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Narrative Review

Pentoxifylline–Tocopherol Therapy for Osteoradionecrosis in the IMRT Era: A Narrative Review with a Conceptual Framework

Efsun Somay[1]*, Erkan Topkan[2] Sibel Bascil[3], Duriye Ozturk[4] and Ugur Selek[5]

[1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Baskent University, Turkey

[2]Department of Radiation Oncology, Faculty of Medicine, Baskent University, Adana, Turkey

[3]Department of Periodontology, Faculty of Dentistry, Baskent University, E-mail: Ankara, Turkey

[4]Department of Radiation Oncology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey

[5]Department of Radiation Oncology, School of Medicine, Koc University, Istanbul, Turkey

***Corresponding Author:** Efsun Somay, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Baskent University, Turkey.

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Abstract

Osteoradionecrosis of the jaw (ORN) remains a significant late complication of head and neck radiotherapy (RT), despite substantial advances in treatment planning and dose optimization. The adoption of intensity-modulated RT (IMRT) has fundamentally altered the mandibular dose distribution, shifting the dominant injury pattern from focal high-dose necrosis toward more diffuse low- to intermediate-dose–related endothelial dysfunction, chronic inflammation, and progressive fibro-atrophic remodeling. Although fibro-atrophy remains implicated as a downstream component of ORN pathogenesis, this shift in radiation injury geometry under IMRT introduces uncertainty as to whether therapeutic strategies developed to counter classic radiation-induced fibro-atrophy—such as pentoxifylline–tocopherol (PENTO)—adequately address the contemporary biological mechanisms driving ORN, given that their clinical rationale and supporting evidence are largely rooted in pre-IMRT paradigms. In this context, this narrative review presents mechanistic insights, along with contemporary clinical data, to examine whether PENTO behaves differently in the IMRT era. Available evidence suggests that variability in reported clinical outcomes is unlikely to reflect altered pharmacological activity of the drug itself, but rather differences in the underlying radiobiological substrate, disease stage, and timing of intervention. Under IMRT, biologically active injury processes may persist within structurally preserved mandibular bone, potentially redefining the therapeutic window during which antifibrotic modulation remains effective. Nevertheless, most published studies derive from mixed or pre-IMRT cohorts and lack systematic stratification by RT technique, mandibular dose–volume parameters, and standardized ORN staging, thereby limiting interpretability. We therefore propose a conceptual framework in which the clinical relevance of antifibrotic therapy is determined primarily by biological stage and tissue activity rather than RT modality alone, underscoring the need for future studies integrating contemporary dosimetry, standardized outcome measures, and biologically informed patient selection to clarify the role of PENTO-based strategies in the management of ORN in the IMRT era.

Keywords: Osteoradionecrosis; Intensity-Modulated Radiotherapy; Radiation-Induced Fibroatrophy; Pentoxifylline; Tocopherol; Antifibrotic Therapy; Mandibular Radiobiology; Head and Neck Cancer

Highlights

- IMRT alters mandibular radiobiology by shifting injury from focal high-dose necrosis to diffuse fibro-atrophic remodeling induced by low-to-intermediate doses.
- The molecular targets of PENTO remain unchanged. Variability in outcomes is due to differences in disease stage and biological context, not changes in drug efficacy.
- In the IMRT era, the optimal timing for antifibrotic therapy may be earlier, during active endothelial dysfunction, inflammation, and fibro-atrophy.
- Most clinical evidence for PENTO-based therapy comes from mixed or pre-IMRT cohorts, which limits its relevance to current practice.
- Biologically informed patient selection, integration of mandibular dosimetry, and standardized outcome measures are essential for future studies.

Introduction

Osteoradionecrosis of the jaw (ORN) is a serious late complication of head and neck radiotherapy (RT), defined by the presence of persistently exposed irradiated bone that fails to heal for at least three months in the absence of tumor recurrence or metastatic disease [1]. Historically, ORN was primarily attributed to radiation-induced hypoxia, hypovascularity, and hypocellularity of bone tissue [1]. Subsequent experimental and clinical investigations expanded this paradigm, leading to the concept of radiation-induced fibro-atrophy (RIFA) as the central biological process underlying progressive post-RT tissue injury. RIF is characterized by endothelial dysfunction, chronic inflammation, oxidative stress, dysregulated fibroblast activity, extracellular matrix remodeling, and progressive tissue atrophy, ultimately resulting in impaired wound healing and necrosis [2]. Importantly, this model was largely established during the era of conventional and three-dimensional conformal RT (3D-CRT), when mandibular radiation exposure was typically high and spatially less constrained.

Building on the radiation-induced fibro-atrophy (RIFA) framework, antifibrotic medical strategies have been proposed to modulate the complex cascade of tissue injury triggered by radiation exposure [2]. Delanian and Lefaix introduced the combination of pentoxifylline and tocopherol (PENTO) as a pharmacological approach specifically designed to counteract key mechanisms of radiation injury, including microvascular dysfunction, persistent inflammatory cytokine signaling, and oxidative stress [2]. Pentoxifylline, a methylxanthine derivative, improves blood flow through hemorheological effects by reducing blood viscosity and enhancing erythrocyte flexibility, and also exerts anti-inflammatory activity, notably by inhibiting tumor necrosis factor-α (TNF-α) production [3]. Tocopherol (vitamin E), a lipid-soluble antioxidant, protects cellular membranes from lipid peroxidation, thereby limiting radiation-induced free radical damage and attenuating fibroblast activation and collagen deposition [4]. Clinical studies have reported that prolonged PENTO therapy may result in partial resolution or stabilization of ORN lesions, which are otherwise challenging to manage [5,6]. Moreover, in cases refractory to PENTO alone, the addition of clodronate—a non-nitrogen-containing bisphosphonate—to the PENTOCLO regimen has been proposed to further modulate bone remodeling by inhibiting osteoclast-mediated bone resorption [5,6]. Collectively, these observations support the concept that radiation-induced tissue injury, once considered largely irreversible, may be at least partially biologically modifiable through targeted pharmacological intervention, with potential implications for improving outcomes in patients with radiation-associated complications [2].

The introduction of intensity-modulated RT (IMRT) has significantly altered mandibular dose distribution in the treatment of head and neck cancer [7]. Compared with conventional RT techniques, IMRT reduces the volume of the mandible exposed to high radiation doses by improving conformality and sparing organs at risk, while concomitantly increasing the extent of low-to-intermediate dose exposure across broader anatomical regions. Dosimetric analyses have consistently demonstrated marked reductions in high-dose parameters, such as V60, alongside increases in moderate-dose volumes, including V30–40 [3]. These shifts in dose distribution have been associated with notable changes in the clinical presentation and epidemiology of ORN, which in the IMRT era tends to present later, exhibits greater heterogeneity in severity, and more frequently reflects multifactorial etiologies involving dental, periodontal, and inflammatory cofactors rather than focal high-dose bone necrosis alone [3,4]. This evolving phenotype likely reflects the interaction between altered radiation injury patterns and changing patient risk profiles, influenced by advances in dental care, comorbidity management, and oncologic outcomes. Despite these substantial radiobiological and clinical

changes, antifibrotic treatment strategies such as pentoxifylline–tocopherol (PENTO), with or without clodronate (PENTOCLO), have not been systematically reevaluated or optimized in the context of IMRT [8]. Most published studies assessing these regimens do not stratify patients by RT technique, detailed mandibular dose–volume parameters, or contemporary risk factors, thereby limiting the applicability of their findings to modern clinical practice [8,9]. Consequently, uncertainty persists regarding whether the biological targets, therapeutic mechanisms, and optimal treatment windows of PENTO-based strategies remain consistent in an era defined by fundamentally altered dose distribution and injury patterns [2,9].

The critical knowledge gap, therefore, lies in whether antifibrotic therapy—particularly regimens such as PENTO—retains comparable efficacy and operates through the same biological mechanisms when applied under the distinct radiobiological conditions created by IMRT, rather than by conventional techniques. By fundamentally altering the spatial and temporal patterns of tissue injury, IMRT may modify both the biological targets of antifibrotic agents and the therapeutic window within which such interventions are most effective. Clarifying the role of PENTO in the IMRT era is essential for optimizing patient selection, refining treatment timing and duration, and interpreting clinical outcomes within the context of contemporary head and neck RT. Addressing this gap will also inform the design of future biologically informed clinical trials and support the development of more personalized antifibrotic strategies to improve outcomes in patients with radiation-associated complications. Accordingly, this narrative review aims to integrate mechanistic insights and contemporary clinical evidence to critically evaluate the biological rationale, therapeutic relevance, and contextual applicability of PENTO-based antifibrotic strategies in the management of ORN in the IMRT era.

Biological Rationale of PENTO: Mechanistic targets within radiation-induced fibro-atrophy

The biological rationale for PENTO therapy is grounded in its capacity to modulate the complex, self-sustaining cascade underlying RIFA, a chronic pathological process distinct from acute radiation injury [2]. RIFA is initiated by radiation-induced endothelial cell damage, leading to capillary rarefaction, impaired nitric oxide signaling with consequent disruption of vasodilation and blood flow, increased vascular permeability with plasma protein extravasation, and ultimately chronic tissue hypoxia due to reduced oxygen delivery [2,10]. These vascular alterations establish a permissive microenvironment that perpetuates tissue injury by sustaining inflammatory signaling—characterized by upregulation of cytokines such as transforming growth factor-β (TGF-β) and tumor necrosis factor-α (TNF-*α)*—and by amplifying oxidative stress through the accumulation of reactive oxygen species (ROS). Persistent inflammation and oxidative damage, in turn, promote fibroblast proliferation and differentiation into myofibroblasts, specialized effector cells responsible for excessive deposition of extracellular matrix (ECM), including collagen and fibronectin [9]. This aberrant ECM remodeling drives progressive tissue stiffening, loss of functional integrity, impaired regenerative capacity, and ultimately irreversible tissue atrophy and organ dysfunction by targeting multiple nodes within this pathological sequence. PENTO therapy is designed to disrupt the progression of RIF and mitigate structural and functional tissue deterioration [10], providing the mechanistic basis for antifibrotic pharmacological intervention.

Pentoxifylline targets several upstream components of the radiation-induced fibrotic process [3,5]. As a non-selective phosphodiesterase inhibitor, pentoxifylline increases intracellular cyclic adenosine monophosphate (cAMP) levels in multiple cell types, including endothelial cells, leukocytes, and fibroblasts [11]. Elevated cAMP exerts broad anti-inflammatory effects by suppressing the production and release of pro-inflammatory cytokines, most notably TNF-α, interleukin-1β (IL-1β), and interleukin-6 (IL-6) [8,9]. TNF-α, in particular, plays a central role in sustaining radiation-induced inflammation by promoting endothelial activation—thereby enhancing leukocyte adhesion and transmigration—stimulating fibroblast proliferation and activation, and driving excessive collagen synthesis and deposition. Persistent TNF-α signaling fosters a pro-fibrotic microenvironment that facilitates the transition from potentially reversible radiation injury to established, self-perpetuating fibrosis, a hallmark of late radiation toxicity [10,11].

Beyond its anti-inflammatory properties, pentoxifylline also modulates blood rheology by improving erythrocyte deformability, reducing blood viscosity, and decreasing platelet aggregation, thereby enhancing microvascular perfusion and oxygen delivery to irradiated tissues [12]. By alleviating microvascular hypoperfusion and chronic hypoxia—key contributors to the perpetuation of fibrosis—pentoxifylline may help restore a more favorable tissue

microenvironment and support tissue repair and remodeling [13]. Taken together, these pleiotropic pharmacological effects position pentoxifylline as a rational candidate for interrupting the feed-forward cycles of inflammation, hypoxia, and fibrosis that underlie radiation-induced tissue injury [14].

Tocopherol (vitamin E) primarily targets oxidative stress pathways that are central to the pathogenesis of radiation-induced tissue injury and fibrosis [15]. Ionizing radiation induces both immediate and sustained generation of ROS, not only as a direct consequence of radiation exposure but also through secondary mechanisms, including mitochondrial dysfunction, chronic inflammation, and activation of oxidase enzymes in irradiated tissues [16]. Persistent ROS drives a cascade of molecular and cellular damage, including lipid peroxidation, DNA strand breaks, and protein oxidation. In addition to their cytotoxic effects, ROS act as signaling molecules that activate redox-sensitive transcription factors—such as nuclear factor-*κB* (NF-*κB*) and activator protein-1 (AP-1)—thereby upregulating profibrotic gene expression, including components of the transforming growth factor-β (TGF-β) signaling pathway [2,17].

As a lipid-soluble antioxidant, tocopherol readily incorporates into cellular membranes, where it scavenges lipid peroxyl radicals and interrupts the chain reactions of lipid peroxidation, thereby preserving membrane integrity [15]. Beyond direct radical neutralization, tocopherol stabilizes endothelial and stromal cells, reducing susceptibility to ROS-mediated injury and dysfunction [18]. By attenuating oxidative stress–driven amplification of fibro-atrophic signaling, tocopherol limits persistent fibroblast activation and excessive extracellular matrix deposition that characterize chronic RIFA

Importantly, oxidative stress remains a key driver of late radiation injury long after completion of RT, sustained by ongoing mitochondrial dysfunction and chronic inflammatory signaling [19]. This provides a biological rationale for antioxidant therapy not only during the acute phase but also as a long-term strategy to mitigate progressive tissue damage and fibrosis in irradiated tissues [20]. Accordingly, tocopherol's membrane-protective and broad-spectrum antioxidant properties constitute a critical component of multimodal antifibrotic strategies aimed at preventing and treating radiation-induced fibro-atrophy.

The combined administration of pentoxifylline and tocopherol—referred to as PENTO therapy—is designed to exert synergistic and complementary effects on the principal pathophysiological mechanisms driving RIFA [2]. Pentoxifylline primarily targets microvascular dysfunction and chronic inflammation by improving blood flow, reducing blood viscosity, and suppressing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (ref). Tocopherol, in contrast, specifically addresses oxidative stress by scavenging ROS within cellular membranes, thereby limiting lipid peroxidation and stabilizing endothelial and stromal cells [2]. Together, these agents disrupt the self-perpetuating cycles of hypoxia, inflammation, and oxidative damage that sustain fibroblast activation and excessive extracellular matrix deposition in irradiated tissues [2,5].

Rather than promoting direct osteogenesis or bone regeneration, PENTO therapy is intended to modify the biological microenvironment by attenuating inflammatory and fibrotic signaling, restoring microvascular perfusion, and slowing the progression of tissue stiffening and atrophy [21]. This mechanistic paradigm is consistent with clinical observations in patients with ORN receiving antifibrotic therapy, in whom therapeutic responses are typically delayed and gradual [5,6]. Such outcomes likely reflect the slow remodeling and reorganization of chronically fibrotic tissue, a process that requires sustained intervention to achieve meaningful structural and functional improvement rather than rapid or complete reversal of established damage [13]. By targeting the underlying biological drivers of fibrosis, PENTO provides a rationale for long-term disease-modifying management to improve tissue viability, alleviate symptoms, and potentially limit disease progression [10].

In selected cases, clodronate has been incorporated into PENTO-based regimens (PENTOCLO) to address abnormalities in bone turnover within irradiated tissue, particularly in the setting of ORN [5]. Clodronate is a first-generation, non-nitrogenous bisphosphonate that inhibits osteoclast activity and survival, thereby reducing osteoclast-mediated bone resorption [5]. By limiting excessive bone breakdown, clodronate may help stabilize bone architecture and prevent further loss of bone mass in regions already compromised by radiation-induced vascular injury and chronic hypoxia [22]. In addition to its anti-resorptive effects, clodronate has demonstrated anti-inflammatory

properties, including attenuation of macrophage activation and downregulation of pro-inflammatory cytokine release, which may further mitigate the chronically inflamed microenvironment characteristic of irradiated tissues [23]. Importantly, clodronate does not profoundly suppress osteoblast function, thereby preserving baseline capacity for bone formation and remodeling [24]. Rather than promoting active osteogenesis, the principal therapeutic objective of clodronate in this context is to stabilize irradiated bone and limit progressive structural deterioration within a compromised microvascular milieu [5]. This distinction is clinically relevant, as excessive suppression of bone remodeling—such as that associated with more potent nitrogen-containing bisphosphonates—may be counterproductive in tissues already marked by impaired healing and regenerative capacity [5]. Accordingly, careful patient selection and close monitoring of bisphosphonate therapy are essential to balance bone stabilization against the risk of further compromising tissue repair [5].

From a mechanistic perspective, the presence of active inflammatory and fibro-atrophic processes within affected tissues is closely linked to the therapeutic efficacy of PENTO therapy [9,10]. In early and intermediate stages of disease, when inflammation, microvascular dysfunction, and aberrant fibrotic activity are most pronounced, PENTO is biologically positioned to exert its maximal anti-inflammatory and antifibrotic effects [6]. By contrast, in advanced stages characterized by extensive cortical bone destruction, secondary infection, and gross structural collapse, the availability of viable biological targets for antifibrotic modulation becomes markedly reduced [6,10]. At this stage, the tissue microenvironment is less responsive to pharmacological intervention, and the potential for meaningful therapeutic benefit is substantially limited [3,6]. This stage-dependent responsiveness highlights the critical importance of treatment timing and biologically informed patient selection, underscoring that optimal outcomes with PENTO depend on intervention during phases of active, modifiable tissue injury rather than end-stage structural failure [3,6,10].

Given that IMRT fundamentally alters the spatial distribution of radiation dose, it also reshapes the biological landscape of late radiation injury. Rather than producing relatively uniform tissue damage, IMRT generates highly heterogeneous injury patterns, with focal high-dose regions interspersed among larger areas exposed to low-to-intermediate doses. This heterogeneity may shift the dominant pathological processes toward more diffuse, persistent inflammation, oxidative stress, and fibro-atrophic remodeling, while sparing adjacent tissues. Whether PENTO effectively targets these IMRT-specific injury patterns—and the altered balance of biological drivers they entail—remains uncertain. This unresolved mechanistic mismatch represents a critical translational gap and sets the stage for reevaluating antifibrotic strategies within the context of modern RT (Table 1, Figure 1).

Study	Study design/ population	Radiotherapy technique	ORN characteristics	PENTO-based regimen	Main outcomes	Relevance to IMRT era
Delanian., *et al*. 2011 [3]	Phase II, single-arm; refractory mandibular ORN	Mixed/not specified	Advanced ORN, exposed bone	PENTOCLO (long-term)	High rates of mucosal healing and symptom resolution	Foundational biological efficacy; pre-IMRT paradigm
Robard., *et al*. 2014 [4]	Observational cohort	Mixed/not specified	Established ORN	PENTOCLO	Partial to complete healing in selected patients	Limited IMRT attribution; heterogeneous RT
Dissard., *et al*. 2020 [16]	Retrospective cohort	Mixed (IMRT included, not stratified)	Stage II–III ORN	PENTOCLO	Clinical improvement in the majority; prolonged treatment required	IMRT is likely represented but not analyzed separately

Martos-Fernández., *et al*. 2018 [17]	Systematic review	Mixed	All ORN stages	PENTO/PENTOCLO	Clinical benefit reported; high heterogeneity	Highlights the lack of RT technique–specific data
Arqueros-Lemus., *et al*. 2023 [18]	Systematic review	Mixed	Variable ORN definitions	PENTO-based regimens	Suggests efficacy in selected cases	Confirms evidence gap in IMRT-specific outcomes
Owosho., *et al*. 2024 [21]	Case series (prophylactic)	IMRT-dominant era	Post-RT extractions	Prophylactic PENTO	Low ORN incidence; feasibility demonstrated	Suggests relevance in trigger-associated IMRT ORN
Carriero and Ouanounou, 2025 [19]	Scoping review	Mixed	All stages	PENTO/PENTOCLO	Evidence low-certainty; no RCTs	Explicitly calls for IMRT-stratified studies
RAPTOR trial (protocol), 2025 [22,23]	Randomized controlled trial (ongoing)	Contemporary RT (IMRT)	Established ORN	PENTOCLO vs standard care	Results pending	First trial designed for modern RT era

Table 1: Clinical studies evaluating PENTO-based therapy and osteoradionecrosis outcomes in the context of radiotherapy technique.

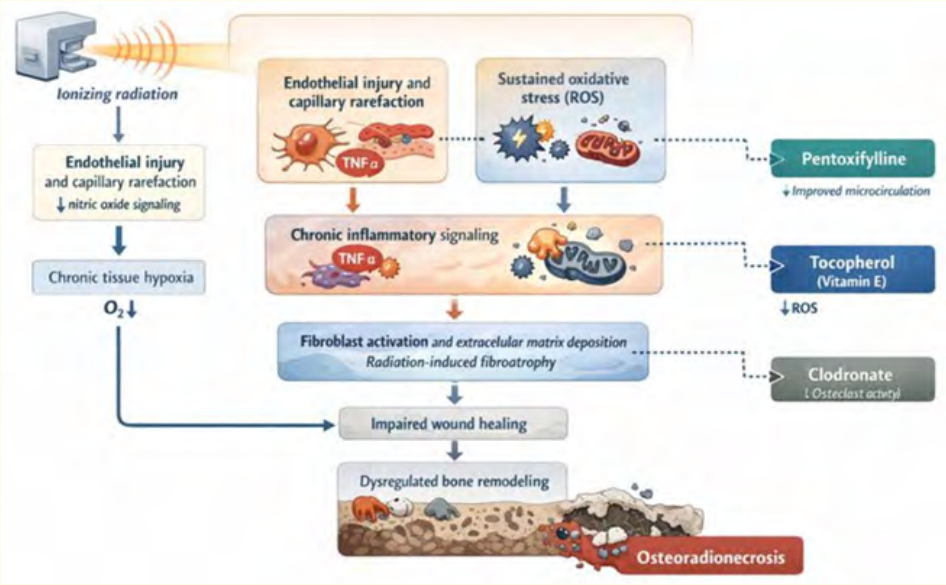

Figure 1: Radiation-induced fibro-atrophy and mechanistic targets of PENTO in osteoradionecrosis.

Note: This figure was created by the authors. Schematic illustrations and graphical elements were generated using BioRender (current academic web-based version, 2025) and Canva (current web-based version, 2025). Final layout optimization, vector refinement, and resolution adjustment for publication were performed using Inkscape (version 1.3.2). No third-party copyrighted images were used.

Impact of IMRT on Mandibular Radiobiology

The transition from conventional RT and 3D-CRT to IMRT has substantially altered the spatial and biological characteristics of radiation exposure to the mandible [25]. IMRT enables highly conformal dose delivery to complex target volumes while reducing high-dose exposure to adjacent organs at risk. As a result, the mandible is less frequently subjected to large contiguous volumes that receive very high radiation doses; however, it is increasingly exposed to broader regions of low- to intermediate-dose irradiation [26]. This shift has important implications for the biological mechanisms underlying mandibular injury and ORN development.

From a dosimetric perspective, IMRT consistently reduces high-dose mandibular parameters such as V60–70 (the percentage of mandible receiving 60–70 Gy), which have traditionally been associated with focal bone necrosis, cortical breakdown, and increased risk of ORN [27]. This reduction in high-dose exposure is a key advantage of IMRT over conventional RT, sparing critical bone structures from severe radiation injury. In parallel, IMRT increases the volume of the mandible exposed to intermediate radiation doses, as reflected by the expansion of the V30–40 ranges [28]. While this redistribution minimizes high-dose hotspots, it exposes a broader proportion of the mandible to lower, yet biologically relevant, radiation levels. Dosimetric studies have demonstrated that diffuse low- and intermediate-dose exposure is particularly prominent in patients requiring bilateral nodal irradiation or complex target coverage [26,28]. Consequently, mandibular injury in the IMRT era may manifest not as focal necrosis but as more widespread, chronic alterations—including progressive fibrosis, vascular injury, and low-grade inflammation—across a larger volume of bone and supporting tissues. These evolving injury patterns have important implications for both the clinical presentation and management of mandibular complications in the IMRT era.

At the tissue level, high-dose focal irradiation predominantly induces direct cellular death, vascular obliteration, and rapid structural compromise [29]. In contrast, low- to intermediate-dose irradiation exerts subtler yet persistent effects on endothelial cells, fibroblasts, immune cells, and the extracellular matrix [30]. Endothelial dysfunction may occur in the absence of overt vessel loss, resulting in impaired nitric oxide signaling, altered vascular permeability, and sustained microvascular instability rather than complete ischemia [31]. These alterations promote a state of chronic low-grade hypoxia and persistent inflammatory signaling, which may predispose irradiated tissues to gradual degeneration and fibro-atrophic remodeling rather than abrupt necrosis [32].

IMRT-associated dose patterns may promote a radiobiological environment characterized by chronic inflammation, oxidative stress, and progressive fibro-atrophic remodeling, rather than predominantly acute necrotic injury [16]. Compared with high-dose radiation damage, these processes tend to evolve more slowly and persist over time. Experimental and clinical evidence suggests that repeated low- to intermediate-dose exposure can sustain long-term activation of profibrotic pathways, including transforming growth factor-β (TGF-β)–mediated signaling and redox-sensitive transcriptional programs, even in the absence of focal high-dose irradiation [2,10]. This biological framework is consistent with the delayed onset of ORN and the longer latency periods frequently reported in patients treated with IMRT compared with earlier RT techniques [8].

Clinically, these radiobiological changes are reflected in altered ORN phenotypes [33]. In the IMRT era, ORN more frequently presents with heterogeneous lesion morphology, variable depth of bone involvement, and a higher prevalence of low-grade or initially asymptomatic disease [5,6]. Rather than manifesting as rapidly progressive cortical necrosis, IMRT-associated ORN often emerges in the setting of compromised mucosal integrity, dental or periodontal inflammation, and impaired wound-healing capacity [5,6]. In this context, local inflammatory and infectious triggers assume a more prominent role in disease initiation, particularly when the underlying bone is biologically weakened by radiation but not yet structurally destroyed [34]. In addition, the expanded low-dose "bath" characteristic of IMRT may involve larger mandibular segments, including regions that were relatively spared with earlier RT techniques [35]. Consequently, fibro-atrophic changes may evolve over broader anatomical areas, potentially reducing the effectiveness of localized surgical or debridement-based interventions and increasing the relevance of systemic therapies aimed at modulating tissue biology [10].

Despite these mechanistic shifts, most clinical frameworks for ORN risk stratification and management continue to emphasize high-dose thresholds derived from pre-IMRT cohorts [1,36,37]. While dose–volume metrics such as V60 remain relevant predictors of mandibular toxicity, they may no longer fully

capture the biological risk landscape in contemporary RT, where dose redistribution rather than absolute peak dose increasingly predominates [36,37]. As IMRT delivers radiation in a more spatially heterogeneous manner, intermediate-dose exposure across larger mandibular volumes—and the associated chronic inflammatory response—becomes increasingly relevant [27]. Moreover, cumulative inflammatory burden and host-related factors, including baseline oral health, periodontal status, and tissue resilience, may become more important in determining mandibular vulnerability in the IMRT era [38-40]. Together, these considerations underscore the need for updated risk models that integrate high-dose metrics with intermediate-dose exposure and individualized patient factors.

In this context, the biological targets of antifibrotic and anti-inflammatory therapies may be more closely aligned with the dominant injury mechanisms observed following IMRT. These mechanisms are characterized by persistent endothelial dysfunction, chronic inflammation, and progressive fibro-atrophic remodeling, rather than the focal high-dose necrosis typical of earlier RT techniques [2,10]. Systemic modulation of inflammatory and oxidative pathways, therefore, represents a biologically plausible therapeutic strategy for patients exposed to diffuse low-to-intermediate radiation doses. Such an approach may address the chronic, low-grade tissue injury and ongoing microvascular dysfunction that increasingly characterize mandibular damage in the IMRT era. However, it remains unclear whether pharmacological interventions originally developed to counteract the consequences of focal, high-dose radiation injury are equally effective against these more diffuse, chronic patterns of tissue damage [5,6].

Clinical Evidence: Are Outcomes Different in the IMRT Era?

The clinical question of whether pentoxifylline–tocopherol–based regimens (PENTO/PENTOCLO) "behave differently" in the IMRT era requires distinction between two related but conceptually distinct evidence domains: (i) changes in baseline ORN incidence and phenotype following the widespread adoption of IMRT, and (ii) therapeutic response to antifibrotic regimens under contemporary RT conditions. Evidence addressing the first domain is derived from multiple clinical cohorts demonstrating a reduction in overall ORN incidence with IMRT-based treatment planning; however, a residual risk persists, particularly among patients with additional local or systemic risk factors and those receiving extensive mandibular irradiation. Beyond incidence alone, several studies have also reported a shift in ORN phenotype in the IMRT era, with a higher proportion of cases presenting as low-grade, indolent, or initially asymptomatic disease rather than rapidly progressive cortical necrosis.

In contrast, evidence informing the second domain—namely, the clinical efficacy of antifibrotic regimens such as PENTO or PENTOCLO in IMRT-treated patients—remains limited. Available studies are constrained by small sample sizes, heterogeneous patient populations, and a lack of systematic stratification according to RT technique, mandibular dose–volume parameters, and contemporary risk profiles. As a result, most published reports do not permit robust assessment of whether antifibrotic therapy performs differently under IMRT-specific dose distributions compared with earlier RT paradigms. This evidentiary gap underscores the need for future studies explicitly designed to evaluate antifibrotic strategies within well-characterized IMRT cohorts, incorporating integrated clinical, biological, and dosimetric assessment.

IMRT-era ORN Incidence and Phenotype: The Moving Baseline Risk

Comparative observational data indicate that IMRT has reduced the overall incidence of ORN compared with conventional RT techniques, consistent with reduced mandibular high-dose exposure and improved sparing of organs at risk [37,41]. Despite these advances, ORN has not been eliminated, and contemporary series increasingly describe more heterogeneous clinical presentations. These include delayed onset, variable depth of bony involvement, a higher proportion of low-grade or slowly progressive disease, and a more prominent contribution of local triggers such as dental extractions and periodontal inflammation [36,38,42]. Several reports further suggest that ORN following IMRT may present with subtler symptoms and be detected later in its course, reflecting a less aggressive clinical trajectory. Consequently, both the baseline probability and clinical phenotype of ORN in IMRT-treated cohorts differ meaningfully from those observed in historical series, complicating direct comparisons of treatment efficacy across RT eras unless careful adjustment is made for dosimetry, disease staging, and co-interventions (Figure 2).

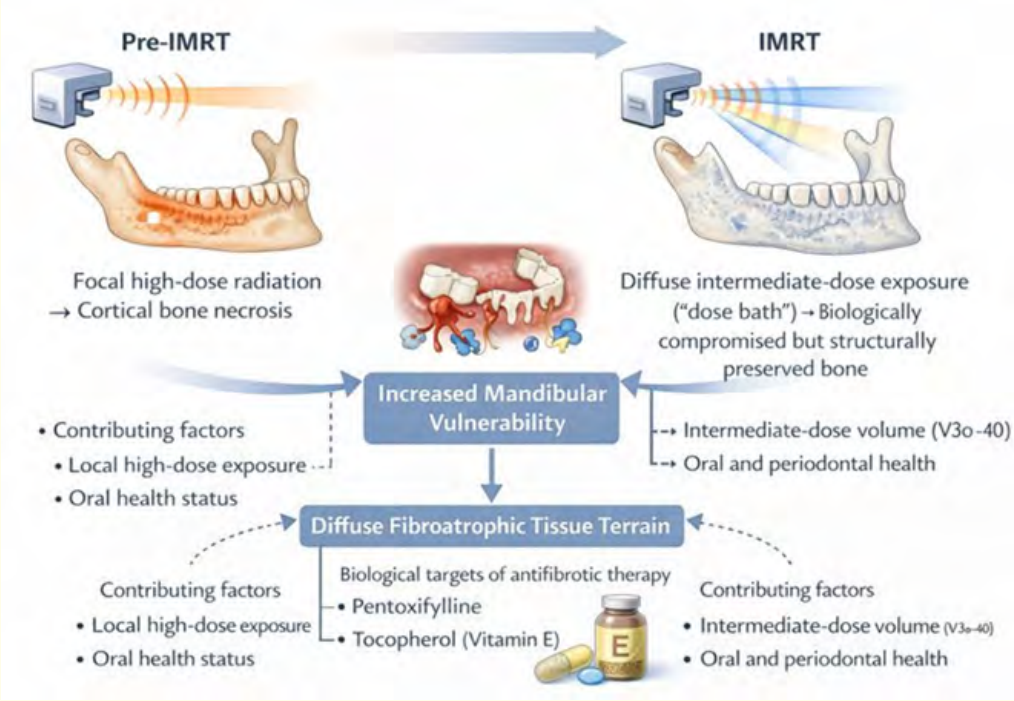

Figure 2: Mechanistic comparison of mandibular radiobiology in the pre-IMRT and IMRT eras and implications for osteoradionecrosis development.

Note: This figure was created by the authors. Schematic illustrations and graphical elements were generated using BioRender (current academic web-based version, 2025) and Canva (current web-based version, 2025). Final layout optimization, vector refinement, and resolution adjustment for publication were performed using Inkscape (version 1.3.2). No third-party copyrighted images were used.

Therapeutic Evidence for PENTO/PENTOCLO: Limited IMRT-specific Attribution

Most clinical studies supporting PENTO-based therapy originate from periods when both conventional RT and IMRT were in use, or else lack sufficient detail on RT technique and mandibular dose distribution to permit IMRT-specific conclusions. The frequently cited phase II experience with prolonged PENTOCLO therapy for refractory mandibular ORN reported high rates of mucosal and bone healing; however, this study was non-randomized and does not allow clear separation of the effects attributable to IMRT-specific dose patterns from selection bias or the influence of concurrent interventions such as surgery or antibiotic therapy [5,6]. More recent institutional cohorts and observational studies have demonstrated variable response rates—often requiring prolonged treatment durations—and have consistently emphasized that disease stage at treatment initiation and the local wound environment play central roles in determining clinical outcomes [10,43]. Notably, many of these studies lack detailed reporting of RT fields and dose–volume parameters, thereby limiting the ability to directly assess the efficacy of PENTO/PENTOCLO in the context of IMRT.

Systematic reviews and meta-analyses reinforce these limitations. Available syntheses consistently conclude that PENTO/PENTOCLO is biologically plausible and associated with clinical improvement in selected cohorts, yet the certainty of evidence remains constrained by heterogeneity in ORN staging, variability in treatment duration, inconsistent use of concurrent surgical or antimicrobial interventions, and incomplete reporting of RT technique [40,44,45]. A 2025 scoping review further

highlighted the absence of adequately powered randomized trials and the difficulty of cross-study comparison due to inconsistent definitions of "healing," variable follow-up intervals, and limited dosimetric characterization [46]. These limitations are particularly consequential in the IMRT era, where intermediate-dose exposure and diffuse tissue compromise may alter both therapeutic targets and the optimal timing of antifibrotic intervention.

Prevention and peri-extraction prophylaxis: Emerging but low-level evidence

A separate and increasingly relevant question in IMRT-treated survivorship is whether PENTO modifies the risk of ORN when administered prophylactically around dental extractions or other mucosal-traumatic events. Early case series and observational reports have explored prophylactic PENTO use in post-radiated patients undergoing extractions; however, these studies are limited by small sample sizes, absence of control groups, and substantial susceptibility to confounding [37,47]. For example, a 2024 initial case series described prophylactic PENTO administration in a small cohort of post-radiated oral and oropharyngeal cancer patients undergoing extractions, with primary emphasis on feasibility and tolerability rather than definitive efficacy outcomes [48]. Although these reports are mechanistically consistent with an IMRT-era model that emphasizes diffuse mandibular vulnerability and the role of local trauma as a trigger for ORN, they do not provide direct evidence that the prophylactic benefit differs specifically with respect to IMRT-related dose distributions. Moreover, interpretation is further limited by potential selection bias, variability in dental technique, differences in baseline mandibular dose, and concurrent preventive measures, thereby precluding firm conclusions regarding efficacy and underscoring the need for controlled, IMRT-stratified prospective studies.

Why IMRT-era "Response" may Appear Different Even if Drug Biology is Unchanged

Even if pentoxifylline and tocopherol exert similar molecular effects across treatment eras, observed clinical response metrics may differ in the IMRT era for several methodological reasons:

- **Shift in lesion substrate:** IMRT reduces focal high-dose necrosis while expanding the volume of tissue exposed to intermediate-dose injury, potentially increasing the proportion of lesions dominated by chronic inflammation and fibro-atrophic remodeling rather than overt cortical devitalization. Consequently, a larger share of cases may present with slowly progressive, low-grade changes rather than rapid bone destruction, making lesions appear more responsive to antifibrotic therapy even when the underlying drug biology is unchanged [36,37].
- **Stage migration and earlier detection:** Enhanced surveillance and advances in imaging have enabled earlier detection of ORN at less advanced stages than in prior eras. As a result, a greater proportion of patients initiate treatment during indolent or low-grade disease phases, which can inflate apparent response rates to therapies such as PENTO, as milder lesions are inherently more likely to stabilize or improve regardless of intervention [42].
- **Confounding by co-interventions:** Many clinical series evaluate PENTO in combination with surgical debridement, sequestrectomy, antibiotics, or other adjunctive measures, making it difficult to isolate the independent effect of antifibrotic therapy. This challenge is amplified in contemporary practice, where multimodality supportive care—including optimized wound management and infection control—is more consistently applied, further complicating attribution of treatment effects [44-46].
- **Inadequate dosimetric stratification:** Many studies fail to report detailed mandibular dose–volume histogram (DVH) parameters, such as V60 or the extent of intermediate-dose exposure. Without such data, comparisons across RT eras or techniques are inherently confounded, as "IMRT" itself is not a biological variable; rather, tissue response is determined by the dose distribution delivered to the mandible. The absence of dosimetric stratification, therefore, limits accurate assessment of treatment effects and cross-study comparability [36,37].

Taken together, these methodological factors underscore that apparent differences in clinical response in the IMRT era should not be interpreted as evidence of altered drug biology, but rather as a reflection of evolving disease substrates, detection practices, and treatment contexts (Figure 3).

Clinical trials and the current evidence gap

The persistence of uncertainty regarding the true efficacy of pentoxifylline–tocopherol–based regimens (PENTO/PENTOCLO),

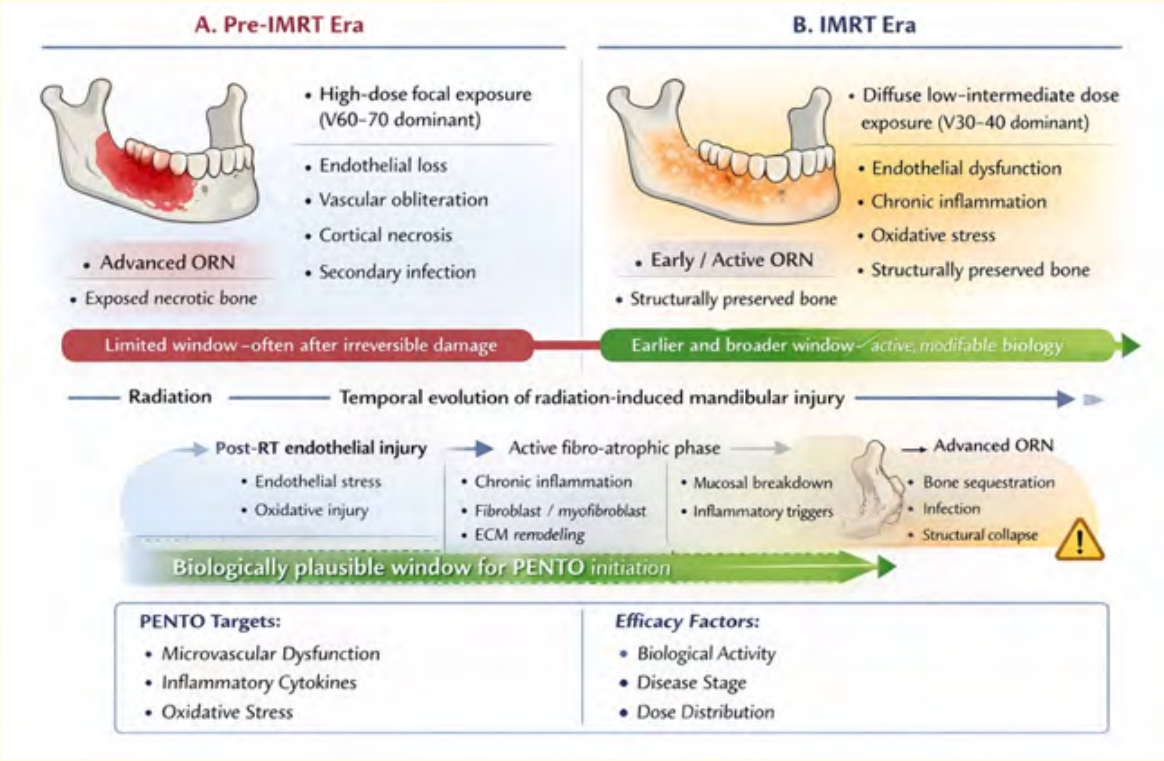

Figure 3: Stage- and biology-dependent window of efficacy for PENTO-based therapy across radiotherapy eras.

Note: This schematic illustrates a conceptual, stage-dependent model of antifibrotic efficacy for pentoxifylline–tocopherol–based therapy (PENTO/PENTOCLO) across radiotherapy eras, incorporating the temporal evolution of radiation-induced mandibular injury. In the pre-IMRT era (left panel), focal high-dose radiation exposure predominates, leading to rapid endothelial loss, vascular obliteration, cortical devitalization, and early structural failure. In this setting, radiation-induced fibro-atrophy typically emerges downstream of irreversible tissue damage, resulting in a narrow therapeutic window in which antifibrotic intervention is biologically relevant. In contrast, the IMRT era (right panel) is characterized by reduced high-dose exposure and expanded low-to-intermediate dose irradiation, promoting persistent endothelial dysfunction, chronic inflammation, oxidative stress, and progressive fibro-atrophic phase.

Note: This figure was created by the authors. Schematic illustrations and graphical elements were generated using BioRender (current academic web-based version, 2025) and Canva (current web-based version, 2025). Final layout optimization, vector refinement, and resolution adjustment for publication were performed using Inkscape (version 1.3.2). No third-party copyrighted images were used.

particularly in the context of IMRT, has prompted the initiation of randomized clinical trials. The NIHR-funded RAPTOR (Randomised Controlled Trial of PENTOCLO in Mandibular Osteoradionecrosis) is a phase II, open-label, multicentre, randomised controlled superiority trial comparing PENTOCLO plus standard of care with standard supportive care alone in patients with mandibular ORN, and is specifically designed to generate higher-certainty evidence regarding therapeutic efficacy [49,50]. Until such randomized data become available, current guideline-level discussions acknowledge medical therapy—including PENTO-based approaches—as a potential option for selected patients, while continuing to emphasize the limited quality of existing evidence and the

importance of individualized decision-making. In this setting, integration of medical therapy with careful assessment of disease stage, optimization of oral health, and appropriate consideration of surgical intervention within a multidisciplinary framework remains essential [42].

Synthesis

Current evidence supports the conclusion that IMRT has altered mandibular dose distribution and the epidemiology of ORN; however, it does not yet demonstrate, with high confidence, that clinical outcomes with pentoxifylline–tocopherol–based regimens (PENTO/PENTOCLO) are systematically different solely as a consequence of IMRT. Although observational reports and case series suggest potential therapeutic benefit, these studies frequently lack appropriate comparator groups and provide insufficient granularity regarding RT technique, mandibular dose–volume histogram (DVH) metrics, and standardized ORN staging. The dominant gap in the current literature is therefore not the absence of encouraging observational signals, but rather the lack of studies that explicitly integrate (i) RT technique with detailed mandibular dosimetry, (ii) standardized definitions of ORN stage and treatment response, and (iii) rigorous controlled comparisons. In the absence of these elements, it remains difficult to determine whether apparent differences in PENTO/PENTOCLO response reflect IMRT-specific biological effects or instead arise from shifts in patient selection, disease stage at treatment initiation, or reporting bias. Addressing this gap is essential to clarify whether antifibrotic therapy in the IMRT era should be repositioned toward earlier-stage disease, trigger-associated prevention strategies, or biologically informed patient selection, rather than extrapolated directly from historical cohorts dominated by focal high-dose necrosis.

A Conceptual Model: Same drug, different window of efficacy

Variability in clinical outcomes reported for PENTO-based therapy across different RT eras can be explained primarily by differences in the temporal and biological context of radiation-induced tissue injury, rather than by changes in the pharmacological properties of the drugs themselves. The core molecular targets of PENTO—microvascular dysfunction, inflammatory cytokine signaling, and oxidative stress—remain unchanged; however, the relative contribution, persistence, and reversibility of these processes differ substantially between pre-IMRT and IMRT radiobiological environments [2,10]. This distinction underpins a stage- and biology-dependent window-of-efficacy model, summarized schematically in Figure X.

In pre-IMRT cohorts, mandibular injury was predominantly driven by focal exposure to high radiation doses, resulting in rapid endothelial loss, vascular obliteration, cortical bone devitalization, and early structural failure [1,36,37]. Under these conditions, radiation-induced fibro-atrophy typically represented a downstream or secondary process occurring after irreversible tissue damage had already developed. Consequently, antifibrotic therapy was often initiated in advanced disease stages characterized by exposed necrotic bone and secondary infection, in which the primary biological targets of PENTO were no longer the dominant drivers of pathology. Reported clinical effects in this setting are therefore more consistent with stabilization of surrounding soft tissues or modulation of inflammatory margins than with reversal of established osseous necrosis [5,6,44].

In contrast, IMRT has shifted mandibular radiation exposure toward diffuse, low-to-intermediate-dose distributions in most patients, with reduced high-dose volumes and expanded regions of subthreshold irradiation [36,37]. This dose pattern favors persistent endothelial dysfunction, chronic low-grade inflammation, and oxidative stress without immediate cortical destruction. Fibro-atrophic remodeling in this context evolves gradually and may remain biologically active for prolonged periods before overt clinical manifestation. As a result, the biological pathways targeted by PENTO are more likely to be present and modifiable at earlier stages of tissue injury in IMRT-treated patients [2,10,39], thereby expanding the potential therapeutic window (Figure 1). Within this conceptual framework, the efficacy of PENTO is primarily determined by disease stage and biological activity at the time of treatment initiation, rather than by the RT technique per se. The therapeutically relevant window is expected to precede extensive bone sequestration and structural collapse, when vascular dysfunction, inflammatory signaling, and oxidative stress remain central components of the injury process. Application of antifibrotic therapy outside this window—particularly in advanced ORN dominated by necrotic bone and infection—is biologically less likely to yield meaningful tissue recovery [42,45].

This model also provides a mechanistic explanation for the heterogeneity observed across clinical studies employing similar

PENTO-based regimens. Differences in reported outcomes are likely driven by variation in mandibular dose–volume distribution, inflammatory burden, timing of intervention, and local triggering factors, rather than inconsistent drug efficacy [36,37,44]. Failure to account for these variables limits the interpretability of existing evidence and complicates comparisons between historical and contemporary cohorts. From a translational perspective, this conceptual framework supports the re-evaluation of PENTO-based therapy with respect to RT technique, dose distribution, and timing, rather than the uniform application across all stages of ORN. Future studies should explicitly integrate mandibular dosimetry, standardized staging, and temporal markers of tissue injury to define biologically appropriate indications for antifibrotic intervention [40,46,49]. In summary, the IMRT era necessitates not the modification of antifibrotic pharmacology, but reassessment of the biological conditions under which these agents are most likely to exert therapeutic benefit.

Clinical implications and future directions

Clinical Implications and Stage-/Biology-informed use of antifibrotic therapy

The mechanistic differences in mandibular radiobiology between pre-IMRT and IMRT eras have direct implications for both the clinical application of antifibrotic therapies and the design of contemporary studies. Unlike older RT techniques, IMRT predominantly induces diffuse low- to intermediate-dose–related injury characterized by persistent endothelial dysfunction, chronic inflammatory signaling, and progressive fibro-atrophic remodeling, rather than focal high-dose–induced tissue necrosis [2,10,36,37]. As a consequence, mandibular ORN in the IMRT era more commonly manifests as slowly progressive, low-grade disease rather than abrupt cortical necrosis. Therapeutic strategies extrapolated from historical, high-dose necrosis–driven models may therefore inadequately address the dominant biological processes operating in IMRT-treated tissues, underscoring the need for updated treatment paradigms that reflect these mechanistic shifts.

Intermediate-dose radiation exposure sustains endothelial activation and microvascular instability without complete vascular obliteration, thereby maintaining a chronic hypoxic and pro-inflammatory tissue microenvironment. This state supports ongoing cytokine release, oxidative stress, and fibroblast-mediated extracellular matrix remodeling—core mechanisms of radiation-induced fibro-atrophy that may remain biologically active over extended periods [2,10]. Under these conditions, antifibrotic therapies targeting vascular dysfunction, inflammatory mediators, and redox imbalance are more likely to engage relevant molecular pathways than in tissues dominated by irreversible, high-dose injury, where cellular and vascular targets may already be lost.

These considerations indicate that clinical responsiveness to antifibrotic intervention is governed primarily by the biological stage of tissue injury at treatment initiation, rather than by RT technique alone. Antifibrotic therapy is therefore most likely to confer benefit when applied during phases of active inflammation and fibro-atrophic remodeling, before the development of extensive bone sequestration, secondary infection, and structural collapse—settings in which therapeutically relevant biological targets are markedly diminished [36,37]. Accordingly, future clinical strategies should emphasize stage- and biology-informed patient selection and timing of intervention. From a research perspective, prospective studies should incorporate standardized ORN staging, detailed mandibular dosimetry, and temporal markers of tissue injury to enable meaningful stratification and to improve the interpretability and translatability of results in the IMRT era.

Integration with dental and supportive care strategies

The IMRT-era phenotype of ORN highlights the increased contribution of local triggering factors—such as dental extractions, periodontal inflammation, and mucosal trauma—to both disease initiation and progression [38,40]. This shift underscores the importance of proactively managing local risk factors as a central component of ORN prevention in IMRT-treated patients. Accordingly, antifibrotic therapy should be viewed not as a stand-alone intervention but as one element of a comprehensive, multimodal supportive care strategy that includes meticulous oral hygiene, atraumatic dental techniques, and prompt identification and treatment of local infection or inflammation [38,40,42]. Close collaboration among radiation oncologists, dental specialists, and oral and maxillofacial surgeons is therefore increasingly important to ensure coordinated care that addresses modifiable risk factors before, during, and after RT.

Observational studies have explored peri-procedural or prophylactic administration of pentoxifylline–tocopherol–based therapy (PENTO) in selected post-radiated patients undergoing

dental extractions, demonstrating that this approach is feasible and generally well tolerated [48]. However, available data remain insufficient to support routine clinical implementation, as evidence regarding long-term efficacy, optimal timing, and appropriate patient selection is limited. Most published reports are constrained by small sample sizes, absence of control groups, and relatively short follow-up, precluding firm conclusions regarding risk reduction. Consequently, current findings should be interpreted as hypothesis-generating and underscore the need for prospective, well-controlled studies integrating dental risk stratification and contemporary RT dosimetry, rather than serving as a basis for generalized prophylactic use.

Implications for outcome assessment

Heterogeneity in outcome definitions has substantially limited interpretation of studies evaluating antifibrotic therapy for ORN. In the IMRT era—where mandibular injury is often diffuse, slowly progressive, and less likely to manifest as rapid tissue necrosis—exclusive reliance on traditional endpoints such as complete mucosal healing or radiographic resolution may fail to capture clinically meaningful benefit. Greater emphasis should therefore be placed on alternative outcome measures, including disease stabilization, prevention of progression, symptom control, and patient-reported functional outcomes such as pain, oral function, and quality of life [44-46]. Adoption of standardized ORN staging systems and uniform response criteria that integrate both objective findings and patient-centered outcomes is essential to enable valid comparisons across studies and RT eras [42,45]. In addition, longer follow-up durations and systematic reporting of adverse events are required to adequately characterize the long-term benefit–risk profile of antifibrotic therapies within this evolving clinical context.

Directions for future research

Future studies should explicitly integrate RT technique, detailed mandibular dose–volume metrics, and biological staging into their design to improve the quality, interpretability, and clinical relevance of evidence. In particular, stratification by intermediate-dose exposure—such as the volume of mandible receiving 30–40 Gy—should be prioritized over exclusive reliance on high-dose thresholds (e.g., V60), as intermediate-dose effects are particularly pertinent in IMRT-treated cohorts, where diffuse tissue injury may predominate [36,37]. In addition, prospective registries and clinical trials should systematically document the timing of antifibrotic therapy relative to both radiation exposure and local triggering events, including dental extractions and mucosal trauma. Such an approach would allow more precise delineation of the biologically plausible therapeutic window suggested by mechanistic models and support evidence-based recommendations regarding the initiation and duration of antifibrotic interventions [40,46].

Randomized controlled trials conducted within contemporary RT frameworks—such as the ongoing RAPTOR trial—are essential to establish higher-certainty evidence regarding the efficacy of PENTOCLO in the management of ORN [49,50]. In parallel, translational research investigating biomarkers of endothelial dysfunction, inflammatory burden, and fibro-atrophic activity may enable biologically informed patient selection and a more personalized application of antifibrotic therapy [2,10]. Incorporating such biomarkers into trial design could help identify patients most likely to benefit from specific interventions and clarify the mechanisms underlying therapeutic responses.

In the IMRT era, the clinical application of PENTO-based therapy should therefore be guided by biological relevance, disease stage, and individual mandibular dose distribution rather than by historical treatment paradigms derived from conventional RT. Aligning antifibrotic strategies with the dominant mechanisms of radiation-induced injury is critical not only for optimizing patient outcomes but also for generating interpretable, generalizable evidence that can support the evolution of personalized approaches to ORN management.

Discussion

This narrative review examined whether PENTO–based therapy exhibits distinct clinical behavior in the IMRT era by integrating mechanistic insights with contemporary clinical evidence. The central conclusion is that apparent variability in reported outcomes is more plausibly explained by changes in mandibular radiobiology and disease substrate than by alterations in drug efficacy. IMRT has reshaped both the spatial and biological characteristics of radiation-induced mandibular injury, shifting the dominant pathological processes from focal, high-dose necrosis typical of earlier techniques toward diffuse, low- to intermediate-dose–driven endothelial dysfunction, chronic inflammation, and progressive fibro-atrophic remodeling. This transition is associated with a more heterogeneous and often indolent clinical phenotype of ORN in the IMRT era [2,10,36,37].

Within this altered radiobiological context, the biological targets of PENTO—microvascular dysfunction, inflammatory cytokine signaling, and oxidative stress—remain relevant but are observed at different stages and spatial distributions of tissue injury than in pre-IMRT cohorts. In earlier RT paradigms, antifibrotic therapy was frequently initiated in advanced disease stages characterized by extensive cortical bone devitalization, secondary infection, and irreversible structural damage—conditions in which fibro-atrophic pathways are no longer the dominant drivers of pathology and the potential for medical intervention is inherently limited [5,6,44]. In contrast, IMRT-treated tissues often retain structural integrity while harboring biologically active, potentially modifiable injury processes such as persistent endothelial dysfunction and chronic inflammation over prolonged periods. This shift alters the therapeutic context rather than the pharmacological mechanism of the therapeutic agent, creating opportunities for earlier intervention in the disease course.

Accordingly, clinical evidence supporting PENTO-based therapy must be interpreted with caution. Most published studies derive from mixed or pre-IMRT cohorts, lack stratification by RT technique or mandibular dose–volume parameters, and employ heterogeneous outcome definitions [44-46]. These limitations preclude definitive conclusions regarding differential efficacy in the IMRT era. Importantly, the absence of IMRT-specific attribution should not be interpreted as evidence of ineffectiveness; rather, it reflects a mismatch between evolving radiobiology and static clinical frameworks traditionally used to evaluate treatment response. Addressing this gap will require studies that integrate detailed dosimetry, standardized staging, and outcome measures tailored to the distinctive features of IMRT-associated injury.

The conceptual model advanced in this revie this narrative review—that the biologically relevant window for antifibrotic therapy has shifted—offers a unifying explanation for heterogeneous clinical observations. In the IMRT era, PENTO-based therapy is most plausibly effective during phases characterized by active endothelial dysfunction, inflammation, and fibro-atrophic remodeling, particularly before the development of extensive bone sequestration or structural collapse [2,10,37]. Failure to consider disease stage, dose distribution, and inflammatory burden at treatment initiation risks underestimating the therapeutic potential of antifibrotic agents when they are applied outside their biologically relevant context.

This framework also informs consideration of prophylactic and peri-procedural strategies. IMRT-associated ORN frequently arises in conjunction with local triggering events such as dental extractions or mucosal trauma, superimposed on biologically compromised yet structurally preserved bone [38,40]. While preliminary observational studies suggest the feasibility and tolerability of prophylactic PENTO use in selected settings, current evidence remains insufficient to support routine implementation, underscoring the need for well-designed, controlled evaluations [48]. Nonetheless, these observations are mechanistically consistent with a model of diffuse mandibular vulnerability rather than focal necrosis, supporting further investigation of risk-adapted, multidisciplinary preventive approaches.

Several limitations inherent to the current literature warrant emphasis, including the paucity of randomized controlled trials conducted within contemporary RT frameworks, inconsistent application of standardized ORN staging systems, and limited incorporation of dosimetric data into outcome analyses [42,45,46]. Ongoing trials such as RAPTOR represent an essential step toward addressing these deficiencies, but future studies will need to extend beyond this by integrating intermediate-dose metrics, biological markers of fibro-atrophic activity, and precise timing of intervention relative to radiation exposure and local insults [49,50]. In summary, the IMRT era does not invalidate antifibrotic therapy for ORN but necessitates a redefinition of its clinical role. PENTO should not be evaluated solely on its capacity to reverse advanced necrosis; rather, its utility should be judged by its ability to modulate biologically active injury processes that predominate under modern dose distributions. Aligning therapeutic intent, patient selection, and outcome assessment with contemporary radiobiology is essential to generate interpretable evidence and optimize supportive care in head and neck RT.

Conclusion

Available evidence indicates that PENTO–based therapy does not exhibit intrinsically altered pharmacological activity in the IMRT era. Rather, its clinical relevance and apparent efficacy are shaped by evolving patterns of mandibular radiobiology driven by modern dose distributions. IMRT shifts radiation injury toward a more diffuse, low- to intermediate-dose–mediated process characterized by persistent endothelial dysfunction, chronic inflammation, and progressive fibro-atrophic remodeling, rather

than the focal high-dose necrosis that predominated with earlier RT techniques. Within this altered biological landscape, the timing of intervention, disease stage, and mandibular dose–volume characteristics become central determinants of therapeutic impact.

Failure to account for these factors risks conflating biological heterogeneity with therapeutic inefficacy and may obscure the true potential of antifibrotic strategies. Future research should therefore integrate contemporary dosimetry, standardized O staging, and biologically informed patient selection to more accurately define the role of antifibrotic therapy in modern clinical practice. In parallel, multidisciplinary care—encompassing close collaboration among radiation oncologists, dental specialists, and surgeons—will be essential to align treatment strategies with the complex and evolving clinical realities of the IMRT era.

Ethics Statement

Ethical approval was not required for this study, as it is a narrative review based exclusively on previously published literature and does not involve human participants, animal subjects, or identifiable personal data.

Author Contributions

The author conceptualized the study, performed the literature review, synthesized the evidence, and drafted the manuscript. The author approved the final version of the manuscript.

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Data Availability Statement

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AI-Assisted Technologies Statement

The figures were created by the authors. Schematic illustrations and graphical elements were generated using BioRender (current academic web-based version, 2025) and Canva (current web-based version, 2025). Final layout optimization, vector refinement, and resolution adjustment for publication were performed using Inkscape (version 1.3.2). No third-party copyrighted images were used. The use of these tools was limited to figure layout, illustration, and visualization. AI-assisted software did not generate scientific content, influence data, or affect the interpretation or conclusions. All scientific concepts, annotations, and figure legends were developed and validated by the authors. The authors confirm that they hold the necessary rights and permissions for the use of all figures in this publication.

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Conflict of Interest

Declare if any financial interest or any conflict of interest exists.

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