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Review Article

Heat Shock Protein 27 as a Driver of Resistance to Radiotherapy and Systemic Therapies in Head and Neck Cancers: From Mechanisms to Therapeutic Targeting

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Abstract

Head and neck cancers (HNCs) constitute a heterogeneous group of malignancies with persistently poor survival outcomes despite significant advances in surgery, radiotherapy, and systemic therapy. Therapeutic resistance—both intrinsic and acquired—remains the principal barrier to cure. Mounting evidence implicates Heat Shock Protein 27 (HSP27), a small molecular chaperone encoded by HSPB1, as a critical mediator of resistance across multiple treatment modalities. HSP27 regulates essential cellular processes, including protein folding, apoptosis inhibition, DNA repair, redox homeostasis, and cytoskeletal stabilization, thereby enabling tumor cells to endure cytotoxic stress. Elevated expression and phosphorylation of HSP27 have been consistently associated with poor responses to chemoradiotherapy, enhanced metastatic potential, and inferior survival in patients with HNC. Furthermore, recent studies highlight its emerging role in resistance to targeted therapies and immunotherapy through stabilization of PI3K/AKT and MAPK signaling pathways and modulation of the immune microenvironment. Accordingly, this review aims to synthesize mechanistic, preclinical, and clinical evidence delineating the multifaceted role of HSP27 in HNC pathobiology and treatment resistance. By integrating data across molecular, translational, and therapeutic domains, it aims to elucidate how HSP27 contributes to radio-, chemo-, and immune resistance; evaluate its potential as a prognostic and predictive biomarker; and outline emerging strategies for therapeutic targeting. A deeper understanding of HSP27's central role in adaptive stress responses may inform biomarker-guided and combinatorial approaches to overcome resistance and improve outcomes in patients with head and neck cancers.

Keywords: Head and Neck Cancer; Heat Shock Protein 27; Treatment Resistance; Radiotherapy; Systemic Therapies

Introduction

Head and neck cancers (HNCs) represent a heterogeneous group of malignancies originating from the mucosal epithelium of the oral cavity, pharynx, larynx, nasal cavity, and paranasal sinuses. Together, they account for approximately 900,000 new cases and more than 400,000 deaths annually worldwide, ranking as the sixth most common malignancy globally and imposing a considerable public health burden [1]. The etiopathogenesis of HNC is multifactorial, driven predominantly by environmental exposures and viral oncogenesis. Tobacco use, including smoking and smokeless forms, alcohol consumption, and betel nut chewing, remain the principal traditional risk factors [2]. In recent decades, the epidemiologic landscape of HNC has shifted with the rising incidence of human papillomavirus (HPV)–associated oropharyngeal cancers, which differ from their HPV-negative counterparts in clinical behavior, molecular characteristics, and therapeutic response [3]. Additionally, inherited genetic susceptibilities, such as polymorphisms in carcinogen-metabolizing enzymes and DNA repair genes, may further modulate individual risk [4].

Despite remarkable advances in diagnostic imaging, surgical techniques, radiation delivery, and systemic therapy, the prognosis of advanced HNC remains suboptimal. The 5-year overall survival (OS) for locally advanced disease generally ranges between 40% and 60%, reflecting the persistent challenges of local recurrence, distant metastasis, and treatment-related toxicities [5]. Prognostic heterogeneity within this patient population is influenced by a variety of clinical and biological factors, including tumor site, stage, performance status, nutritional condition, smoking history, HPV status, and molecular subtype [6]. Moreover, the frequent coexistence of comorbidities such as malnutrition, sarcopenia, and cachexia in HNC patients further complicates therapeutic decision-making and negatively impacts survival outcomes [7].

Optimal management of HNCs demands a multidisciplinary approach involving head and neck surgical oncology, oral and maxillofacial surgery, radiation oncology, medical oncology, pathology, and rehabilitation specialists [8]. Surgery remains the cornerstone of treatment for resectable tumors, aiming to achieve complete excision with negative margins while preserving organ function and quality of life. For patients with unresectable or locally advanced disease, radiotherapy (RT) or concurrent chemoradiotherapy (CRT) constitutes the standard of care [9]. RT, particularly with intensity-modulated RT (IMRT), has markedly improved locoregional control by enhancing dose conformity and sparing surrounding normal tissues [10]. Concurrent administration of systemic agents such as cisplatin exploits radiosensitization mechanisms, leading to improved local control and OS [11]. Nevertheless, a significant subset of patients exhibits intrinsic or acquired resistance to RT and chemotherapy, undermining long-term efficacy [12].

Radiation resistance remains a formidable clinical obstacle in the management of HNC. Multiple molecular and microenvironmental mechanisms contribute to this phenomenon. Tumor hypoxia, a common feature of many HNCs, impairs the oxygen-dependent fixation of radiation-induced DNA damage, thereby reducing the formation of lethal DNA lesions and ultimately impairing tumor cell death [13]. In addition, activation of prosurvival signaling cascades, including the PI3K/AKT, NF-κB, and ERK pathways, enhances DNA repair capacity, inhibits apoptosis, and fosters a radioresistant phenotype [14]. The epithelial–mesenchymal transition (EMT) further contributes to radioresistance by conferring stem-like properties and motility, enabling residual tumor cell repopulation after therapy [15]. Moreover, cancer stem cells (CSCs) within HNCs possess robust DNA damage response systems, slow proliferation rates, and high expression of anti-apoptotic proteins, all of which facilitate recurrence following irradiation [16]. The tumor microenvironment (TME), comprising stromal fibroblasts, immune infiltrates, extracellular matrix components, and vasculature, also plays a pivotal role by secreting cytokines, growth factors, and exosomes that promote repair, angiogenesis, and immunosuppression after RT exposure [17].

Similarly, chemotherapy resistance is a significant determinant of therapeutic failure. Platinum-based regimens, including cisplatin and carboplatin, remain the backbone of systemic therapy for

HNC, often combined with 5-fluorouracil or taxanes [18]. However, resistance frequently arises through increased drug efflux mediated by ATP-binding cassette (ABC) transporters, enhanced DNA damage repair, inactivation of apoptotic pathways, and detoxification mechanisms such as glutathione conjugation [19]. These adaptive responses not only limit cytotoxic efficacy but also contribute to cross-resistance between different chemotherapeutic classes, further complicating disease management [20].

Amid these challenges, heat shock proteins (HSPs) have garnered increasing attention as critical molecular mediators of treatment resistance. HSPs are highly conserved stress-responsive chaperones that maintain cellular proteostasis by assisting in protein folding, stabilization, and degradation under stressful conditions such as hypoxia, heat, and oxidative stress [21]. Among them, HSP27, also known as HSPB1, has emerged as a particularly influential player in HNC biology. HSP27 functions as a molecular chaperone that modulates numerous signaling networks involved in survival, apoptosis, and cytoskeletal integrity. Its expression is upregulated in response to diverse cellular stresses, including radiation, chemotherapy, and oxidative injury [22]. Mechanistically, HSP27 interacts with key regulators such as caspase-3, cytochrome c, AKT, and NF-κB, thereby suppressing apoptosis, enhancing cell survival, and promoting DNA repair [23].

In most HNC studies, elevated HSP27 expression has been correlated with aggressive clinical behavior, advanced stage, metastasis, and reduced sensitivity to RT and chemotherapy [24]. HSP27 also facilitates EMT, cytoskeletal remodeling, and enhanced motility, thereby promoting metastatic dissemination [25]. Importantly, its antioxidant properties enable tumor cells to neutralize reactive oxygen species (ROS) and mitigate radiation-induced DNA strand breaks, thereby contributing directly to radioresistance [26]. Furthermore, by stabilizing anti-apoptotic proteins such as Bcl-2 and modulating p53 activity, HSP27 supports chemoresistance in HNC cell lines exposed to cisplatin and 5-FU [27].

Given these multifaceted roles, the present review aims to provide an integrative analysis of HSP27 in HNC, encompassing its molecular biology, its involvement in RT and chemotherapy resistance, its impact on tumor microenvironment interactions, and its potential clinical applications as a prognostic biomarker and therapeutic target. By synthesizing emerging evidence from preclinical and clinical studies, we seek to delineate how modulation of HSP27 could overcome treatment resistance, improve response rates, and enhance outcomes for patients with HNCs [28].

Methods

This narrative review was conducted through a comprehensive search of the PubMed, Scopus, and Web of Science databases for English-language publications up to September 2025. The search terms included combinations of “Heat Shock Protein 27,” “HSP27,” “HSPB1,” “head and neck cancer,” “radiotherapy,” “radioresistance,” “chemoresistance,” “resistance to targeted agents,” and “immunotherapy resistance.” Relevant preclinical, translational, and clinical studies were reviewed, with particular emphasis on mechanistic investigations and prognostic correlations. The reference lists of key articles were also screened to ensure the inclusion of pertinent studies. As this is a narrative review, data were synthesized qualitatively to highlight mechanistic pathways, translational relevance, and potential therapeutic implications of HSP27 in treatment resistance of HNCs.

Molecular biology of HSP27

Overview and structural organization

HSP27, encoded by the HSPB1 gene located on chromosome 7q11.23, is a small, ATP-independent molecular chaperone with an approximate molecular weight of 27 kilodaltons (kDa) [21]. As a member of the small HSP (sHSP) family, HSP27 plays essential roles in maintaining cellular proteostasis, ensuring that proteins retain their proper structure and function under both physiological conditions and stresses like heat shock, oxidative stress, and toxic insults [22]. Unlike its larger, ATP-dependent counterparts, such as HSP70 and HSP90, which aid in protein folding and refolding through ATP hydrolysis, HSP27 functions without the energy provided by ATP, enabling it to respond swiftly to cellular stress [23].

HSP27 exerts its protective effects primarily through two interrelated mechanisms: dynamic oligomerization and reversible phosphorylation. HSP27 can form various multimeric complexes through dynamic oligomerization, thereby enhancing its capacity to interact with aggregated and misfolded proteins, prevent their accumulation, and promote their proper refolding or degradation [24]. Reversible phosphorylation, especially at serine residues, can alter the conformation and activity of HSP27 [25]. This process, in turn, affects its chaperone function, subcellular localization, and interactions with other proteins [26]. These phosphorylation events are also essential for regulating HSP27's role in cellular signaling pathways and in stress responses [27]. Together, these mechanisms underscore HSP27's vital role in cellular resilience, its implications in various diseases, and its potential as a therapeutic target for conditions such as neurodegenerative disorders, cardiac diseases, and cancer [28].

Structurally, HSP27 comprises three major domains with distinct but complementary functions that are integral to its role in cellular stress response and proteostasis [29] (Table 1, Figure 1):

- **N-terminal domain (NTD):** This region is pivotal for oligomerization, allowing HSP27 to form large multimeric complexes. These complexes, which can range widely in size, are essential for buffering misfolded proteins and maintaining proteostasis within the cell. The NTD not only promotes the formation of high-order oligomers but also plays a role in the stabilization of these complexes under various stresses [30].
- **Alpha-crystallin domain (ACD):** The highly conserved central domain is fundamental for substrate recognition and binding. This domain enables HSP27 to interact specifically with misfolded or aggregated proteins, which is crucial for preventing their accumulation within the cell [31]. By facilitating proper protein folding and preventing aggregation, the ACD contributes significantly to the cellular stress response, particularly during conditions that destabilize protein structure [32].
- **C-terminal extension (CTE):** This flexible tail region extends from the ACD and enhances HSP27's versatility in coordinating the stress response. The CTE facilitates critical interactions with client proteins and co-chaperones, effectively broadening HSP27's functionality under various stressors [33]. Its dynamic nature allows for intricate regulatory mechanisms that optimize protein folding under stress [34].

Mechanistic Aspect	Description	Key Molecular Partners/ Pathways	Functional Consequence
Structural Domains	NTD, ACD, CTE organization	–	Determines chaperone flexibility and oligomerization
Phosphorylation Sites	Ser15, Ser78, Ser82	p38 MAPK/MAPKAPK2	Modulates oligomerization and stress response
Interaction with Apoptotic Proteins	Caspase-3, Cytochrome c, DAXX	–	Inhibits apoptosis and enhances survival
Redox Regulation	SOD, GPx, Catalase stabilization	Nrf2	Maintains oxidative balance
Cytoskeletal Stabilization	Actin, Microtubules	–	Supports motility and metastasis
Transcriptional Regulation	HSF1 activation and feedback	HSPB1 promoter	Induces adaptive stress response

Table 1: Key Molecular Functions and Regulatory Mechanisms of HSP27.

Abbreviations: ACD, α-Crystallin Domain; CTE, C-terminal Extension; DAXX, Death-domain Associated Protein; GPx, Glutathione Peroxidase; HSF1, Heat Shock Factor 1; HSPB1, Heat Shock Protein Beta-1; MAPK, Mitogen-Activated Protein Kinase; MAPKAPK2, MAPK-Activated Protein Kinase 2; Nrf2, Nuclear Factor Erythroid 2–Related Factor 2; NTD, N-terminal Domain; SOD, Superoxide Dismutase.

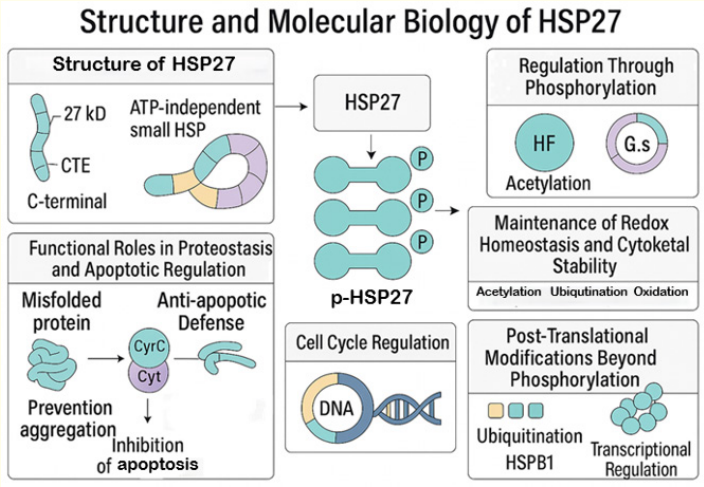

Figure 1

Abbreviations: ATP, Adenosine Triphosphate; CTE, C-terminal Extension; Cyt c, Cytochrome c; DNA, Deoxyribonucleic Acid; HF, Heat Factor; HSP, Heat Shock Protein; HSP27, Heat Shock Protein 27; HSPB1, Heat Shock Protein Beta-1; NTD, N-terminal Domain; p-HSP27, Phosphorylated Heat Shock Protein 27.

Under basal (non-stressed) conditions, HSP27 predominantly exists as large oligomeric complexes that can range in weight from 200 to 800 kDa [35]. However, in response to post-translational modifications (PTMs), such as phosphorylation at specific serine residues, these oligomers can dynamically dissociate into smaller oligomeric forms, including dimers or even monomers [36]. This oligomeric plasticity is vital for the rapid adaptation to a wide range of cellular stressors, such as heat shock, oxidative stress, hypoxia, and exposure to cytotoxic agents, ensuring that HSP27 can effectively perform its chaperone functions and enhance cell survival in challenging environments [37]. The ability to transition between different oligomeric states allows HSP27 to fine-tune its activity in response to the cellular milieu, underscoring its role as a key player in the maintenance of cellular health and resilience [38].

Regulation through phosphorylation

Phosphorylation is the primary regulatory mechanism that governs the chaperone and signaling functions of HSP27. This protein is notable for having three key serine phosphorylation sites, namely Ser15, Ser78, and Ser82 [39]. These sites are critical targets for a variety of kinases, which include but are not limited to p38 mitogen-activated protein kinase (MAPK), MAPK-activated protein kinase 2 (MAPKAPK-2), and protein kinase D (PKD) [40,41]. When HSP27 undergoes phosphorylation at these sites, it triggers a series of conformational changes that facilitate the disassembly of larger oligomeric structures into smaller, more functionally active forms [42]. The resulting phosphorylated HSP27, often referred to as p-HSP27, exhibits an increased affinity for several client proteins that play essential roles in cellular processes such as apoptosis regulation, cytoskeletal organization, and maintaining redox balance [43].

One key interaction of phosphorylated HSP27 is with caspase-3, which is crucial in apoptosis execution. By binding to caspase-3, p-HSP27 effectively inhibits its activation, thereby providing a protective effect against programmed cell death during conditions of cellular stress [44]. Similarly, p-HSP27 interacts with DAXX, a protein involved in apoptotic signaling, and F-actin, which is a significant component of the cytoskeleton. This interaction helps to maintain cytoskeletal integrity and function under stress conditions [45,46].

In essence, HSP27 operates as a dynamic molecular switch that is responsive to cellular stress. Its ability to rapidly transition between different structural states, mediated by phosphorylation, allows it to adapt to the specific requirements of stressed or damaged cells [47]. This modulation is essential for facilitating a protective response, enhancing cell survival, and ensuring proper cellular function under adverse conditions. Thus, the phosphorylation of HSP27 not only regulates its chaperone activity but also positions it as a crucial player in the orchestration of cellular stress responses [48].

Functional roles in proteostasis and apoptotic regulation

HSP27 functions as a multifunctional guardian of cellular homeostasis, playing a crucial role in protecting cells from stress through several interconnected mechanisms.

- **Protein Quality Control:** HSP27 actively binds to misfolded or denatured proteins, thereby preventing their aggregation, which can lead to cellular dysfunction [49]. This chaperone activity not only aids in the refolding of misfolded proteins into their appropriate functional conformations but also promotes their correct assembly into protein complexes [50]. For proteins that cannot be successfully refolded, HSP27 guides them toward degradation pathways, including the ubiquitin-proteasome system and autophagy [51]. This targeted degradation is essential for maintaining proteome integrity and ensuring that only correctly folded, functional proteins are available within the cell [52].
- **Anti-Apoptotic Defense:** HSP27 exerts potent anti-apoptotic effects through its direct interactions with several key apoptotic regulators, significantly influencing cell survival [4]. Specifically, it binds to cytochrome c, effectively inhibiting the assembly of the apoptosome complex, which consists of Apaf-1 and caspase-9 [53]. This critical blockade prevents the subsequent activation of downstream caspases, which are essential mediators of the apoptotic process [54].

In addition to its role in blocking apoptosome formation, HSP27 plays a crucial role in maintaining mitochondrial function [55]. It interacts with members of the Bcl-2 family of proteins, which are vital in regulating the apoptosis pathway. By modulating the balance between pro-apoptotic proteins (Bax, Bak) and anti-apoptotic proteins (Bcl-2, Bcl-xL), HSP27 helps inhibit mitochondrial outer membrane permeabilization (MOMP)—a critical step that leads to the release of cytochrome c into the cytosol [55,56]. By preventing MOMP, HSP27 preserves mitochondrial integrity, thereby averting the release of pro-apoptotic factors that trigger cell death. This multifaceted approach not only highlights the essential functions of HSP27 in regulating apoptosis but also underscores its potential as a therapeutic target in diseases characterized by dysregulated apoptosis, such as cancer and neurodegenerative disorders [56].

Cell cycle regulation

HSP27 plays a crucial role in the meticulous regulation of cell cycle progression, especially under conditions of cellular stress. This protein is known to modulate the expression levels of critical proteins involved in cell cycle control [57]. For instance, it influences the production of cyclin D1, which is essential for the transition from the G1 phase to the S phase of the cell cycle, promoting DNA replication and cell division [58]. Additionally, HSP27 regulates the expression of p21, a significant cyclin-dependent kinase inhibitor (CDKI) that functions to pause cell cycle progression in response to various stressors, thereby preventing the propagation of damaged cells [59,60].

This adaptive regulatory mechanism facilitated by HSP27 is vital for cellular survival, as it enables cells to withstand genotoxic challenges and supports their recovery and re-entry into the cell cycle once stress conditions are resolved [61]. By ensuring that cells can respond appropriately to adverse environments, HSP27 significantly contributes to maintaining cellular homeostasis and genomic stability [62].

Maintenance of redox homeostasis and cytoskeletal stability

Reactive oxygen species (ROS) are highly reactive molecules that play a significant role in mediating cellular damage, particularly during therapeutic interventions like RT and chemotherapy [63]. These species can cause oxidative stress, leading to cellular dysfunction and death. HSP27 (Heat Shock Protein 27) is a crucial player in cellular defense mechanisms, particularly in redox regulation, by upregulating the activity of key antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GPx) [64,65]. This antioxidative capacity is critical for mitigating the damage induced by ROS, thereby promoting cell survival in the challenging environments created by oxidative stress [48].

Beyond its role in redox homeostasis, HSP27 is also known to interact intimately with cytoskeletal components, specifically actin filaments and microtubules [66]. This interaction plays a vital role in stabilizing the cytoskeletal architecture, which is essential for various cellular processes, including cell motility, adhesion, and invasion [67]. These processes are frequently hijacked by tumor cells to facilitate metastatic diffusion and spread [68]. Therefore, the cytoskeletal association of HSP27 not only supports normal cellular mechanics, ensuring structural integrity and functionality, but also enhances the aggressiveness and migratory capacity of tumor cells [69]. This dual role of HSP27 highlights its importance in both maintaining healthy cellular functions and promoting cancer cell behavior, underlining the complexities of its involvement in tumor progression [70] (Figure 2).

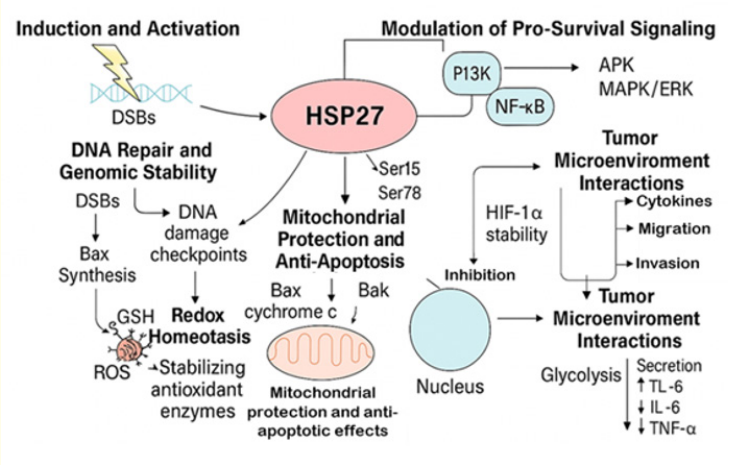

Figure 2: Mechanisms of HSP27-mediated radioresistance in head and neck cancer.

Abbreviations: Akt, Protein Kinase B; Bak, Bcl-2 Antagonist/Killer; Bax, Bcl-2–Associated X Protein; DSBs, Double-Strand Breaks; ERK, Extracellular Signal–Regulated Kinase; GSH, Glutathione; HIF-1α, Hypoxia-Inducible Factor 1-alpha; HSP27, Heat Shock Protein 27; MAPK, Mitogen-Activated Protein Kinase; NF-κB, Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells; PI3K, Phosphoinositide 3-Kinase; ROS, Reactive Oxygen Species; TNF-α, Tumor Necrosis Factor Alpha; IL-6, Interleukin-6.

Post-translational modifications beyond phosphorylation

In addition to phosphorylation, several post-translational modifications (PTMs) such as acetylation, ubiquitination, and oxidation contribute significantly to the intricate regulation of HSP27 [71]. These modifications profoundly influence HSP27's structural dynamics, its binding preferences for client proteins, and its localization within various subcellular compartments [72].

Oxidative modifications, which are often induced by reactive oxygen species (ROS), can disrupt the oligomerization of HSP27 [73]. This disruption can lead to alterations in its chaperone efficiency, potentially impairing its ability to assist in protein folding and protect against aggregation [74]. Specifically, when HSP27 oligomers are destabilized, its capacity to promote cellular survival under stress conditions may be compromised [75].

Acetylation of lysine residues in HSP27 has been associated with a decrease in substrate affinity, which can diminish the chaperone's overall protective role [76]. Furthermore, this modification is linked to a weakened anti-apoptotic effect, suggesting that acetylated HSP27 may be less effective in inhibiting programmed cell death, particularly in adverse environmental conditions [77].

Ubiquitination, another vital PTM, can function in two distinct ways: it may tag HSP27 for proteasomal degradation, thereby regulating its levels within the cell, or it may alter HSP27's interactions with various signaling intermediates [78]. This dual role highlights the complexity of ubiquitination, as it can either diminish HSP27 availability or enhance its functional interactions, depending on the cellular context [79].

Collectively, these PTMs equip HSP27 with the necessary adaptability to respond dynamically to the shifting biochemical milieu and redox state of the tumor microenvironment (TME). This is particularly critical under conditions of hypoxia and metabolic stress that are frequently encountered in head and neck cancers (HNCs), where effective modulation of stress responses can significantly influence tumor survival and progression [79].

Transcriptional regulation of HSPB1

At the transcriptional level, the expression of HSP27, also known as HSPB1, is predominantly regulated by heat shock factor 1 (HSF1), a pivotal master transcription factor that orchestrates the cellular stress response [80]. In response to various forms of cellular stress, such as heat shock, oxidative stress, or injury, HSF1 undergoes a conformational change that promotes its trimerization [81]. This trimerized form of HSF1 then translocates to the nucleus, where it specifically binds to heat shock elements (HSEs) located within the promoter region of the HSPB1 gene [82]. This binding triggers a cascade of events that leads to the rapid transcriptional activation of HSP27, ultimately enhancing the cell's capacity to withstand stressors [83].

The persistent activation of HSF1 has been frequently documented across diverse malignancies, including breast, lung, and colon cancers [84]. This sustained activation leads to the constitutive overexpression of HSP27, enhancing cellular tolerance to genotoxic stress, enabling malignant cells to survive exposure to DNA-damaging agents that would typically induce apoptosis [85]. Furthermore, HSP27 mediates anti-apoptotic effects by stabilizing cytoskeletal components, inhibiting pro-apoptotic signaling cascades, and modulating multiple stress response pathways [86]. Importantly, a positive feedback mechanism exists within this regulatory axis: once synthesized, HSP27 stabilizes HSF1 by preventing its proteasomal degradation [87]. This stabilization prolongs HSF1's transcriptional activity, thereby maintaining elevated chaperone protein expression in cancer cells. Collectively, this interplay enhances tumor cell survival under stress conditions, facilitates cancer progression, and contributes to therapeutic resistance [88].

Extracellular HSP27 and immune modulation

Beyond its established intracellular functions, extracellular HSP27 has been identified in the bloodstream of cancer patients, where it acts as a damage-associated molecular pattern (DAMP) molecule [89]. This secreted form of HSP27 engages with specific cell surface receptors, including Toll-like receptors 2 and 4 (TLR2 and TLR4), as well as CD91, leading to significant modulation of immune cell behaviors [90,91]. The role of extracellular HSP27 in cancer biology is notably context-dependent, exhibiting the dual capability to provoke either pro-tumor immune responses or facilitate immune suppression [92]. In the case of head and neck cancers (HNCs), for instance, extracellular HSP27 predominantly contributes to the establishment of an immunosuppressive tumor microenvironment [93]. This occurs mainly through the promotion of macrophage polarization towards the M2 phenotype, which is characterized by its anti-inflammatory properties, enhanced tissue repair functions, and support for tumor progression [94].

Research has demonstrated that M2 macrophages can secrete a variety of cytokines, such as IL-10 and TGF-β, which further suppress the activity of effector immune cells and promote angiogenesis, providing additional support for tumor growth [95]. Moreover, the presence of extracellular HSP27 has been shown to diminish the cytotoxic activity of T cells, impairing their ability to target and eradicate cancer cells effectively [96]. This mechanism of immune evasion not only allows tumors to progress unchecked but also complicates therapeutic interventions. As a result, patients with HNCs often face a significantly unfavorable prognosis, underscoring the critical need for targeted therapies that can disrupt the immunosuppressive effects of HSP27 to enhance anti-tumor immunity [97].

HSP27 and cancer-related inflammation

HSP27 plays a central role in orchestrating inflammatory processes within the tumor microenvironment (TME), bridging cellular stress responses with chronic inflammation that fuels cancer progression [98]. Under physiological conditions, HSP27 maintains cellular homeostasis and restrains excessive inflammation by stabilizing the actin cytoskeleton, inhibiting nuclear factor kappa B (NF-κB) activation, and reducing the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and TNF-α [99,100]. In malignancy, however, this tightly regulated balance becomes disrupted, and HSP27 frequently adopts a pro-inflammatory phenotype that favors tumor survival and immune evasion [101]. Elevated HSP27 expression in cancer cells and tumor-associated stromal cells enhances the secretion of IL-6, TNF-α, and vascular endothelial growth factor (VEGF), promoting angiogenesis, epithelial–mesenchymal transition (EMT), and resistance to apoptosis [102,103]. Moreover, extracellular HSP27, released through active secretion or passive leakage from damaged cells, acts as a damage-associated molecular pattern (DAMP) molecule that binds to TLR2 and TLR4 on macrophages and dendritic cells, triggering downstream activation of NF-κB and the release of additional cytokines and chemokines [104]. This creates a self-sustaining feedback loop that not only recruits immunosuppressive cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), but also remodels the extracellular matrix (ECM) in ways that enhance the metastatic potential of the tumor [105]. In this context, HSP27 emerges as a pivotal mediator of cancer-associated inflammation, integrating stress adaptation with pro-tumorigenic signaling pathways. As such, targeting HSP27 may represent a promising therapeutic strategy aimed at disrupting inflammation-driven cancer progression and restoring immune competency within the tumor microenvironment [106].

HSP27 and the cellular radiation response

Ionizing radiation induces complex and multifactorial cellular damage, including DNA double-strand breaks (DSBs), single-strand breaks, base modifications, oxidative stress through the generation of ROS, and disturbances in mitochondrial and plasma membrane integrity [107]. The survival of irradiated tumor cells is influenced not only by their DNA repair mechanisms but also by the intricate maintenance of redox homeostasis, mitochondrial integrity, apoptosis regulation, and the activation of pro-survival signaling networks [108]. HSP27 plays a pivotal role in orchestrating these adaptive responses [109]. In HNCs, HSP27 contributes to radioresistance by promoting survival signaling, preserving genomic stability, and modulating the tumor microenvironment to facilitate post-irradiation recovery [110]. Beyond its intracellular cytoprotective effects, HSP27 also exerts extracellular and stromal influences, engaging in crosstalk that promotes tissue remodeling, angiogenesis, immune evasion, and metabolic reprogramming, thereby ensuring tumor persistence even after exposure to high-dose RT [111]. Collectively, these multifaceted functions position HSP27 as a central mediator of adaptive and therapeutically relevant radioresistance [109]. The mechanisms by which HSP27 confers radioresistance can be summarized as follows [43] (Table 2, Table 3).

Mechanism	Molecular Effect	Downstream Pathways/ Targets	Impact on Radio response
DNA Repair Facilitation	Stabilization of Ku70/Ku80, RAD51	NHEJ, HR pathways	Enhanced DNA repair fidelity
Antioxidant Defense	Activation of SOD, GPx, and catalase	Nrf2 signaling	Reduction of ROS-induced apoptosis
Mitochondrial Protection	Inhibition of Bax/Bak, Cytochrome c release	Intrinsic apoptosis pathway	Sustained mitochondrial function
Pro-survival Signaling	Stabilization of p-Akt, ERK, NF-κB	PI3K/AKT, MAPK	Increased cell survival
TME Modulation	Cytokine secretion, M2 macrophage recruitment	IL-6, IL-10, HIF-1α	Enhanced angiogenesis, immune evasion

Table 2: Mechanisms of HSP27-Mediated Resistance to Radiotherapy.

Abbreviations: Akt, Protein Kinase B; Bax, Bcl-2-associated X Protein; Bak, Bcl-2 Antagonist/Killer; ERK, Extracellular Signal–Regulated Kinase; GPx, Glutathione Peroxidase; HIF-1α, Hypoxia-Inducible Factor 1-alpha; HR, Homologous Recombination; IL, Interleukin; MAPK, Mitogen-Activated Protein Kinase; NF-κB, Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells; NHEJ, Non-Homologous End Joining; Nrf2, Nuclear Factor Erythroid 2–Related Factor 2; RAD51, DNA Repair Protein RAD51 Homolog 1; ROS, Reactive Oxygen Species; SOD, Superoxide Dismutase; TME, Tumor Microenvironment.

Mechanism	Target/Pathway	Effect	Representative Evidence
Apoptosis Inhibition	Caspase-3, Apaf-1	Blocks apoptosome formation	Lo Muzio et al., 2005
p53 Modulation	Wild-type and mutant p53	Inhibits transcriptional activation	Lang., *et al.* 2010
DNA Repair Enhancement	ERCC1, XRCC1	Promotes cisplatin adduct removal	Mese., *et al.* 2002
ROS Neutralization	SOD, GPx, GSH	Protects from oxidative injury	Chai., *et al.* 2020
Drug Efflux Regulation	MDR1 (P-gp)	Enhances drug efflux	Zhu., *et al.* 2010

Table 3: Mechanisms of HSP27-Induced Chemoresistance in Head and Neck Cancers.

Abbreviations: Apaf-1, Apoptotic Protease-Activating Factor 1; ERCC1, Excision Repair Cross-Complementation Group 1; GPx, Glutathione Peroxidase; GSH, Glutathione; MDR1, Multidrug Resistance Protein 1; P-gp, P-glycoprotein; SOD, Superoxide Dismutase; XRCC1, X-ray Repair Cross-Complementing Protein 1.

Induction and activation of HSP27

Ionizing radiation quickly triggers the expression of HSP27 through the activation of HSF1 and the p38 MAPK/MAPKAPK-2 signaling cascade, which reacts to DNA damage and oxidative stress [112]. Phosphorylation at Ser15, Ser78, and Ser82 leads to oligomeric remodeling, resulting in the formation of smaller and more dynamic units that move to the cytoplasm, nucleus, and mitochondria [113]. This redistribution process augments interactions with DNA repair proteins, apoptotic regulators, cytoskeletal components, and key kinases [114]. These processes also aid in the sequestration of denatured proteins, prevent their aggregation, and maintain proteostasis under radiation-induced stress by boosting HSP27's chaperone activity [43]. When HSP27 or its upstream kinases are experimentally suppressed, tumor cells become more sensitive to ionizing radiation because it impairs their ability to adapt to stress, delays DNA repair, and promotes the activation of apoptotic pathways [110]. These findings collectively and strongly suggest HSP27 as a rapid-response effector that integrates stress sensing, molecular chaperoning, and survival signaling, all of which are crucial for tumor radioresistance [109].

DNA repair and genomic stability

HSP27 plays a crucial role in preserving genomic integrity following ionizing radiation exposure by stabilizing key DNA repair mediators, including Ku70/Ku80 (non-homologous end joining), RAD51 (homologous recombination), and XRCC1 (base excision repair) [110]. It aids in their recruitment to sites of DNA damage and interacts with checkpoint kinases ATR and Chk1, thus ensuring proper cell-cycle arrest and repair fidelity [94]. Additionally, HSP27 can modulate chromatin accessibility and the dynamics of mediator proteins, thereby enhancing repair efficiency [115]. Hence, HSP27 safeguards both repair efficiency and genomic stability, which can negatively impact RT outcomes in HNCs due to an induced radioresistance, akin to other cancers [109]. Contrasting with its elevated levels, the depletion of HSP27 can have detrimental effects on cellular health. Specifically, reduced levels of HSP27 may lead to delayed repair kinetics, meaning that cells take longer to fix DNA damage, which can result in an accumulation of damaged DNA over time [116]. This accumulation not only impairs cellular function but may also initiate a cascade of events leading to mitotic catastrophe, where cells experience abnormal division, and ultimately trigger apoptosis. This sequence of events significantly enhances the sensitization of cells to radiation therapy, making them more susceptible to the damaging effects of radiation [117].

Redox homeostasis

Ionizing radiation generates high levels of ROS, causing oxidative damage to DNA, proteins, and lipids [118]. HSP27 mitigates oxidative stress by promoting glutathione synthesis, stabilizing antioxidant enzymes (SOD, catalase, GPx), and binding oxidized proteins to prevent aggregation [64]. These mechanisms help maintain proteostasis and redox balance, thereby preventing apoptosis, cellular senescence, and ferroptosis induced by ROS [48]. Furthermore, HSP27 indirectly supports redox-sensitive transcription factors like Nrf2, enhancing adaptive antioxidant responses [119]. The loss of HSP27 leads to excessive ROS accumulation, increased lipid peroxidation, protein oxidation, and heightened radiation-induced cell death, highlighting its central role in oxidative stress-mediated radioresistance [116]. HSP27's protective effect is especially more relevant in hypoxic tumor niches, which are inherently more resistant to RT due to their altered redox dynamics [120].

Mitochondrial protection and anti-apoptotic effects

Mitochondrial integrity plays a crucial role in determining the response to ionizing radiation [121]. HSP27 helps to preserve mitochondrial potential, inhibits the pro-apoptotic proteins Bax and Bak, and prevents the release of cytochrome c, thereby blocking the activation of the caspase cascade [44]. Within the cytosol, HSP27 directly interacts with cytochrome c and caspase-3 to inhibit the execution of apoptosis [122]. By stabilizing mitochondria, it ensures sustained energy production and redox control, thereby supporting survival signaling during ionizing radiation stress [123]. On the contrary, the inhibition or downregulation of HSP27 can lead to mitochondrial destabilization. This destabilization activates the release of cytochrome c and the activation of caspases, which triggers intrinsic apoptosis [116]. As a result, the cells exhibit increased radiosensitivity, highlighting HSP27's critical function in mitochondrial-mediated resistance pathways, especially relevant in HNCs, where tumor cells often rely on these mechanisms to evade apoptosis and promote survival under stress conditions. Thus, theoretically, targeting the regulation of HSP27 could provide therapeutic strategies to enhance the efficacy of RT in combating HNCs [109].

Modulation of pro-survival signaling

HSP27 functions as a signaling hub, intensifying pro-survival cascades including PI3K/AKT, NF-κB, and MAPK/ERK [124]. It stabilizes phosphorylated AKT, promotes NF-κB nuclear translocation for anti-apoptotic gene transcription, and prolongs ERK1/2 activity to sustain proliferation under stress [43]. HSP27 also interacts with scaffold proteins to coordinate cross-talk among these networks, integrating DNA repair, stress adaptation, and apoptosis suppression [51]. Disruption of HSP27 signaling diminishes AKT and ERK activation, inhibits NF-κB, and heightens radiation-induced apoptosis, underscoring its role as a master coordinator of survival signaling [109].

Tumor microenvironment interactions

HSP27 influences tumor-extrinsic survival mechanisms within the microenvironment [111]. It cooperates with HIF-1α to enhance glycolysis under hypoxia [125], stabilizes the cytoskeleton to promote migration, invasion, and metastasis [126], and, when secreted, activates TLR signaling in stromal and immune cells, triggering pro-survival cytokines (IL-6, IL-8, TNF-α) [127]. These mechanisms may significantly contribute to tumor repopulation, metabolic adaptation, angiogenesis, and immune evasion following RT [116]. In this context, inhibiting HSP27 may potentially disrupt tumor adaptations to hypoxia, oxidative stress, and inflammatory signals, ultimately increasing radiosensitivity. This effect could be particularly noteworthy in HNCs, which often possess dense stromal components and hypoxic regions that impede the effectiveness of RT. Consequently, targeting HSP27 presents a promising therapeutic strategy to improve patient outcomes in patients with HNC [109].

Preclinical and clinical evidence of HSP27-related radioresistance in head and neck cancers

Clinical studies, excluding a few exceptions, consistently demonstrate that high HSP27 expression is associated with poor local tumor control and inferior OS following RT in patients with HNCs [111]. Immunohistochemical analyses of various HNC subtypes, including oral cavity carcinoma (OCC), laryngeal carcinoma, and tongue carcinoma, reveal that intense cytoplasmic and nuclear staining for HSP27 is associated with radioresistant phenotypes, lower rates of complete response, and a higher risk of recurrence. In one cohort of HNC patients treated with definitive RT, elevated HSP27 levels were shown to be an independent prognostic factor for local recurrence, with hazard ratios > 2.0 after adjustment for tumor stage, nodal involvement, and performance status. These observations suggest that elevated HSP27 expression can serve as a valuable predictive biomarker for anticipating RT response in HNCs.

Borowczak., *et al*. conducted a retrospective study to evaluate the prognostic significance of HSP27 and HSP70 expression in 158 laryngeal squamous cell carcinoma (LSCC) tissue samples from 40 patients who underwent total laryngectomy [128]. Immunohistochemical analysis revealed that low expression levels of both HSP27 and HSP70 were significantly associated with reduced overall survival, findings that appear paradoxical compared with most reports in HNCs. Multivariate analysis confirmed the independent prognostic relevance of HSP27, emphasizing its potential as a biomarker in LSCC. Nonetheless, these divergent results underscore the complexity of heat shock protein biology in cancer. Supporting this notion, Kaigorodova., *et al*. demonstrated that subcellular localization of HSP27 bears distinct prognostic implications: nuclear HSP27 is involved in transcriptional regulation and DNA repair, whereas cytoplasmic HSP27 predominantly mediates anti-apoptotic functions [129]. Failure to account for this spatial heterogeneity may obscure clinically meaningful associations and contribute to inconsistencies across studies [130].

Zheng., *et al*. conducted an examination of 158 specimens of tongue squamous cell carcinoma, including metastatic lymph nodes, focusing on HSP27 expression [131]. Their immunohistochemical analysis revealed that low levels of HSP27 expression were significantly correlated with poorer OS. Multivariate Cox regression analysis further affirmed HSP27 as an independent prognostic factor. However, it is worth noting that the study was limited to a single center and did not incorporate functional studies to investigate the mechanistic role of HSP27 in therapy resistance.

Experimental evidence further supports these clinical observations. In HNC cell lines, the knockdown of HSP27 using siRNA or antisense oligonucleotides, such as OGX-427, significantly enhances radiation-induced apoptosis, delays DNA repair kinetics, and diminishes clonogenic survival. Hadchity., *et al*. demonstrated that the inhibition of HSP27 through OGX-427 (Apatorsen), an antisense oligonucleotide designed to suppress HSP27 expression, in SQ20B cells improved radiosensitivity by increasing apoptotic and clonogenic cell death while decreasing Akt phosphorylation, thereby underscoring HSP27's role in modulating pro-survival signaling pathways [23]. Although this study benefited from a targeted intervention and provided mechanistic insights, in vitro nature and absence of direct clinical validation limit the broader applicability of the findings.

Guttmann and colleagues have provided further mechanistic insights into the interaction between HSP27 and Akt in human neutrophils [132]. Their results demonstrated that the dissociation of HSP27 from Akt leads to increased apoptosis, highlighting the critical role of HSP27 in sustaining Akt-mediated pro-survival signaling. Although the study focused on immune cells rather than malignant models, it still offers valuable mechanistic clarity that may be relevant to tumor cell survival pathways. Supporting this result, research in various cancer systems has revealed that HSP27 depletion disrupts the stabilization of DNA repair proteins, compromises mitochondrial integrity, and diminishes pro-survival signaling. Logically, these effects cumulatively underscore HSP27's multifaceted contribution to radiation resistance. In support, the concurrent targeting of HSP27 and the PI3K/AKT pathway has been shown to induce synergistic radiosensitization, positioning HSP27 as both a critical modulator of intrinsic tumor resilience and a potentially exploitable therapeutic vulnerability in HNCs and other tumor sites (Table 4).

Study Author, Year	Tumor Type	N	Method	HSP27 Expression Pattern	Clinical Correlation/Outcome
Lo Muzio., *et al*. 2005	OSCC	128	IHC	High cytoplasmic	↓ Chemo response, ↓ OS
Mese., *et al*. 2002	OSCC	75	IHC	High cytoplasmic	↑ Stage, ↓ Survival
Chai et al., 2020	NPC	102	IHC	High nuclear	↓ Response to CCRT
Borowczak., *et al*. 2025	LSCC	40	IHC	Low expression	↓ OS
Zheng., *et al*. 2022	Tongue SCC	158	IHC	Low expression	↓ OS

Table 4: Clinical Studies Evaluating HSP27 in Head and Neck Cancers.

Abbreviations: CCRT, Concurrent Chemoradiotherapy; HSP27, Heat Shock Protein 27; IHC, Immunohistochemistry; LSCC, Laryngeal Squamous Cell Carcinoma; NPC, Nasopharyngeal Carcinoma; OS, Overall Survival; OSCC, Oral Squamous Cell Carcinoma; SCC, Squamous Cell Carcinoma.

HSP27 in resistance to chemotherapy and other systemic therapies

Chemotherapy continues to be a fundamental component of multimodal treatment for HNCs; however, both intrinsic and acquired resistance often curtail its therapeutic effectiveness [48]. Among the various molecular factors contributing to chemoresistance, HSP27 has surfaced as a significant mediator, impacting apoptosis regulation, drug efflux, DNA repair, and mechanisms of stress adaptation [43]. Increased expression of HSP27 has consistently been linked to diminished responsiveness to platinum-based therapies, 5-fluorouracil (5-FU), taxanes, and targeted biological agents, highlighting its pervasive influence across diverse systemic treatment modalities [133]. The fundamental mechanisms underlying HSP27-induced chemoresistance can be summarized as follows [134] (Figure 3).

Inhibition of apoptosis

HSP27's anti-apoptotic function is crucial in development of resistance to many chemotherapeutic agents, a significant challenge in cancer treatment [43]. Cytotoxic agents, including widely used drugs such as cisplatin, carboplatin, and 5-FU, induce apoptosis primarily by promoting mitochondrial outer membrane permeabilization (MOMP), which results in the release of cytochrome c, a strong triggering factor in the apoptotic cascade [135]. However, HSP27 plays a protective role by directly binding to cytochrome c and Apaf-1, effectively thwarting the assembly of the apoptosome and preventing the subsequent activation of caspase-9, a key initiator of apoptosis [44]. Additionally, HSP27 disrupts the cleavage process of caspase-3, another critical enzyme involved in the execution phase of apoptosis, thereby further impeding apoptotic signaling [122]. It also inhibits the DAXX-mediated apoptotic path-

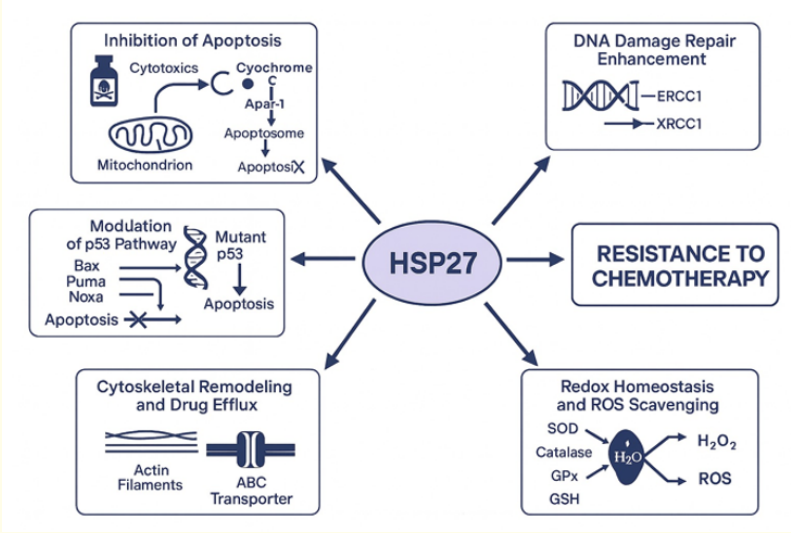

Figure 3: Mechanistic Overview of HSP27-Mediated Chemoresistance in Head and Neck Cancers.

Abbreviations: ABC, ATP-Binding Cassette; Apaf-1, Apoptotic Protease-Activating Factor 1; Bax, Bcl-2–Associated X Protein; Cyto c, Cytochrome c; ERCC1, Excision Repair Cross-Complementation Group 1; GPx, Glutathione Peroxidase; GSH, Glutathione; H_2O_2, Hydrogen Peroxide; HSP27, Heat Shock Protein 27; p53, Tumor Protein p53; Puma, p53 Upregulated Modulator of Apoptosis; ROS, Reactive Oxygen Species; SOD, Superoxide Dismutase; XRCC1, X-ray Repair Cross-Complementing Protein 1.

way, which is associated with the intrinsic signaling response to cellular stress and damage [55]. By blocking these pathways, both intrinsic and extrinsic, HSP27 diminishes the cytotoxic potential of DNA-damaging agents. This protective mechanism significantly enhances tumor cell survival, even in the face of aggressive high-dose chemotherapy regimens, ultimately contributing to treatment resistance and recurrence in cancer patients [109].

Modulation of the p53 pathway

HSP27 plays a pivotal role in mediating chemoresistance through its modulation of the tumor suppressor p53, a master regulator of apoptosis and the cellular response to genotoxic stress [94]. In various malignancies, including HNCs, HSP27 has been shown to bind directly to the DNA-binding domain of p53, thereby impairing its transcriptional activation of critical pro-apoptotic target genes such as Bax, Puma, and Noxa [136]. This inhibitory interaction suppresses the intrinsic apoptotic pathway, enabling tumor cells to withstand chemotherapy-induced DNA damage [137]. Furthermore, HSP27 contributes to the stabilization of mutant p53 isoforms that are frequently expressed in malignant tissues [138]. Although these mutant variants are deficient in canonical tumor-suppressive functions, they often acquire oncogenic gain-of-function properties that enhance cell survival, proliferation, and invasion [139]. By preserving the structural stability of these aberrant p53 forms, HSP27 reinforces a pro-survival cellular phenotype and diminishes therapeutic efficacy. Collectively, this intricate HSP27–p53 interplay fosters an anti-apoptotic milieu that allows tumor cells to evade apoptosis and persist under cytotoxic stress induced by chemotherapy or RT [109].

DNA damage repair enhancement

Platinum-based chemotherapeutic agents, such as cisplatin, exert their cytotoxic effects primarily by forming intra- and inter-strand crosslinks within DNA, thereby disrupting essential processes of replication and transcription [140]. HSP27 plays a piv-

otal role in the cellular defense against such genotoxic stress by promoting DNA damage repair [116]. Specifically, HSP27 stabilizes key DNA repair proteins, including excision repair cross-complementation group 1 (ERCC1) and X-ray repair cross-complementing protein 1 (XRCC1), which are critical components of the nucleotide excision repair (NER) and base excision repair (BER) pathways, respectively [141]. Upregulation of HSP27 enhances the efficiency of cisplatin-induced DNA adduct removal and facilitates the restoration of genomic integrity, thereby mitigating the cytotoxic consequences of platinum-based therapy [142]. This protective mechanism, while beneficial for normal cellular survival, paradoxically contributes to the emergence of chemoresistance in cancer cells and remains a major obstacle to the long-term efficacy of platinum-based regimens [109].

Redox homeostasis and ROS scavenging

Chemotherapeutic agents frequently exert their therapeutic effects by generating ROS, which are highly reactive molecules that can inflict significant oxidative damage to cellular components, including DNA and proteins [143]. HSP27 plays a critical role in mitigating the cytotoxic effects associated with ROS by enhancing the activity of various antioxidant enzymes [48]. These include superoxide dismutase (SOD), which dismutates superoxide radicals into hydrogen peroxide; catalase, which converts hydrogen peroxide into water and oxygen; and glutathione peroxidase (GPx), which reduces lipid peroxides and hydrogen peroxide using glutathione as a cofactor [64]. Moreover, HSP27 supports the synthesis of glutathione (GSH), a vital antioxidant that helps detoxify harmful peroxides and maintains redox balance within cells, by regulating the enzyme γ-glutamylcysteine synthetase [144]. This function is particularly important in cancer cells, which often face elevated levels of oxidative stress during chemotherapy [145]. By reinforcing this antioxidative defense mechanism, HSP27 protects cancer cells from oxidative stress–induced apoptosis, especially during treatment with chemotherapeutics such as cisplatin and 5-FU, thereby contributing to the therapeutic resistance often observed in malignancies [109] (Table 5).

Strategy	Model/Context	Mechanism of Action	Therapeutic Effect	Reference
OGX-427 (Apatorsen)	HNC cell lines	Antisense inhibition of HSP27	↑ Radiosensitivity, ↑ Apoptosis	Hadchity., *et al*. 2009
HSP27 siRNA	HNSCC lines	Knockdown	↓ Akt signaling, ↑ ROS	Zhu., *et al*. 2010
Combined HSP27 + PI3K inhibition	*In vitro*	Dual pathway targeting	Synergistic radiosensitization	Guttmann., *et al*. 2013
HSP27 blockade + PD-1 inhibitor	Preclinical ICI model	Immune reactivation	↑ $CD8^+$ infiltration, ↓ M2 macrophages	Experimental studies (2024)

Table 5: Experimental and Translational Studies Targeting HSP27.

Abbreviations: Akt, Protein Kinase B; $CD8^+$, Cluster of Differentiation 8 Positive T Cell; HNC, Head and Neck Cancer; HNSCC, Head and Neck Squamous Cell Carcinoma; HSP27, Heat Shock Protein 27; ICI, Immune Checkpoint Inhibitor; M2, Type 2 Macrophage; PI3K, Phosphoinositide 3-Kinase; PD-1, Programmed Death-1; ROS, Reactive Oxygen Species; siRNA, Small Interfering RNA.

Cytoskeletal remodeling and drug efflux

HSP27 plays a critical role in regulating cytoskeletal dynamics, a process that significantly contributes to the development of drug resistance in cancer therapy [68]. By stabilizing actin filaments and microtubules, HSP27 preserves cellular morphology and structural integrity while promoting vesicular trafficking essential for the optimal function of ATP-binding cassette (ABC) transporters, particularly P-glycoprotein (MDR1) [51]. Through this cytoskeletal support, HSP27 facilitates efficient intracellular transport and enhances the efflux of xenobiotic compounds, including chemotherapeutic agents [133]. Elevated HSP27 expression has been correlated with increased drug efflux capacity, resulting in reduced intracellular accumulation of cytotoxic agents and consequently attenuated therapeutic efficacy [43].

This mechanism has been well documented in head and neck cancer (HNC) cell lines exhibiting resistance to cisplatin and paclitaxel, where dual suppression of HSP27 and MDR1 effectively restores chemosensitivity in a synergistic manner [146]. These findings underscore the functional interplay between HSP27-mediated cytoskeletal stabilization and drug transporter regulation, highlighting HSP27 as a crucial mediator of multidrug resistance. Targeting HSP27, either directly or in combination with conventional cytotoxic therapies, therefore represents a promising strategy to overcome chemoresistance and enhance treatment outcomes in refractory malignancies [109].

Clinical and translational evidence linking HSP27 to chemoresistance and prognosis in head and neck cancers

Clinical and translational investigations provide compelling evidence that elevated expression of HSP27 contributes to chemotherapy resistance and adverse clinical outcomes in HNCs [43]. In a comprehensive immunohistochemical analysis of 128 patients with oral squamous cell carcinoma (OSCC), Lo Muzio., *et al*. demonstrated that strong cytoplasmic HSP27 expression was significantly correlated with decreased sensitivity to cisplatin-based chemotherapy and increased recurrence rates, with multivariate analysis confirming HSP27 as an independent prognostic factor for OS and disease-free survival (DFS) [147]. Similarly, Ciocca and colleagues, in a multicenter HNSCC cohort, reported that nuclear accumulation of HSP27 was associated with resistance to 5-FU and poor pathologic response to CRT, underscoring its role in cytoprotective signaling and apoptotic suppression [111]. Chai., *et al*. further showed that nasopharyngeal carcinoma patients with high HSP27 expression had reduced response rates to cisplatin–5-FU-based induction chemotherapy and significantly shorter OS, with a median survival reduction of nearly 20 months compared to low-expression counterparts [148]. Mechanistically, these clinical findings align with preclinical data showing that HSP27 stabilizes anti-apoptotic proteins such as Bcl-2 and Akt, enhances DNA double-strand break repair, and supports cytoskeletal organization necessary for drug efflux via ATP-binding cassette transporters [149]. Earlier observations by Mese and colleagues revealed that elevated HSP27 expression correlated with advanced tumor stage and poor prognosis in OSCC [150], while Lang., *et al*. later confirmed that upregulated HSP27 was associated with lower complete response rates and shorter progression-free survival following cisplatin-based therapy [151]. Ramalingam and colleagues extended these results by demonstrating a stepwise increase in HSP27 expression from normal mucosa through dysplasia to invasive carcinoma, implicating the protein in malignant transformation and tumor aggressiveness [152]. However, not all reports are concordant. Suzuki and colleagues found that high HSP27 expression correlated with improved prognosis in a subset of OSCC cases, possibly reflecting site-specific or differentiation-dependent functions [153]. Likewise, Torres and colleagues found no significant prognostic association in oral tongue squamous cell carcinoma (OTSCC), emphasizing variability due to tumor site, post-translational modifications, or methodological differences in immunohistochemical evaluation [154]. Functional studies reinforce HSP27's biological role in treatment resistance. Zhu and colleagues demonstrated that silencing HSP27 in HNSCC cell lines reduced invasiveness and metastatic potential [155], while Hadchity and colleagues showed that targeting HSP27 with the antisense oligonucleotide OGX-427 enhanced radiosensitivity and chemotherapy-induced apoptosis [156]. Interestingly, Borowczak and colleagues reported an inverse pattern in laryngeal squamous cell carcinoma (LSCC), where reduced HSP27 and HSP70 expression correlated with poorer OS and higher recurrence risk, suggesting a context-dependent role that may vary by differentiation status or microenvironmental conditions [157].

Taken together, the preponderance of evidence indicates that HSP27 overexpression—whether cytoplasmic or nuclear—is closely associated with reduced chemosensitivity, accelerated tumor progression, and inferior survival outcomes in head and neck cancers. However, the heterogeneity among existing studies underscores the need for standardized, prospective validation. Future research should incorporate quantitative assessments of both total and phosphorylated HSP27, stratification by HPV status, and harmonized immunohistochemical scoring systems. Such methodological uniformity will be essential to establish HSP27 as a robust predictive and prognostic biomarker and to facilitate the rational development of HSP27-targeted therapeutic strategies in head and neck oncology [109] (Table 6).

Therapeutic Concept	Mechanistic Rationale	Potential Combination Partners	Expected Outcome
HSP27 inhibition (antisense or small molecules)	Disrupts stress adaptation	PI3K/AKT, MAPK inhibitors	Enhanced sensitivity
Integration with RT	Radiosensitization via DNA repair suppression	IMRT or proton therapy	Improved local control
Combination with ICIs	Reverses immunosuppressive TME	PD-1/PD-L1 blockade	Improved immunotherapy efficacy
Biomarker-driven trials	Stratify by total/p-HSP27	Precision oncology cohorts	Predictive response selection

Table 6: Proposed Translational and Clinical Implications of HSP27 Targeting.

Abbreviations: HSP27, Heat Shock Protein 27; ICIs, Immune Checkpoint Inhibitors; IMRT, Intensity-Modulated Radiotherapy; MAPK, Mitogen-Activated Protein Kinase; PD-1, Programmed Death-1; PD-L1, Programmed Death-Ligand 1; PI3K, Phosphoinositide 3-Kinase; RT, Radiotherapy; TME, Tumor Microenvironment.

HSP27 and resistance to targeted agents and immunotherapy

While the contribution of HSP27 to RT/CRT resistance in HNCs is well established, emerging data indicate that this chaperone also plays a pivotal role in resistance to molecularly targeted therapies and immunotherapeutic agents [109]. The cytoprotective, anti-apoptotic, and signaling-modulatory properties of HSP27 enable tumor cells to adapt to pharmacologic inhibition of oncogenic pathways, particularly those involving the EGFR, phosphoinositide 3-kinase (PI3K)/Akt, and mitogen-activated protein kinase (MAPK) cascades [43] (Figure 4).

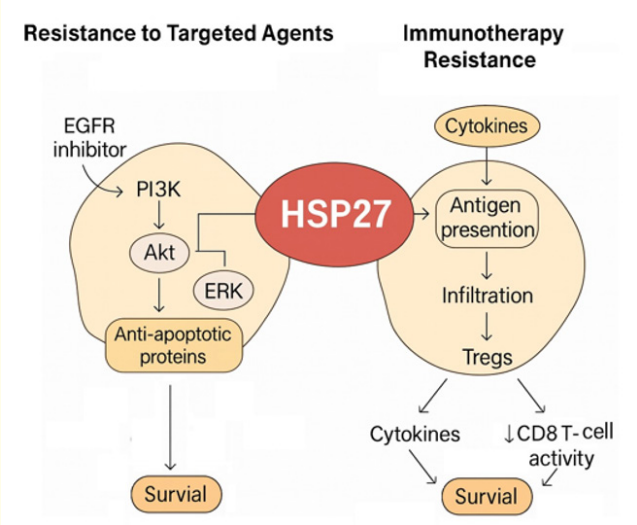

Figure 4: Mechanisms of HSP27-Mediated Resistance to Targeted Agents and Immunotherapy in Head and Neck Cancer.

Abbreviations: Akt, Protein Kinase B; CD8, Cluster of Differentiation 8; EGFR, Epidermal Growth Factor Receptor; ERK, Extracellular Signal–Regulated Kinase; HSP27, Heat Shock Protein 27; PI3K, Phosphoinositide 3-Kinase; Tregs, Regulatory T Cells.

Resistance to EGFR-Targeted therapies

EGFR overexpression is a hallmark of most HNCs, and the monoclonal antibody cetuximab remains the only approved targeted therapy in this disease [158]. However, clinical response rates are modest, and acquired resistance is common. Several studies have implicated HSP27 in mediating resistance to EGFR inhibition [159]. Mechanistically, HSP27 directly interacts with phosphorylated Akt and maintains downstream survival signaling even under EGFR blockade. In cetuximab-resistant HNSCC cell lines, upregulation of HSP27 preserves Akt phosphorylation and inhibits apoptosis by stabilizing anti-apoptotic Bcl-2 family proteins.

Pharmacologic inhibition or siRNA-mediated knockdown of HSP27 re-sensitizes resistant cells to cetuximab and erlotinib, restoring apoptosis and growth arrest [160]. Furthermore, HSP27 enhances the proteasomal degradation of EGFR inhibitors through its chaperone function, effectively reducing intracellular drug retention. Clinically, increased cytoplasmic HSP27 expression has been linked to inferior responses to EGFR-targeted regimens and shorter PFS, highlighting its role as a predictive biomarker of anti-EGFR therapy resistance [161].

Cross-Talk with PI3K/AKT/mTOR and MAPK pathways

HSP27's ability to stabilize key nodes within the PI3K/Akt and MAPK signaling networks contributes to its broad influence on targeted therapy outcomes [162]. Following EGFR or mTOR inhibition, compensatory activation of these pathways frequently occurs, driven in part by HSP27-mediated phosphorylation events. HSP27 forms complexes with Akt, Raf-1, and ERK1/2, preventing their dephosphorylation and degradation [163]. Experimental suppression of HSP27 disrupts these complexes, decreases downstream signaling activity, and enhances tumor cell sensitivity to dual PI3K/mTOR inhibitors such as BEZ235 and temsirolimus [164]. Moreover, in HNC cell models treated with tyrosine kinase inhibitors (TKIs), HSP27 upregulation promotes EMT, which confers additional drug resistance through increased migratory capacity and survival signaling [165]. These findings suggest that co-targeting HSP27 alongside pathway inhibitors could delay or overcome resistance mediated by adaptive signaling plasticity.

HSP27 and immunotherapy resistance

Beyond its cytoprotective functions, HSP27 also influences the tumor immune microenvironment, contributing to resistance to immune checkpoint inhibitors (ICIs) [166]. HSP27 modulates antigen presentation and cytokine release, facilitating an immunosuppressive milieu [167]. High HSP27 expression in tumor and stromal cells correlates with increased infiltration of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), alongside reduced cytotoxic $CD8^+$ T-cell activity [168]. Mechanistically, extracellular HSP27 released via exosomes or stress-induced secretion binds TLR2 and TLR4 on macrophages, inducing IL-10 and TGF-β secretion and promoting an M2-like polarization that dampens anti-tumor immunity [169]. Recent studies have linked HSP27 upregulation with reduced efficacy of PD-1/PD-L1 blockade in HNCs [170]. In preclinical models, HSP27 silencing enhanced interferon signaling and increased MHC class I expression, augmenting T-cell recognition and tumor clearance under anti-PD-1 treatment, suggesting that HSP27 may serve as both a biomarker and potential therapeutic target for overcoming immunotherapy resistance [171]. Early-phase research is exploring combined inhibition of HSP27 with ICIs or small-molecule checkpoint regulators to reprogram the tumor immune microenvironment toward a more inflamed, therapy-responsive state [172]. Considering the facts above, the multifaceted role of HSP27 across cytoprotective, signaling, and immune-modulatory axes positions it as a central regulator of treatment escape in HNCs [43].

Targeting HSP27, either through antisense oligonucleotides such as OGX-427 or novel small-molecule inhibitors, has shown preclinical promise in reversing resistance to EGFR-targeted agents and ICIs [173]. Integration of HSP27 inhibition into multimodal regimens, particularly in tumors exhibiting high baseline expression or post-treatment induction, could enhance durable responses. Prospective studies incorporating HSP27 expression profiling and immune phenotyping are warranted to validate its predictive value and to define rational combination strategies that leverage its inhibition for improved outcomes in HNC patients [133].

Future perspectives

Despite extensive evidence implicating HSP27 as a critical mediator of resistance to RT and systemic therapies in HNCs, significant gaps remain before its translation into an established biomarker or therapeutic target can be realized [102]. The heterogeneity among clinical findings underscores the urgent need for methodological standardization. Therefore, future studies should adopt harmonized immunohistochemical protocols, including clearly defined scoring systems, subcellular localization (cytoplasmic versus nuclear), and differentiation between total and p-HSP27 isoforms [174]. Given that phosphorylation status directly governs HSP27's oligomeric state and functional activity, quantifying these isoforms is essential for accurately correlating expression with clinical outcomes [175]. Stratification by tumor subsite, HPV status, and therapeutic context is also imperative to resolve discrepancies observed across oral, oropharyngeal, laryngeal, and other HNCs [176].

Therapeutically, HSP27 represents a promising yet underexploited vulnerability. The antisense oligonucleotide apatorsen (OGX-427) has shown the capacity to enhance radiosensitivity and chemosensitivity in preclinical HNC models by disrupting HSP27-mediated stress tolerance, DNA repair, and pro-survival signaling [177]. However, its clinical utility remains to be tested in this setting [178]. Parallel efforts to develop small-molecule inhibitors targeting HSP27 oligomerization or phosphorylation cycles may further potentiate conventional treatments by dismantling the adaptive stress networks that protect tumor cells from cytotoxic injury [179]. Rational combination approaches, particularly those coupling HSP27 blockade with inhibitors of the PI3K/AKT or MAPK pathways, or with immune checkpoint blockade, should be prioritized to overcome redundant survival signaling and immune evasion mechanisms [180].

Emerging multi-omic and computational approaches provide powerful opportunities to dissect the broader chaperone interactome in which HSP27 operates [181]. Integrative proteomic and transcriptomic profiling can uncover co-chaperone dependencies and synthetic-lethal vulnerabilities, guiding the rational design of combination regimens [182]. Liquid biopsy–based quantification of circulating or exosomal HSP27 also holds promise as a noninvasive biomarker for monitoring therapeutic response, residual disease, and recurrence risk [183]. Moreover, the extracellular and immune-modulatory roles of HSP27, especially its capacity to polarize macrophages toward the M2 phenotype, attenuate cytotoxic T-cell activity, and sustain a pro-inflammatory yet immunosuppressive tumor microenvironment, warrant further mechanistic and translational investigation, given their implications for immunotherapy resistance [184]. Translational bridge studies that connect mechanistic insight with patient-level validation are now a critical priority [185]. Incorporating HSP27-targeted strategies into adaptive, biomarker-driven clinical trials could accelerate therapeutic evaluation and identify predictive markers of benefit [186]. Artificial intelligence and systems biology modeling may further facilitate the mapping of HSP27-centered stress and proteostasis networks, illuminating actionable nodes for drug development [187]. Ultimately, the clinical realization of HSP27-directed therapy will depend on a precise understanding of its contextual duality, cytoprotective in normal tissues yet pro-survival in malignancy, and the ability to exploit tumor-specific dependencies without compromising normal tissue repair. By integrating molecular diagnostics, precision therapeutics, and real-time biomarker monitoring, targeting HSP27 may evolve from an experimental concept to a clinically transformative strategy capable of enhancing radiosensitivity, overcoming systemic resistance, and improving survival in patients with HNCs.

Conclusion

HSP27 has emerged as a pivotal regulator of treatment resistance in HNCs, integrating multiple cytoprotective functions that enable tumor persistence under therapeutic stress. Through its dynamic phosphorylation, chaperone activity, and broad network of client proteins, HSP27 preserves DNA repair fidelity, sustains redox equilibrium, stabilizes mitochondrial integrity, and suppresses apoptosis, thereby conferring resilience to RT and systemic agents alike. Its capacity to maintain PI3K/AKT, MAPK, and NF-κB signaling, facilitate EMT, and support ATP-binding cassette–mediated drug efflux underscores its central role in mediating both radio-

and chemoresistance. Beyond intrinsic tumor cell mechanisms, extracellular HSP27 also shapes the TME, promoting immunosuppression and inflammation that further attenuate therapeutic efficacy. Collectively, these multifaceted actions position HSP27 as both a biomarker of resistance and a therapeutic target of high translational relevance. Although early preclinical studies and limited clinical data support the feasibility of targeting HSP27, particularly through antisense oligonucleotides and small-molecule inhibitors, prospective validation remains imperative. Future integration of HSP27 inhibition into rational combination regimens, especially with PI3K/AKT or immune checkpoint blockade, may redefine therapeutic paradigms in resistant HNCs. Ultimately, translating the molecular understanding of HSP27 into precision oncology frameworks holds the potential to enhance radiosensitivity, restore chemosensitivity, and improve long-term disease control for patients confronting this biologically complex and clinically challenging malignancy.

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Conflict of Interest

None.

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