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Review

Genetic Determinants of Radiotherapy Resistance in Uveal Melanoma

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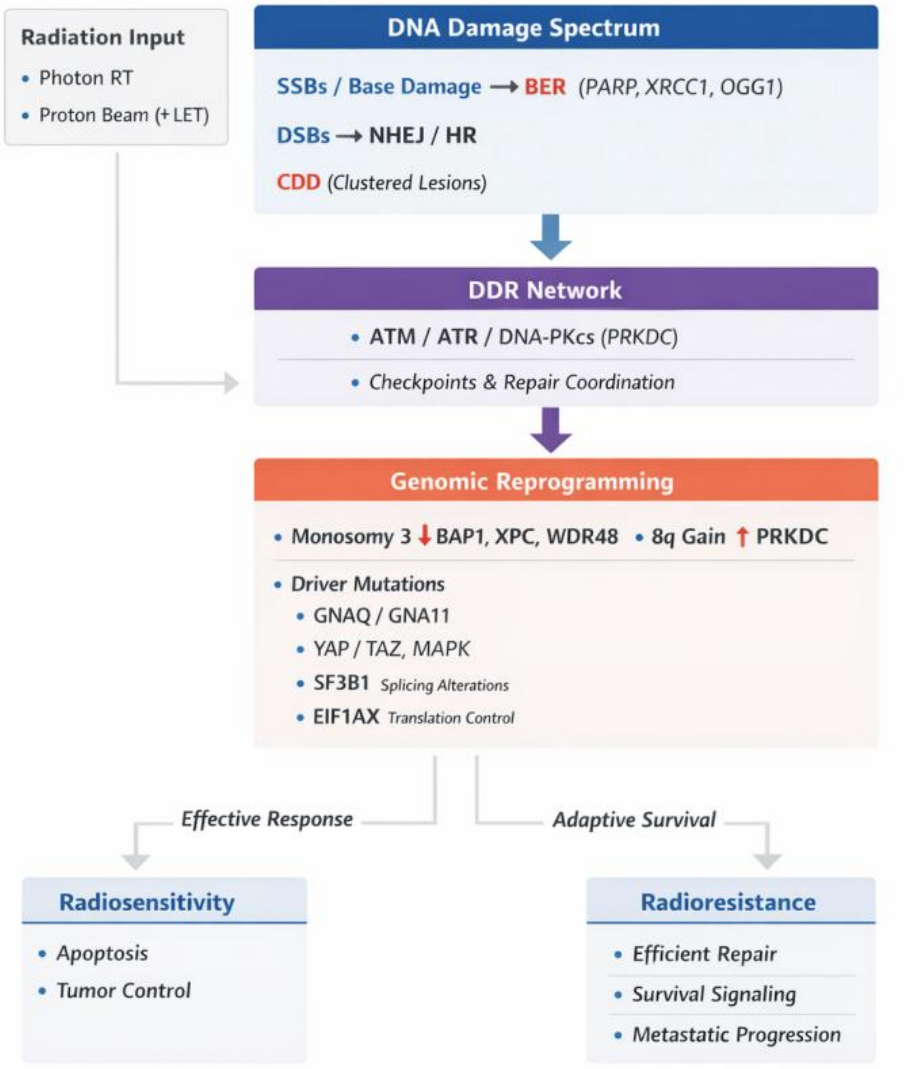
Abstract

Radiotherapy remains the cornerstone of local treatment for uveal melanoma (UM), achieving high rates of primary tumor control. Nevertheless, a substantial proportion of patients experience disease progression and metastatic relapse, underscoring a fundamental biological limitation of radiotherapy efficacy in this malignancy. Accumulating evidence indicates that radioresistance in UM is not driven by high mutational burden, but rather by a distinctive genetic architecture dominated by chromosomal alterations and adaptive DNA damage response programs. High-risk cytogenetic states in UM, particularly those defined by large-scale chromosomal imbalance, have emerged as key biological contexts shaping radiotherapy tolerance. Rather than acting as passive prognostic markers, these configurations appear to remodel genome maintenance capacity by selectively dampening tumor-suppressive safeguards while favoring DNA damage tolerance and survival-oriented repair responses. In parallel, early oncogenic events that drive tumor initiation indirectly reinforce radioresistance by sustaining pro-survival signaling programs, transcriptional adaptability, and stress resilience. Together, these features establish a cellular state in which radiation-induced damage is accommodated rather than eliminated, permitting clonogenic persistence despite adequate local dose delivery. This review integrates genomic, cytogenetic, and radiobiological evidence to propose a unifying framework in which UM radioresistance arises from coordinated genetic reprogramming of DNA repair and survival pathways. Understanding these determinants is essential for the rational development of radiosensitization strategies and for improving long-term disease control in UM.

Graphical Abstract



1. Introduction

Despite remarkable advances in local treatment modalities, including brachytherapy and proton beam therapy (PBT), uveal melanoma (UM) remains a highly lethal malignancy driven by its strong metastatic propensity rather than by inadequate primary tumor control. Contemporary radiotherapeutic approaches achieve excellent local control rates, exceeding 95% in most large series. However, local treatment failure, although infrequent, is clinically significant, as it has been consistently associated with an increased risk of metastatic death [1-3].

In patients treated with PBT, local tumor control rates approach 96%-97%, yet local recurrence may occur even a decade after primary treatment, underscoring the long latency and biological persistence of UM [1,4]. Importantly, local recurrence is not merely a regional event but serves as a surrogate marker of aggressive tumor biology, frequently heralding subsequent metastatic dissemination.

More strikingly, successful eradication of the primary ocular tumor does not translate into long-term survival benefit for a substantial proportion of patients. Longitudinal studies indicate that approximately 25% and 34% of UM patients develop metastases within 5 and 10 years, respectively, and nearly 45%-50% ultimately develop metastatic disease within 15-25 years after initial treatment [1,5]. Once metastasis occurs, most commonly involving the liver in nearly 90% of cases, the disease is almost invariably fatal [3].

Survival outcomes for metastatic UM remain dismal. The mean survival following diagnosis of metastatic disease is approximately 12 months, and although a small subset of patients may survive beyond 3-4 years, overall survival (OS) has not meaningfully improved over the past three decades based on clinical data reported from treatment centers such as Massachusetts Eye and Ear Infirmary and the Harvard Cyclotron in the United States [1]. OS is defined as the time from diagnosis or initiation of treatment until death from any cause. Recent clinical trials evaluating chemotherapies, targeted agents, and immunotherapies have demonstrated limited clinical efficacy, often accompanied by substantial toxicity [6]. Notably, no adjuvant systemic therapy has yet been approved for UM, a stark contrast to the growing precision of molecular prognostication [2].

Beyond survival, treatment-related morbidity represents another critical limitation of current radiotherapeutic strategies. While brachytherapy has become a standard eye-sparing alternative to enucleation, exposure of radiosensitive ocular structures, including the macula, fovea, and optic nerve, frequently results in radiation-induced vision loss, with up to 50% of patients experiencing significant visual impairment following treatment [5].

At the pathological and biological level, multiple features of the primary tumor have been robustly associated with metastatic risk and poor outcome. These include large tumor size, increased thickness, ciliary body involvement, extrascleral extension, epithelioid cell morphology, high mitotic activity, and the presence of angiogenic patterns such as closed extravascular matrix loops. Cytogenetically, monosomy 3 and gain of chromosome 8q represent the most powerful predictors of metastatic progression. Consistent with other solid malignancies, angiogenesis plays a central role in UM growth and dissemination, further reinforcing the link between tumor microenvironment and lethal progression [5].

Importantly, emerging evidence suggests that initial responses to advanced radiotherapy techniques may mask deeper biological resistance mechanisms. Tumors that initially regress can later recur or metastasize, potentially driven by adaptive molecular programs, including activation of hypoxia-inducible factor-1α (HIF-1α) and related stress-response pathways. These adaptive responses may enable tumor cells to survive radiation-induced damage and ultimately fuel systemic spread [7].

Collectively, these observations underscore a critical paradox in UM management: primary disease is effectively controlled by surgery or RT, yet up to half of patients succumb to metastatic disease for which no effective treatment exists. This disconnect highlights that treatment failure in UM is not primarily technical, but rather biological and genetic in origin, strongly implicating tumor-intrinsic molecular determinants in radioresistance, metastatic escape, and therapeutic inefficacy.

Accordingly, in this review, we systematically analyze genes implicated in UM pathogenesis alongside key DNA repair and damage response genes involved in the cellular response to RT, with the overarching goal of elucidating genetic determinants of RT inefficacy and highlighting potential targets to overcome resistance and limit metastatic dissemination.

2. Uveal Melanoma

UM is a rare but aggressive malignancy arising from melanocytes located within the uveal tract of the eye, which comprises the choroid, ciliary body, and iris. Among ocular melanomas, UM represents the predominant subtype, accounting for approximately 85-90% of cases, whereas conjunctival melanoma originates from the ocular surface epithelium and remains comparatively rare [8-10].

Although melanoma most frequently develops in the skin, the eye constitutes the second most common anatomical site for melanoma occurrence. UM is the most common primary intraocular malignancy in adults, responsible for nearly 70% of all primary eye cancers. Its annual incidence is estimated at 2-8 cases per million population, with consistent reports converging around 5-6 cases per million per year, underscoring its rarity at the population level [11-15].

Clinically, UM is characterized by a strong predilection for hematogenous dissemination, most notably to the liver, which represents the initial site of metastasis in the majority of cases. Despite effective local tumor control achieved through RT or enucleation, approximately 50% of patients ultimately develop metastatic disease. Once metastasis is detected, prognosis is poor, with reported median survival ranging from 4 to 7 months, reflecting the limited efficacy of current systemic therapies [16,17].

3. Treatment Strategies for Uveal Melanoma

Contemporary treatment strategies for UM are broadly categorized into radical approaches, involving removal of the globe by enucleation, and conservative approaches, aimed at preserving the eye and, when possible, useful vision. Historically, surgical enucleation represented the cornerstone of treatment for UM, reflecting the primary goal of achieving local tumor eradication. This paradigm shifted following the landmark Collaborative Ocular Melanoma Study (COMS), which demonstrated no significant difference in OS between patients with medium-sized UM treated by enucleation and those receiving iodine-125 plaque brachytherapy [18]. This pivotal finding established eye-preserving RT as an oncologically sound alternative to radical surgery.

For small-to medium-sized tumors, ocular brachytherapy constitutes the standard-of-care in most ocular oncology centers. This technique involves the surgical placement of a saucer-shaped radioactive plaque, most commonly containing iodine-125 or ruthenium-106, directly over the sclera adjacent to the tumor. Iodine-125 brachytherapy, in particular, has proven to be an effective and widely adopted eye-sparing treatment, offering high rates of local control while maintaining acceptable toxicity profiles [19,20]. Among external beam techniques, PBT has emerged as a cornerstone of modern UM management. PBT is a highly precise form of RT that employs charged protons rather than photons, allowing for sharp dose localization within the tumor while minimizing irradiation of adjacent normal ocular structures [21,22].

From a radiobiological perspective, proton therapy introduces additional complexity relevant to treatment resistance. As protons decelerate near the distal end of the Bragg peak, linear energy transfer (LET) increases, resulting in a higher density of ionization events along the radiation track. This leads to the induction of complex DNA damage (CDD), including clustered double-strand breaks and chemically modified DNA lesions, which are inherently more difficult for tumor cells to repair than isolated DNA damage [6,23]. While

this property contributes to the increased relative biological effectiveness (RBE) of protons, it also places greater selective pressure on tumor cells with enhanced DNA damage response (DDR) and repair capabilities, an issue of central relevance when considering genetically driven radioresistance in UM.

4. Radiotherapy in Uveal Melanoma

A comprehensive understanding of RT and its cytotoxic mechanisms is fundamental to identifying the biological pathways that underlie treatment resistance and post-therapy metastatic progression in UM. In recent years, RT has undergone substantial paradigm shifts. These advances have transformed RT from a purely local cytotoxic intervention into a biologically complex, precision-guided anticancer strategy.

At the cellular level, ionizing radiation exerts antitumor effects primarily through genomic DNA damage. Damage occurs directly via DNA ionization or indirectly through radiolysis of intracellular water, generating highly reactive oxygen species (ROS) [24]. ROS-mediated oxidation produces base lesions and single-strand breaks (SSBs). When SSBs occur in close proximity on opposing strands, they can form double-strand breaks (DSBs), the most lethal type of radiation-induced DNA damage [25]. Molecular oxygen further stabilizes damaged DNA ends, producing irreversible lesions that critically compromise genomic integrity.

Beyond direct cytotoxicity, RT damages other cellular organelles, including the endoplasmic reticulum, triggering immunogenic cell death (ICD). ICD is characterized by the release of tumor-associated antigens (TAAs) and a spectrum of cytokines, chemokines, and danger-associated molecular patterns [26-28]. These signals activate innate and adaptive immune responses, facilitating immune-mediated elimination of irradiated tumor cells. Importantly, the immunological consequences of RT depend on dose, fractionation, and spatial delivery, which critically influence treatment outcomes [29-32].

Conventional multifractionated RT delivers relatively low doses per fraction over multiple sessions. While this can elicit antitumor immune responses, repeated daily irradiation may also eliminate infiltrating immune effector cells, potentially limiting sustained immune activation. In contrast, hypofractionated or stereotactic regimens deliver high doses in fewer fractions, better preserving tumor-infiltrating immune cells and enhancing the immunostimulatory potential of RT [7]. This distinction has important implications for both tumor control and resistance evolution.

PBT represents a modern precision RT modality. Despite its widespread clinical use, the radiobiological response of UM to PBT remains incompletely understood. As protons decelerate near the distal edge of the Bragg peak, LET increases, causing densely clustered DNA damage. Such clustered lesions, including DSBs and chemically modified bases, challenge the cellular repair machinery. The efficacy of PBT depends on its ability to overwhelm tumor DNA repair systems, driving irreversible cell death [6]. However, these same features may select for tumor cells with enhanced DDR capabilities, potentially promoting radioresistance.

Following radiation-induced DNA damage, cells activate tightly regulated biological responses, including DNA repair, damage tolerance, cell-cycle checkpoint control, senescence, and apoptosis. The specific pathway engaged is dictated by the type, complexity, and severity of the damage. In cases of extensive or irreparable genomic injury, cells undergo permanent growth arrest or programmed cell death. Conversely, tumors with efficient or dysregulated DDR pathways may survive radiation exposure, contributing to treatment failure [33-35].

Despite these advances, it remains unclear to what extent DNA repair pathways contribute to UM initiation, progression, and, critically, radioresistance following treatment [1,36,37]. Characterizing the expression patterns and functional status of DDR-related genes in UM therefore represents a crucial step toward understanding variability in RT response and identifying novel therapeutic vulnerabilities. Accordingly, in this review, we systematically analyze genes implicated in UM pathogenesis alongside key DNA repair and damage response genes involved in the cellular response to RT, with the overarching goal of elucidating genetic determinants of RT inefficacy and highlighting potential targets to overcome resistance and limit metastatic dissemination.

5. Radioresistance in Uveal Melanoma

Despite RT constituting the cornerstone of local treatment for UM, surprisingly few studies have systematically investigated the radiobiology and mechanisms of radioresistance in this malignancy. Consequently, much of the current understanding of UM radiosensitivity is derived from a limited number of in vitro studies employing established UM cell lines, with relatively sparse integration of molecular or genetic correlates (Table 1).

Table 1. Genetic and cytogenetic landscape of UM with implications for metastasis and radioresistance.

Category	Gene	Chromosome	Pathway/role
Potential driver mutations	GNAQ	9q21.2	Constitutive Gαq activation; PLCβ-PKC-MAPK signaling; YAP/TAZ survival pathway
	GNA11	19p13.3	Activating Gαq mutation; PKC/MAPK signaling; pro-survival driver
	CYSLTR2	13q14.2	Oncogenic GPCR; upstream Gαq activator; PLCβ-PKC signaling
	PLCB4	20p12.3	Gαq effector; DAG/IP3 signaling; PKC/MAPK activation
	SF3B1	2q33.1	Spliceosome component; aberrant RNA splicing; late-metastasis subtype
	EIF1AX	Xp22.12	Translation initiation factor; ribosomal start-site regulation; low-risk biology
	SRSF2	17q25.1	Splicing factor; exon recognition defects; transcriptomic instability
	U2AF1	21q22.3	Splice-site recognition factor; splicing errors; stress-adaptation dysregulation
	TP53	17p13.1	DDR regulator; cell-cycle arrest; apoptosis mediator
Metastasis drivers	MYC (8q)	8q24.21	Oncogenic transcription factor; proliferation driver; metabolic reprogramming
	ASAP1 (DDEF1 / AMAP1)	8q24.21	ARF-GAP scaffold; cytoskeletal remodeling; invasion and migration
	PRAME	22q11.22	Cancer-testis antigen; transcriptional repression; immune evasion marker
Chromosomal	Monosomy 3	Chr 3	Tumor suppressor loss; high-risk cytogenetics; metastatic phenotype
	Isodisomy 3	Chr 3	Copy-neutral LOH; tumor suppressor inactivation; aggressive subtype
	8q gain	Chr 8q	Oncogene amplification; dosage-driven signaling; metastatic competence
	6p gain	Chr 6p	Copy-number gain; favorable prognosis marker; low-risk subtype
	1p loss	Chr 1p	Chromosomal deletion; genomic instability; adverse prognostic marker
	CNKSR3	6q25.2	Signaling scaffold; MAPK pathway modulation; rare CNA-associated role
Radioresistance genes	PRKDC (DNA-PKcs)	8q11.21	NHEJ kinase; DSB repair mediator; radioresistance driver
	ATM	11q22.3	DSB sensor kinase; checkpoint activation; DDR coordinator
	ATR	3q23	Replication-stress sensor; HR repair regulator; genome stability mediator
	CHEK2 (CHK2)	22q12.1	ATM effector kinase; checkpoint enforcement; irradiation response
	H2AX (H2AFX; γH2AX readout)	11q23.3	DSB chromatin marker; γH2AX signaling; repair kinetics indicator
	PARP1	1q42.12	SSB/BER mediator; DNA repair facilitator; radiosensitization target
	PARG	10q11.23	PAR turnover enzyme; PARP signaling regulator; BER resolution
	OGG1	3p26.2	BER glycosylase; oxidative lesion repair; ROS-damage tolerance
	XPC	3p25.1	Global-genome NER sensor; bulky-lesion repair; genome surveillance
	WDR48 (UAF1)	3p22.2	USP1 cofactor; Fanconi anemia regulation; ICL repair support
	USP1	1p31.3	Deubiquitinase; Fanconi pathway regulator; replication-stress tolerance
	FANCD2	3p25.3	Fanconi anemia effector; interstrand crosslink repair; fork protection
	MLH1	3p22.2	Mismatch repair core protein; replication fidelity; repair-capacity regulator
	BAP1	3p21.1	Chromatin regulator; deubiquitinase; HR-associated DDR mediator
	MBD4	3q21	DNA glycosylase; BER at CpG sites; genome maintenance regulator

Early radiobiological investigations, largely based on single UM cell line models, suggested that UM cells exhibit an intrinsically radioresistant phenotype. Initial experiments using the SP6.5 and OM431 cell lines reported limited sensitivity to γ-irradiation at doses up to 3-4 Gy, reinforcing the notion that UM may be broadly resistant to conventional photon-based RT [38-40]. However, these early conclusions were constrained by the narrow experimental scope and limited biological diversity represented by single-cell-line analyses.

Subsequent studies employing larger and more diverse panels of UM cell lines substantially refined this view. Investigations using multiple primary (OCM-1, Mel202, Mel270, 92.1) and metastatic (OMM1, OMM2.2, OMM2.3, OMM2.6) UM cell lines demonstrated (Table 2) a broad spectrum of radiosensitivity following X-ray irradiation [41,42]. Importantly, no consistent differences were observed between cell lines derived from primary tumors versus metastatic lesions, indicating that radiosensitivity in UM is not intrinsically linked to metastatic origin.

These observations were further corroborated by later studies examining additional UM cell lines (SP6.5, Mel270, µ2, TP17, 92.1, and MKT-BR). These analyses confirmed pronounced inter-line variability in response to X-ray irradiation and showed that radiosensitivity was not significantly influenced by cell-cycle status (asynchronous versus G0/G1-arrested cells) or by hypoxic conditions (1% oxygen) before or after irradiation [43]. Collectively, these findings underscore that UM radioresponse is governed by intrinsic cellular properties rather than by simple microenvironmental or proliferative parameters.

Table 2. Information on UM cell lines reported in the literature.

Cell Line	Origin (Primary/Metastatic)	Racial Background	Histologic Info (Tumor Type)	Cytogenetic Features	Genetic Mutations (key)
92.1	Primary UM	—	Primary choroidal melanoma	Disomy 3 (normal chr3)	GNAQ Q209L; BAP1 WT; EIF1AX mutation
Mel270	Primary UM	—	Primary ciliary body / recurrent UM	Disomy 3	GNAQ Q209P; BAP1 WT
Mel202	Primary UM	—	Primary choroidal melanoma (recurred after irradiation)	Disomy 3	GNAQ Q209L
OCM-1	Primary UM (originally)	Caucasian†	Choroidal melanoma	Variable/complex karyotype; reported tetraploid	BRAF V600E (misidentified lineage issues reported)
OMM1	Metastatic UM (subcutaneous/liver)	—	Metastatic site	Disomy 3 (typical for many cultured lines)	GNA11 Q209L
OMM2.2	Metastatic UM (liver)	Male donor (population not reported)	Metastatic	Disomic/derived alongside Mel270	—
OMM2.3	Metastatic UM (liver; same patient as Mel270)	—	Metastatic	Disomic (same origin as Mel270)	GNAQ Q209P
OMM2.5	Metastatic UM (liver; same patient as Mel270)	—	Metastatic	Disomy 3	GNAQ Q209P
OMM2.6	Metastatic UM (liver; same patient family as OMM2.2/OMM2.3/ Mel270)	—	Metastatic	Typically disomic	Similar profiles to OMM2.2 & OMM2.3
OM431	Primary UM	Caucasian	Uveal melanoma (eye/uvea)	—	—

While the majority of these studies focused on low-LET radiation such as X-rays or γ-rays, limited evidence suggests that high-LET radiation may exert enhanced cytotoxic effects in UM. Specifically, exposure to carbon ion irradiation was shown to markedly reduce UM cell survival compared with low-LET photons, highlighting the potential importance of radiation quality in overcoming UM radioresistance [44,45].

A particularly notable advance was reported by Hussain et al. [46], who demonstrated that the heterogeneity of radiosensitivity among UM cell lines is conserved across radiation modalities, including both photon and proton irradiation. In this study, Mel270 and OMM2.5 consistently exhibited the highest levels of radioresistance, whereas OMM1 and 92.1 were among the most radiosensitive cell lines, irrespective of whether X-rays or protons were used. These findings suggest that intrinsic biological determinants, rather than radiation modality alone, play a dominant role in shaping UM radioresponse.

Despite the widespread clinical use of PBT in UM, experimental studies investigating UM cellular responses to protons remain remarkably scarce. Available data indicate that Mel270 cells display comparable clonogenic survival following exposure to low-LET protons and X-rays, although proton irradiation may uniquely affect cell motility, suggesting modality-specific biological effects beyond cell killing [46]. Notably, comprehensive analyses of DNA damage signaling and repair pathway activation in UM cells following photon versus proton irradiation have not yet been systematically reported.

Taken together, existing evidence indicates that radioresistance in UM is not uniform, but instead reflects substantial intertumoral and intercellular heterogeneity. However, the molecular and genetic determinants underlying this variability remain poorly defined. Given the central role of DNA damage induction and repair in RT response, elucidating the contribution of DDR pathways to UM radioresistance represents a critical unmet need and provides the rationale for the analyses discussed in the following sections.

6. Genetic and DNA Damage Response Determinants of Radiotherapy Inefficacy

6.1 DNA Damage Complexity and Repair Pathway Choice

RT generates a broad spectrum of DNA lesions, yet the biological outcome in UM is largely determined by lesion complexity and the repair pathway “choice” that follows. As repeatedly emphasized in radiobiology, the most frequent products of irradiation are SSBs and oxidized base lesions. However, these injuries are often resolved quickly and with high fidelity; accurate repair kinetics for SSB/base lesions can occur on the scale of minutes in many cell types, reflecting the efficiency of base excision repair (BER). In practical terms, BER acts as the cell’s “rapid response unit” for oxidative base damage and abasic sites, limiting the long-term lethality of these abundant but typically reparable lesions [6,47-49].

In contrast, DSBs and CDD represent the lesions most strongly linked to durable clonogenic death after RT. DSBs are particularly dangerous because they sever chromosomal integrity, and classical radiobiological models support the notion that even a single unrepaired DSB can be catastrophic for survival [50,51]. Accordingly, cells deploy two principal DSB repair programs: non-homologous end joining (NHEJ) and homologous recombination (HR). NHEJ is active throughout the cell cycle and is therefore frequently positioned as the default DSB repair option. Importantly, NHEJ itself is not monolithic: classical NHEJ (cNHEJ) and alternative NHEJ (aNHEJ) differ in kinetics and fidelity [52,53]. While NHEJ can rapidly restore DNA continuity, it does so without a homologous template and is therefore intrinsically error-prone, often leaving small insertions or deletions [54,55]. By contrast, HR achieves high-fidelity repair by using the sister chromatid as a template, but this accuracy comes at a cost, HR is largely restricted to S/G2 phases, when a sister chromatid is available [56].

The concept of CDD adds a crucial layer of complexity to this lesion hierarchy. CDD is typically defined as two or more lesions within one to two helical turns of DNA, effectively representing “clustered” injury rather than isolated breaks. Several authors have highlighted that CDD can be operationally categorized into non-DSB clusters (dense base/SSB lesions) and DSB clusters, and that its resolution likely requires coordinated engagement of BER/SSB repair together with DSB repair mechanisms [57,58]. However, the relative contribution of BER versus NHEJ versus HR to CDD repair remains incompletely resolved, and the field continues to debate whether specific radiation qualities shift pathway engagement in predictable directions [59,60].

This controversy becomes especially relevant to UM because PBT is widely used for ocular tumors and introduces a distinct microdosimetric environment. The physical signature of PBT is the Bragg peak, where dose deposition rises sharply at a controlled depth, one of the key reasons protons can treat intraocular lesions while limiting exit dose. Yet the same physics that improves geometric precision can also reshape biology: as protons slow near the Bragg peak, LET increases, leading to denser ionization events that can favor clustered injury patterns. Recent work has reported that BER/SSB repair proteins, particularly PARP-1, PARG, and OGG1, are critical for repairing DNA damage induced by relatively higher-LET protons delivered around the Bragg peak, suggesting that a substantial component of proton-associated damage in this context is SSB/oxidative-base-linked and therefore BER-dependent. Notably, this BER-leaning interpretation sits alongside conflicting reports arguing that increasing LET may preferentially engage either NHEJ or HR for the repair of DSBs after proton/neutron-like irradiation, underscoring that lesion complexity and pathway utilization are not fixed properties, but may be context-dependent and cell-type specific [6,57,58].

Taken together, the emerging picture is that radiation modality and LET do more than change the spatial distribution of dose; they influence the architecture of DNA damage, which in turn constrains repair pathway choice. In UM, where PBT is a mainstay, tumor control may hinge on whether irradiation produces predominantly BER-manageable SSB/base lesions, or instead generates DSBs and CDD that overwhelm DSB repair capacity. Conceptually, UM radioresistance can be viewed as a phenotype arising from efficient management of high-risk lesions (DSBs/CDD) and/or adaptive routing between BER, NHEJ, and HR under modality-specific conditions such as increased LET at the Bragg peak.

6.2 DDR Signaling Kinases and Radiotherapy Response

Beyond the physical dose distribution delivered by photons or protons, the cellular DDR is ultimately "decisive" for whether irradiated UM cells recover or collapse. Within this network, the apical signaling kinases Ataxia-Telangiectasia Mutated (ATM), a DNA double-strand break-activated serine/threonine kinase that phosphorylates key repair and checkpoint proteins, ATM and Rad3-related (ATR), a replication-stress-responsive serine/threonine kinase that coordinates single-stranded DNA damage signaling and HR repair, and DNA-PKcs act as command nodes that translate DNA lesions into repair pathway engagement, checkpoint activation, and, when damage is irreparable, cell death. Yet, despite the centrality of these kinases, the DDR to PBT in UM remains surprisingly underexplored, leaving an important mechanistic gap between clinical practice and molecular explanation [3,61].

ATM has emerged as a plausible determinant of UM radioresponse, but not without controversy. Hussain et al. [46] reported that intrinsic radioresistance across UM cell lines correlates strongly with ATM levels, consistent with ATM's role as a master coordinator of DSB signaling and repair. Strikingly, in their study, pharmacologic ATM inhibition enhanced the cytotoxic impact of both photons and protons, reducing clonogenic survival and positioning ATM as a rational radiosensitization target in UM. These findings mirror a broader oncology trend: ATM targeting is being pursued as a radiosensitization strategy in other malignancies, most prominently glioblastoma and head-and-neck cancers, where combinations with photon irradiation have been actively investigated [62-65]. In parallel, the development of more potent and selective ATM inhibitors (e.g., AZD1390) strengthens the translational appeal of this axis and raises the question of whether UM, especially PBT-treated UM, could be an appropriate clinical setting for DDR-directed combinations [3,61].

Nevertheless, translating ATM into a clinically reliable biomarker is complicated by discordant findings across datasets. In several tumor types, ATM phosphorylation and nuclear relocalization have been proposed as predictors of radiotherapy response and clinical outcome, prompting similar investigations in UM focusing on ATM activation and downstream signaling markers such as γH2AX and CHK2 after irradiation [3]. However, while Hussain et al. [46] emphasized ATM expression as a correlate of radioresistance in UM cell-line models, other studies have reported minimal changes in ATM levels despite differences in tumor behavior. Moreover, some reports suggest that loss of ATM and ATR occurs in subsets of UM associated with higher metastatic risk, indicating that DDR kinase status may vary across molecular subtypes or stages of disease progression [66]. These observations suggest that functional parameters, including localization, activation kinetics, and signaling competence, may provide more informative indicators of ATM activity than bulk expression alone.

DNA-PKcs (PRKDC) represents a second major signaling axis within the DDR network and plays a central role in cNHEJ, the dominant pathway for repairing radiation-induced DSBs [6]. Rather than restating the general principle that efficient DSB repair underlies radioresistance (Section 6.1), DNA-PKcs can be viewed here as a key effector of this process, with elevated activity potentially accelerating DSB repair and buffering lethal genomic damage. Gene-expression profiling studies in primary UM further highlight the importance of this pathway in tumor progression and therapy response. Dogrusöz et al. [3] analyzing the expression of 121 DNA repair genes, identified PRKDC as significantly associated with unfavorable prognosis, with higher PRKDC expression observed in metastasizing tumors.

Importantly, the dysregulation of PRKDC does not occur in isolation but appears to be embedded within broader chromosomal alterations that reshape DNA repair capacity in UM. The same study revealed that tumors with poor prognosis, particularly those harboring monosomy 3, exhibit reduced expression of a chromosome 3p DNA repair gene cluster that includes BAP1, WDR48 (UAF1), and XPC [3]. In validation analyses, decreased expression of BAP1/WDR48/XPC together with increased PRKDC levels was significantly associated with adverse clinical outcomes, suggesting coordinated functional remodeling of DDR pathway engagement rather than isolated gene-level alterations. Additional support for this concept comes from observations that MLH1, another chromosome 3p gene, also shows prognostic associations in some UM cohorts, reinforcing the idea that chromosome 3 loss may simultaneously attenuate multiple genome-maintenance mechanisms.

Conversely, 8q gain or amplification, another recurrent chromosomal alteration in UM, may promote a complementary gain-of-function survival advantage. Increased copy number of 8q can elevate PRKDC expression, potentially strengthening DNA-PKcs-dependent NHEJ activity and enabling tumor cells to better tolerate genotoxic stress [3]. Functional studies further support this interpretation, demonstrating that pharmacological inhibition of DNA-PKcs reduces UM cell survival and may suppress malignant phenotypes such as proliferation, invasion, and metastatic potential [67]. Together, these findings suggest a model in which chromosome-level alterations

functionally modulate DDR capacity, with chromosome 3 loss weakening specific repair and checkpoint pathways, whereas 8q gain reinforces DNA-PKcs-mediated repair capacity.

ATR constitutes a third critical DDR signaling axis linking DSB processing with replication stress responses and HR competence. Emerging evidence indicates that reduced ATR expression, or complete loss, may correlate with significantly poorer OS in UM, suggesting that ATR status captures biologically meaningful differences in tumor behavior [66]. Functionally, ATR acts as a key regulator of replication fork stability and HR-associated repair pathways. ATR deficiency could therefore reshape cellular responses to radiation in multiple ways: by increasing catastrophic replication stress, which may sensitize cells to DNA damage, or by selecting for alternative repair adaptations that promote tumor aggressiveness [6,66]. The reported co-occurrence of ATM and ATR alterations in high-risk UM further highlights that DDR signaling networks are not static but may evolve during tumor progression, influencing both metastatic potential and therapy response [3,6].

Taken together, current evidence supports a model in which radiotherapy outcomes in UM reflect the dynamic interplay between ATM-mediated signaling, DNA-PKcs-driven end-joining repair, ATR-regulated replication stress responses, and chromosome-level alterations that reconfigure the broader DNA repair landscape. Within this framework, both DDR kinases and associated repair gene clusters may function as biomarkers of treatment response or as therapeutic targets for radiosensitization.

However, an important limitation of the current literature is that most mechanistic studies of DDR in UM have been conducted using X-ray or γ-ray irradiation, whereas the biological responses to proton irradiation remain less well characterized. Because proton beams, particularly near the Bragg peak, can produce distinct patterns of DNA damage, including complex clustered lesions, the repair requirements imposed on tumor cells may differ from those induced by conventional photon irradiation. Future studies should therefore integrate molecular profiling with functional analyses of DDR activity, compare photon- and proton-induced responses directly, and extend experimental systems beyond two-dimensional cultures to more physiologically relevant UM models such as tumor spheroids. Such approaches may ultimately clarify why radiotherapy fails in certain UM cases and guide the development of rational combination strategies capable of converting precision irradiation into durable tumor control.

6.3 Chromosomal Alterations and DNA Repair Gene Clusters

Cytogenetic evolution is a defining feature of UM progression, and multiple studies have converged on a consistent message: Copy-number architecture is a dominant determinant of UM risk biology, repeatedly outperforming mutational burden for prognostication. Large integrative analyses of UM genomes have emphasized that UM stratification is largely "CNA-driven," with recurrent events including monosomy 3, 8q gain, 1p loss, 6p gain, and 6q alterations, which together define molecular programs linked to metastatic competence and therapy tolerance [68-71]. Importantly, these chromosomal alterations do not merely label aggressive disease; they appear to reshape DNA repair capacity through coordinated perturbation of gene clusters that sit at the intersection of genome stability and therapy response [72].

Amaro et al. [1] reported a strong association between monosomy 3 and death from metastasis, and further connected this karyotype to adverse histopathological features (e.g., epithelioid morphology, vascular patterns, ciliary body involvement, and larger tumor dimensions). Notably, their work and others' profiling efforts also suggest that monosomy 3 and 8q gain can occur independently, yielding karyotype classes with distinct prognostic trajectories (e.g., disomy 3/disomic 8q versus monosomy 3/8q gain), and that 8q copy number can expand to multiple copies in high-risk disease. Consistent with a stepwise evolutionary model, these chromosomal aberrations correlate with increasing tumor size, implying acquisition during progression rather than initiation [12].

8q gain/amplification is one of the most reproducible high-risk CNAs in UM, and broad genomic studies repeatedly show 8q gains enriched in poor-outcome disease. Within the logic of RT inefficacy, 8q gain is compelling because it can raise the expression dosage of genes that support survival under genotoxic stress [72].

Beyond chromosome 3 and 8q, large-scale genomic profiling indicates that 1p loss is a recurrent alteration in UM and is enriched in higher-risk copy-number patterns. Broad analyses report 1p loss among the common CNAs in UM cohorts, supporting its inclusion as an adverse "risk architecture" component rather than a rare outlier [72]. Additionally, in high-risk evolutionary models, 1p loss is frequently discussed as a co-traveling event with other aggressive CNAs (e.g., monosomy 3 and 8q gain), consistent with stepwise karyotypic escalation [73,74].

Importantly, chromosome 3 risk biology is not restricted to physical loss. Harbour and colleagues emphasized that some high-risk tumors display isodisomy 3 (copy-neutral LOH), creating biallelic functional inactivation patterns at key loci despite retaining two copies. In their synthesis, isodisomy 3 is discussed as an alternative route to high-risk molecular phenotypes, conceptually consistent with "LOH-driven" unmasking of tumor suppressor disruption and downstream transcriptional reprogramming [73,74].

While most CNA discussion in UM highlights "bad actors," there is credible evidence that some focal alterations correlate with improved outcome [75]. Notably, Lake et al. [76] (SNP array analysis) reported that CNKSR3 amplification (6q) was correlated with improved patient survival, suggesting that CNKSR3 marks a distinct subset rather than simply mirroring aggressive CNA load.

Within this cluster, BAP1 occupies a particularly influential position. While widely recognized as a tumor

suppressor associated with metastatic risk [77,78], BAP1 also intersects directly with the DDR: its protein product is a nuclear deubiquitinase linked to double-strand break repair via HR and broader chromatin/transcriptional control [79]. Dogrusöz et al. [3] reported lower BAP1 expression in tumors with poor survival, and the cytogenetic context provides a plausible biological rationale: in monosomy 3 tumors, UM often retains only a single BAP1 allele, making somatic inactivation of the remaining allele especially consequential. In this context, chromosome 3 loss primarily reflects a copy-number-driven risk architecture rather than a fully resolved functional DDR model, converting a dosage-sensitive vulnerability into a durable metastatic phenotype.

WDR48 (UAF1) extends this repair cluster beyond HR, tying chromosome 3p loss to Fanconi anemia pathway regulation via the USP1/UAF1 complex and its control of FANCD2 deubiquitination [80-82]. Dogrusöz et al. [3] noted low WDR48 expression in metastasizing UM and linked this reduction to adverse clinicopathologic characteristics, supporting its inclusion within a broader CNA-defined high-risk profile rather than reiterating a functional DDR rewiring mechanism. In parallel, XPC, a sensor component of nucleotide excision repair (NER), was also reduced in poor-outcome tumors in their cohorts. Although the etiologic role of UV in UM remains debated, the prognostic linkage of XPC downregulation suggests that NER components may influence UM biology beyond canonical UV photoproduct repair, potentially through genome surveillance functions and transcription-coupled repair [83].

6.4 UM Driver Mutations and Their Indirect Impact on Radioresistance

Although UM is clinically notable for RT resistance, its genome is paradoxically characterized by a low frequency of recurrent coding mutations. Whole-exome sequencing efforts, including TCGA-based analyses, have consistently suggested that UM displays limited mutational complexity and lacks the classical pattern of widespread genomic instability [1]. Within this relatively “quiet” mutational landscape, a small set of founder driver alterations, most prominently GNAQ and GNA11 [84,85], and less frequently CYSLTR2 and PLCB4 [86,87], appear to initiate tumor formation by enforcing persistent oncogenic signaling. Multiple studies have emphasized that GNAQ/GNA11 mutations cluster at conserved hotspots, particularly Q209 (and less commonly R183) within the Ras-like GTPase domain, consistent with constitutive activation [88]. Notably, reports have indicated that GNA11 mutations may be enriched in metastatic UM compared with GNAQ, hinting that closely related drivers can still channel tumors toward distinct evolutionary endpoints [12].

Crucially, these initiating mutations are widely regarded as insufficient for full malignant competence. As proposed across genomic and clinicogenetic studies, UM progression toward invasion and metastasis typically requires additional “hits,” which may be genetic (e.g., BAP1 pathway disruption) or shaped by permissive systemic contexts such as inflammation and angiogenesis. In this framework, RT response is unlikely to be dictated by GNAQ/GNA11 alone; rather, these drivers may indirectly reinforce radioresistance by sustaining pro-survival transcriptional states, remodeling cell-cycle dynamics, and engaging adaptive stress responses that allow irradiated cells to endure and recover. Indeed, UM biology has been linked to oncogenic signaling programs capable of activating YAP/TAZ in a HIPPO-independent manner, alongside contributions from conventional MAPK signaling, circuits that plausibly buffer radiation-induced lethal stress through enhanced survival signaling, metabolic flexibility, and microenvironmental adaptation [1].

Importantly, UM treatment tolerance cannot be explained by founder drivers alone; accumulating evidence indicates that tumors also leverage “damage-management” circuitry, particularly DDR kinases and end-joining repair capacity, to endure irradiation. Consistent with the framework outlined in Section 6-1, these mechanisms should be interpreted as modulators of DNA damage handling rather than independent definitions of radioresistance, with ATM inhibition further supporting DDR dependency in UM [46].

Complementing ATM, DNA-PKcs (PRKDC), the catalytic core of cNHEJ, represents an additional DDR-dependent tolerance mechanism in UM. Rather than reiterating its prognostic and functional roles described above (Section 6.2), it is important to emphasize here that enhanced NHEJ capacity may act downstream of aggressive tumor biology to support survival following irradiation.

Thus, PRKDC should be viewed in this context primarily as a component of DDR-mediated damage tolerance, linking genomic alterations (e.g., 8q gain) to functional resilience against DNA damage, rather than as an independent prognostic axis.

Beyond DSB-centric kinases, UM radioresistance may also be indirectly reinforced by enzymes that manage oxidative/SSB-associated damage and repair signaling dynamics (e.g., PARP1-PARG and BER nodes). While these factors are not UM “founder drivers” in the classical sense, they can function as adaptive enablers, especially under RT conditions rich in oxidative base lesions, SSBs, and clustered damage. In parallel, repair surveillance modules (e.g., NER sensors such as XPC) and replication-associated repair regulators (e.g., USP1-WDR48/UAF1 control of FANCD2/FANCI deubiquitination) provide additional layers of stress tolerance that can indirectly stabilize survival programs after irradiation, particularly when tumors evolve toward aggressive, therapy-resilient phenotypes [89].

A distinct but clinically important route linking genetics to treatment behavior is represented by germline DNA repair defects that create atypical UM subsets. Rodrigues et al. identified germline MBD4 loss-of-function as a predisposition mechanism that can generate hypermutated UM, highlighting that, although rare, such

genome-maintenance defects reshape the evolutionary landscape of UM and may alter how tumors respond to DNA damage and therapy selection pressures (including RT) [90].

Beyond G-protein drivers, later-occurring lesions help stratify UM into biologically distinct trajectories with different metastatic timing, an evolutionary structure that can also shape therapy outcomes. Large-scale profiling has repeatedly shown that BAP1, SF3B1, and EIF1AX mutations are near-mutually exclusive, aligning with early, late, or minimal metastatic propensity, respectively [91-93]. In particular, SF3B1 mutations, often affecting recurrent residues such as R625 and K666, have been described as defining a subgroup of UM that maintains chromosome 3 disomy yet still develops metastasis after a prolonged latency [93-95]. As several studies have highlighted, SF3B1 alters splice-site selection and promotes widespread usage of cryptic splice junctions, thereby perturbing the processing of multiple transcripts. While not “DNA repair genes” in the canonical sense, splicing-factor mutations can plausibly rewire cellular stress handling by shifting isoform balance across pathways relevant to apoptosis, checkpoint control, and damage tolerance, an indirect but potentially powerful route to radioresistant phenotypes [3,36,37,77].

By contrast, EIF1AX mutations are enriched in disomic, lower-risk UM and cluster in the conserved N-terminus of the encoded translation initiation factor, with occasional frameshift deletions and splice-site hotspots described in other tumor types. Consistent with independent validation studies, EIF1AX-mutant UM generally maps to a comparatively favorable risk profile [38,96]. Nevertheless, the mechanistic implication for RT is conceptually interesting: alterations in translation initiation can recalibrate proteostasis and stress-adaptive translation, potentially influencing how efficiently cells execute damage responses and recover after irradiation-again, an indirect influence rather than a direct repair defect [1,97].

Finally, an additional signaling hub, ARF6, has been described as a major integrator of oncogenic inputs in UM and as a responder to multiple receptor pathways (including EGFR, VEGFR, and WNT). While this axis is typically discussed in the context of invasion, trafficking, and tumor progression, its broader implication for RT is that UM driver circuitry is not merely proliferative; it is architected for survival and plasticity [1,97]. Taken together, the emerging literature supports a model in which UM radioresistance can arise not only from classical DNA damage repair proficiency, but also from driver mutation-anchored survival programs that enable irradiated cells to avoid apoptosis, maintain clonogenic potential, and exploit microenvironmental cues, thereby converting sublethal damage into long-term persistence and relapse.

7. Conclusion

UM represents a malignancy in which RT resistance is governed not by physical dose parameters alone, but by a coordinated network of genomic, cytogenetic, and DDR determinants. This review integrates these layers to propose a unifying framework in which radioresistance arises from adaptive reprogramming of DNA repair pathway choice, DDR signaling, and survival circuitry.

At the core of this model lies DNA damage architecture and repair pathway utilization. While radiation-induced SSBs and oxidative lesions are efficiently resolved through BER, the cellular fate of UM is largely dictated by its capacity to process high-risk lesions-DSBs and CDD. The dynamic balance between error-prone but rapid NHEJ and high-fidelity HR enables tumor cells to preserve viability under genotoxic stress. Importantly, in the context of PBT, increased LET near the Bragg peak promotes clustered damage, potentially shifting repair dependency toward BER-and NHEJ-dominant programs and reinforcing adaptive repair plasticity.

Superimposed on lesion-level biology, DDR signaling kinases-ATM, ATR, and DNA-PKcs-function as central regulatory nodes that orchestrate repair pathway engagement, checkpoint activation, and cell fate decisions. ATM coordinates DSB signaling, ATR integrates replication stress and HR competence, and DNA-PKcs drives cNHEJ. However, their functional impact in UM is highly context-dependent, shaped by activation dynamics, subcellular localization, and tumor evolutionary state. Notably, PRKDC (DNA-PKcs) emerges as a critical effector of radioresistance, linking enhanced NHEJ capacity to both survival under RT and aggressive tumor behavior.

Crucially, these DDR dependencies are embedded within a cytogenetically defined repair landscape. Recurrent alterations such as monosomy 3 and 8q gain act as active drivers of DDR rewiring rather than passive prognostic markers. Loss of chromosome 3p-associated repair genes (including BAP1, WDR48 (UAF1), and XPC) impairs multiple genome maintenance pathways (HR, Fanconi anemia signaling, and NER), while 8q amplification increases PRKDC dosage, reinforcing NHEJ. This creates a state of functional repair imbalance, in which selective loss of high-fidelity repair is coupled with gain of damage-tolerant pathways, enabling both genomic plasticity and resistance to RT-induced cytotoxicity.

Beyond structural alterations, driver mutations and oncogenic signaling networks (e.g., GNAQ/GNA11-MAPK and YAP/TAZ pathways) further potentiate radioresistance by sustaining pro-survival transcriptional programs, modulating apoptosis thresholds, and promoting metabolic and stress adaptation. Additional modifiers [including splicing factor mutations (SF3B1), translational regulators (EIF1AX), and auxiliary repair systems (e.g., PARP1-PARG, USP1-WDR48)] extend this resilience by reshaping cellular responses to DNA damage at multiple regulatory levels.

Collectively, these findings support a model in which UM radioresistance is an emergent phenotype driven by the integration of DNA damage complexity, repair pathway plasticity, DDR kinase signaling, and cytogenetic reprogramming. This framework provides a strong rationale for targeted radiosensitization strategies,

particularly those exploiting synthetic lethality by inhibiting compensatory pathways such as DNA-PKcs-dependent NHEJ or modulating ATR/ATM signaling under defined genomic contexts.

However, a critical gap remains: most mechanistic insights derive from photon-based systems, whereas PBT, the clinical standard in UM, induces distinct, high-LET-associated damage profiles. Addressing this discrepancy through integrated, modality-specific studies combining genomic profiling with functional DDR assays in physiologically relevant models will be essential for translating molecular understanding into clinical benefit.

In conclusion, defining the genetic and DDR determinants of RT resistance in UM is fundamental to bridging the gap between precision irradiation and durable disease control, enabling the development of mechanism-based therapeutic strategies to overcome resistance and limit metastatic progression.

Abbreviation

aNHEJ: Alternative NHEJ

ATM: Ataxia-telangiectasia mutated

ATR: ATM and Rad3-related

BER: Base excision repair

CDD: Complex DNA damage

cNHEJ: Classical NHEJ

COMS: Collaborative ocular melanoma study

DDR: DNA damage response

DSBs: Double-strand breaks

HIF-1α: Hypoxia-inducible factor-1α

HR: Homologous recombination

ICD: Immunogenic cell death

LET: Linear energy transfer

NER: Nucleotide excision repair

NHEJ: Non-homologous end joining

OS: Overall survival

PBT: Proton beam therapy

RBE: Relative biological effectiveness

ROS: Reactive oxygen species

SSBs: Single-strand breaks

TAAs: Tumor-associated antigens

UM: Uveal melanoma

Authors' Contributions

H.CH. conceived and designed the study, served as the senior author, and contributed to conceptualization, writing - original draft, and project administration.

M.H.M.D., S.N.H., Z.S., and V.P. carried out Investigation, data collection, and preparation of tables and figures.

Ş.B.T. contributed to data curation, validation, supervision, and assisted with manuscript revision as academic advisors.

Z.B. contributed to study design, data interpretation, overall supervision, and writing - review & editing.

All authors reviewed the manuscript critically, provided feedback, and approved the final submitted version.

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