non-healing wounds	Microvascular injury; bone remodeling failure; immune dysregulation	[2,38–40]
Local mechanical trauma	Ill-fitting dentures, mucosal irritation, sharp restorations	Repetitive mucosal injury can expose devitalized bone in compromised tissues	Microbiome disruption; immune dysregulation	[23,35]
Systemic comorbidities	Diabetes mellitus, smoking, vascular disease, osteoporosis	Impaired angiogenesis, endothelial dysfunction, and delayed wound healing increase susceptibility to radiation injury	Microvascular injury; oxidative stress; impaired bone remodeling	[25,36,41,42]
Hematologic and nutritional status	Anemia, malnutrition, weight loss	Reduced oxygen delivery and impaired tissue regeneration promote chronic hypoxia and delayed healing	Microvascular injury; oxidative stress; systemic susceptibility	[25,41,42]
Systemic inflammatory burden	Elevated inflammatory–nutritional indices (CAR/WL, GINI, PINI, SIS)	Reflect host’s inflammatory and metabolic stress that may amplify radiation-induced tissue injury	Oxidative stress; immune dysregulation; systemic susceptibility	[14,43,44]

Abbreviations: CAR/WL, C-reactive protein–to-albumin ratio with weight loss; GINI, Global Immune-Nutrition Index; IMRT, intensity-modulated radiotherapy; PINI, Prognostic Inflammatory-Nutritional Index; RT, radiotherapy; SIS, systemic inflammation score; V60/V70, mandibular volume receiving ≥ 60 Gy or ≥ 70 Gy.

2.3.1. Radiotherapy Dose–Volume Effects

Mandibular exposure to >60 – 70 Gy remains the strongest predictor of ORNJ, even with IMRT/PT [2–4]. High-dose subvolumes (V70, V75) correlate with microvascular rarefaction, osteoblast impairment, and progressive hypoxia [7,8].

2.3.2. Dental Health, Extractions, and Oral Trauma

Periodontal disease, periapical infections, and mucosal trauma increase susceptibility [11]. Extractions before or after RT (especially in regions > 60 – 65 Gy) are major triggers [38,39]. Ill-fitting prostheses or repetitive trauma can convert minor injuries into chronic non-healing wounds [23,35].

2.3.3. Systemic Comorbidities and Host Factors

Diabetes, smoking, malnutrition, osteoporosis, vascular disease, and low hemoglobin impair angiogenesis, collagen synthesis, immune function, and oxygen delivery [25,36,41,42]. These amplify radiation injury and explain divergent outcomes among similarly dosed patients.

2.3.4. Microbial Dysbiosis and Infection

RT-induced dysbiosis shifts the oral microbiome toward pathogen enrichment [45]. Once bone is exposed, bacterial products accelerate osteoclastogenesis and chronic inflammation [24,46,47]. Radiation-impaired immune cells are unable to clear infection, sustaining a destructive inflammatory cycle.

2.3.5. Soft-Tissue Fibrosis and Mucosal Integrity

Radiation induces fibroblast senescence, myofibroblast persistence, and excessive ECM deposition [9,10,19]. Suppression of bFGF and PDGF impairs angiogenesis and wound

repair, promoting persistent mucosal fragility and hypovascular fibrosis. These alterations synergize with hypoxia to sustain non-healing states.

2.3.6. Systemic Inflammation, Oxidative Stress, and Hypoxia

Elevated inflammatory indices (CARWL, PIV, Valero host index, GINI, SIS) predict mandibular and periodontal radiation injuries [14,25,36,43,47]. Systemic oxidative stress reduces antioxidant capacity, promoting ROS-driven injury. Hypoxia—whether from microvascular rarefaction or anemia—impairs bone turnover and fosters fibroblast activation [4,8,9].

2.3.7. Timing of Trauma and Surgical Procedures

Late post-RT extractions occur during advanced fibro-atrophic change and carry a higher ORNJ risk [48]. Chronic microtrauma from dentures or bruxism may precipitate necrosis in similarly vulnerable tissues.

2.3.8. Integrative Risk Model

ORNJ arises from the convergence of multiple interacting determinants, including RT dose–volume characteristics, impaired bone turnover, fibro-atrophic soft-tissue remodeling, dysregulated immunity and microbiome alterations, systemic vulnerabilities, and traumatic or dental triggers. These factors do not operate independently; rather, they interact within a complex pathogenic network that shapes both the likelihood and severity of mandibular injury after RT. Table 2 provides an integrated summary of the principal clinical, dosimetric, and host-related determinants associated with ORNJ development, complementing the pathogenic domains outlined in Table 1 and illustrating how diverse clinical risk factors converge on the underlying biological pathways of radiation-induced mandibular injury. Because HSP27 regulates endothelial survival, redox homeostasis, fibroblast activation, and cytoskeletal stability [15–17,19–21], the interplay among these risk domains further underscores its potential influence on individual susceptibility to ORNJ and the trajectory of disease evolution.

2.4. Integrative Synthesis and Conceptual Transition Toward Molecular Mediators

ORNJ represents a dynamic failure of tissue homeostasis, arising from microvascular compromise, persistent oxidative injury, fibro-atrophic remodeling, impaired bone turnover, and immune dysregulation. Radiation initiates acute ROS generation, mitochondrial and cytoskeletal injury, and endothelial apoptosis, which progressively evolve into chronic hypoxia, senescence, fibrosis, dysbiosis, and skeletal collapse. Despite similar dosimetric profiles, patients exhibit striking heterogeneity in clinical outcomes, suggesting intrinsic differences in molecular resilience and cellular stress-response capacity.

HSP27 is a particularly strong mechanistic candidate for explaining this variability. It is rapidly induced by ionizing radiation, cytokines, oxidative stress, and hypoxia, and it modulates many of the very processes central to ORNJ pathogenesis—endothelial protection, redox homeostasis, apoptosis resistance, fibroblast activation, and osteoclast–osteoblast cytoskeletal dynamics. As summarized in Figure 2, these domains closely correspond to the biological pathways governing ORNJ evolution, reinforcing the plausibility of HSP27 as an integrative mediator.

Yet, despite this strong biological alignment, HSP27 has not been investigated in osteoradionecrosis tissues, highlighting a notable gap in current mechanistic understanding. This absence underscores the need for mechanistic, biomarker-driven, and translational studies to determine whether HSP27 contributes to susceptibility, progression, or therapeutic responsiveness in ORNJ. Addressing this question may clarify how molecular stress-response systems shape tissue resilience following irradiation, providing the ratio-

nale for examining HSP27 in greater detail in the sections that follow. More broadly, these considerations suggest that the clinical expression of ORNJ may depend not only on the magnitude of radiation exposure but also on the intrinsic capacity of mandibular tissues to withstand radiation-induced cellular stress—thereby implicating stress-response pathways such as HSP27 as potential modulators of tissue resilience after irradiation.

3. Molecular Biology and Stress-Response Functions of HSP27

HSP27 is a highly conserved molecular chaperone involved in cellular adaptation to oxidative, mechanical, metabolic, inflammatory, and radiation-induced stress. Its canonical functions include cytoprotection, regulation of apoptosis, cytoskeletal organization, redox homeostasis, endothelial stability, fibroblast activation, and bone-cell regulation [15–17,19–21]. This section summarizes the principal biological functions of HSP27 that provide the mechanistic basis for its potential relevance to radiation-induced mandibular injury.

3.1. Structure and Biochemical Architecture of HSP27

HSP27 belongs to the small HSP family and contains an α -crystallin domain flanked by flexible terminal regions that enable dynamic oligomer formation [15]. These assemblies range from tetramers to large multimers exceeding 800 kDa, with oligomeric state influencing chaperone capacity, cytoskeletal interaction, and anti-apoptotic activity. Phosphorylation at Ser15, Ser78, and Ser82 by MAPKAPK2/3 downstream of p38 MAPK promotes oligomer disassembly and shifts HSP27 toward functions such as actin regulation and cell motility [15]. These conformation-dependent transitions allow rapid adaptation to cellular stress.

3.2. Gene Regulation and Induction Pathways

HSP27 transcription is primarily regulated by heat shock factor 1, which is activated by stressors including heat shock, ROS, radiation-induced DNA damage, inflammatory cytokines, and hypoxia [15]. Additional regulatory pathways include p38 MAPK signaling during oxidative stress [17], ATM/ATR and p53 activation following DNA damage, NF- κ B/MAPK signaling induced by TNF- α and IL-1 β [16,22,29], and mechanical stress-responsive pathways involving HSP27-mediated actin stabilization. These regulatory inputs place HSP27 at the intersection of oxidative, inflammatory, genotoxic, and mechanical stress responses.

3.3. HSP27 as a Molecular Chaperone and Guardian of Proteostasis

HSP27 prevents the aggregation of misfolded proteins and supports their refolding or degradation via the ubiquitin–proteasome system and autophagy [15]. This proteostatic function becomes particularly important under chronic ROS exposure, mitochondrial dysfunction, and metabolic stress, all of which are characteristic features of radiation-injured tissues [8–11,15].

3.4. Regulation of Oxidative Stress and Redox Homeostasis

HSP27 stabilizes glutathione pools, limits ROS generation, and inhibits redox-sensitive apoptotic cascades [18,28]. Through these functions, HSP27 may influence whether stressed cells undergo adaptive survival, apoptosis, or senescence under conditions of persistent oxidative injury [8–10].

3.5. Anti-Apoptotic and Pro-Survival Functions

HSP27 inhibits cytochrome c-mediated caspase-9 activation, prevents Bax-driven mitochondrial permeabilization, and modulates stress kinases including DAXX and

ASK1 [15,17]. These cytoprotective effects may preserve cell survival during acute injury, although prolonged survival of dysfunctional or senescent cells may also contribute to chronic tissue pathology. This duality is especially relevant in tissues where endothelial apoptosis and vascular rarefaction are central features of radiation injury [3,4].

3.6. Cytoskeletal Stabilization, Cell Motility, and Matrix Remodeling

By binding actin and regulating polymerization, HSP27 maintains cytoskeletal integrity during oxidative and mechanical stress [15]. This function supports endothelial barrier stability, fibroblast contractility, osteoclast cytoskeletal organization [21], and reparative cell migration. Dysregulated HSP27 activity may therefore affect mechanotransduction, matrix remodeling, and cellular repair responses in chronically stressed tissues.

3.7. HSP27 in Endothelial Biology and Angiogenic Signaling

HSP27 contributes to endothelial integrity by stabilizing actin structures, supporting nitric oxide signaling, and modulating VEGF-driven angiogenesis. Ernst et al. demonstrated that HSP27 regulates endothelial senescence and angiogenic signaling [29]. These functions suggest that HSP27 may influence vascular survival and repair capacity in radiation-injured microenvironments [1–4].

3.8. HSP27 in Fibroblast Activation, Senescence, and Radiation-Induced Fibrosis

TGF- β -driven fibroblast activation, senescence, and fibrosis are central features of chronic radiation injury [9–11,19]. HSP27 intersects with these pathways by regulating TGF- β 1 signaling, cytoskeletal contractility, and myofibroblast differentiation [49]. Inhibition of HSP27 disrupts TGF- β 1 signaling and suppresses fibrosis in in vitro fibrotic cell systems and an experimental rat pulmonary fibrosis model [19], supporting its potential relevance to fibrotic remodeling after irradiation.

3.9. HSP27 in Bone Remodeling Cells: Osteoblasts, Osteoclasts, and Osteocytes

HSP27 influences osteoblasts, osteoclasts, and osteocytes, three cell populations central to bone remodeling and skeletal adaptation [7,20,21,27,33,50–52]. HSP27 has been shown to regulate osteoblast-related functions, including osteocalcin synthesis and mineralization, in osteoblast models [20]. In osteoclasts, HSP27 regulates cytoskeletal organization, podosome formation, and resorptive activity [21]. Although less extensively studied in osteocytes, HSP27-associated stress-response pathways may influence mechanosensitivity, survival, and signaling within the bone remodeling network.

3.10. Evidence Context and Limitations of Extrapolation

Taken together, these biological functions support the hypothesis that HSP27 may act as a stress-response regulator linking oxidative injury, endothelial survival, fibroblast activation, cytoskeletal remodeling, inflammatory signaling, and bone-cell function. However, the evidence supporting these associations is indirect and derives from heterogeneous sources, including in vitro systems, non-mandibular animal models, radiation-injury studies, bone-biology experiments, and mechanistic reviews. These data provide a biologically plausible rationale for considering HSP27 in radiation-induced mandibular injury, but they do not establish an ORNJ-specific role.

In endothelial cells, HSP27 may influence the balance between apoptosis, senescence, and adaptive survival. In fibroblasts, it may modulate TGF- β 1 signaling and extracellular matrix remodeling. In osteoblasts and osteoclasts, it may affect cytoskeletal organization, survival, and resorptive behavior. More broadly, its roles in redox buffering, NF- κ B modulation, and apoptotic regulation place HSP27 within pathways relevant to chronic radiation injury. Figure 2 visually summarizes the principal molecular domains

through which HSP27 may intersect with radiation-injured tissues, including fibroblast activation, inflammatory signaling, redox homeostasis, and osteoblast–osteoclast dynamics. This framework provides a conceptual bridge to Section 4, where these HSP27-linked mechanisms are considered as hypothesis-generating intersections rather than established ORNJ-specific mechanisms.

Although multiple HSPs participate in cellular stress responses, HSP27 may be particularly relevant in this context because its functions extend beyond protein folding. Larger chaperones, such as HSP70 and HSP90, primarily act as ATP-dependent regulators of client protein stability and global proteostasis [15]. In contrast, HSP27 plays prominent roles in cytoskeletal stabilization, endothelial barrier maintenance, redox buffering, and TGF- β -mediated fibroblast activation [15–17,19]. These activities partially overlap with biological domains implicated in radiation-induced mandibular injury, including microvascular compromise, persistent oxidative stress, fibro-atrophic remodeling, and impaired skeletal turnover.

Importantly, the evidence supporting these associations derives from heterogeneous study types, including in vitro cell-line experiments, animal models of radiation-induced fibrosis or bone remodeling, clinical observational studies, and narrative or mechanistic reviews. These sources differ substantially in biological context, tissue specificity, and translational relevance. Therefore, findings from pulmonary fibrosis, vascular injury, osteoclast biology, or general bone metabolism should not be interpreted as direct evidence for HSP27 involvement in ORNJ. Rather, they provide indirect mechanistic rationale for hypothesis generation. Direct validation in irradiated mandibular tissues, periodontal structures, and ORNJ specimens remains necessary.

4. Mechanistic Intersections Between HSP27 Biology and ORNJ Pathogenesis

Rather than reiterating established ORNJ mechanisms or canonical HSP27 biology, this section integrates these two domains to identify plausible mechanistic intersections and testable hypotheses. ORNJ is characterized by microvascular injury, oxidative stress, fibroblast senescence, dysregulated bone remodeling, and impaired immune function. HSP27 regulates several overlapping stress-response pathways, including redox homeostasis, cytoskeletal stabilization, apoptotic signaling, endothelial protection, fibroblast activation, and inflammatory regulation. Although HSP27 has not been directly examined in ORNJ tissues, these mechanistic overlaps support targeted investigation of HSP27 as a potential regulator of radiation-induced mandibular tissue resilience.

4.1. HSP27 and Endothelial Injury: Implications for Mandibular Microvascular Failure

Endothelial apoptosis and chronic microvascular loss are early drivers of ORNJ pathogenesis [3,4]. HSP27 stabilizes the endothelial cytoskeleton, enhances nitric oxide signaling, and promotes survival under oxidative or mechanical stress [29]. Experimental models indicate that HSP27 overexpression can limit radiation-induced senescence and preserve angiogenic capacity. Therefore, variability in endothelial HSP27 induction or phosphorylation may help explain why patients receiving comparable mandibular doses develop divergent ORNJ outcomes.

However, the proposed involvement of HSP27 in radiation-induced endothelial injury within ORNJ remains inferential and is extrapolated from studies of endothelial stress responses and radiation-induced vascular injury in other tissues.

4.2. HSP27 and Oxidative Stress in Irradiated Bone and Soft Tissue

Persistent oxidative stress is a major determinant of late radiation injury [8–10]. HSP27 acts as a redox-buffering protein that limits ROS accumulation, protects mitochondrial integrity, and modulates antioxidant pathways [28]. Reduced or delayed HSP27 activation may therefore permit excessive ROS-mediated injury, accelerating fibroblast senescence, osteoblast apoptosis, and progressive hypoxia, all of which contribute to ORNJ development. However, the potential role of HSP27 in oxidative-stress regulation during ORNJ should currently be regarded as hypothesis-generating rather than evidence-based.

4.3. HSP27 and Fibroblast Activation: Connecting Chaperone Biology to Fibro-Atrophic Remodeling

Radiation induces fibroblast senescence and exaggerated TGF- β 1 responsiveness, leading to collagen accumulation and fibrosis [9,19]. HSP27 regulates cytoskeletal architecture and interacts with mediators of myofibroblast differentiation and ECM remodeling [19,49]. Pharmacologic inhibition of HSP27 attenuates TGF- β 1-driven fibrosis in in vitro fibrotic cell systems and an experimental rat pulmonary fibrosis model [19]. These observations are consistent with a potential role for HSP27 in fibro-atrophic remodeling, but they do not constitute direct evidence of HSP27-mediated fibrosis in ORNJ.

4.4. HSP27 in Osteoblast and Osteoclast Biology: Potential Determinant of Bone Turnover Failure

ORNJ is marked by osteocyte apoptosis, impaired osteoblast function, dysregulated osteoclast activity, and altered irradiated bone microstructure [9,27,33,50,51]. HSP27 has been shown to regulate osteoblast-related functions, including osteocalcin synthesis [20], and to influence osteoclast cytoskeletal organization and resorptive activity [21]. Accordingly, HSP27 may influence whether irradiated bone retains residual remodeling capacity or progresses toward non-regenerative skeletal failure. Importantly, the available evidence derives from structural and biochemical characterization of irradiated mandibular bone and from non-ORNJ bone-cell models rather than direct investigation of HSP27-mediated bone remodeling pathways in ORNJ.

4.5. HSP27 and Immune Dysregulation in the Irradiated Microenvironment

Radiation compromises neutrophil and macrophage function and promotes persistent low-grade inflammation [17,22,30]. HSP27 modulates macrophage polarization, regulates NF- κ B-dependent cytokine output, and influences immune-cell apoptosis. Altered HSP27 responses may therefore affect whether immune activation resolves appropriately or evolves into chronic, destructive inflammation.

4.6. Integrative Framework: HSP27 as a Molecular Determinant of ORNJ Susceptibility

Across endothelial, fibroblast, osteogenic, and immune pathways, HSP27 intersects with the major biological disturbances that characterize ORNJ. These intersections support three complementary conceptual models. First, in a susceptibility model, insufficient or delayed HSP27 induction after RT may permit greater endothelial loss, fibro-atrophic remodeling, and impaired skeletal repair, thereby increasing ORNJ risk. Second, in a progression model, aberrant HSP27 phosphorylation or downstream signaling may impair cytoskeletal remodeling and apoptotic resolution, promoting persistence of senescent or dysfunctional stromal cells and facilitating chronic non-healing lesions. Third, in a protective resilience model, robust and appropriately timed HSP27 activation may preserve microvascular integrity, limit oxidative injury, and maintain stromal resilience, thereby reducing ORNJ risk even in regions exposed to high mandibular radiation doses.

These models position HSP27 as a plausible molecular regulator of radiation-induced mandibular tissue resilience and provide a rationale for systematic experimen-

tal and translational studies evaluating its role in ORNJ susceptibility, progression, and therapeutic responsiveness.

4.6.1. Temporal Duality of HSP27 Signaling During the Evolution of ORNJ

The biological effects of HSP27 in radiation-induced tissue injury are likely to be highly dependent on the temporal stage of the tissue response. Although direct evidence in ORNJ is lacking, findings from radiation biology, fibrosis research, and cellular stress-response studies suggest that HSP27 may exert both protective and maladaptive effects during different phases of tissue injury evolution.

During the acute radiation phase, HSP27 activation may promote tissue resilience through several cytoprotective mechanisms, including suppression of oxidative stress, stabilization of mitochondrial and cytoskeletal integrity, inhibition of apoptosis, and preservation of endothelial function [15,17,28,29]. In this context, robust HSP27 induction may limit acute radiation-induced cellular injury and support adaptive tissue repair responses.

During the subacute phase, persistent oxidative stress, inflammatory signaling, and fibroblast activation may alter the biological consequences of HSP27 signaling [8–10,19,28]. During this transitional period, HSP27 may simultaneously support cellular survival while promoting the persistence of activated fibroblasts, senescent stromal cells, and maladaptive repair processes. Thus, HSP27 activity may become increasingly context-dependent, exhibiting both protective and potentially deleterious effects.

During the chronic fibro-atrophic phase, sustained or dysregulated HSP27 activity may contribute to the maintenance of pathological tissue states. Persistent inhibition of apoptosis, continued support of TGF- β -responsive fibroblast populations, stabilization of dysfunctional stromal networks, and altered bone-cell survival dynamics may collectively reinforce fibro-atrophic remodeling and impaired skeletal repair [15–17,19,21,49]. Under these conditions, HSP27-mediated cytoprotection may paradoxically contribute to the persistence of the non-healing, hypoxic, and remodeling-deficient microenvironment characteristic of advanced ORNJ.

Taken together, these observations suggest that HSP27 may function as a temporally dynamic regulator of tissue resilience following irradiation. Whereas early HSP27 activation may facilitate adaptive repair and cellular recovery, persistent or dysregulated activation during chronic injury may contribute to the persistence of pathological tissue states. This temporal duality provides a potential mechanistic explanation for the apparently ambivalent role of HSP27 in radiation-induced tissue injury and represents an important hypothesis for future investigation.

4.6.2. Mandibular Microenvironment Specificity and Limits of Extrapolation

Although the biological functions of HSP27 have been extensively investigated in vascular, pulmonary, fibrotic, and oncologic models, extrapolating these findings to ORNJ requires caution, as the mandibular microenvironment possesses several unique anatomical and biological characteristics. Unlike many other irradiated tissues, the mandible is subjected to continuous mechanical loading during mastication, depends on highly coordinated osteoblast–osteoclast–osteocyte interactions for skeletal homeostasis, and exists in close proximity to the oral microbiome and periodontal tissues [7,11,20,21]. Furthermore, mandibular tissues exhibit relatively limited collateral vascularization, making them particularly susceptible to persistent hypoxia and impaired repair following radiation exposure [3,4].

The biological behavior of fibroblasts and mesenchymal stromal cells within irradiated mandibular tissues may also differ substantially from that observed in skin, lung, or other fibrotic organs because of differences in extracellular matrix composition, biomechanical

stress, vascular supply, and local inflammatory signaling [9,10,19]. Likewise, HSP27-mediated regulation of osteocyte survival, osteoclast cytoskeletal function, periodontal ligament homeostasis, and oral mucosal barrier integrity remains largely unexplored [15,20,21].

Therefore, although the mechanistic overlap between HSP27 biology and ORNJ pathogenesis is compelling, the present framework should be regarded as hypothesis-generating. Direct investigation of HSP27 expression, phosphorylation status, cellular localization, and functional activity within irradiated mandibular tissues, periodontal structures, and ORNJ specimens is essential before definitive conclusions regarding its role in ORNJ can be established.

4.7. Why HSP27 Has Been Overlooked in ORNJ Research

HSP27 has likely been overlooked in ORNJ research because traditional mechanistic models have emphasized vascular compromise, surgical trauma, infection, and radiation dose–volume effects rather than molecular stress-response mediators. Its multifunctional biology—spanning endothelial, fibroblast, osteogenic, and immune pathways—also makes it difficult to isolate within single-pathway models of radiation injury. In addition, access to well-preserved ORNJ tissue suitable for molecular analysis remains limited. However, recent advances in stress-response biology, molecular biomarker discovery, and biologically informed RT risk stratification now provide a strong context for systematic investigation of HSP27 in ORNJ.

4.8. Translational Relevance and Opportunities

Despite the lack of direct ORNJ-specific evidence, the mechanistic convergence between HSP27 biology and radiation-induced mandibular injury supports translational investigation in three domains.

First, biomarker studies could assess whether HSP27 expression or phosphorylation reflects baseline susceptibility, early tissue stress during RT, or progression of fibro-atrophic remodeling and impaired bone turnover. Such studies may help identify patients at increased ORNJ risk before overt clinical manifestations develop.

Second, mechanistic targeting studies could determine whether modulation of HSP27 signaling alters endothelial recovery, oxidative stress burden, fibroblast activation, or skeletal remodeling after irradiation. Because HSP27 governs cytoskeletal stability, apoptotic signaling, redox homeostasis, and fibrotic remodeling, this pathway may influence several interdependent components of ORNJ pathogenesis.

Third, therapeutic adjunct strategies may be considered in future preclinical work. Preclinical studies in fibrosis models have demonstrated that pharmacological modulation of HSP27 signaling may alter fibrotic responses, although such approaches have not been evaluated in ORNJ. Therefore, any HSP27-targeted strategy should first be tested in radiation-induced mandibular injury models before clinical relevance can be assumed.

4.9. Integrative Perspective

Direct evidence linking HSP27 to ORNJ remains unavailable, but the mechanistic convergence is substantial. HSP27 occupies nodal positions within pathways central to radiation-induced tissue injury, including microvascular dysfunction, oxidative stress responses, fibroblast activation, impaired bone remodeling, inflammatory signaling, and dysregulated apoptosis. Variability in HSP27 induction, phosphorylation, or downstream signaling may therefore contribute to interindividual differences in ORNJ susceptibility among patients receiving comparable radiation doses.

Systematic investigation of HSP27 in irradiated mandibular tissues could refine existing pathogenetic models and support biologically informed approaches to risk stratification, prevention, and therapeutic development. Integrating molecular stress-response pathways

with clinical and dosimetric predictors may improve identification of patients at elevated risk and guide mechanism-based strategies to preserve vascular integrity, limit fibro-atrophic remodeling, and maintain skeletal resilience following RT. Table 3 summarizes the principal HSP27-related biomarker domains and potential therapeutic opportunities relevant to ORNJ.

Table 3. Emerging Molecular Pathways and Candidate Biomarkers Potentially Relevant to Osteoradionecrosis of the Jaw.

Molecular Mediator/Pathway	Principal Biological Function	Evidence in Radiation-Induced Tissue Injury or Fibrosis	Potential Relevance to ORNJ Pathogenesis	Representative References
HSP27 (HSPB1)	Molecular chaperone regulating cytoskeletal stability, oxidative stress responses, and apoptosis	Demonstrated roles in endothelial protection, redox homeostasis, and fibrosis modulation in experimental radiation models	May influence tissue resilience, microvascular integrity, and fibroblast responses in irradiated mandibular tissues	[15–17,19–21]
TGF- β signaling	Central regulator of fibroblast activation and extracellular matrix deposition	Strong experimental and clinical evidence of radiation fibrosis	Drives fibro-atrophic remodeling in soft tissues surrounding irradiated bone	[9–11,19,30]
NF- κ B signaling	Master regulator of inflammatory transcriptional responses	Activated following radiation-induced oxidative stress and tissue injury	Sustains chronic inflammatory microenvironment and macrophage activation	[23,45,47]
Reactive oxygen species (ROS)–related pathways	Cellular redox regulation and oxidative stress signaling	Persistent ROS generation is a hallmark of radiation injury	Contributes to endothelial dysfunction, osteocyte damage, and fibroblast senescence	[8–10,14]
Matrix metalloproteinases (MMPs)	Extracellular matrix degradation and remodeling	Dysregulated MMP activity is reported in radiation-induced fibrosis	May influence periodontal and mucosal tissue remodeling adjacent to irradiated bone	[30,40]
Hypoxia-inducible factor-1 α (HIF-1 α)	Cellular adaptation to hypoxia and angiogenic signaling	Activated in chronically hypoxic irradiated tissues	May modulate vascular remodeling and hypoxic stress in mandibular tissues	[5,29]
Inflammatory cytokines (IL-1 β , IL-6, TNF- α)	Regulators of inflammatory signaling and immune activation	Elevated in radiation-induced tissue injury and chronic inflammatory states	May amplify local inflammatory responses and osteoclast activation in ORNJ	[23,36]

Abbreviations: HIF-1 α , hypoxia-inducible factor-1 α ; HSP27, heat shock protein 27; MMP, matrix metalloproteinase; NF- κ B, nuclear factor kappa B; ORNJ, osteoradionecrosis of the jaw; ROS, reactive oxygen species; TGF- β , transforming growth factor- β .

5. Future Directions and Research Priorities

Despite advances in RT techniques and supportive care, ORNJ remains a complex, heterogeneous, and incompletely understood late effect of head and neck cancer treatment. The mechanistic synthesis presented in earlier sections indicates that ORNJ reflects a dynamic interaction among microvascular injury, oxidative stress, fibroblast senescence, disrupted bone remodeling, and immune–metabolic dysregulation rather than a static post-radiation complication. Important gaps remain in understanding biological susceptibility, detecting early tissue destabilization, and developing mechanism-based interventions. The priorities outlined below define a research agenda aimed at advancing ORNJ biology and evaluating molecular mediators—including HSP27—which remain unexplored yet mechanistically compelling. These priorities can be broadly organized into four interconnected research domains: mechanistic characterization of radiation-induced tissue injury, development of predictive biomarker systems, establishment of high-fidelity experimental models, and exploration of mechanism-based therapeutic strategies.

The central hypothesis proposed in this review is that HSP27 may influence mandibular tissue resilience following radiotherapy by regulating the balance between acute cytoprotection and chronic fibro-atrophic remodeling. Insufficient, delayed, or dysregulated HSP27 signaling may be associated with impaired endothelial recovery, increased oxidative

stress, altered fibroblast and stromal-cell persistence, and disrupted osteoblast–osteoclast remodeling dynamics, thereby increasing susceptibility to ORNJ. This hypothesis does not assume a causal role for HSP27 in ORNJ, but instead provides a focused framework for future experimental and clinical investigation.

The present hypothesis-driven framework builds upon broader concepts of stress-response resilience in radiation-induced injury [16], but applies these principles specifically to the unique biological environment of irradiated mandibular tissues. Accordingly, the research priorities outlined below are intended to provide a focused roadmap for validating the role of HSP27 in ORNJ susceptibility, progression, and therapeutic response.

Among the numerous unanswered questions surrounding HSP27 and ORNJ, several research priorities appear particularly urgent from both mechanistic and translational perspectives. First, validation studies examining HSP27 expression, phosphorylation status, and cellular localization in irradiated mandibular tissues and ORNJ specimens represent the highest priority, as they would establish whether HSP27 is biologically relevant to human ORNJ. Second, mechanistic studies investigating the temporal and cell type-specific effects of HSP27 during radiation-induced mandibular injury are needed to clarify its potentially protective and maladaptive roles across different stages of ORNJ evolution. Third, translational studies integrating HSP27-related biomarkers with established clinical and dosimetric risk factors may determine whether stress-response profiling improves prediction of ORNJ susceptibility and progression. Together, these priorities provide a framework for the rational development of future experimental and clinical investigations.

5.1. Testable Hypotheses Emerging from the HSP27–ORNJ Framework

Three testable hypotheses emerge from the proposed HSP27–ORNJ framework. First, patients who develop ORNJ after comparable mandibular radiation exposure may demonstrate lower or delayed HSP27 induction, altered phosphorylation, or impaired endothelial localization compared with irradiated patients who do not develop ORNJ. Second, in established ORNJ, sustained or dysregulated HSP27 activation may correlate with fibro-atrophic remodeling, persistent senescent stromal cells, impaired bone turnover, and higher clinical stage. Third, experimental modulation of HSP27 signaling in radiation-injury models may alter endothelial survival, oxidative stress burden, fibroblast activation, and osteoblast–osteoclast remodeling dynamics, thereby changing the severity or reversibility of mandibular radiation injury.

5.2. Mechanistic Priorities: Defining the Biological Trajectory of ORNJ

ORNJ pathogenesis reflects the convergence of vascular injury, fibro-atrophic remodeling, impaired skeletal turnover, immune dysfunction, and systemic inflammatory susceptibility [1–4,7–11,19,50,51]. Although these domains have been individually characterized, their temporal hierarchy and causal relationships remain poorly understood. Three fundamental questions therefore define the next phase of mechanistic ORNJ research: at what stage reversible radiation injury transitions into irreversible fibro-atrophic remodeling; which tissue compartments—endothelial, stromal, or skeletal—represent the primary rate-limiting steps in disease progression; and how systemic metabolic or inflammatory states modify local radiation responses.

Addressing these questions will require integrated multi-omics profiling of irradiated mandibular tissues across defined post-RT intervals. Transcriptomic, proteomic, and spatial metabolomic analyses may clarify the evolving interactions among endothelial cells, fibroblasts, osteocytes, and immune subsets within developing lesions. Early transcriptomic and proteomic studies already suggest persistent inflammatory and fibrotic signatures years after irradiation [53,54]. Spatial transcriptomics may be particularly

valuable for mapping the cellular architecture of evolving ORNJ lesions and identifying regulatory networks—including stress-response pathways such as HSP27—that may influence disease progression.

5.3. Development of Predictive Biomarker Systems

Validated biomarkers capable of predicting ORNJ susceptibility or detecting early tissue destabilization remain unavailable. Existing prediction models rely primarily on dosimetric parameters, dental status, and general systemic risk factors [2–4,9], which explain only a portion of the observed clinical variability.

5.3.1. Imaging Biomarkers

Advanced imaging techniques may enable earlier detection of radiation-induced mandibular injury. MRI-based approaches—including diffusion-weighted imaging, dynamic contrast enhancement, and ultrashort echo-time imaging—can identify marrow hypoxia, early fibrosis, or microstructural alterations in bone before cortical breakdown occurs [22,33]. Molecular imaging strategies such as hypoxia PET tracers (^{18}F -FMISO) and fibroblast-activation imaging (FAPI-PET) may further improve early risk stratification by detecting biologically active tissue remodeling [32].

5.3.2. Circulating Biomarkers

Systemic inflammatory and oxidative indices—including CRP/albumin ratios, neutrophil-to-lymphocyte ratios, and immune-nutrition scores—have been associated with radiation-induced tissue injury in other contexts [31,33], but remain poorly studied in ORNJ cohorts. Because HSPs are highly stress-responsive, circulating HSPs—including HSP27—represent promising yet unexplored biomarker candidates for detecting radiation-induced tissue stress [10].

5.3.3. Tissue Biomarkers

Histopathological studies consistently demonstrate osteocyte depletion, microvascular rarefaction, and fibro-atrophic tissue replacement in ORNJ [7,9,19]. Expanding immuno-histochemical profiling to include markers of endothelial injury (VE-cadherin, CD31), fibroblast activation (α -SMA, COL1A1), apoptotic signaling, and oxidative DNA damage could provide mechanistic insight into lesion development. Incorporating HSP27 expression and phosphorylation mapping into such analyses may allow direct visualization of stress-response activity within irradiated mandibular tissues. Ultimately, a tiered biomarker model integrating imaging, circulating markers, and tissue-based indicators may enable earlier diagnosis and individualized risk prediction.

5.4. Establishing High-Fidelity Preclinical Models

A major limitation in ORNJ research is the absence of experimental models that accurately reproduce the complexity of human disease. Existing rodent models often rely on extreme radiation doses, surgical trauma, or combined insults and rarely replicate the chronic fibro-atrophy, microbial dysbiosis, and immune-metabolic interactions observed in clinical ORNJ. Future efforts should therefore prioritize the development of fractionated RT regimens that mirror clinical treatment protocols, the incorporation of relevant cofactors such as dental trauma, periodontal disease, or microbiome disruption, and the application of transgenic or molecular approaches to interrogate endothelial injury, TGF- β signaling dynamics, and cellular stress-response systems such as HSP27. In parallel, emerging experimental platforms—including tissue-engineered mandibular constructs and microfluidic bone-on-chip systems—offer promising opportunities to study radiation-induced stress

signaling, osteoblast–endothelial interactions, and fibroblast senescence within controlled, physiologically relevant environments [55].

5.5. Translational Therapeutic Opportunities

Current management strategies—including surgical debridement, resection, antibiotics, pentoxifylline–tocopherol therapy, hyperbaric oxygen, and laser therapy—offer variable benefit and do not directly target the underlying biological mechanisms of ORNJ. Future therapeutic approaches should address the core pathogenic processes outlined in Section 2.

5.5.1. Anti-Fibrotic Strategies

Inhibitors targeting TGF- β , CTGF, or Smad signaling—currently under investigation for pulmonary and dermal fibrosis—may hold promise for limiting fibro-atrophic progression in irradiated mandibular tissues [9,10,19]. Therapies directed at fibroblast senescence or SASP signaling pathways represent additional potential avenues.

5.5.2. Endothelial-Protective Agents

Radioprotective agents such as statins and ACE inhibitors demonstrate endothelial-preserving effects in experimental models of radiation injury [56]. Given HSP27's established role in maintaining endothelial cytoskeletal integrity and survival [29], modulation of this pathway may represent a promising strategy for protecting mandibular microvasculature following RT.

5.5.3. Redox-Modulating Therapies

Because oxidative stress contributes to both early and late radiation injury [8–11,15], therapies targeting mitochondrial dysfunction and redox imbalance—such as mitochondria-targeted antioxidants (e.g., MitoQ), Nrf2 activators, or NAD⁺-restoration strategies—warrant further investigation.

5.5.4. Microbiome-Centered Approaches

Radiotherapy alters oral microbial ecology, and dysbiosis contributes to the amplification of inflammation within exposed bone lesions. Microbiome-directed strategies—including probiotics, targeted antimicrobial approaches, or biofilm-modulating therapies—may help reduce inflammatory burden and infection risk in susceptible patients [22,30,34,57,58].

5.6. Integrating HSP27 into Future ORNJ Research

Given its established roles in oxidative stress regulation [28], apoptosis control [28,29], endothelial stability [29], fibroblast activation [26], and osteoblast–osteoclast cytoskeletal dynamics [50,51], HSP27 represents a particularly compelling candidate for mechanistic and translational investigation in ORNJ. Notably, the biological domains most strongly implicated in ORNJ pathogenesis—vascular injury, fibro-atrophy, oxidative stress, immune dysregulation, and bone remodeling failure—closely correspond to well-recognized functions of HSP27.

Despite this striking mechanistic alignment, no studies have examined HSP27 expression, activation, or regulatory dynamics within irradiated mandibular tissues or ORNJ-specific patient cohorts. This complete evidentiary absence represents a significant scientific gap. Even foundational descriptive investigations—such as mapping HSP27 localization, phosphorylation states, or stress-induced regulatory shifts across stages of ORNJ—could substantially refine pathogenetic models and identify early susceptibility markers.

Future research should therefore prioritize evaluating whether stress-response pathways involving HSP27 contribute to the biological variability observed in ORNJ suscep-

tibility. Experimental studies examining HSP27 expression and activation in irradiated mandibular bone and surrounding soft tissues may clarify how stress-response signaling evolves during radiation-induced tissue injury. Complementary preclinical models will be necessary to determine whether modulation of HSP27 influences key pathogenic processes, including endothelial dysfunction, fibro-atrophic remodeling, and impaired bone turnover. In parallel, clinical investigations assessing associations between circulating or tissue-level HSP27 expression and ORNJ risk may establish the translational relevance of this pathway.

Integrating molecular stress-response markers with conventional dose–volume parameters may ultimately enable the development of biologically informed predictive models that improve risk stratification and guide preventive strategies in modern precision RT. Achieving this goal will require coordinated research efforts that integrate mechanistic biology, biomarker discovery, advanced experimental modeling systems, and biologically rational therapeutic development. Within such a framework, investigating HSP27 offers a promising opportunity to bridge radiation-induced cellular stress responses with the pronounced interindividual heterogeneity observed clinically, thereby advancing the field toward predictive, preventive, and mechanism-based management of radiation-induced mandibular injury. Viewed in this light, ORNJ can be understood not solely as a consequence of radiation dose exposure but also as a disorder of impaired tissue resilience to radiation-induced cellular stress.

6. Conclusions

ORNJ is a clinically significant late toxicity of head and neck radiotherapy, resulting from the combined effects of microvascular injury, hypoxia, oxidative stress, fibro-atrophic remodeling, immune dysregulation, impaired bone turnover, and systemic susceptibility. In this context, HSP27 is identified as a potential, but as yet unvalidated, mediator of tissue resilience. Its roles in redox regulation, endothelial protection, cytoskeletal stabilization, apoptosis control, fibroblast activation, inflammatory signaling, and osteoblast–osteoclast function are closely aligned with pathways involved in ORNJ pathogenesis.

Direct investigation of HSP27 expression, phosphorylation, or functional relevance in irradiated mandibular tissues or ORNJ cohorts has not yet been conducted. The current review is intended as a hypothesis-generating framework rather than an assertion of causality. It remains to be determined whether HSP27 primarily supports adaptive repair following radiation injury or, under conditions of chronic hypoxia and fibro-inflammatory remodeling, contributes to the persistence of dysfunctional stromal and bone-cell populations. This context-dependent role requires experimental and clinical validation.

Future research priorities include molecular profiling of irradiated mandibular tissues, stage-specific assessment of HSP27 expression and phosphorylation, integration of tissue-, salivary-, or serum-derived HSP27 markers with clinical and dosimetric risk models, and mechanistic testing in radiation-injury models. These approaches may clarify the role of HSP27 as a biomarker of susceptibility, a mediator of disease progression, or a therapeutically targetable stress-response pathway in ORNJ.

Author Contributions: Conceptualization, E.T., D.T., E.S., D.O., S.B. and U.S.; methodology, E.T., D.T., E.S., D.O., S.B. and U.S.; software, E.T., D.T., E.S., D.O., S.B. and U.S.; validation, E.T., D.T., E.S., D.O., S.B. and U.S.; formal analysis, E.T., D.T., E.S., D.O., S.B. and U.S.; investigation, E.T., D.T., E.S., D.O., S.B. and U.S.; resources, E.T., D.T., E.S., D.O., S.B. and U.S.; data curation, E.T., D.T., E.S., D.O., S.B. and U.S.; writing—original draft preparation, E.T., D.T., E.S., D.O., S.B. and U.S.; writing—review and editing, E.T., D.T., E.S., D.O., S.B. and U.S.; visualization, E.T., D.T., E.S., D.O., S.B. and U.S.; supervision, E.T., D.T., E.S., D.O., S.B. and U.S.; project administration, E.T., D.T., E.S., D.O., S.B. and U.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study.

Acknowledgments: The authors confirm that all figures included in the manuscript were created by the authors specifically for this study. The figures are original and were prepared using BioRender.com. The authors clarify that AI-based tools (Grammarly Premium, web version) were used solely for language editing and improvement of English clarity and readability. The scientific content, data interpretation, figure design, and overall intellectual contribution are entirely the authors' work. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

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