RESEARCH ARTICLE

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Genetic Polymorphisms in Genes Involved in Oxidative Stress and Their Association with Radiotherapy Toxicity among Head and Neck Cancer Patients

Anand K. Gudur[1], Suresh J. Bhosale[1], Rashmi A. Gudur[1], Kailas D. Datkhile[2]*

Abstract

Background: The present study was planned to examine the possible association of polymorphisms in the superoxide dismutase and catalase genes with adverse normal tissue effects or injury resulting from radiotherapy in HNC patients. **Methods:** A total of two hundred and fifty head and neck cancer (HNC) patients undergoing therapeutic radiotherapy were enrolled in this study, wherein acute radiation induced toxicity and treatment response were systematically documented. The investigation aimed to assess the potential association between oxidative stress-related gene polymorphisms and susceptibility to acute skin toxicity. Specifically, single nucleotide polymorphisms (SNPs) in *SOD1* (A251G, rs2070424), *SOD2* (C299T, rs1141718), *SOD3* (G172A, rs2536512), and two SNPs in the *CAT* gene (A21T, rs7943316; C262T, rs1001179) were genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methodology. **Results:** The findings revealed a statistically significant negative association between both the combined variant genotype and the heterozygous *SOD3* G172A genotype and the risk of acute radiation-induced skin toxicity, suggesting a potential protective effect (OR = 0.48, 95% CI: 0.26–0.88; p = 0.018). In contrast, the homozygous recessive *SOD3* 172A/A genotype demonstrated a strong positive correlation with the incidence of oral mucositis in HNC patients, exhibiting a markedly elevated risk (OR = 10.47, 95% CI: 4.48–24.44; p < 0.0001). Additionally, individuals carrying the heterozygous 172G/A genotype showed a 2.25-fold increased susceptibility to severe mucositis (OR = 2.25, 95% CI: 1.21–4.17; p = 0.009). Furthermore, the heterozygous A21T genotype of the *CAT* gene (rs7943316) was significantly associated with an increased risk of oral mucositis following radiotherapy in HNC patients (OR = 1.79, 95% CI: 1.00–3.22; p = 0.049). **Conclusion:** The analysis of genetic polymorphisms in extracellular superoxide dismutase (*SOD3*) revealed a statistically significant association with radiation-induced skin toxicity and mucositis among HNC patients in the studied population.

Keywords: Head and neck cancer- Radiotherapy- SOD- Catalase- Genetic polymorphism- acute radiation toxicity

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Introduction

Head and neck cancer (HNC) represents a significant global health burden, with an estimated 890,000 new cases (accounting for 4.5% of all cancer) and approximately 450,000 deaths (4.6% of global cancer mortality) reported in 2020 which comprises the incidence of approximately 380 000 cases of cancer of lip and oral cavity, 185 000 of laryngeal cancer, 133 000 of nasopharyngeal cancer, 98 000 of oropharynx, 84 000 of hypopharynx and 54 000 of salivary gland cancers [1]. Over recent decades, the global incidence of HNC has shown a marked upward trend, with the highest prevalence observed in South Asia, followed by Central and Eastern Europe and South America [1, 2]. Notably, India has witnessed a disproportionately high and escalating incidence of HNC, contributing to nearly 80% of the global HNC burden in 2020. In 2022 alone, India reported 245,811 new HNC cases and 130,139 related deaths, underscoring the urgent need for region specific epidemiological surveillance, early detection strategies, and personalized therapeutic interventions [3-5]. Radiotherapy (RT) remains a cornerstone in the management of HNC, commonly administered either as adjuvant radiotherapy (aRT) or in combination with chemotherapy as concurrent chemoradiotherapy (cRT) [6]. Ionizing radiation interacts with biological tissues to generate reactive oxygen species and free radicals, which induce DNA damage and trigger cell death through necrotic or apoptotic pathways. Tumor cells, characterized by high proliferative activity, are generally more vulnerable to radiation induced genotoxic stress compared to adjacent normal tissues. Nonetheless, therapeutic

*[1]Department of Oncology, Krishna Vishwa Vidyapeeth "Deemed to be University", Taluka-Karad, Dist- Satara, Pin-415 539, (Maharashtra), India. [2]Department of Molecular Biology & Genetics, Krishna Institute of Science and Technology, Krishna Vishwa Vidyapeeth "Deemed to be University", Taluka-Karad, Dist- Satara, Pin-415 539, (Maharashtra), India. *For Correspondence: hodgeneticslab@kvv.edu.in*

radiation inevitably exposes surrounding normal tissues, leading to a spectrum of acute and late toxicities. Acute adverse effects such as mucositis, dysphagia, and radiation dermatitis are primarily attributed to damage in rapidly dividing epithelial and mucosal cells [7, 8], whereas late toxicities including subcutaneous fibrosis and osteoradionecrosis are associated with radiation injury to slowly proliferating stromal and osseous tissues [7-9]. A substantial proportion of patients experience varying degrees of normal tissue reactions, and the inter individual variability in toxicity severity remains inadequately explained by clinical parameters alone. Emerging evidence suggests that host genetic factors, particularly polymorphisms in genes governing DNA repair, oxidative stress response, and cell cycle regulation, may significantly contribute to differential radiosensitivity and toxicity profiles among HNC patients. Radiation induced oxidative stress is a key initiator of radiation associated normal tissue toxicities in cancer patients. The endogenous antioxidant enzyme system is an important defense system help to inhibit radical induced DNA strand breaks and improve radiotherapy related aftereffects. The polymorphism of antioxidant enzyme coding genes seems to play a role in development of radiation injury resulting from radiotherapy in cancer patients. The polymorphism of superoxide dismutase (*SOD*) was studied earlier for its association with radiotherapy induced normal tissue toxicity in cancer patients [10] such as subcutaneous fibrosis in breast cancer [11, 12], and severe adverse effects in prostate cancer [13] and acute radiation induced toxicity in lung cancer patients [14]. Conversely, other studies found no association of SNPs of *SOD* with risk of developing acute normal tissue toxicities [15] in breast cancer [16-18]. Similarly the genetic variants of catalase gene did not show an association with risk of acute toxicity in breast cancer patients [16]. Thus, number of studies demonstrated involvement of polymorphisms of antioxidant enzyme coding genes, with contradictory opinions, however there remained further scope to explore the association of polymorphic variants of *SOD* and catalase genes with radiotherapy induced toxicity effects on normal tissue of HNC patients. To date, no systematic investigations have been conducted to evaluate the association between oxidative stress related gene polymorphisms and radiotherapy induced toxicity specifically within the Maharashtrian population. This represents a significant gap in the regional oncogenomic landscape, given the potential influence of genetic variability on treatment outcomes.

Some other studies attempted to assess the association of SNPs in DNA damage response, DNA repair and antioxidant response genes with the normal tissue adverse reactions in HNC patients undergoing chemoradiotherapy and radiotherapy treatment which showed nonsignificant correlation of any of the studied genes with radiotherapy toxicity [19]. Despite the biological plausibility and mechanistic relevance of these candidate genes, the findings across these studies have largely demonstrated non-significant correlations between the studied SNPs and the severity or incidence of radiotherapy related toxicity [19]. This lack of statistical association may be attributed to limited sample sizes, population heterogeneity, or the multifactorial nature of radiation-induced tissue injury, which involves complex gene environment interactions and compensatory molecular pathways. Consequently, while these studies provide foundational insights, they underscore the need for larger, population-specific genomic analyses and integrative biomarker approaches to better elucidate the genetic determinants of radiotherapy tolerance in HNC patients. Therefore, the preliminary objective of present study was to examine the possible association of polymorphisms of Cu, Zn-*SOD*, Mn-*SOD*, EC-*SOD* and catalase genes with adverse normal tissue effects or injury resulting from radiotherapy in HNC patients. We evaluated possible association of *SOD1* (A251G, A>G, SNP: rs2070424), *SOD2* (C299T, C>T, SNP: rs1141718), *SOD3* (G172A, G>A, SNP: rs2536512) polymorphisms and two SNPs of catalase gene including (A21T, A>T, rs7943316; C262T, C>T, rs1001179) with risk of acute skin toxicity reactions after therapeutic radiotherapy in HNC patients.

Materials and Methods

Study Design

Cross sectional/ Observational/Analytical study.

Study Period

The study was carried out between 2019-2022.

Patient enrollment and Clinical Information

Two hundred and fifty (250) histopathologically confirmed HNC patients visiting to Medical Oncology Out Patient Department (OPD) for the treatment at the Department of Oncology of Krishna Hospital & Medical Research Center, Karad were enrolled based on predefined inclusion and exclusion criteria. The predefiened Inclusion critera are;

Patients with 18 to 85 years age diagnosed with HNC on histopathology; No metastasis at diagnosis; Clinically localised or locally advanced according to standard staging system, and normal skin and oral mucosa before the first radiotherapy fraction. Exclusion criteria are; patients with no pathological diagnosis; relapsed disease or metastasis; patients with severe co-morbidities; patients with incomplete treatment taken; incomplete follow-up.

Treatment of HNC patients with radiotherapy & chemo-radiotherapy

Radiotherapy treatment parameters including total dose, dose per fraction, and overall treatment duration were adapted from standard institutional protocols. All enrolled HNC patients received Intensity Modulated Radiation Therapy (IMRT), guided by computed tomography (CT) based planning, simulation, and verification procedures, with rigorous quality assurance measures in place. Target volumes were delineated using CT imaging: Gross Tumor Volume (GTV) encompassed all clinically and radiologically evident disease; Clinical Target Volume (CTV) included regions at risk for microscopic spread; and Planning Target Volume (PTV) accounted for setup uncertainties and organ motion.

Radiotherapy was delivered using a 6-Mega Volt (MV) linear accelerator (Model: Unique Performance; Manufacturer: Varian Medical Systems, USA) employing Volumetric Modulated Arc Therapy (VMAT) technique. Patients received a total dose ranging from 60 to 66 Gy, administered in 33 fractions. Concurrent chemotherapy was administered when clinically indicated, consisting of weekly cisplatin at a dose of 40 mg/m² for up to six cycles during the radiotherapy course.

Follow up and Toxicity assessment

To assess acute normal tissue toxicity following radiotherapy, patients were monitored for a period of three months post treatment. Clinical outcomes including partial, complete, or no response; disease stability or progression; and early mortality due to disease, treatment related toxicity, or other causes were systematically recorded. The facial and cervical skin regions were designated as anatomical sites for evaluating radiation-induced cutaneous toxicity, given their direct exposure during HNC radiotherapy. Acute adverse effects, specifically oral mucositis and skin reactions, were documented throughout the treatment course and during follow-up using standardized grading criteria established by the Radiation Therapy Oncology Group (RTOG). Acute radiation toxicity was defined as any tissue injury manifesting from the initiation of radiotherapy up to three months following its completion. Post-radiotherapy toxicity involving normal skin and oral mucosa was systematically documented on a weekly basis throughout the treatment course. Follow up assessments were conducted at one and three months after completion of radiotherapy to evaluate the persistence and progression of acute adverse effects. The severity of radiation induced injuries including acute radiation dermatitis and oral mucositis was clinically assessed by a radiation oncologist and graded according to the standardized RTOG criteria. For comparative analysis, HNC patients exhibiting grade >2 toxicities, such as severe mucositis and fibrotic skin reactions, were classified as radiosensitive, whereas those with grade ≤2 reactions were categorized as relatively radioresistant. Patients exhibiting radiosensitive phenotypes defined by grade >2 radiation induced toxicities were classified as cases and compared to those with grade ≤2 toxicities (controls) to evaluate the association between oxidative stress related gene polymorphisms, specifically in *SOD* and *CAT* genes. Comprehensive clinical and demographic data were recorded for all participants, who were prospectively followed for a period of three months post radiotherapy to monitor treatment-related outcomes. Prior to enrollment, all patients were thoroughly informed about the study objectives, procedures, and ethical considerations. Written informed consent was obtained from each participant in accordance with institutional ethics committee guidelines.

Blood sample collection and genomic DNA isolation from blood

Five milliliter (mL) of whole blood from patients was collected in sterile EDTA containing vacutainer after receiving informed consent. The blood sample from patients was collected before initiation of radiotherapy treatment. The genomic DNA extraction was carried out by salting out method where the whole blood was processed with lysis buffer-1 containing 10mM Tris-HCl pH-7.6, 320mM sucrose, 5mM $MgCl_2$, 1% triton X-100, pH 7.6 to lyse RBCs, thereafter the sample was treated with the lysis buffer 2 to lyse out WBCs (10mM Tris- HCl, 11.4mM sodium citrate, 1mM EDTA, 1% SDS, pH-8.0). The sample was further treated with Proteinase K (200µg/µl) to digest the proteins and subsequently RNase A (200µg/µl). The genomic DNA was precipitated by addition of twice the volume of ice cold ethanol and 1/10th volume of 3M Sodium acetate (pH-5.2). The precipitated DNA was aggregated together by centrifugation. The obtained pellet of DNA was then resuspended in T10E1 buffer and was checked on 1% agarose gel for its quality and quantity. This purified DNA was used for further genotyping assays after quantitative and qualitative analysis.

Genotyping assays of oxidative stress related SOD and CATALASE genes

The PCR conditions for amplification of 570 bp of *SOD1*, codon -251, exon-10, 251 A>G; 139 bp of *SOD2*, codon -399, exon-3, 399 C>T; 245 bp of *SOD3*, codon -40, exon-3, 172 G>A and catalase (250bp) codon-326, exon 7 A21T, and 185 bp of 262 region of promoter of catalase gene are represented in Table 1.

Restriction Fragment Length Polymorphism

After confirmation of DNA amplification, each PCR product was digested with an appropriate restriction enzyme for genotyping. Ten micro liters of the PCR products digested at 37°C overnight with specific restriction enzymes in 20 µL reaction mixtures containing buffer supplied with each restriction enzyme (Table 1). After the overnight incubation, digestion products were separated on a 2-3% low EEO agarose (GeNei) gel at 100 V for 30 min stained with ethidium bromide and photographed with Gel Documentation System (BioRad).

Statistical Analysis

The genotypic frequencies for oxidative stress related genes of HNC patient's were determined. The relative risk and Odds Ratio (OR) and corresponding 95% confidence intervals (CI) were determined through unconditional multiple logistic regression. The OR estimated to test whether any association exists between the grade of acute toxicity and selected SNPs.

Results

The primary objective of this study was to evaluate the incidence and severity of acute radiation induced toxicities specifically dermatitis and oral mucositis in HNC patients undergoing therapeutic radiotherapy. Acute toxicity grading was performed according to the RTOG criteria, wherein grade 2 reactions are generally self-limiting and manageable without clinical intervention, while toxicities exceeding grade 2 typically necessitate therapeutic management. Based on this classification, patients were stratified into two groups: those exhibiting

Table 1. The List of Candidate *SOD1, SOD2, SOD3* and *CAT* Genes with Details of PCR and RFLP Procedures Including Primers and Restriction Enzymes and Expected Products of Selected Genes

Gene Genotype	rs number	Nucleotide change	Primer Sequence Forward/Reverse	PCR Conditions	PCR product size	Enzyme / Digestion conditions	Dominant (Wild type)	Heterozygous	Recessive (Mutant)
SOD1 codon-251 exon-10 (A251G)	rs2070424	(A>G)	FP: 5′-AGT ACT GTC AAC CAC TAG CA-3′ RP: 5′-CCA GTG TGC GGC CAA TGA TG-3′	95^0C- 5 min, 30 cycles of 95^0C- 30 sec, 58^0C- 30 sec, 720C- 30 sec, 72^0C- 5 min	570 bp	1 U of MspI 370C Incubation for 16 hrs	570 bp	570 bp, 369 bp, 201 bp	369 bp, 201 bp
SOD2 Codon-399 exon-3 C399T	rs1141718	C>T	FP: 5'-AGC TGG TCC CAT TAT CTA ATA G-3' RP: 5'-TCA GTG CAG GCT GAA GAGAT-3'	95^0C- 5 min, 35 cycles of 95^0C- 30 sec, 52^0C- 30 sec, 720C- 1 min, 72^0C- 5 m	139bp	1 U of EcoRV 370C Incubation for 16 hrs	117bp, 22bp	139bp, 117bp, 22bp	139bp
SOD3 codon-40 exon-3 (G172A)	rs2536512	(G>A)	FP: 5'-GAC ATG TAC GCC AAG GTC AC-3' RP: 5'-AAC TGG TGC ACG TGG ATG-3'	95^0C- 5 min, 35 cycles of 95^0C- 30 sec, 650C-30 sec, 72^0C-1 min, 720C-5 min	245 bp	1 U of BsshII 370C Incubation for 16 hrs	183 bp, 62 bp,	245 bp, 183 bp, 62 bp,	245 bp
Catalase codon-326 exon-7 (A21T)	rs7943316	(A>T)	FP: 5′-AAT CAG AAG GCA GTC CTC CC-3′ RP: 5′-TCG GGG AGC ACA GAG TGT AC-3′	95^0C- 5 min, 35 cycles of 95^0C- 30 sec, 55^0C- 30 sec, 720C- 30 sec , 72^0C- 5 m	250 bp	1 U of HinFI 370C Incubation for 16 hrs	177 bp, 73 bp	250 bp, 177 bp, 73 bp	250 bp
Catalase 262 region of promoter (C262T)	rs1001179	(C>T)	FP: 5'-AGA GCC TCG CCC CGC CGG ACC G-3' RP: 5-' TAA GAG CTG AGA AAG CAT AGC T-3'	95^0C- 5 min, 30 cycles of 95^0C- 20 sec, 66^0C- 30 sec, 720C- 30 Sec, 72^0C- 5 m	185 bp	1 U of SmaI 37^0C Incubation for 16 hrs 37˚C for 16h	155 bp, 30 bp	185 bp, 155 bp, 30 bp	185 bp

Table 2. Univariate Analysis of Polymorphisms of Superoxide Dismutase and Catalase Genes and Radiation Induced Skin Reactions and Mucositis in Head and Neck Cancer Patients

Gene Name (SNP)	Genotype	Skin reaction ≤2 n=187	Skin reaction >2 n=63	OR 95% CI	p value	Oral mucositis ≤2 n=118	Oral mucositis >2 n=132	OR 95% CI	p value
SOD1 A251G (rs2070424)	A/A	122	44	1 (Reference)		74	92	1(Reference)	
	A/G	57	18	0.87 (0.46-1.64)	0.68	38	37	0.78 (0.45-1.35)	0.38
	G/G	8	1	0.34 (0.04-2.85)	0.324	6	3	0.40 (0.09-1.66)	0.208
	A/G +G/G	65	19	0.81 (0.43-1.50)	0.504	44	40	0.73 (0.43-1.23)	0.243
SOD2 C399T (rs1141718)	C/C	179	62	1 (Reference)		113	128	(Reference)	
	C/T	0	0	NC		0	0	NC	
	T/T	8	1	0.36 (0.04-2.94)	0.341	5	4	0.70 (0.18-2.69)	0.61
	C/T +T/T	8	1	0.36 (0.04-2.94)	0.341	5	4	0.70 (0.18-2.69)	0.61
SOD3 G172A (rs2536512)	G/G	45	25	1 (Reference)		48	22	1(Reference)	
	G/A	97	25	0.46 (0.24-0.89)	0.022*	60	62	2.25 (1.21-4.17)	0.009*
	A/A	45	13	0.52 (0.23-1.14)	0.103	10	48	10.47 (4.48-24.44)	<0.0001*
	G/A +A/A	142	38	0.48 (0.26-0.88)	0.018*	70	110	3.42 (1.90-6.16)	<0.0001*
Catalase A21T (rs7943316)	A/A	73	18	1 (Reference)		49	42	1(Reference)	
	A/T	70	24	1.39 (0.69-2.78)	0.351	37	57	1.79 (1.00-3.22)	0.049*
	T/T	44	21	1.93 (0.93-4.02)	0.077	32	33	1.20 (0.63-2.27)	0.569
	A/T +T/T	114	45	1.60 (0.86-2.97)	0.137	69	90	1.52 (0.90-2.55)	0.112
Catalase C262T (rs1001179)	C/C	108	34	1 (Reference)		65	77	1 (Reference)	
	C/T	61	28	1.45 (0.80-2.63)	0.21	45	44	0.82 (0.48-1.40)	0.478
	T/T	18	1	0.17 (0.02-1.37)	0.097	8	11	1.16 (0.44-3.05)	0.763
	C/T +T/T	79	29	1.16 (0.65-2.07)	0.6	53	55	0.87 (0.53-1.44)	0.604

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval; Significance $p< 0.05$; *, Indicates significant Odds Ratio ($p<0.05$); p value determined based on $\chi 2$; NC, Not calculated

Table 3. Association of Polymorphisms of Superoxide Dismutase and Catalase Genes with Risk of Skin Reaction after Radiotherapy in Head and Neck Cancer Patients

Gene /SNP	Genotypes	All Patients	Radiosensitive patients	OR 95% CI	p value
SOD1 (rs2070424)	A/A	166	44	1 (Reference)	
	A/G	75	18	0.90 (0.49-1.67)	0.75
	G/G	9	1	0.41 (0.05-3.39)	0.415
	A/G +G/G	84	19	0.85 (0.46-1.55)	0.603
SOD2 (rs1141718)	C/C	241	62	1 (Reference)	
	C/T	0	0	NC	
	T/T	9	1	0.43 (0.05-3.47)	0.429
	C/T +T/T	9	1	0.43 (0.05-3.47)	0.429
SOD3 (rs2536512)	G/G	70	25	1 (Reference)	
	G/A	122	25	0.57 (0.30-1.07)	0.082
	A/A	58	13	0.62 (0.29-1.33)	0.226
	G/A +A/A	180	38	0.59 (0.33-1.05)	0.073
Catalase (rs7943316)	A/A	91	18	1 (Reference)	
	A/T	94	24	1.29 (0.65-2.53)	0.459
	T/T	65	21	1.63 (0.80-3.30)	0.172
	A/T +T/T	159	45	1.43 (0.78-2.61)	0.245
Catalase (rs1001179)	C/C	196	34	1 (Reference)	
	C/T	52	28	3.10 (1.72-5.57)	0.0002*
	T/T	2	1	2.88 (0.25-32.67)	0.392
	C/T +T/T	54	29	3.09 (1.73-5.52)	0.0001*

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidential interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05); p value determined based on χ^2; NC, Not calculated

grade ≤2 toxicity and those with grade >2 toxicity for both cutaneous and mucosal reactions. Among the 250 patients treated, 63 individuals (25.20%) developed grade 3 skin toxicity characterized by bright erythema, moderate edema, patchy moist desquamation, increased pain, yellow exudate secretion, pruritus, and cutaneous tightening. In contrast, 187 patients (74.80%) experienced grade ≤2 skin reactions, which included faint erythema, mild itching, and skin tightening.

Among the 250 HNC patients evaluated, 132 individuals (52.80%) developed grade >2 oral mucositis (grades 3 and 4) following radiotherapy, characterized by severe pain, fibrinous mucosal inflammation, ulceration, hemorrhage, and tissue necrosis. In contrast, 118 patients (47.20%) exhibited grade ≤2 mucositis, presenting with mild to moderate symptoms such as mucosal irritation, patchy inflammation, serosanguinous discharge, and moderate pain. Furthermore, the administration of radiotherapy in combination with chemotherapy demonstrated a statistically significant association with the occurrence of grade >2 skin toxicity ($p < 0.001$) and grade >2 oral mucositis ($p < 0.001$), indicating an enhanced risk of acute normal tissue reactions in patients receiving multimodal treatment. Similarly, the influence of potential confounding variables comprising demographic factors such as age, gender, dietary habits, and tobacco and alcohol use, as well as clinicopathological attributes including treatment modality, tumor subsite, disease stage, and therapeutic response to chemotherapy and radiotherapy was systematically addressed in a previously published study involving the same study subjects [20]. Considering other potential confounding variables, a higher prevalence of grade >1 skin toxicity was observed among patients with a history of tobacco smoking (92.68%) compared to those reporting alcohol consumption (34.14%). Additionally, 93.20% of tobacco users exhibited grade >1 mucositis, a statistically significant association ($p = 0.04$). While grade 1 toxicities are generally self-limiting and managed without clinical intervention, toxicities exceeding grade 1 typically necessitate therapeutic management to mitigate treatment-related morbidity.

Genotype distribution of SOD1, SOD2, SOD3 and CAT genes and radiotherapy toxicity in HNC patients

Univariate logistic regression analysis was employed to investigate the association between specific genetic polymorphisms in *SOD1* (rs2070424), *SOD2* (rs1141718), *SOD3* (rs2536512), and *CAT* (rs7943316 and rs1001179) and the incidence of acute radiation induced toxicities, including Skin reactions reactions and oral mucositis, in HNC patients. As summarized in Table 2, the analysis revealed that among the studied SNPs, only the *SOD3* rs2536512 variant demonstrated a statistically significant association with acute skin toxicity. No significant correlations were observed between the remaining SNPs and either skin reactions or mucositis in HNC patients. The presence of the combined variant genotype and heterozygous *SOD3* G172A genotype was significantly associated with a reduced risk of acute radiation-induced skin toxicity, indicating a potential protective effect (OR = 0.48; 95% CI: 0.26–0.88; $p = 0.018$). In contrast, analysis of oral mucositis as a radiotherapy-related

Table 4. Association of Polymorphisms of Superoxide Dismutase and Catalase Genes with Risk of Mucositis after Radiotherapy in Head and Neck Cancer Patients

Gene /SNP	Genotypes	All Patients	Radiosensitive patients	OR 95% CI	p value
SOD1 (rs2070424)	A/A	166	92	1 (Reference)	
	A/G	75	37	0.89 (0.55-1.42)	0.626
	G/G	9	3	0.60 (0.15-2.27)	0.454
	A/G +G/G	84	40	0.85 (0.54-1.35)	0.513
SOD2 (rs1141718)	C/C	241	128	1 (Reference)	
	C/T	0	0	NC	
	T/T	9	4	0.83 (0.25-2.77)	0.77
	C/T +T/T	9	4	0.83 (0.25-2.77)	0.77
SOD3 (rs2536512)	G/G	70	22	1 (Reference)	
	G/A	122	62	1.61 (0.91-2.85)	0.097
	A/A	58	48	2.63 (1.42-4.86)	0.002*
	G/A +A/A	180	110	1.94 (1.13-3.31)	0.014*
Catalase (rs7943316)	A/A	91	42	1 (Reference)	
	A/T	94	57	1.31 (0.80-2.14)	0.276
	T/T	65	33	1.10 (0.63-1.91)	0.736
	A/T +T/T	159	90	1.22 (0.78-1.91)	0.371
Catalase (rs1001179)	C/C	196	77	1 (Reference)	
	C/T	52	44	2.15 (1.33-3.48)	0.001*
	T/T	2	11	14.00 (3.03-64.62)	0.0007*
	C/T +T/T	54	55		

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidential interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05); p value determined based on χ^2; NC, Not calculated

adverse outcome revealed a strong positive association with the homozygous recessive *SOD3* 172A/A genotype, which conferred a markedly elevated risk (OR = 10.47; 95% CI: 4.48–24.44; p < 0.0001). Additionally, the heterozygous 172G/A genotype was associated with a 2.25-fold increased likelihood of developing severe mucositis (OR = 2.25; 95% CI: 1.21–4.17; p = 0.009). The findings of this study indicate that genetic polymorphisms in *SOD3* may contribute to individual susceptibility to radiotherapy induced adverse effects in HNC patients. Specifically, the variant alleles of *SOD3* were significantly associated with increased risk of mucocutaneous toxicity, suggesting a functional role in modulating oxidative stress responses during radiation exposure. In contrast, analysis of the *CAT* gene polymorphisms A21T (rs7943316) and C262T (rs1001179) revealed no statistically significant association with acute skin toxicity following radiotherapy. No meaningful differences were observed between recessive and heterozygous genotypes of *CAT* in relation to cutaneous adverse effects. However, the heterozygous A21T genotype (rs7943316) demonstrated a positive association with oral mucositis (OR = 1.79; 95% CI: 1.00–3.22; p = 0.049), indicating a potential genotype-specific influence on mucosal radiosensitivity in HNC patients receiving radiotherapy.

Association of SOD1, SOD2, SOD3 and CAT gene polymorphisms with risk of toxicity effects of radiotherapy in HNC patients

Multivariate logistic regression analysis revealed no statistically significant association between polymorphic variants of *SOD1* (rs2070424), *SOD2* (rs1141718), and *SOD3* (rs2536512) and the incidence of acute radiation-induced toxicities, including cutaneous reactions and oral mucositis, in HNC patients. The calculated odds ratios (ORs) for these genotypes did not demonstrate predictive value for increased susceptibility to adverse effects. Specifically, no correlation was observed between superoxide dismutase gene polymorphisms and the development of radiation-induced dermatitis, as detailed in Table 3. The multivariate logistic regression analysis revealed that the homozygous recessive genotypes of *SOD1* (OR = 0.41; 95% CI: 0.05–3.39; p = 0.415), *SOD2* (OR = 0.43; 95% CI: 0.05–3.47; p = 0.429), and *SOD3* (OR = 0.62; 95% CI: 0.29–1.33; p = 0.226) exhibited odds ratios below unity, suggesting a potential protective trend; however, none of these associations reached statistical significance. Similarly, analysis of the *CAT* gene polymorphism rs7943316 showed that the recessive allele was associated with an increased risk of acute radiation-induced dermatitis (OR = 1.63; 95% CI: 0.80–3.30; p = 0.172), while the heterozygous A/T genotype demonstrated a modest, non-significant association (OR = 1.29; 95% CI: 0.765–2.53; p = 0.459). The heterozygous C/T genotype of the *CAT* gene rs1001179 single nucleotide polymorphism (SNP) exhibited a statistically significant association with an increased risk of acute radiation-induced skin toxicity in head and neck cancer (HNC) patients, conferring a 3.10-fold elevated risk (OR = 3.10; 95% CI: 1.72–5.57; p = 0.0002). Furthermore, multivariate logistic regression analysis revealed a significant correlation between

Table 5. Association between Genotypes of Superoxide Dismutase and Catalase Genes with Tumor Stage and Tumor Grade in Head and Neck Cancer Patients

Gene Name (SNP)	Genotype	Tumor stage		OR 95% CI	p value	Histological Grade		OR 95% CI	p value
		T1, T2 n=134	T3, T4 n=116			I, II n=103	III, IV n=147		
SOD1 A251G (rs2070424)	A/A	92	74	1 (Reference)		72	94	1(Reference)	
	A/G	37	38	1.27 (0.73-2.20)	0.38	27	48	1.36 (0.77-2.39)	0.282
	G/G	5	4	0.99 (0.25-3.83)	0.993	4	5	0.95 (0.24-3.69)	0.949
	A/G+ G/G	42	42	1.24 (0.73-2.10)	0.417	31	53	1.30 (0.76-2.24)	0.326
SOD2 C399T (rs1141718)	C/C	127	114	1 (Reference)		98	143	1(Reference)	
	C/T	0	0	NC		0	0	NC	
	T/T	7	2	0.31 (0.06-1.56)	0.158	5	4	0.54 (0.14-2.09)	0.379
	C/T+ T/T	7	2	0.31 (0.06-1.56)	0.158	5	4	0.54 (0.14-2.09)	0.379
SOD3 G172A (rs2536512)	G/G	38	32	1 (Reference)		32	38	1(Reference)	
	G/A	65	57	1.04 (0.57-1.87)	0.892	49	43	0.73 (0.39-1.37)	0.341
	A/A	31	27	1.03 (0.51-2.07)	0.924	22	36	1.37 (0.67-2.79)	0.375
	G/A+ A/A	96	84	1.03 (0.59-1.80)	0.892	71	79	0.93 (0.53-1.65)	0.822
Catalase A21T (rs7943316)	A/A	50	41	1 (Reference)		38	53	1 (Reference)	
	A/T	33	41	1.51 (0.81-2.80)	0.186	45	49	0.78 (0.43-1.39)	0.403
	T/T	31	34	1.33 (0.70-2.53)	0.371	20	45	1.61 (0.82-3.15)	0.162
	A/T+ T/T	64	75	1.42 (0.84-2.43)	0.187	65	94	1.03 (0.61-1.74)	0.891
Catalase C262T (rs1001179)	C/C	81	61	1 (Reference)		64	78	1 (Reference)	
	C/T	46	43	1.24 (0.72-2.11)	0.426	33	56	1.39 (0.89-2.39)	0.231
	T/T	7	12	2.27 (0.84-6.12)	0.103	6	13	1.77 (0.63-4.94)	0.27
	C/T+ T/T	53	55	1.37 (0.83-2.27)	0.211	39	69	1.45 (0.86-2.42)	0.154

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidential interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05); p value determined based on χ^2; NC, Not calculated

polymorphisms in both *SOD* and *CAT* genes and the occurrence of severe radiotherapy-related toxicities, including acute dermatitis and oral mucositis, as detailed in Table 4. Multivariate analysis demonstrated a significant association between the *SOD3* rs2536512 polymorphism and radiotherapy-induced oral mucositis in HNC patients. The homozygous recessive A/A genotype was linked to a 2.63-fold increased risk (OR = 2.63; 95% CI: 1.42–4.86; p = 0.002), while the combined heterozygous G/A and homozygous A/A genotypes showed a 1.94-fold elevated risk (OR = 1.94; 95% CI: 1.13–3.31; p = 0.014). Similarly, the *CAT* gene rs1001179 SNP exhibited strong associations with mucositis, with the T/T genotype conferring a markedly increased risk (OR = 14.00; 95% CI: 3.03–64.62; p = 0.0007) and the C/T genotype showing a moderate association (OR = 2.15; 95% CI: 1.33–3.48; p = 0.001). In contrast, the rs7943316 SNP of the *CAT* gene did not show a significant correlation with mucosal toxicity following radiotherapy.

Association of SOD1, SOD2 COD3 and CAT gene polymorphisms with tumor and node response towards radiotherapy in HNC patients

Logistic regression analysis was performed to evaluate the association between polymorphisms in *SOD1* (rs2070424), *SOD2* (rs1141718), *SOD3* (rs2536512), and *CAT* (rs7943316 and rs1001179) genes with tumor grade and radiotherapy response in HNC patients, as presented in Tables 4 and 5. Univariate analysis revealed no statistically significant correlation between these genetic variants and clinical or histopathological tumor grading, indicating that the studied SNPs do not association with clinical and histological tumor grades. The *SOD2* gene polymorphism, including both recessive and heterozygous genotypes, demonstrated no statistically significant association with advanced tumor stage (OR = 0.31; 95% CI: 0.06–1.56; p = 0.158) or higher histological grade (OR = 0.54; 95% CI: 0.14–2.09; p = 0.379). Similarly, the recessive genotype of *SOD3* showed no correlation with tumor grade >3 (OR = 1.03; 95% CI: 0.51–2.07; p = 0.924), as presented in Table 5. The heterozygous and homozygous recessive genotypes of *CAT* gene SNPs rs7943316 and rs1001179 showed no significant association with clinical or histological tumor staging in HNC patients. Similarly, polymorphisms in *SOD1*, *SOD2*, and *CAT* genes were not correlated with radiotherapy response. However, the *SOD3* rs2536512 SNP demonstrated a statistically significant protective effect, with a negative association observed for complete tumor response following radiotherapy (OR = 0.47; 95% CI: 0.23–0.96; p = 0.038) at three-month follow-up. The polymorphisms *SOD1* (rs2070424), *SOD2* (rs1141718), and *CAT* (rs7943316, rs1001179) with odds ratios below one showed no significant association with complete or partial tumor response in HNC patients, nor with acute radiation-induced toxicities such as dermatitis or mucositis when stratified by body mass index. However,

Table 6. Association between Genotypes of Superoxide Dismutase and Catalase Genes with Tumor and Node Response in Head and Neck Cancer Patients towards Radiotherapy

Gene Name (SNP)	Genotype	Tumor Response		Risk Ratio 95% CI	p value	Node Response		Risk Ratio 95% CI	p value
		CR n=209	PR/NR n=41			CR n=217	PR/NR n=33		
SOD1 A251G (rs2070424)	A/A	135	31	1 (Reference)		142	24	1(Reference)	
	A/G	65	10	0.67 (0.30-1.44)	0.309	67	8	0.70 (0.30-1.65)	0.423
	G/G	9	0	0.22 (0.01-3.99)	0.31	8	1	0.73 (0.08-6.18)	0.78
	A/G+ G/G	74	10	0.58 (0.27-1.26)	0.175	75	9	0.71 (0.31-1.60)	0.41
SOD2 C399T (rs1141718)	C/C	200	41	1 (Reference)		208	33	1(Reference)	
	C/T	0	0	NC		0	0	NC	
	T/T	9	0	0.25 (0.01-4.45)	0.348	9	0	0.32 (0.01-5.76)	0.445
	C/T+ T/T	9	0	0.25 (0.01-4.45)	0.348	9	0	0.32 (0.01-5.76)	0.445
SOD3 G172A (rs2536512)	G/G	53	17	1 (Reference)		60	10	1(Reference)	
	G/A	106	16	0.47 (0.22-1.00)	0.051	110	12	0.65 (0.26-1.60)	0.354
	A/A	50	8	0.49 (0.19-1.25)	0.14	47	11	1.40 (0.54-3.58)	0.477
	G/A+ A/A	156	24	0.47 (0.23-0.96)	0.038*	157	23	0.87 (0.39-1.95)	0.7561
Catalase A21T (rs7943316)	A/A	79	12	1 (Reference)		79	12	1 (Reference)	
	A/T	77	17	1.45 (0.65-3.24)	0.361	81	13	1.05 (0.45-2.45)	0.898
	T/T	53	12	1.49 (0.62-3.56)	0.369	57	8	0.82 (0.35-2.40)	0.871
	A/T+ T/T	130	29	1.46 (0.70-3.04)	0.301	138	21	1.00 (.46-2.14)	0.996
Catalase C262T (rs1001179)	C/C	118	24	1 (Reference)		125	17	1 (Reference)	
	C/T	74	15	0.99 (0.49-2.02)	0.992	76	13	1.25 (0.57-2.73)	0.562
	T/T	17	2	0.57 (0.12-2.67)	0.483	16	3	1.37 (0.36-5.22)	0.636
	C/T +T/T	91	17	0.91 (0.46-1.81)	0.806	92	16	1.27 (0.61-2.66)	0.511

SNP, Single nucleotide polymorphism; CR, Complete Response; PR, Partial Response; NR, No Response; RR, Risk ratio, CI, Confidential interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05), p value determined based on χ^2; NC, Not Calculated

Table 7. Association of Superoxide Dismutase and Catalase Gene Polymorphisms with Risk of Acute Toxicity Effects of Radiotherapy in Head and Neck Cancer Patients Stratified by BMI

Gene Name (SNP)	Genotype	Normal Weight (BMI ≤20)				Overweight (BMI ≤20)			
		All Patients	RS patients	OR 95% CI	p value	All Patients	RS patients	OR 95% CI	p value
SOD1 A251G (rs2070424)	A/A	73	43	1 (Reference)		93	49	1 (Reference)	
	A/G	34	18	0.89 (0.45-1.78)	0.759	41	18	0.83 (0.43-1.60)	0.584
	G/G	4	2	0.84 (0.14-4.83)	0.853	5	3	1.13 (0.26-4.96)	0.862
	A/G+ G/G	38	20	0.89 (0.46-1.72)	0.738	46	21	0.86 (0.46-1.61)	0.651
SOD2 C399T (rs1141718)	C/C	108	63	1 (Reference)		133	64	1 (Reference)	
	C/T	0	0	NC		0	0	NC	
	T/T	3	1	0.57 (0.05-5.61)	0.631	6	3	1.03 (0.25-4.28)	0.957
	C/T+ T/T	3	1	0.57 (0.05-5.61)	0.631	6	3	1.03 (0.25-4.28)	0.957
SOD3 G172A (rs2536512)	G/G	36	23	1 (Reference)		34	19	1 (Reference)	
	G/A	51	31	0.95 (0.47-1.89)	0.887	71	36	0.90 (0.45-1.80)	0.782
	A/A	24	10	0.65 (0.26-1.61)	0.354	34	14	0.73 (0.31-1.70)	0.475
	G/A+ A/A	75	41	0.85 (0.44-1.63)	0.636	105	50	0.85 (0.44-1.63)	0.631
Catalase A21T (rs7943316)	A/A	57	36	1 (Reference)		34	40	1 (Reference)	
	A/T	43	23	0.84 (0.43-1.63)	0.619	51	22	0.36 (0.18-0.72)	0.003*
	T/T	11	5	0.71 (0.23-2.24)	0.57	54	6	0.09 (0.03-0.24)	<0.0001*
	A/T+ T/T	54	28	0.82 (0.44-1.52)	0.531	105	28	0.22 (0.12-0.42)	<0.0001*
Catalase C262T (rs1001179)	C/C	83	52	1 (Reference)		59	55	1 (Reference)	
	C/T	27	15	0.88 (0.43-1.82)	0.743	62	13	0.22 (0.11-0.45)	<0.0001*
	T/T	1	1	1.59 (0.09-26.07)	0.742	18	1	0.05 (0.007-0.46)	0.006*
	C/T+ T/T	28	16	0.91 (0.45-1.84)	0.798	80	14	0.18 (0.09-0.36)	<0.0001*

RS, Radiosensitive; SNP, Single nucleotide polymorphism; CR, Complete Response; PR, Partial Response; NR, No Response; RR, Risk ratio; CI, Confidential interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05), p value determined based on χ^2

CAT gene variants rs7943316 (OR = 0.09; 95% CI: 0.03–0.24; p < 0.00001) and rs1001179 (OR = 0.05; 95% CI: 0.007–0.46; p = 0.006) demonstrated a significant negative association with oral mucositis, suggesting a potential protective role against mucosal toxicity in this patient cohort (Table 7).

Discussion

Genetic factors play a critical role in modulating individual susceptibility to radiation induced toxicities. Understanding polymorphisms in DNA repair and oxidative stress pathway genes may elucidate their contribution to differential radiation responses during radiotherapy and aid in mitigating treatment-related adverse effects. While extensive research has explored the role of DNA repair genes in carcinogenesis, their association with radiotherapy outcomes remains underexplored, highlighting a gap in translational evidence. Radiation response varies across ethnic populations due to underlying genetic susceptibility, contributing to heterogeneity in treatment outcomes and toxicity profiles. In normal tissues, the antioxidant defense system particularly enzymes such as superoxide dismutase and catalase play a critical role in mitigating oxidative stress-induced damage. The genetic variations including SNPs of antioxidant enzyme coding genes (*SO*D and *catalase*) have been considered as candidate genes for cancer susceptibility [21-23]. Polymorphisms in *SOD* and *CAT* genes have previously been investigated for their potential role in cancer susceptibility across various malignancies, including prostate [24, 25], cervical [26, 27], lung [22] and colorectal cancer [28, 29]. However, findings from epidemiological studies remain inconsistent, with several reports indicating no significant association between these genetic variants and cancer risk in diverse populations [30-33]. Parallel investigations have explored their relevance to radiotherapy-induced toxicities, with select studies confirming a significant correlation between these polymorphisms and acute skin reactions following radiation exposure [13, 16, 34]. Contradictory findings have been reported by other research groups, indicating no significant association between *SOD* gene variants and the risk of radiotherapy-induced normal tissue toxicities [15, 17, 18, 35]. In view of these inconsistencies, the present study aimed to evaluate the role of SNPs in *SOD* and *CAT* genes in modulating susceptibility to acute radiation-induced toxicities in HNC patients. Univariate logistic regression analysis identified a significant protective association between the heterozygous *SOD3* G172A genotype (rs2536512) and acute skin toxicity following radiotherapy in HNC patients (OR = 0.48; 95% CI: 0.26–0.88; p = 0.018). Conversely, the same *SOD3* variant was strongly associated with increased risk of oral mucositis, both in its homozygous form (OR = 10.47; 95% CI: 4.48–24.44; p < 0.0001) and heterozygous form (OR = 2.25; 95% CI: 1.21–4.17; p = 0.009). Additionally, the heterozygous *CAT* A21T genotype (rs7943316) showed a modest but significant association with oral mucositis (OR = 1.79; 95% CI: 1.00–3.22; p = 0.049), while the heterozygous C/T genotype of *CAT* rs1001179 was significantly linked to acute skin reactions (OR = 3.10; 95% CI: 1.72–5.57; p = 0.0002). Assessment of the correlation between *SOD1* (rs2070424), *SOD2* (rs1141718), *SOD3* (rs2536512), and *CAT* (rs7943316, rs1001179) gene polymorphisms with clinicopathological features and radiotherapy response in HNC patients revealed a significant protective association for *SOD3* rs2536512 (OR = 0.47; 95% CI: 0.23–0.96; p = 0.038). In contrast, no significant associations were observed for the remaining SNPs with tumor response or clinicopathological parameters. These findings align with previous reports examining the role of pathway-specific genetic variants in modulating radiation-induced toxicities across various malignancies [36]. While previous studies have highlighted the role of Mn-*SOD* (*SOD2*) polymorphisms in modulating radiosensitivity across various cancer types, our findings underscore the significance of extracellular *SOD3* genetic variants, specifically rs2536512, in influencing radiotherapy-induced toxicities in HNC patients. To the best of our knowledge, this study is of first of its own kind in India to study the variations related to oxidative stress related genes after radiotherapy on the risk of developing acute toxicity reactions in HNC patients.

In conclusion, analysis of *SOD1*, *SOD2*, and *SOD3* gene polymorphisms in relation to radiotherapy induced normal tissue toxicity revealed a significant association between the *SOD3* rs2536512 SNP and acute skin reactions in HNC patients. The heterozygous G172A and combined variant genotypes demonstrated a protective effect against acute cutaneous toxicity. In contrast, both the homozygous recessive 172A/A and heterozygous 172G/A genotypes of *SOD3* were significantly associated with an increased risk of developing oral mucositis following radiotherapy.

Author Contribution Statement

Concept: AKG, SJB Design: KDD, SJB, AKG, Experimental Studies: KDD Clinical studies: AKG, RAG, Data analysis: KDD, AKG, Statistical analysis: KDD, Manuscript preparation: AKG, RAG, KDD, SJB. All authors read and approved the final manuscript.

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Approval

The study protocol was approved by protocol committee of Krishna Vishwa Vidyapeeth (Deemed to be University)

Declaration of Conflict of interest

The authors declare that they have no competing financial or any other conflict of interests that could have appeared to influence the work reported in this paper.

Ethics Committee Approval

The study protocol was approved by Institutional Ethics Committee of Krishna Vishwa Vidyapeeth 'Deemed to be University', Karad.

Abbreviations

HNC: Head and Neck Cancer
RT: Radiotherapy
Gy: Gray
RTOG: Radiation Therapy Oncology Group
PCR-RFLP: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism
SNP: Single Nucleotide Polymorphism
ROS: Reactive Oxygen Species
SOD: Superoxide dismutase
CAT: Catalase
IMRT: Intensity modulated radiation
GTV: Gross tumor volume
CTV: Clinical Target Volume
PTV: Planning target volume
CT: Computed tomography
OR: Odds Ratio
CI: Confidence Interval
SD: Standard deviation
µL: Microliter
µg: Microgram
DNA: Deoxyribose Nucleic acid
EDTA: Ethylene Diamine Tetra Acetate

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